Osteoporosis Screening and Diagnosis: BMD, FRAX and Assessment of Secondary Osteoporosis

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Disclosure and Conflicts of Interest
Steven T Harris MD 2018-2019
* None

Bone Loss

- Slow loss may begin before menopause in women, late 40s in men
- Accelerates at menopause due to estrogen deficiency
- Continues throughout life
- Influenced by many factors: nutrition, diseases, medications, lifestyle, etc.


Bone Density: Major Determinant of Fracture Risk

Bone density accounts for 60% to 80% of bone strength and resistance to fractures

**Who Should Be Considered for BMD Testing?**

National Osteoporosis Foundation Guidelines for Women

- Women ≥65 years of age regardless of additional risk factors
- Postmenopausal women <65 years of age with at least one risk factor for osteoporosis (in addition to menopause)
- Postmenopausal women ≥65 years of age with fractures (to confirm diagnosis and determine disease severity)
- Women considering therapy for osteoporosis, if BMD testing would facilitate the decision
- Women who have been on HRT for prolonged periods

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**Central DXA Bone Density Measurements**

![Central DXA Bone Density Measurements](image-url)
DXA Interpretation

- **T-score:** SD from young normal average values
- **Z-score:** SD from age-matched average values
- This example, X is a 55-year-old patient:
  - T-score = -3.2
  - Z-score = -2.0

WHO Bone Density Criteria

**BMD Measured by Central DXA at the Spine or Hip**

<table>
<thead>
<tr>
<th>Diagnostic criteria*</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>T-score is above or equal to -1</td>
<td>Normal</td>
</tr>
<tr>
<td>T-score is between -1 and -2.5</td>
<td>Osteopenia (low bone mass)</td>
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<td>T-score is -2.5 or lower</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>T-score is -2.5 or lower + fragility fracture</td>
<td>Severe, established osteoporosis</td>
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*Measured in "T-scores;" the T-score indicates the number of standard deviations above or below the average peak bone mass in young adults.

Pathogenesis of Osteoporosis

**Diagnosis criteria**

- **T-score is above or equal to -1:** Normal
- **T-score is between -1 and -2.5:** Osteopenia (low bone mass)
- **T-score is -2.5 or lower:** Osteoporosis
- **T-score is -2.5 or lower + fragility fracture:** Severe, established osteoporosis

**WHO Bone Density Criteria**

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**Pathogenesis of Osteoporosis**

**Bone Loss**

- **LOW BONE DENSITY**
- **POOR BONE QUALITY**
- **FRACTURES**
- **FALLS**

**Modifed from Riggs BL and Melton LJ III. Osteoporosis: Etiology, Diagnosis, and Management. New York: Raven Press; 1986.**

**T-Scores and the Spectrum of Bone Disease**

- **T-Score: 0.0 = Normal**
- **T-Score: -2.0 = Osteopenia**
- **T-Score: -2.5 = Osteoporosis**
  - Reduced bone mass and increased bone fragility
  - Osteomalacia
  - Softening of bones caused by deficiencies in vitamin D, phosphate, or calcium

1Harris VW and Brown TT. Clin Rev Bone Miner Metab. 2012;10:246-256.

WHO Bone Density Criteria: Caveats

* The terms “osteopenia” and “osteoporosis” were originally developed as epidemiologic tools to compare the prevalence of low bone densities in one country with those in another.
* The terms were based on studies of fracture risk in older postmenopausal women, and were never originally intended for application to men or to premenopausal women.
* There is a continuous relationship between bone density and fracture risk, making the dividing lines between “normal,” “osteopenia” and “osteoporosis” somewhat arbitrary.
* The bone density range for osteopenia is in essence statistically “low normal” for a young adult.

Bone Densitometry: Caveats

* The first bone density measurement provides a “snapshot” of the skeleton at one point in time, as a function of genetic factors, diet, exercise, illnesses and medications—anything that might affect skeletal homeostasis.
* That first bone density measurement does not indicate whether the density is moving up, down or sideways.

Caveats

BMD testing is valuable, but—

* A T-score ≤ -2.5 is consistent with—but not diagnostic of—osteoporosis.
* A clinical diagnosis of osteoporosis may be made with a T-score greater than -2.5.
  - Example: atraumatic vertebral fracture with T-score = -1.9.

Risk Factors for Fracture: Beyond Age + T-score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Fracture</td>
<td>1.62</td>
<td>(1.30-2.01)</td>
</tr>
<tr>
<td>Parental History of Hip Fracture</td>
<td>2.28</td>
<td>(1.48-3.51)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>1.60</td>
<td>(1.27-2.02)</td>
</tr>
<tr>
<td>Systemic Corticosteroids</td>
<td>2.25</td>
<td>(1.60-3.15)</td>
</tr>
<tr>
<td>Alcohol Intake ≥ 3 Units Daily</td>
<td>1.70</td>
<td>(1.20-2.42)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.74</td>
<td>(0.94-3.20)</td>
</tr>
</tbody>
</table>

Patients With Prior Fracture Have a High Risk of Future Fragility Fractures

<table>
<thead>
<tr>
<th>Prior fracture</th>
<th>Relative risk of future fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>3.3</td>
</tr>
<tr>
<td>Vertebra</td>
<td>1.7</td>
</tr>
<tr>
<td>Hip</td>
<td>1.9</td>
</tr>
<tr>
<td>Wrist</td>
<td>1.4</td>
</tr>
<tr>
<td>Vertebra</td>
<td>4.4</td>
</tr>
<tr>
<td>Hip</td>
<td>2.3</td>
</tr>
<tr>
<td>Hip</td>
<td>NA</td>
</tr>
</tbody>
</table>


Calculating Absolute Fracture Risk: FRAX

FRAX® Model: Benefits

- Validated in large cohort of ~60,000 patients
- Quantitative estimation of fracture risk – more comprehensible to patients
- Applicability to men and women worldwide
- Can be used with economic modeling to determine cost-effective intervention thresholds
- Can also be used as a powerful tool to counsel individual patients about the benefits of intervention

http://www.sheffield.ac.uk/FRAX/tool.aspx, accessed 26 JUN 17

52-Year-Old Woman With T-score -2.0:
Effect Of Additional Risk Factors

<table>
<thead>
<tr>
<th>15-Year Fracture Risk (%)</th>
<th>Risk of Major Fractures</th>
<th>Risk of Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>20</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>30</td>
<td>11</td>
<td>11.5</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Age & BMD, Age & BMD Smoking, Age & BMD Smoking Parental Hip Fx, Age & BMD Smoking Parental Hip Fx Wrist Fx
Benefits of FRAX®

- Guides the treatment decisions in osteopenic patients because the decisions are based on the risk of fracture, not T-score alone
- Identifies patients at high risk for fracture to ensure that they are offered treatment to lower risk
- Helps avoid giving medication to those who are at low risk and have little to gain from treatment

“Specific treatment decisions must be individualized”

FRAX® Model: Caveats

- The model is not intended for application in patients who are already on pharmacologic therapy
- The model is based on femoral neck BMD only—not spine BMD
- Limited to 4 ethnicities in US (Caucasian, Black, Hispanic, Asian)
- It is not clear what margin of error is present in the fracture risk estimates
- It is not obvious that all risk factors carry equal weight in predicting the response to pharmacologic treatment

FRAX® Model: Additional Caveats

When Clinical Judgment is Needed

FRAX® may underestimate fracture risk:

- Some risk factors (glucocorticoids, smoking, alcohol, previous fractures) are dose-dependent, but FRAX® doesn’t incorporate “dose response”—it only incorporates those variables in a dichotomous way
- Some factors that increase the risk of fracture independently of their effect on BMD are not included in FRAX®:
  - Falls
  - Some diseases and medications (immobilization, diabetes, anticonvulsants, SSRIs, PPIs, TZDs)

Rewards of Osteoporosis Treatment

- Reduction in the risk of fracture
- Reduction in pain and disability
- Preservation of independence
- Reduction in height loss
- Positive effect on mortality (?)
- Positive effect of being “proactive”
- Positive effect on a surrogate such as BMD
Risks of Osteoporosis Treatment

- Economic cost of treatment
- Other costs of treatment: nuisance value of taking another medication, reminder of illness, worry about consequences of therapy
- Side effects of treatment

2008/2013 NOF Guidelines: Treatment Initiation

Post-menopausal Women And Men ≥50

Assess Risk Factors and Measure BMD if Patient Has Risk Factors

T-score between -1.0 and -2.5

Hip or Vertebral Fractures or
T-score ≤ -2.5 (Spine, Femoral Neck or Total Hip)

10-year Probability of Hip Fracture ≥ 3%

Probability of All Major Fractures ≥ 20%

These thresholds were based on a pharmacoeconomic analysis that is already out of date

Bone Density Testing: Caveat

BMD testing is valuable, but--
A T-score ≤ -2.5 is consistent with—but not diagnostic of—osteoporosis

Differential Diagnosis Of Low BMD

- Primary osteoporosis (postmenopausal or age-related)
- Secondary osteoporosis (caused, wholly or in part, by other diseases or medications)
  - Secondary causes are not rare
- Idiopathic osteoporosis (disease characterized by low bone density and fractures in young adults without known cause)
- Other bone diseases
  - Osteogenesis imperfecta
  - Osteomalacia
  - Renal osteodystrophy
Some Causes Of Secondary Osteoporosis In Adults

<table>
<thead>
<tr>
<th>Endocrine/Metabolic</th>
<th>Nutritional Conditions</th>
<th>Drugs</th>
<th>Collagen Disorders</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism</td>
<td>Malabsorption syndromes</td>
<td></td>
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<tr>
<td>Hyperadrenocorticism</td>
<td>Malnutrition</td>
<td></td>
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<tr>
<td>Hyperparathyroidism</td>
<td>Chronic cholestasis</td>
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<tr>
<td>Hyperparathyroidism</td>
<td>Dialysis</td>
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<td></td>
<td>Renal transplantation</td>
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<td></td>
<td>Vitamin D deficiency</td>
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<td></td>
<td>Calcium deficiency</td>
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<td></td>
<td>Alkalosis</td>
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<td></td>
<td>Hypercalcitria</td>
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<td></td>
<td>Glucocorticoids</td>
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<td></td>
<td>Excess thyroid hormone</td>
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<tr>
<td></td>
<td>Hyperparathyroidism</td>
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<td></td>
<td>Cushing’s disease</td>
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<tr>
<td></td>
<td>Vitamin D deficiency</td>
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<td></td>
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<tr>
<td></td>
<td>Hypercalcitria</td>
<td></td>
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<tr>
<td></td>
<td>Osteogenesis imperfecta</td>
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<td></td>
<td>Myeloma</td>
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<td></td>
<td>Rickets</td>
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<td></td>
<td>Celiac disease</td>
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<td></td>
<td>Hyperparathyroidism</td>
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<td>Marfan syndrome</td>
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<td></td>
<td>Ehlers-Danlos syndrome</td>
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<tr>
<td></td>
<td>Connective tissue</td>
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</tr>
<tr>
<td></td>
<td>Tissue manipulation</td>
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Most Common Causes Of Secondary Osteoporosis

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Conditions</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Hypogonadism</td>
<td>Malabsorption</td>
<td>Steroid therapy</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>Antiepileptics</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>GnRH agonists</td>
</tr>
<tr>
<td></td>
<td>Myeloma</td>
<td>Depo-Provera</td>
</tr>
<tr>
<td></td>
<td>Vitamin D deficiency</td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Hypercalcitria</td>
<td>Excess thyroxine</td>
</tr>
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</table>

Data reanalyzed from Tannenbaum C, et al. J Clin Endocrinol Metab. 2002;87(10):4431 using current definition of vitamin D deficiency (personal communication: Luckey MM)

How Often Do Healthy Women With Osteoporosis Have Unsuspected Disorders?

Study population: 664 consecutive postmenopausal women with a T-score of -2.5 or below

- 54% excluded for a known secondary cause
- 173 females (ages 46-87) without known secondary osteoporosis or prior lab abnormalities underwent lab evaluation
  - CBC, chemistry, 24-hour urine calcium, PTH, 25-OH vitamin D, most also had TSH, SPEP
  - 44% of patients were found to have a secondary cause

Data reanalyzed from Tannenbaum C, et al. J Clin Endocrinol Metab. 2002;87(10):4431 using current definition of vitamin D deficiency (personal communication: Luckey MM)

Osteoporotic Women With New Diagnoses

- Vitamin D deficiency (25-OH D <20 ng/mL) 20%
- Hypercalcitria 10%
- Malabsorption 7%
  - Celiac disease (3)
  - Hyperparathyroidism 3%
    - Primary (1)
    - Secondary (5)
- Over-replacement with T4 (4) 2%
- Cushing’s disease (1) <1%
- Other 1%

Data reanalyzed from Tannenbaum C, et al. J Clin Endocrinol Metab. 2002;87(10):4431 using current definition of vitamin D deficiency (personal communication: Luckey MM)
Prevalence of Occult Secondary Osteoporosis

- Prevalence in studies that assessed urinary calcium and vitamin D:
  - Women and men, varying ages: 1-4 37%–63%
  - Post-hip fracture patients: 2 60%–80%
  - Bone loss on pharmacologic therapy: 5 50% ≤50%

No large, population-based studies; studies from referral centers vary by criteria for inclusion, extent of testing, and definition of vitamin D deficiency

References:
2. Haden S T et al, Calcif Tissue Int. 1999;64:275

Identifying the Patient with an Occult Disorder

- All patients deserve at least a limited laboratory evaluation prior to treatment
- No clinical parameter (even age or disease severity) identifies those most likely to have an occult disorder
- The available data do not suggest that occult disease is more likely in patients with low Z-scores (i.e., in those whose density is lower than expected for age)
- “Persistent” additional testing is appropriate if there is a statistically significant BMD decrease on therapy

References:
1. Tannenbaum C et al, J Clin Endocrinol Metab 2002;87:4431

Evaluation of the Patient with Osteoporosis

- Careful history and examination
- Laboratory testing
  - Comprehensive Metabolic Panel
  - CBC
  - 24-hour urinary calcium (and creatinine if worried about the adequacy of the collection)
  - 25-OH vitamin D (NOT 1,25-dihydroxyvitamin D)
  - PTH
  - Total testosterone and gonadotropins in younger men
  - Thyroid function tests (TFTs) if symptoms warrant or the patient is on thyroid replacement therapy
  - Fasting serum phosphorus if osteomalacia is suspected

Laboratory test | Looking for
--- | ---
CBC | myeloma; malabsorption of iron, B12, folate
Serum chemistry
- Albumin
- Globulin
- Alkaline phosphatase
- Calcium (high or low)
- Phosphate
- BUN, creatinine
| malabsorption; malnutrition
| myeloma
| malignancy, cirrhosis, vitamin D deficiency
| hyperparathyroidism, malabsorption
| malnutrition, osteomalacia
| renal disease
25-OH vitamin D | vitamin D deficiency
24-hour urine calcium (and creatinine) | hypercalcuria, malabsorption

Other tests as indicated by symptoms or results of above tests:
- PTH if urine or serum calcium abnormally high or low
- SPEP if CBC abnormal
- Test for celiac disease if low 24-hour urine calcium or anemia

NOF Clinician’s Guide to Prevention and Treatment of Osteoporosis 2013. www.nof.org—with some personal opinion from ST Harris
Importance of 24-hour Urine Calcium

- Effectively identifies both hypercalciuria and malabsorption when results fall outside normal values (60-300 mg/day)—with a calcium intake around 1000 mg daily
- Both disorders associated with higher rates of bone loss
- Calcium deficiency associated with diminished or absent BMD response to therapy
- Each condition requires a specific intervention for optimal patient management
- Spot urine calcium does not detect malabsorption
- 38% of new diagnoses would have been missed without 24-hour urine calcium results

When to Test Further?

- Osteoporosis is unexpected or unexpectedly severe
- Osteoporosis and fractures in:
  - Healthy premenopausal women
  - Men under 50
  - Both groups have a high prevalence of secondary causes (44-90%)
- Significant bone loss on treatment without an identified cause

Additional Testing

- Immunofixation/light chains
- Celiac disease antibodies
- 24-hour urinary cortisol
- HIV testing
- Testing for mastocytosis
- Biochemical markers of bone turnover?
- Bone biopsy?

Evaluate for other causes of bone loss, especially those that are serious or correctable

Low T-score → Treatment