Osteoporosis—Defining the Problem

Introduction
Osteoporosis is a major public health concern. In fact, 1 of every 2 women and 1 of every 4 men age 50 years or older experience an osteoporosis-related fracture during her or his remaining lifetime. Osteoporosis is, however, both under recognized and undertreated. In the United States, only 20% of patients at high risk for osteoporotic fracture are evaluated or treated. Moreover, the costs associated with osteoporotic fractures are considerable. In 2005, these costs were estimated to be $19 billion. But the true costs often go beyond economics—osteoporotic fractures are associated with increased morbidity, disability and loss of independence, decreased quality of life (QOL) and mortality. Preventing fractures would preserve limited medical resources and reduce losses in terms of poorer QOL. Bisphosphonates have been shown to reduce not only fracture risk but also mortality in patients with osteoporosis. Primary care practitioners play a critical role in the identification of many diseases and conditions, and are in the best position to identify patients at increased risk for fractures due to low bone mass. Testing of at-risk patients is an important step toward improving patient care and reducing the disability and healthcare costs associated with this common condition.

Osteoporosis—A Growing Problem
Osteoporosis is defined as a reduction in bone strength that increases the risk of fractures. It is characterized by low bone mass and structural deterioration of the bone microarchitecture. A patient is defined as having osteoporosis when the T-score is ≤ –2.5 and as having osteopenia when the T-score is between -1 and -2.5. The T-score is a measurement of bone mineral density (BMD) as compared to “young normal” adults of the same sex. It has been suggested that a patient aged older than 50 years who sustains a low-trauma vertebral or hip fracture has a clinical diagnosis of osteoporosis. With the rapid aging of the American population, the prevalence of osteoporosis and associated fractures is expected to increase. Currently, an estimated 10 million Americans have osteoporosis and another 34 million have osteopenia (or low bone mass). The prevalence of osteoporosis in the United States is expected to reach more than 14 million by 2020. The most common fracture sites are the hip, spine, and wrist. In 2005, osteoporosis was the cause of more than 2 million fractures, and this number is expected to rise to 3 million fractures by 2025. See the following Figure.
Figure. Distribution of fractures associated with osteoporosis. Data from 2005.  

The effect of fractures on patients and the health care community is substantial. Approximately 24% of patients who experience hip fracture die within the following year, and 20% who were ambulatory before hip fracture require long-term care afterward.  

For elderly nursing home patients, the mortality risk is higher yet—40% die within a year of a hip fracture, and there is a 6% to 12% risk for refracture in these patients.  

Although hip fractures are 2 to 3 times more common in women than men, the one-year mortality after hip fracture is nearly twice as high in men compared with women.  

The National Osteoporosis Foundation estimates that costs associated with fractures will reach $25.3 billion by 2025.  

Risk Factors  
Despite the prevalence of this condition, many people with risk factors fail to appreciate their risk for fracture.  

A study of 60,393 individuals found that among women with a diagnosis of osteoporosis, only 43% believed themselves to be at increased risk for fracture.  

Furthermore, only 41% receiving treatment for osteoporosis believed they were at increased risk for fracture.  

The risk for osteoporosis and subsequent fracture increases with age, and although this condition affects both men and women, 80% of those affected are women.  

By age 80 years or older, approximately 87% of women have osteoporosis as measured by dual-energy X-ray absorptiometry (DXA) testing.  

While osteoporosis affects all races and ethnic groups, the risk is greater among some groups than others.  

See the following Table.
Table. Odds Ratio for Osteoporosis by Race/Ethnicity\textsuperscript{12}

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>African American</td>
<td>0.55</td>
<td>0.48-0.62</td>
</tr>
<tr>
<td>Native American</td>
<td>0.97</td>
<td>0.82-1.14</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.31</td>
<td>1.19-1.44</td>
</tr>
<tr>
<td>Asian*</td>
<td>1.56</td>
<td>1.32-1.85</td>
</tr>
</tbody>
</table>

Adapted from Siris ES et al. \textit{JAMA}. 2001;286(22):2815-2822.
* Predominantly of East Asian descent (Chinese, Japanese, Korean)

A higher body mass index (BMI) has been associated with a decreased risk of developing osteoporosis.\textsuperscript{13} Some evidence, however, suggests that while a BMI of 25 to 29.9 kg/m\textsuperscript{2} may be protective, a BMI ≥30 kg/m\textsuperscript{2} may be associated with an increased risk. Furthermore, a higher proportion of body fat, regardless of BMI, appears to increase the risk for osteoporosis and nonskeletal fracture.\textsuperscript{14} The Global Longitudinal Study of Osteoporosis in Women (GLOW) study found that obesity was not protective and was, in fact, associated with an increased risk for ankle and upper leg fractures.\textsuperscript{15} These findings may be explained by evidence linking different components of the metabolic syndrome (ie, increased triglycerides, reduced high-density lipoprotein cholesterol, hypertension) to the development of low bone mineral density and osteoporosis.\textsuperscript{14} In addition, obese women are more likely to have early menopause, and have a higher fall risk.\textsuperscript{14} Interestingly, in a study conducted in nearly 200,000 postmenopausal women, African American women had the highest BMD and Asian women the lowest; however, the BMD score differences were explained by size difference (larger bones are more dense by DXA) in all but the African American group.\textsuperscript{16}

People with a family history of osteoporosis are predisposed to develop osteoporosis, and a broken bone in these individuals suggests osteoporosis may be present.\textsuperscript{1,8,13} A parental history of hip fracture increases an individual’s risk for fracture independent of BMD scores.\textsuperscript{17} Low levels of testosterone and estrogen in men, and amenorrhea, menopause, or low estrogen levels in women increases the risk of osteoporosis.\textsuperscript{1,9} In a study of 200,160 postmenopausal women with no previous diagnosis of osteoporosis, 39.6% had osteopenia and 7.2% had osteoporosis.\textsuperscript{13} This suggests that in the average waiting room of a primary care practice, nearly half of postmenopausal women have osteoporosis or osteopenia that has never been evaluated. Furthermore, in the wake of the Women's Health Initiative findings in 2002, many women stopped taking hormone replacement therapy, placing them at greater risk for osteoporosis.\textsuperscript{7,18}

A diet low in calcium and vitamin D also has been implicated in the development of osteoporosis, and high intake of protein, sodium and caffeine are also associated with increased risk.\textsuperscript{1,19} More than half of North American women receiving therapy to treat or prevent osteoporosis receive inadequate amounts of vitamin D.\textsuperscript{19} But deficiencies are
even more widespread—it is estimated that the majority of Americans receive less than recommended amounts of vitamin D and calcium. An inactive lifestyle is also associated with an increased risk for developing this condition, and conversely exercise appears to be protective.

Use of certain medications can increase the likelihood of developing osteoporosis. Corticosteroids, commonly used, are a major contributor. Proton pump inhibitors (PPIs) and SSRI (selective serotonin reuptake inhibitor)-type antidepressant medications also are among the more commonly used drugs that may increase the risk for osteoporosis. The risk with PPIs is particularly important because they are available over-the-counter. Long-term use of heparin, or use of immunosuppressants, anticonvulsants, aromatase-inhibitor therapy for breast cancer, tamoxifen (premenopausal), gonadotropin-releasing hormone agonist therapy for prostate cancer, parenteral medroxyprogesterone acetate, supraphysiologic thyroxine doses, and total parenteral nutrition also increase the risk for osteoporosis.

Smoking is an important risk factor—with current smokers being at greater risk than former smokers. Excessive consumption of alcohol, defined as 3 or more units of alcohol per day (30 mL of spirits, 285 mL of beer, or 120 mL of wine), also appears to increase risk.

Comorbidities are also important to consider when evaluating risk factors for osteoporosis. Among the more common diseases associated with increased fracture risk are rheumatoid arthritis, chronic obstructive pulmonary disease, certain gastrointestinal diseases, and diabetes mellitus. The complete list is extensive; additional information can be found in the National Osteoporosis Foundation (NOF) Clinician’s Guide to Prevention and Treatment of Osteoporosis at: http://www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v7.pdf.

Fracture Risk and Prevention
Prevention of fractures by stopping bone loss and increasing bone mass and strength is the main concern in the management of osteoporosis. Although osteoporosis itself places the patient at risk, other factors are also important. Skeletal risk factors include a prior hip fracture, which increases the risk for subsequent hip fracture 4-fold, and prior vertebral fracture, which increases the risk for subsequent vertebral fracture. The major nonskeletal risk factor for osteoporotic bone fracture is falls. In fact, 98% of hip fractures are the result of falls, although the proportion of vertebral fractures attributable to falls is lower. Poor balance, use of sedating medication, and cognitive problems, as well as lack of muscle strength—all contribute to the risk for falls, and should be addressed in the comprehensive management plan for at-risk patients. Somewhat surprisingly, although patients with osteoporosis are at greater risk for fracture, more fractures occur in patients with “osteopenia” because these patients constitute a larger portion of the population. Thus, determining a patient’s fracture risk is an important component of fracture prevention. FRAX® is an online fracture risk
assessment tool developed by the World Health Organization and released in 2008. It is available at http://www.shef.ac.uk/FRAX/; the NOF recommends its use in postmenopausal women and men aged 50 years and older.\textsuperscript{7,21} FRAX® is most useful in helping to determine if treatment is needed in patients with osteopenia because it identifies those patients with osteopenia who are at elevated risk because of age and other clinical risk factors.\textsuperscript{7,21}

Although BMD serves as a good indicator of fracture risk, it is not the only relevant factor. FRAX® incorporates several validated and weighted risk factors in the algorithm to determine the 10-year probability for hip fracture and for major osteoporotic fractures (wrist, proximal humerus, hip, and clinical vertebral fracture).\textsuperscript{21} These risk factors in FRAX® include age, height and weight, the T-score or BMD at the hip, prior fracture after age 45, parental hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, and consumption of 3 or more units of alcohol per day. This tool has limitations, however; some important risk factors have not been included in the algorithm—vitamin D deficiency, the propensity for or history of falls, level of physical activity, bone turnover markers, previous treatment for osteoporosis, and the use of certain medications, among others. But the greatest limitation is that few clinicians use FRAX®,\textsuperscript{21} a situation that should improve if more clinicians become aware of its clinical utility.

QOL is adversely affected by fracture. Fractures may result in both acute and chronic pain and may increase dependence and depression. Evidence suggests that multiple fractures appear to have an additive impact on QOL. The GLOW study explored the effect of common fractures on QOL in women aged 55 years and older. More than 55,000 women participated. Spine, hip, and upper leg fractures resulted in the greatest reduction in QOL, with a European Quality of Life 5 Dimensions Index (EQ-5D) score of 0.62, 0.64, and 0.61, respectively, compared with a score of 0.79 for patients who had no history of fracture.\textsuperscript{22} A history of multiple fractures also reduced EQ-5D scores, with scores of 0.74 for 1 prior fracture, 0.68 for 2, and 0.58 for 3 or more. These women experienced reductions in health-related QOL that were similar to those faced by women with other chronic diseases such as diabetes (0.67), arthritis (0.69), and lung disease (0.71).\textsuperscript{22}

Depression and anxiety, pain, mobility issues, self-care problems, and difficulty performing usual activities all affect patients who experience fractures. Compared with individuals who had not experienced fractures, those in the GLOW study who had had 3 or more fractures were more likely to suffer from depression or anxiety (56% vs 40% for those with no fractures); to have pain (88% vs 67%) or to have difficulty with mobility (62% vs 26%) and self-care (26% vs 6%) or performing usual activities (60% vs 26%). Women with 1 or 2 fractures also experienced greater degrees of depression, anxiety, pain, and difficulty with mobility, self-care, and usual activities than those without.\textsuperscript{22} Reductions in QOL associated with fracture are long-term, though some improvement may occur with time.\textsuperscript{22}
**Diagnosis**

Underdiagnosis is a substantial problem, with only 14% of women aged 65 years or older enrolled in Medicare having undergone BMD testing at least once.\(^2\) NOF has established guidelines regarding testing and diagnosis. The decision to test a particular patient is based on the individual’s fracture risk profile and skeletal health assessment. However, NOF recommends testing all women aged 65 years and older and all men aged 70 years and older, regardless of clinical risk factors. It does not recommended testing in children or adolescents, nor does it recommend routine testing in healthy young men or premenopausal women.\(^7\) Likewise, the US Preventive Services Task Force recommends screening for osteoporosis in women aged 65 years or older and in younger women with a fracture risk equal to that of a 65-year-old white woman with no additional risk factors.\(^24\) The American Association of Clinical Endocrinologists recommends screening for all women aged 65 years or older and in younger postmenopausal women at increased risk of fracture.\(^25\)

DXA is considered the gold standard for measuring BMD,\(^7,26\) and DXA testing of both spine and hip should be performed. Results can be stated in terms of Z-scores or T-scores. Z-scores are based on a comparison with others of the same sex and age as the patient, while T-scores compare the patient’s results with those of young normal adults of the same sex, and serve as the basis for making a diagnosis of osteoporosis or low bone mass.\(^7\) The scores are expressed in terms of standard deviations above or below the mean. If the T-score at the spine or hip is \(\leq -2.5\), that provides the basis for a diagnosis of osteoporosis.\(^7\) Although other modes of measurement exist, including peripheral DXA, quantitative computed tomography (QCT), peripheral QCT, and quantitative ultrasonometry (QUS), DXA is the preferred method of measurement.\(^7\)

In the adult skeleton, bone remodeling occurs constantly, an ongoing balancing act between osteoblasts and osteoclasts. This process can be assessed and bone loss detected through the measurement of biochemical markers of bone turnover in the serum and urine. Resorption markers include serum C-telopeptide (CTX) and urinary N-telopeptide (NTX), while formation markers include serum bone-specific alkaline phosphatase (BAP) and osteocalcin.\(^7,9\) Procollagen type 1 amino-terminal propeptide (P1NP) is a more useful marker of formation than either BAP or osteocalcin,\(^27\) but it is not widely available. Evidence indicates that anti-bone-resorption therapy reduces levels of bone turnover markers.\(^28\)

**Barriers to Testing of At-Risk Individuals**

Clearly, there is opportunity to increase the number of patients who are appropriately tested for osteoporosis based on current recommendations. Determining potential barriers to more effective identification of those with osteoporosis may help overcome this challenge and increase the percentage of those who are tested. In recent years, a number of studies have attempted to determine why such a low percentage of at-risk patients are tested for osteoporosis.
In 1 setting, community screening at no cost to participants targeted individuals between 40 and 60 years of age who were evaluated using an ultrasound heel bone density scanner. Of 1048 individuals who participated, 147 had a T-score of –1.5 or less. Letters were sent to these patients’ primary care physicians requesting that they order a DXA. Only 37% of the patients, however, actually obtained a DXA scan. When asked why they had not gotten a test, participants stated that they did not think it was important, because if it had been, their primary care physician would have had them tested.

A survey of more than 1200 individuals aged 60 years and older found that while most believed osteoporosis to be a serious condition, few thought they themselves were susceptible. Men were less likely to believe in both the severity of osteoporosis and their own susceptibility to the condition than were women. Overall, only 44.6% of respondents believed they were at risk for osteoporosis, and only 26.3% thought they were likely to develop it. Despite the fact that age is strongly associated with increased risk for osteoporosis, older respondents were less likely to believe in the severity of osteoporosis and in the value of screening. Given the prevalence of this condition, it appears that patient education may be necessary to increase identification of individuals with osteoporosis.

Conclusions
Osteoporosis and low bone mass are under recognized and underdiagnosed conditions with serious consequences for patients. Fractures resulting from osteoporosis or osteopenia are associated with increased morbidity and mortality and decreased independence and QOL. Important risk factors include decreased BMD as determined by DXA; age; use of medications such as glucocorticoids, anticonvulsants, PPIs, and agents used to treat malignancies; cigarette smoking and excessive alcohol consumption. Regardless of other clinical risk factors, however, all women aged 65 years or older and all men aged 70 years or older should have their BMD assessed using DXA. Improving the detection of patients at elevated risk for fracture in order to prevent future fractures will require increased patient education about lifelong bone health.

References:


