Osteoporosis Diagnosis: BMD, FRAX and Assessment of Secondary Osteoporosis

Steven T Harris MD FACP
Clinical Professor of Medicine
University of California, San Francisco

steve.harris@ucsf.edu

Disclosure and Conflicts of Interest
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• Advisory Board/Consulting:
  – Eli Lilly & Co
  – Merck
  – Radius Health

• Speakers’ Bureaus
  – Amgen
  – Eli Lilly & Company
  – Radius Health
  – Shire
Pathogenesis of Osteoporosis

AGING  MENOPAUSE  OTHER RISK FACTORS

RESORPTION > FORMATION

Bone Loss

LOW PEAK BONE MASS

POOR BONE QUALITY

LOW BONE DENSITY

FRACTURES

FALLS


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>
</thead>
<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>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

* Measured in “T-scores;” the T-score indicates the number of standard deviations above or below the average peak bone mass in young adults

T-Scores and the Spectrum of Bone Disease

**T-Score: -2.0 = Osteopenia**
Low BMD but not low enough to be “osteoporosis”

**T-Score: -2.5 = Osteoporosis**
Reduced bone mass and increased bone fragility

*or*

**Osteomalacia**
Softening of bones caused by deficiencies in vitamin D, phosphate, or calcium

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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.

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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 $\leq -2.5$ 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></td>
<td>Wrist</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.3</td>
</tr>
<tr>
<td>Vertebra</td>
<td>1.4</td>
</tr>
<tr>
<td>Hip</td>
<td>NA</td>
</tr>
</tbody>
</table>

Calculating Absolute Fracture Risk: FRAX

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>Risk of Major Fractures</th>
<th>Risk of Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &amp; BMD</td>
<td>5.8 0.8</td>
</tr>
<tr>
<td>Age &amp; BMD Smoking</td>
<td>6.1 1.4</td>
</tr>
<tr>
<td>Age &amp; BMD Smoking Parental Hip Fx</td>
<td>11 1.5</td>
</tr>
<tr>
<td>Age &amp; BMD Smoking Parental Hip Fx Wrist Fx</td>
<td>20 3.0</td>
</tr>
</tbody>
</table>

10-Year Fracture Risk (%)
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

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)

Gnudi S et al. J Bone Miner Res 2001;16:2102-08
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
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% or Probability of All Major Fractures ≥ 20%

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

http://www.nof.org

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>Glucocorticoids</td>
<td>Osteogenesis imperfecta</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
<td>Malnutrition</td>
<td>Excess thyroid hormone</td>
<td>Homocystinuria</td>
<td>Myeloma and some cancers</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Chronic cholestatic</td>
<td>Heparin</td>
<td>Ehlers - Danlos syndrome</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>liver disease</td>
<td>GnRH agonists</td>
<td>Marfan syndrome</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Gastric operations</td>
<td>Phenytin</td>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Vitamin D deficiency</td>
<td>Phenobarbital</td>
<td></td>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Hypophosphatasia, in adults</td>
<td>Calcium deficiency</td>
<td>Depo-Provera</td>
<td></td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 1</td>
<td>Alcoholism</td>
<td>Aromatase inhibitors</td>
<td></td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Hypercalciuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from AACE Guidelines on Osteoporosis
### Most Common Causes Of Secondary Osteoporosis

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

Some unsuspected

### 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%
Hypercalcuiuria  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%

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: 5 60%–80%
  – Bone loss on pharmacologic therapy: 6,7 ≥50%

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

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)1,2
- “Persistent” additional testing is appropriate if there is a statistically significant BMD decrease on therapy

1. Tannenbaum C et al. J Clin Endocrinol Metab 2002;87:4431
2. Gabaroi DC et al. Menopause. 2010;17:135

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

NOF Clinician’s Guide to Prevention and Treatment of Osteoporosis 2013. www.nof.org.--with some personal opinion from ST Harris
<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Looking for</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>myeloma; malabsorption of iron, B12, folate</td>
</tr>
<tr>
<td>Serum chemistry</td>
<td></td>
</tr>
<tr>
<td>– Albumin</td>
<td>malabsorption; malnutrition</td>
</tr>
<tr>
<td>– Globulin</td>
<td>myeloma</td>
</tr>
<tr>
<td>– Alkaline phosphatase</td>
<td>malignancy, cirrhosis, vitamin D deficiency</td>
</tr>
<tr>
<td>– Calcium (high or low)</td>
<td>hyperparathyroidism, malabsorption</td>
</tr>
<tr>
<td>– Phosphate</td>
<td>malnutrition, osteomalacia</td>
</tr>
<tr>
<td>– BUN, creatinine</td>
<td>renal disease</td>
</tr>
<tr>
<td>25-OH vitamin D</td>
<td>vitamin D deficiency</td>
</tr>
<tr>
<td>24-hour urine calcium (and creatinine)</td>
<td>hypercalciuria, malabsorption</td>
</tr>
</tbody>
</table>

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

**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

Tannenbaum C, et al. J Clin Endocrinol Metab. 2002;87:4431-7
When to Test Further?

- Osteoporosis is unexpected or unexpectedly severe
- Osteoporosis and fractures in:
  - Healthy premenopausal women 1-3
  - Men under 50 4
  * 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?

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3 Kulak C et al. Endocrine Practice 2000;5:336
Evaluate for other causes of bone loss, especially those that are serious or correctable.