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# The Diagnosis and Workup of Patients for Osteoporosis or Osteopenia (Low Bone Mass)

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## 1. Introduction

The rate of screening and treatment for osteoporosis remains low. Osteoporosis affects approximately 200 million women worldwide and two thirds of women 80 or older have this disease. It causes more than 1.6 million hip fractures worldwide. (International Osteoporosis Foundation, 2006) In the United States, more than 10 million Americans have osteoporosis and 3.6 million have low bone mineral density of the hip. In 2005 in the United States, there were more than 2 million osteoporotic fractures in men and women. These fractures caused more than 432,000 hospitalist admissions, 2.5 million physician office visits and about 180,000 nursing home admissions yearly in the United States. In 2005, the cost of osteoporotic fractures was approximately 17 billion dollars. (U.S. Department of Health and Human Services, 2004) Osteoporosis is responsible for approximately 90% of all spine and hip fractures in Caucasian females age 65-84 in the United States.

Fifty percent of women and twenty-five percent of men greater than age 50 will experience an osteoporotic fracture in their remaining lifetime. (National Osteoporosis Foundation, Feb. 2008) Less than 5 percent of patients with a clinical low trauma fragility fracture are referred for medical evaluation and treatment. (Bonura, 2009) In 2005, a population based study reported that the proportion of women screened and treated for osteoporosis after a fragility fracture was 10.2 percent and 12.9 percent respectfully. In males, studies indicate that a low proportion of men are evaluated for osteoporosis or receive anti-resorptive therapy after a fragility fracture. (Feldstein, 2005) Most patients with hip fractures receive no pharmacologic treatment for osteoporosis.

Physician frequently fail to diagnose and treat osteoporosis, even in the elderly patients who have suffered a fractures. (Bonura, 2009) Less than 20 percent of women with wrist fractures are screened for osteoporosis, and only 12.9 percent are treated for osteoporosis after a fracture. (Cuddihy, 2002) In a clinical study the majority of patients with clinical vertebral fractures (80 percent) did not receive osteoporosis therapy. (Lindsay, 2005) A prior osteoporotic fracture increases the risk of future fractures. A forearm fracture is associated with a two fold increased risk of fractures. Radiographic vertebral fractures are associated with a higher risk of subsequent hip and other fractures. In the year following a vertebral fracture, 26 percent of patients will fracture a hip, pelvis, vertebrae, wrist, humerus, or leg. (Klotzbuecher, 2000)

Following a hip fracture in women, the mortality ranges between 20-24% within one year. 25% of patients are admitted to a long term healthcare facility and only 40% are able to obtain their pre-fracture level of independence. Worldwide, one-third of hip fractures occur

in men and more men than women die after a hip fracture with a mortality rate of about 37.5%. (Jiang, 2005) The most common of all the osteoporotic fractures are vertebral fractures. They are usually painless, but can cause back pain, height loss, deformity, reeducated respiratory function, disability, and a reduced quality of life. There is also an increase in mortality in women of about 23% over 8 years and they can cause an increase in future vertebral and non vertebral fractures. (Kado, 1999)

Prior Fracture	Relative Risk of Future Fractures		
	Wrist	Vertebral	Hip
Wrist	3.3	1.7	1.9
Vertebral	1.4	4.4	2.3
Hip	Not Available	2.5	2.3

Table 1. Prior Fracture as a Predictor of Fracture Risk (Klotzbuecher, 2000))

2. Evaluation

Postmenopausal women and men after age 50 should be evaluated for their risk factors for osteoporosis and fracture, and their risk factors of falling. This evaluation includes a history and a physical exam, including a height measurement and, if necessary diagnostic testing. Several clinical risk factors for osteoporosis have been indentified and should be evaluated. Non-modifiable risk factors include advancing age, female sex, Asian or Caucasian ethnicity, history of a fracture as an adult, family history of a fracture in a first degree relative (maternal or paternal history of a hip fracture) and rheumatoid arthritis. Modifiable risk factors comprise low body weight, hormone deficiency, long term use of medications that affect bone homeostasis (e.g., glucocorticoids), causes of secondary osteoporosis, smoking, excessive alcohol consumption, an inactive lifestyle, and a lifetime diet low in calcium and vitamin D. The more risk factor that a patient has, the greater the risk of a fracture. (Bonura, 2009)

The most important of all these risk factors are age (65 or greater in women and 70 or greater in men) and the occurrence of a low trauma fracture after age 40. Other risk factors of importance are bone mineral density, genetics, menopause, BMI, and lifestyle.

As a woman ages, their fracture risk increases. After age 50, their fracture risk doubles every 7 or 8 years. The average age of a hip fracture in women is 82 years and in men 50% of their hip fractures occur before age 80. Vertebral fractures usually occur in women and men in their seventies. (Chang, 2004) A prior osteoporotic fracture increases the risk of future osteoporotic fracture risk. If a postmenopausal female sustains an osteoporotic fracture, she has approximately a two fold increase of sustaining another osteoporotic fracture in her lifetime.

Bone mineral density also is a risk factor for future fractures. Bone mineral density affects fracture risk. The lower the bone mineral density (BMD), the higher the risk for fractures. A decrease of 1 standard deviation of bone mineral density (BMD) represents a 10-12% decrease in BMD and can increase fracture risk by 1.5 to 2.6 times. (Marshall, 1996) Genetics plays a role in osteoporosis and future fracture risk. Daughters of women who have had an osteoporotic fracture, and daughters of first degree relatives (mother or sisters) or have osteoporosis have lower bone mineral density (BMD) for their age. Also a history of an

<b>Lifestyle Factors</b>		
Low calcium intake	Vitamin D insufficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum (in antacids)
Alcohol (3 or more drinks/d)	Inadequate physical activity	Immobilization
Smoking (active or passive)	Falling	Thinness
<b>Hypogonadal States</b>		
Androgen insensitivity	Hyperprolactinemia	Premature ovarian failure
Anorexia nervosa and bulimia	Panhypopituitarism	Turner’s & Klinefelter’s syndromes
Athletic amenorrhea		
<b>Endocrine Disorders</b>		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing’s syndrome	Hyperparathyroidism	
<b>Gastrointestinal Disorders</b>		
Celiac disease	Inflammatory bowel disease	Pancreatic disease
Gastric bypass	Malabsorption	Primary biliary cirrhosis
GI surgery		
<b>Genetic Factors</b>		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher’s disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan syndrome	Riley-Day syndrome
Hemochromatosis	Menkes steely hair syndrome	
<b>Hematologic Disorders</b>		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell diseases	Thalassemia
<b>Rheumatic and Autoimmune Diseases</b>		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
<b>Miscellaneous Conditions and Diseases</b>		
Alcoholism	Emphysema	Muscular dystrophy
Amlyloidosis	End stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Post-transplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis
<b>Medications</b>		
Anticoagulants (heparin)	Cancer chemotherapeutic drugs	Glucocorticoids (≥ 5 mg/d of prednisone or equivalent for ≥ 3 mo)
Anticonvulsants	Cyclosporine A and tacrolimus	Gonadotropin releasing hormone agonists
Aromatase inhibitors	Depo-medroxyprogesterone	Lithium
Barbiturates		

Table 2. Conditions, Diseases and Medications That Cause or Contribute to Osteoporosis and Fractures (National Osteoporosis Foundation, 2008)

osteoporotic fracture in a first degree relative increases an individual’s risk of osteoporotic fractures. (Seaman, 1989) During the late menopausal transition (2-3 years before menopause) and during menopause, there is an increase in bone resorption due to a decrease in estrogen production. Women lose approximately 2% of BMD annually for about 5 years during menopause. After which they lose 1-2% per year. They can lose 10.5% in their spine and 5.3% in their hip over this 5-7 year period in this time. (Recker, 2000) In men bone loss increases after age 70 and it is more common in men who are deficient in testosterone or estradiol. (Fink, 2006)

If a woman is thin, a weight of less than 127 pounds, it is a risk factor for a low BMD and a high risk for fracture, A high BMI may be protective. In older women, low BMI is associated with a higher fracture risk. (Van Der Voort, 2001)

The lifestyle factors that are associated with low bone mass and fracture risk are cigarette smoking, alcoholism, poor nutrition, and lack of physical activity, There are also secondary causes of low bone mineral density, including medications, genetic disorders, and various disease states.

Also, in all menopausal women and men after age 50, their risk for falls should be evaluated. About one-third of men and women age 65 years of age or older fall each year. They should be questioned about their history of falls, muscle weakness, dizziness, difficulty walking, impaired vision, balance problems, or medications that affect balance (e.g., sedatives, narcotics, anti-hypertensives). Some of the medications that have the highest association with falls are the serotonin-reuptake inhibitors, antiarrhythmic drugs, tricyclic antidepressants, neuroleptic agents, benzodiazepines, and the anticonvulsants. (Leipzig, 1999) Ten percent of these falls result in hip fractures and 90% of hip fractures are due to falls. An excellent screening test is the “Get Up and Go” test. Have a senior patient get up from a chair, without using their arms, and then have them walk and observe for unsteadiness. (Mathias, 1986) The more number of risk factors of falling, the greater risk of falls.

Medical Risk Factors		
Age	Medications causing over-sedation (narcotic analgesics, anticonvulsants, psychotropics)	
Anxiety and agitation	Orthostatic hypotension	
Arrhythmias	Poor vision and use of bifocals	
Dehydration	Previous fall	
Depression	Reduced problem solving and mental acuity and diminished cognitive skills	
Female gender	Urgent urinary incontinence	
Impaired transfer and mobility	Vitamin D insufficiency [serum 25-hydroxyvitamin D (25(OH)D) < 30 ng/ml (75 nmol/L)]	
Malnutrition		
Environmental Risk Factors	Neuro and Musculoskeletal Risk Factors	Other Risk Factors
Lack of assistive devices in bathrooms	Kyphosis	Fear of falling
Loose throw rugs	Poor balance	
Low level lighting	Reduced proprioception	
Obstacles in the walking path	Weak muscles	
Slippery outdoor conditions		

Table 3. Risk Factors for Falls (National Osteoporosis Foundation, 2008)

During a patient’s examination, height measurement may be useful to indicate occult vertebral compression fractures, which are indicative of osteoporosis. They are the most common osteoporotic fractures in postmenopausal women, and two-thirds of these fractures are not clinically recognized. (Cauley, 2007) The loss of height, kyphosis, and back pain may be signs of vertebral fractures. Normally after achieving maximal height, women can lose up to 1.0 – 1.5 inches (2.0 – 3.8 cm) of height as part of the normal aging process, due to degenerative arthritis and shrinkage of intervertebral disks. Height loss of greater than 1.5 inches (3.8 cm) increases the risk of a vertebral fracture. One must suspect a vertebral fracture in postmenopausal women with a historical height loss greater than 4 cm (1.6 in.) or a prospective height loss greater than 2 cm (0.8 in.). In men, a historical height loss greater than 6 cm (2.4 in.) or a prospective height loss greater than 3 cm (1.2 in.). Vertebral fractures are associated with an increase of vertebral and nonvertebral fractures in the future. Nineteen percent of patients who have a vertebral fracture will sustain another fracture within one year. (Laster, 2007) Across a range of BMD, prevalent vertebral fractures increase fracture risk by up to 12 times. Risk assessments based only on BMD may overestimate the risk of future fractures in patients without vertebral fractures and under estimate the risk of future fractures in patients with vertebral fractures. (Siris, 2007) When measuring height annually, it should be performed with a stadiometer or a wall mounted ruler. If there is a historical height loss of more than 1.5 inches (3.8 cm) in menopausal women or than 2.4 inches (6 cm) in men, an evaluation to rule out vertebral fractures should be performed. This can be accomplished by a vertebral fracture assessment (VFA) or by a lateral thoracolumbar radiograph. It is also important in patients who have acute or chronic back pain or kyphosis (to rule out vertebral fractures).

3. Bone mineral density assessment

The diagnosis of osteoporosis is made by BMD. The decision to assess bone density should be based on the skeletal health and risk profile of the individualized patient. Table 4 and 5 summarizes the Internal Society of Clinical Densitometry and the North American Menopausal Society indications for Bone Mineral Density (BMD).

Indications for Bone Mineral Density (BMD) Testing - ISCD	
Women aged 65 and older	Adults with a disease or condition associated with low bone mass or bone loss
Postmenopausal women under age 65 with risk factors for fracture	Adults taking medications associated with low bone mass or bone loss
Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture or high-risk medication use	Anyone being considered for pharmacologic therapy
Men aged 70 and older	Anyone being treated, to monitor treatment effect
Men under age 70 with clinical risk factors for fracture	Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
Adults with a fragility fracture	Women discontinuing estrogen should be considered for bone density testing according to the indications listed above

Table 4. Indications for Bone Mineral Density (BMD) Testing - ISCD (Baim, 2008))



Indications for Bone Mineral Density (BMD) Testing - NAMS	
BMD Should Be Measured in the Following Populations:	Testing should be considered for postmenopausal women age 50 and over when one or more of the following risk factors for fracture have been identified
<ul style="list-style-type: none"><li>• All women age 65 and over regardless of clinical risk factors</li></ul>	<ul style="list-style-type: none"><li>• Fracture (other than skull, facial bone, ankle, finger, and toe) after menopause</li></ul>
<ul style="list-style-type: none"><li>• Postmenopausal women with medical causes of bone loss (eg, steroid use, hyperparathyroidism), regardless of age</li></ul>	<ul style="list-style-type: none"><li>• Thinness (body weight &lt; 127 lbs. [57.7 kg] or BMI &lt; 21 kg/m<sup>2</sup>)</li></ul>
<ul style="list-style-type: none"><li>• Post menopausal women age 50 and over with additional risk factors (see below)</li></ul>	<ul style="list-style-type: none"><li>• History of hip fracture in a parent</li></ul>
<ul style="list-style-type: none"><li>• Postmenopausal women with a fragility fracture (eg, fracture from a fall from standing height)</li></ul>	<ul style="list-style-type: none"><li>• Current smoker</li></ul>
	<ul style="list-style-type: none"><li>• Rheumatoid arthritis</li></ul>
	<ul style="list-style-type: none"><li>• Alcohol intake of more than two units per day (one unit is 12 oz. of beer, 4 oz. of wine, or 1 oz. of liquor)</li></ul>

Table 5. Indications for Bone Mineral Density (BMD) Testing of the North American Menopause Society (NAMS) (North American Menopause Society, 2010)

There are many techniques that measure BMD. The gold standard in diagnosis of osteoporosis is made by central DXA using dual energy absorptiometry. Using two different x-ray energies, a DXA device can record attenuation profiles at two different photon energies. At low energy (30-50 keV) bone attenuation is greater than soft tissue attenuation; where as high energy (greater than 70 keV) bone attenuation is similar to soft tissues attenuation. Thus, two types of tissue are distinguished: bone (hydroxyapatite) and soft tissue (everything else). (International Society of Clinical Densitometry, 2010) DXA measures areal BMD. The results are reported as grams of mineral per square centimeter (g/cm<sup>2</sup>).

The skeletal sites that are measured with central DXA are both the PA spine (L<sub>1</sub> – L<sub>4</sub>) and the hip (femoral neck or total proximal femur of either hip). In certain circumstances when a hip or a spine cannot be measured then a forearm (33% radius or one third radius of the non dominant arm) should be measured (e.g., patients who are obese and whose weight is above the limit of the DXA table). Results of DXA are reported as a comparison of two norms. A T-score uses a Caucasian female 20-29 NHANES III database, for women of all ethnic groups. In men, a Caucasian male 20-29 NHANES III database is used in all ethnic groups. The difference between the patient’s score is expressed in standard deviation above or below the norm. Also, a Z-score will be generated. The patient’s BMD is compared to individuals of the same age, sex, and ethnicity. Z-scores should be population specific where adequate reference data exists (International Society for Clinical Densitometry, 2009).

The lower the BMD (T-score) the higher the fracture risk. A decrease of 1 standard deviation represents a 10 - 12% decrease in BMD and an increase in fracture risk by a factor of 1.5 to 2.6, depending on fracture type. The risks of spine and hip fracture increase 2.3 fold and 2.6 fold respectively, for each decrease of 1 standard deviation at the spine and hip. A Z-score of -2.0 or lower is defined as below expected range for age. A Z-score above -2.0 is within the expected range for age.

Peripheral Dual Energy X-Ray Absorptiometry (pDXA) measures areal bone density of the forearm, finger, or heel. It can indentify individuals at risk for fracture but this modality cannot be used for the diagnosis of osteoporosis or for follow up of patients. The measurement of peripheral sites are useful only in screening patients for the need of a central DXA, they are not useful for follow up in patients or in patients taking medications for osteoporosis. (Recker, 2000) Quantitative Computed Tomography (QCT) can measure spinal BMD and can predict vertebral fractures in women, but there is a lack of evidence of a prediction of vertebral fractures in men. There is no evidence that spine QCT can predict hip fractures in women or men. Peripheral Quantitative Computed Tomography (pQCT) of the ultra distal radius can predict hip fracture risk, but not spine fracture risk in postmenopausal women. Quantitative Ultrasound (QUS) can predict fragility fractures in postmenopausal women (hip and vertebral) and men over age 65 (hip and nonvertebral fractures). (Baim, 2008)

According to the World Health Organization (WHO) only the measurement of BMD by central DXA can be used for the diagnosis of osteoporosis, the follow up of individuals and the monitoring of treatment efficacy. (National Osteoporosis Foundation, 2008)

The WHO has defined low bone mass (Osteopenia) as a BMD between -1.0 and 2.5 SD below the normal for young healthy adults of the same sex (T-score < 1.0 and > -2.5), osteoporosis by a BMD of -2.5 SD or below (T-score ≤ -2.5) and severe osteoporosis with a T-score of ≤ -2.5 and a fragility fracture. (World Health Organization, 2003)

The World Health Organization has established the following definitions based on BMD measurement at the spine, hip, or forearm by DXA devices:		
Normal	Low Bone Mass (Osteopenia)	Osteoporosis
BMD is within 1 SD of a “young normal” adult (T-score at -1.0 and above.	BMD is between 1.0 and 2.5 SD below that of a “young normal” adult (T-score between -1.0 and -2.5).	BMD is 2.5 SD or more below that of a “young normal” adult (T-score at or below -2.5). Patients in this group who have already experienced one or more fracture are deemed to have severe or “established” osteoporosis.”

**Note:** Although these definitions are necessary to establish the presence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

Table 6. Defining Osteoporosis by BMD (Kanis, 1994)

In postmenopausal women and men age 50 and older, T-scores are preferred, using the WHO criteria. In women prior to menopause and in males younger than age 50, Z-scores, not T-scores are preferred. The WHO diagnostic criteria may be applied to women in the menopausal transition with risk factors for osteoporosis.

At the time of a central DXA, a vertebral fracture assessment (VFA) can be performed. It is a densitometric spine imaging than can detect vertebral fractures. (Schousboe, 2008) Most vertebral fractures are asymptomatic and if present can increase an individual’s future risk of fracture. A Vertebral Fracture Assessment (VFA) is a diagnostic method in which low intensity or dual x-ray absorptiometry is used to examine the lateral spine (T<sub>4</sub>-L<sub>4</sub>), thereby identifying vertebral fractures. (Leipzig, 1999) There is much less radiation with a VFA in comparison to a lateral spine x-ray (3μSV for VFA versus 600μSV for a radiograph).

According to the International Society of Clinical Densitometry a vertebral fracture assessment should be performed in the following circumstances:



<b>Consider VFA when results may influence management.</b>	
<b>Postmenopausal women with low bone mass (Osteopenia) by BMD criteria PLUS any one of the following:</b>	<b>Men with low bone mass (Osteopenia) by BMD criteria, PLUS any one of the following:</b>
• Age greater than or equal to 70 years	• Age 80 years or older
• Historical height loss greater than 4 cm (1.6 in.)	• Historical height loss greater than 6 cm (2.4 in.)
• Prospective height loss greater than 2 cm (0.8 in.)	• Prospective height loss greater than 3 cm (1.2 in.)
• Self-reported vertebral fracture (not previously documented)	• Self-reported vertebral fracture (not previously documented)
• Two or more of the following:	• Two or more of the following:
• Age 60 to 69 years	• Age 70 to 79 years
• Self-reported prior non-vertebral fracture	• Self-reported prior non-vertebral fracture
• Historical height loss of 2 to 4 cm	• Historical height loss of 3 to 6 cm
• Chronic systemic diseases associated with increased risk of vertebral fractures (e.g., moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn’s disease)	• Chronic systemic diseases associated with increased risk of vertebral fractures (e.g., moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn’s disease)
	On pharmacologic androgen deprivation therapy or following orchiectomy
<b>Women or men on Chronic Glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for three (3) months or longer).</b>	<b>Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management.</b>

Table 7. Indications for VFA (Schousboe, 2008)

The VFA is interpreted using a semi-quantitative visual inspection with assignment of fracture grade by the radiologist or the clinician. Using Genant’s method, the clinician determines if a vertebra is fractured or normal. The thoracic and lumbar spine is scanned for deformities and height loss exceeding twenty percent in the anterior, middle, or posterior dimensions. What the clinician determines visually using the semiquantitative method of Genant are morphological changes in the vertebrae. Clinicians should look for end plate deformities (horizontal edges), lack of parallelism of the end plates, buckling of the cortices (vertical edges) and loss of vertical continuity with the adjacent vertebrae. Clinicians then grade the fracture deformity. If a fracture is suspected, it is compared to a standard:

- Grade 1 (mild fracture) height loss 20-25%
- Grade 2 (moderate) height loss of 25-40%
- Grade 3 (severe) height loss of > 40%

Depending on where deformities are present in the vertebra, fractures are classified as wedge (loss of anterior height), crush (loss of posterior height) and biconcave (loss of middle height). (Genant, 1993)

In a study comparing VFA to spine radiographs, VFA had a sensitivity of 95% to detect vertebral fractures indentified by spine radiographs and a specificity of 82% to exclude fractures not visualized in a radiograph. (Vokes, 2003)

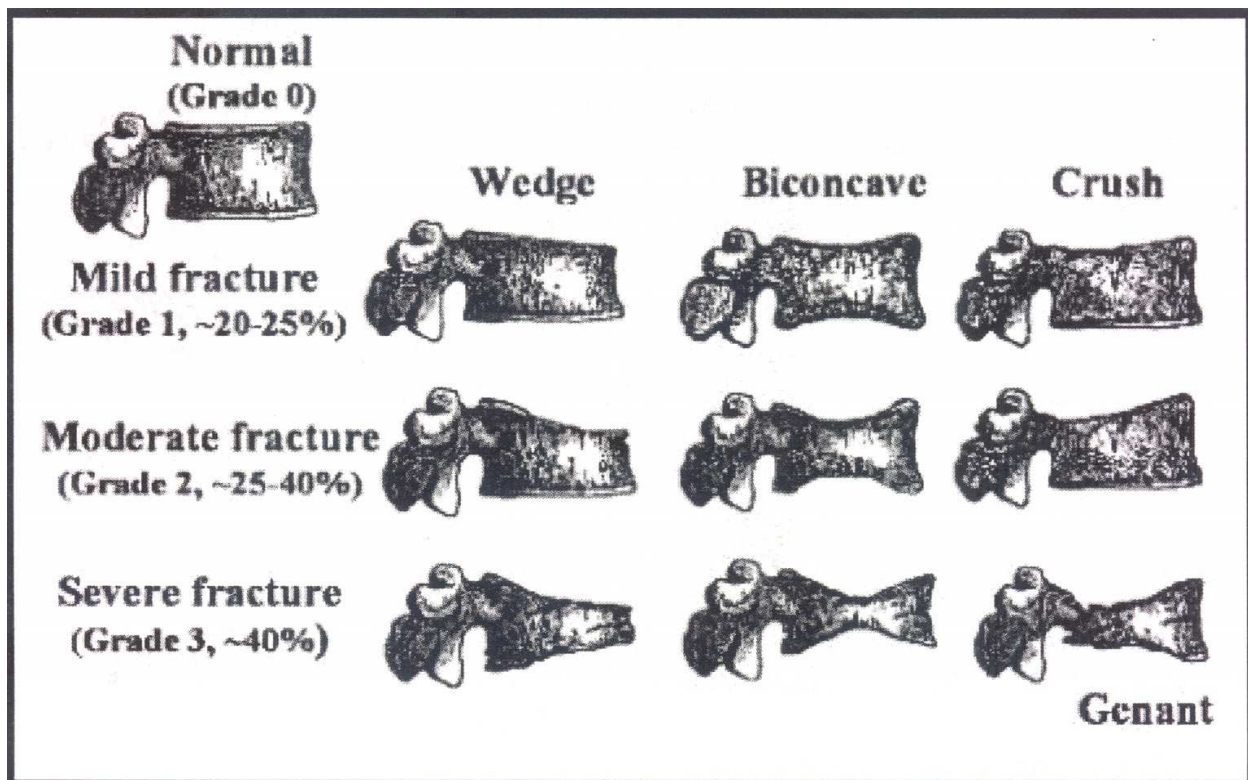


Fig. 1. Genant's Semiquantitative Analysis Grading of Fracture Deformity (Genant, 1993)

#### 4. Follow up bone mineral density testing

Follow up DXA testing by central DXA should be performed every 2-5 years in untreated menopausal women and in men age 70 or older. In patients who are receiving osteoporosis therapy, BMD testing should be performed every 1-2 years. (Van Der Voort, 2001) In order to determine if the change in BMD over time is a real biological change and not due to chance, a precision study must be performed. Each DXA facility should determine its precision error and calculate the least significant change (LSC), within a 95% statistical confidence. The precision error that is supplied by the manufacturer should not be used.

To perform a precision analysis, the technologist measures 15 patients 3 times or 30 patients 2 times, repositioning the patient after each scan. They then calculate the root mean square standard deviation and obtain the LSC at 95% confidence. This is a real biological change over time and is not due to chance. The minimum acceptable precision for an individual technologist is: lumbar spine 1.9% (LSC = 5.3%), total hip 1.8% (LSC = 5.0%), and femoral neck 2.5% (LSC = 6.9%). (International Society for Clinical Densitometry, 2007)

#### 5. Evaluation for treatment

Within one year of a hip fracture 10-20% of patients die, 20% are placed in nursing homes, and only 40% regain independent functioning. (U.S. Department of Health and Human

Services, 2004) There are more low-trauma fractures in patients with low bone density (Osteopenia) than in those with a DXA diagnosis of osteoporosis. This occurs because there are more individuals with Osteopenia than osteoporosis. (Khosla, 2007) In the study of osteoporotic fractures (SOF), 54% of women with hip fractures did not have osteoporosis according to their BMD results. (Wainwright, 2005) Therefore, it is important to identify and treat individuals who have Osteopenia (low bone density) who have the highest chance of a fracture. Not all patients with low bone mass will fracture.

## 6. FRAX assessment tool

The WHO sponsored the development of the FRAX assessment tool to identify which individuals with low bone mineral density have the greatest chance of fracture and which patients need to be treated. (Kanis, 2008) It identifies which patients, who have Osteopenia (low bone mass) who have a higher fracture risk and need to be treated. (Internal Society for Bone Densitometry Course) FRAX is based on an analysis of approximately 60,000 patients that were studied in Europe, North American, Asia, and Australia. The FRAX tool is for untreated individuals with low bone density and identifies which individuals are at the highest risk of fracture. The NOF recommends the FRAX tool for untreated postmenopausal and men 50 or more years of age with a T-score in the osteopenic range (low bone mass). FRAX predicts the 10 year probability for hip fracture and for major osteoporotic fractures (hip, proximal humerus, distal forearm, and clinical vertebral fractures). FRAX uses clinical risk factors with or without femoral neck BMD. Economic modeling was performed to identify the 10 year hip fracture risks above which is cost effective, from the societal perspective, to treat with pharmacological agents.

NOF criteria for using FRAX to assist with treatment decisions are:

- a. An untreated postmenopausal women or a man age 50 or older
- b. With low bone mass (T-score between -1.0 and -2.5)
- c. With no prior hip or vertebral fracture (clinical or morphometric)
- d. An evaluable hip for DXA study

Examples of "untreated" patients include:

- a. No ET/HT or estrogen agonist/antagonist (SERM) for the past one year
- b. No calcitonin for the past one year
- c. No PTH for the past one year
- d. No denosumab for the past one year
- e. No bisphosphonate for the past two years (unless it is an oral taken for < 2 months)

This model uses femoral neck BMD but, in women, if femoral neck BMD is unavailable, total hip BMD may be used. In men, only femoral neck BMD can be used in FRAX. (World Health Organization, 2003) Spine or peripheral BMD measurements should not be used in FRAX. (Kanis) There are multiple limitations of FRAX. It does not consider the other risk factors for fracture. These include a history of falls, patients with clinical vertebral fractures, doses of glucocorticoids, exposure dose of alcohol, nicotine, drugs which lower BMD (anticonvulsants, anticoagulants, antineoplastics, antiestrogenic or antiandrogenic agents), parental history of non hip fractures and lumbar spine BMD. This tool only recognizes a hip fracture of a parent. Spinal fractures of a parent due to osteoporosis also may increase fractures risk in the offspring. The therapeutic thresholds that are proposed in the FRAX tool are for clinical guidance and are not rules. They do not preclude clinicians from considering intervention strategies in patients who do not have osteoporosis, nor should they mandate treatment in patients with osteopenia. The decision to treat a patient must be made on a case by case basis.

Risk Factor	Type of Variable	Description
Age	Continuous	40-90 years. For ages below or above this range, the model computes fracture risks as of age 40 or 90.
Sex	Male/female	Model validated for men and women.
Weight	Continuous	Expressed in kilograms.
Height	Continuous	Expressed in centimeters. The modal calculates body mass index and uses it as a continuous variable.
Previous fracture	Yes/no	Includes adult fractures occurring spontaneously or with low trauma (e.g., osteoporosis-related fractures), including morphometric vertebral fractures.
Parental hip fracture	Yes/no	Any hip fracture affecting either parent.
Current smoking	Yes/no	Dose-dependence of fracture risk has been observed but is not reflected in the model.
Oral glucocorticoid use	Yes/no	Present or past exposure to doses equivalent to 5 mg/d prednisolone for ≥ 3 months. Dose-dependence of fracture risk has been observed but is not reflected in the model.
Rheumatoid arthritis	Yes/no	Only a confirmed diagnosis of rheumatoid arthritis should be scored.
Secondary osteoporosis	Yes/no	Secondary osteoporosis occurs in the presence of conditions including, but not limited to, insulin-dependent diabetes, adult osteogenesis imperfecta, uncontrolled hyperthyroidism, menopause at 45 years, hypogonadism, chronic malnutrition/malabsorption, or chronic liver disease.
Alcohol ≥ 3 units daily	Yes/no	1 unit is 285 mL beer, 120 mL wine, 60 mL aperitif, or 30 mL distilled spirits. Dose-dependence of fracture risk has been observed but is not reflected in the model.
Femoral neck BMD	Continuous	Enter BMD value and select DXA machine model used to obtain it, or enter T-score. Risk estimates can also be produced without BMD. If only total hip BMD is available, that can be used. Spinal or peripheral BMD are not to be used.
Clinical vertebral fractures and multiple osteoporosis-related fractures confer additional risk beyond what the model calculates; clinical judgment should be used.		
For a “yes” answer to smoking, alcohol, or glucocorticoid use, the model assumes average levels of exposure. With high exposures, facture risk may increase more than the model accounts for, and clinical judgment should be used.		
When a femoral neck T-score is entered into the online FRAX model, the secondary osteoporosis button becomes inactivated.		

Table 8. Risk Factors Included in the FRAX Algorithm (Siris, 2010)



The image shows the FRAX WHO Fracture Risk Assessment Tool interface. At the top, there is a header with the FRAX logo and the text 'WHO Fracture Risk Assessment Tool'. Below the header is a navigation bar with links: HOME, CALCULATION TOOL, PAPER CHARTS, FAQ, and REFERENCES. A 'Select a Language' dropdown menu is also present. The main section is titled 'Calculation Tool' and contains the instruction: 'Please answer the questions below to calculate the ten year probability of fracture with BMD.' On the left side, there are two conversion tools: 'Weight Conversion' (pound to kg) and 'Height Conversion' (inch to cm), each with a 'convert' button. The main questionnaire area is titled 'Questionnaire:' and includes fields for 'Country' (US(Caucasian)), 'Name / ID', and 'About the risk factors' (with an information icon). The questionnaire consists of 12 numbered questions: 1. Age (between 40-90 years) or Date of birth (with sub-fields for Year, Month, and Day); 2. Sex (Male/Female radio buttons); 3. Weight (kg) (text input); 4. Height (cm) (text input); 5. Previous fracture (No/Yes radio buttons); 6. Parent fractured hip (No/Yes radio buttons); 7. Current smoking (No/Yes radio buttons); 8. Glucocorticoids (No/Yes radio buttons); 9. Rheumatoid arthritis (No/Yes radio buttons); 10. Secondary osteoporosis (No/Yes radio buttons); 11. Alcohol 3 more units per day (No/Yes radio buttons); 12. Femoral neck BMD (dropdown menu and text input). At the bottom right of the questionnaire, there are 'Clear' and 'Calculate' buttons.

Fig. 2. FRAX Calculation Tool

7. Whom should we treat: NOF guidelines

Consider FDA approved medical therapies for patients with:

- A hip or vertebral (clinical or morphometric) fracture
- Osteoporosis diagnosed by a BMD T-score  $\leq -2.5$  (femoral neck or spine) after appropriate evaluation to exclude secondary causes of osteoporosis
- Low bone density (a BMD score between -1 and -2.5 at the femoral neck or spine) and a FRAX 10 year probability of hip fracture  $\geq 3\%$  or a major osteoporotic fracture (hip, wrist, proximal humerus, clinical vertebral fracture) of  $\geq 20\%$

Physicians should use clinical judgment to treat patients at lower FRAX risk levels if additional risk factors for fracture are present.

Before developing a management plan, the clinician should rule out secondary causes of osteoporosis or bone loss. About 20% of postmenopausal women with osteoporosis and 40% of men with osteoporosis have a secondary cause that can be indentified and treated. (Fitzpatrick, 2002) Secondary osteoporosis can result from a variety of medical conditions including endocrine, hematopoietic or nutritional disorders, and vitamin D deficiency. Diseases such as celiac (malabsorption), liver and renal diseases, the use of glucocorticoids, aromatase inhibitors, antiandrogen therapy (GNRH) and chemotherapy can cause bone loss. These secondary causes must be ruled out before staring pharmacological therapy.

Some of the routine tests would be a complete blood count, serum levels of calcium and phosphate, 25-hydroxyvitamin D, bone specific alkaline phosphatase, creatinine and a 24-hour urine for calcium. Some of the specialized tests may include a thyroid stimulating hormone (TSH), serum levels of parathyroid hormone (PTH) to screen for hyperparathyroidism, a serum protein electrophoresis to indentify abnormal protein produced by multiple myeloma and antitissue transglutaminase antibodies for celiac disease. (Hodgson, 2003)



Test	Diagnostic Result	Possible Secondary Cause
Completed blood cell count	Anemia	Multiple myeloma
Serum calcium	Elevated	Hyperparathyroidism
	Low	Vitamin D deficiency, Gastrointestinal (GI) malabsorption
Serum phosphate	Elevated	Renal failure
	Low	Hyperparathyroidism
Serum 25-hydroxyvitamin D	Low	Undersupplemenataion, GI malabsorption, celiac disease
Serum albumin	Used to interpret serum calcium, nutritional deficiencies	
Serum alkaline phosphatase	Elevated	Vitamin D deficiency, GI malabsorption, hyperparathyroidism, Paget's disease, liver/biliary disease
Urinary calcium excretion	Elevated	Renal calcium leak, multiple myeloma, metastatic cancer involving bone, hyperparathyroidism, hyperthyroidism
	Low	GI malabsorption, inadequate intake of calcium and vitamin D
Thyroid-stimulating hormone (TSH)	Low	Hyperthyroidism (causes excess bone turnover)
	High	Hypothyroidism
Serum protein electrophoresis	Monoclonal band	Multiple myeloma
Tissue transglutaminase antibody (gluten enteropathy)	Elevated	Predictive of celiac disease
Creatinine	Elevated	Renal osteodystrophy, possible contraindication to bisphosphonates
PTH	Elevated	Hyperparathyroidism, vitamin D deficiency

Table 9. Laboratory Tests for Osteoporosis Evaluation (North American Menopause Society, 2010)

8. Bone turnover markers

Bone turnover markers are proteins that are produced by the activity of osteoclasts and by osteoblasts. The resorption markers of osteoclastic activity are the breakdown products of type I collagen (N-telopeptides, C-telopeptides, deoxypyridinolone). There are markers of osteoblastic synthesis of bone matrix (bone-specific alkaline phosphatases, osteocalcin, procollagen type I N-terminal propetide).

Suppression of biochemical markers of bone turnover occur 3-6 months of specific antiresorptive therapies and they increase after 1-3 months of anabolic therapies. The NOF recommends a baseline and a repeat bone resorption marker after initiation of therapy as a method of monitoring the therapeutic effect of an antiresorptive agent.

The changes of bone turnover markers occur more rapidly than changes in BMD and they can also predict patient compliance or poor response to antiresorptive therapy. There is a high degree of biological and analytical variability in the measurement of biochemical markers. This variability can be reduced by obtaining samples in the early morning after an overnight fast. (National Osteoporosis Foundation, 2008)

## 9. Conclusion

In all senior men and in all postmenopausal women a history should be obtained to evaluate a patient's risk factors for osteoporosis and for fractures. As part of a patient's physical exam, a height measurement should be performed. This can identify when there is a significant height loss or an asymptomatic vertebral fracture. When necessary, a central DXA and sometimes a Vertebral Fracture Assessment (VFA) may be performed. Clinicians should estimate a patient's 10-year probability of a hip or a major osteoporotic related fracture using FRAX. We should use the WHO criteria to determine who we should treat and which individuals whom we should not treat. Clinicians also must perform a laboratory workup on patients, to rule out secondary causes of osteoporosis, before starting a pharmacological treatment regimen.

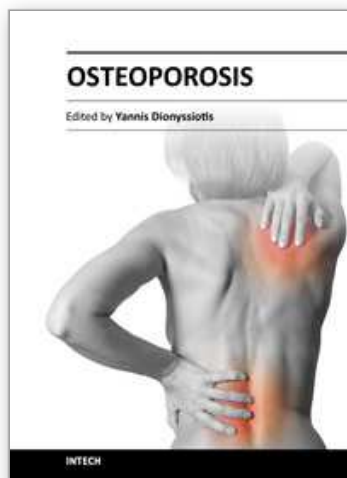
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## **Osteoporosis**

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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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