# Osteoporosis: Screening, Evaluation, and Monitoring

*Michael W. Schaefer, MD, and Geetha Gopalakrishnan, MD*

**Osteoporosis is the most common skeletal** disorder. It is characterized by a decrease in bone mineral density resulting in fractures. According to the **National Osteoporosis Foundation (NOF)**, 10 million Americans are affected by osteoporosis and an additional 34 million are at risk for osteoporosis. Although osteoporosis is more common among women, men account for approximately 20% of all cases. It is estimated that 50% of women and 25% of men over the age of 50 years will have an osteoporosis related fracture in their lifetime. Osteoporotic fractures typically involve the spine, hip and forearm and result from minimal or no trauma. The morbidity, mortality, and cost associated with these fractures are significant. Mortality rates as high as 25% are reported one year after a hip fracture. If patients survive, 25% will require long-term nursing home care and only 40% will achieve their pre-fracture level of independence. The estimated cost of these fractures to our health care system is more than $17 billion per year and this cost is anticipated to triple by 2040. Therefore, prevention of osteoporosis, particularly fractures, is a public health priority.[1]

## What are the current evidence-based recommendations on screening for osteoporosis?

### Choice of Screening Test

The goal of screening is to identify individuals at risk for osteoporotic fractures. **Dual Energy X-ray Absorptiometry (DXA)** is the gold standard for diagnosing osteoporosis and monitoring changes in **bone mineral density (BMD)**. BMD measurement by DXA strongly predicts fracture risk. It is estimated that each **standard deviation (SD)** decrease in BMD increases the risk of fracture by 2-3 fold.[2] BMD can be expressed as a number of SD away from a sex-matched young normal adult population (T-score) or a population of the same age and gender (Z-score). Osteoporosis is defined by a clinical history of fragility fractures or by a DXA assessment of the lumbar spine, hip, and forearm BMD (see Table 1).[1]

Other screening tools include quantitative ultrasound (QUS), quantitative CT (QCT), and peripheral QCT. Although these scans also predict fracture risk, they are not currently recommended for screening purposes. Cost, radiation exposure and lack of normative data limit the use of these tests for screening and monitoring therapy (see Table 2).[3]

### Population to be screened

Due to the increased risk of fractures noted with age, the NOF currently recommends screening all postmenopausal women over the age of 65 years and all men over the age of 70 years. This recommendation is based on an outcomes analysis conducted by the **United States Preventive Service Task Force (USPSTF)**. Based on prevalence rates of osteoporosis, screening 10,000 postmenopausal women between the age of 65 and 69 would identify approximately 1,200 individuals at high risk for fracture (T-score ≤ -2.5). If this high-risk population were offered treatment, it is estimated that 14 hip fractures and 40 vertebral fractures could be prevented, assuming 70% compliance. These conclusions were based on published evidence that bisphosphonates reduce the risk of hip fractures by 37% and vertebral fractures by 50%. In this analysis, fracture prevention utilizing anti-resorptive therapy became more favorable with increasing age.[6]

Furthermore, the NOF recommends screening in younger postmenopausal women and men aged 50 to 69 years based on the presence of risk factors (see Table 3). The USPSTF analyzed the use of risk factors as a guide to screening. In women aged 60-64, screening would prevent only

**TABLE 1: WORLD HEALTH ORGANIZATION CLASSIFICATION [1]**

| | |
|---|---|
| **Normal** | T-score at -1.0 and above |
| **Low bone mass (Osteopenia)** | T-score between -1.0 and -2.5 |
| **Osteoporosis** | T-score at or below -2.5 |
| **Established Osteoporosis** | One or more fragility fractures |

T-score: a number of standard deviations (SD) away from a sex-matched young normal adult population

**TABLE 2: SCREENING TOOLS FOR OSTEOPOROSIS [2-5]**

| Type of Test | Ability to Predict Fracture | Advantages |
|---|---|---|
| **Dual Energy X-ray Absorptometry (DXA)** | + | Gold standard for screening and monitoring changes in BMD. Advantage: Low cost, ease of use, excellent precision and minimal radiation exposure. |
| **Quantitative Ultrasound (QUS)** | + | Can be considered for screening but should not be used to diagnose or monitor therapy. Individuals with a low QUS measurement need to be reassessed by DXA for diagnostic purposes. Advantage: Low cost, ease of use and lack of radiation exposure. |
| **Quantitative computed tomography (QCT) & peripheral QCT** | + | Utilized in research studies. Higher radiation exposure and expense has limited use in clinical settings. Advantage: Provides a detailed assessment of the geometrical and structural elements of bone. |

| TABLE 3: COMMON RISK FACTORS FOR OSTEOPOROSIS & FRACTURE [1, 7] | |
|---|---|
| General | History of prior low trauma fracture as an adult, Low BMD in patient with or without fractures, Low body mass, Frequent falls |
| Lifestyle factors | Low calcium intake, Smoking, Alcohol use (> 3 drinks per day), High caffeine intake, Inadequate physical activity |
| Medications | Glucocorticoids (> 5mg Prednisone daily for at least 3 months), Aromatase inhibitors, Anticonvulsants, Selective serotonin reuptake inhibitors, Proton pump inhibitors, Anticoagulants, Depo-medroxyprogesterone |
| Medical conditions | Thyrotoxicosis, Hyperparathyroidism, Diabetes Mellitus, Vitamin D deficiency, Cushing's syndrome, Hypogonadism, Rheumatoid arthritis, Malabsorption, Multiple Myeloma |
| Genetic factors | Hip fracture in a first degree relative |

five hip fractures over five years. However, in the presence of one risk factor, the rate of fracture prevention doubled and approached that of the group over age 65. Based on these estimates, the presence of a risk factor should prompt screening in younger postmenopausal women and men over the age of 50 years.[6]

Lastly, individuals with secondary causes of osteoporosis such as steroid use or hyperparathyroidism should be screened for osteoporosis irrespective of age. Routine BMD assessment is not recommended for healthy young men, premenopausal women, or children.[1]

### Frequency of Testing

Despite having established guidelines on when to start screening for osteoporosis, limited data is available on how often to repeat BMD assessments after the initial exam. Hillier and colleagues prospectively followed 4,124 postmenopausal women with a mean age of 72 and a total hip T score of -1.3 for a period of eight years. On average, the subjects showed a 0.59% loss in BMD per year and the mean T score at follow up decreased to -1.64. After eight years, there were 877 non-vertebral fractures including 275 hip fractures. After a detailed ROC analysis, the BMD at follow up could not predict fractures any better than the original BMD evaluation. The authors concluded that repeat DXA analysis was not useful in further estimating fracture risk in this population.[8]

Considering the low rate of bone loss noted in this study, these findings are not surprising, and therefore should not be extrapolated to other populations with higher rates of bone loss, such as early menopausal women or individuals with osteoporotic risk factors. The American Association of Clinical Endocrinologists (AACE) currently recommends that in patients with a normal BMD (T-score > -1) at baseline, repeat screening should be done every three to five years. If a patient has a BMD significantly above the lower limits of normal, further testing may not be needed. For patients at risk for osteoporosis (i.e., patients with risk factors or low bone mass), DXA should be performed every one to two years until stability in BMD is established, after which testing frequency can decrease.[9]

| TABLE 4: FDA- APPROVED PHARMACOLOGIC AGENTS FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS [1] | | | |
|---|---|---|---|
| Class | Agents | Prevention | Treatment |
| Bisphosphonates | Alendronate | + | + |
| | Risedronate | + | + |
| | Ibandronate | + | + |
| | Zoledronic Acid | + | + |
| Calcitonin | Salmon Calcitonin | - | + |
| Estrogen Agonist/Antagonist | Raloxifene | + | + |
| Hormone Replacement Therapy | Estrogen | + | - |
| Parathyroid Hormone | Teriparatide | - | + |
| RANK Ligand (RANKL) Inhibitor | Denosumab | - | + |

## How should response to treatment be assessed?

Once a diagnosis is established, calcium and vitamin D supplementation along with pharmacological therapy can be considered for the prevention and treatment of osteoporosis (see Table 4).

Even though treatment can be associated with a decrease in the incidence of osteoporotic fractures, development of a new fracture does not necessarily represent failure of therapy. At best, pharmacological agents reduce fracture rates by 30-70% [10]. Therefore, monitoring changes in BMD can help determine the effectiveness of a treatment strategy and guide management decisions.

The NOF, AACE, and **International Society for Clinical Densitomtery (ISCD)** all recommend using DXA for monitoring treatment. In order to compare BMD, the measured change in BMD must be greater than the precision error of the machine.[9] In general, precision errors range between 2-4% for the spine and 3-6% for the hip. Changes that are greater than the precision error are considered clinically significant.[1] However, changes in BMD with aging or upon initiation of therapy tend to be small in magnitude compared with the expected error in measurement, and therefore, waiting at least a year before repeating a BMD measurement (and preferably two years) is recommended.[2]

In addition to serial DXA measurements, assessment of bone turnover can be considered in certain circumstances. Bone resorption makers such as **N-terminal crosslinking telopeptide of type 1 collagen (NTX-1)** and **C-terminal crosslinking telopeptide of type 1**

**collagen (CTX-1)** are elevated in high turnover states like menopause.[10] They have been shown to predict fracture risk independent of BMD in postmenopausal women[11]. These markers decrease rapidly with antiresorptive therapy and can be used to monitor response to treatment. Urine NTX is the most common biochemical marker used in clinical practice. Considering the biological variability of this marker, levels should be obtained in the morning after an overnight fast. Large change (i.e. > 50% reduction) is required for clinical significance. Routine measurement of bone turnover markers is not recommended. [10] Measurement of bone turnover can be considered in cases when a discrepancy exists between serial DXA measurement and the clinical senario (i.e. loss in BMD despite therapy with bisphosphonates). In these cases, bone turnover markers can assess degree of compliance or absorption of oral medications.

## Who should undergo workup for secondary causes and what should that workup include?

Traditionally, menopausal or age-related osteoporosis is considered primary osteoporosis. Secondary osteoporosis results from a variety of medical conditions and external factors. All patients with osteoporosis should have a comprehensive history and physical examination to identify risk factors for osteoporosis (i.e. family history, medication use, medical history). A more extensive work-up to evaluate secondary causes of bone loss may be indicated in patients with low BMD (Z-score < -2.0), fragility fractures, failure to respond to therapy, or a decline in BMD at a rate greater than expected for age.[12]

The AACE recommends that all patients with osteoporosis, regardless of suspicion for secondary causes, have a routine baseline laboratory evaluation. These studies include serum calcium, phosphorous, creatinine, electrolytes, total protein, albumin, liver enzymes and complete blood count. A 25-hydroxy Vitamin D level should also be checked in any osteoporotic patient, given the prevalence of Vitamin D deficiency. The AACE recommends more extensive laboratory workup depending on history and or physical exam findings including urinary calcium excretion, TSH, PTH, serum and urine protein electrophoresis, urinary free cortisol or other assessment of cortisol excess (1 mg overnight dexamethsone suppression test).[8]

## Conclusion

Osteoporosis is a common condition with a significant impact on morbidity, mortality, and health care costs. With this in mind, it is important to screen not only postmenopausal women, but also older men and younger individuals with risk factors for bone loss and osteoporotic fractures. DXA is not only useful as a screening tool, but is an excellent way to monitor response to therapy. Finally, all patients with osteoporosis should have a routine comprehensive evaluation including history, physical, and laboratory assessment; however, a subset of these patients should have a more detailed laboratory workup to rule out secondary causes.

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*Michael W. Schaefer, MD, is an Endocrinology Fellow at the Warren Alpert Medical Shool of Brown Univerisity.*

*Geetha Gopalakrishnan, MD is an Associate Professor of Medicine at the Warren Alpert Medical School of Brown University.*


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## Correspondence


Geetha Gopalakrishnan, MD
900 Warren Ave, Suite 300
East Providence, RI 02914
phone: (401) 444-3420
e-mail: Geetha_Gopalakrishnan@brown.edu