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
  - Gilead Sciences
  - Merck
  - Radius Health

Pathogenesis of Osteoporosis


WHO Bone Density Criteria
BMD Measured by Central DXA at the Spine or Hip

Diagnostic criteria*
- T-score is above or equal to -1
- T-score is between -1 and -2.5
- T-score is -2.5 or lower
- T-score is -2.5 or lower + fragility fracture

Classification
- Normal
- Osteopenia (low bone mass)
- Osteoporosis
- Severe, established osteoporosis

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

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></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.shef.ac.uk/FRAX/tool.jsp
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>5.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

**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”

**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

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)

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%
  - OR
  - Probability of All Major Fractures ≥ 20%

http://www.nof.org

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Gnudi S et al. J Bone Miner Res 2001;16:2102-08
Bone Density Testing: Caveat

BMD testing is valuable, but--

A T-score ≤ -2.5 is consistent with—but not diagnostic of—osteoporosis

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

Differential Diagnosis Of Low BMD

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>Homozygosity</td>
<td>Myeloma and some cancers</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Chronic cholestatic liver disease</td>
<td>Heparin</td>
<td>Ehlers - Danlos syndrome</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Gastric operations</td>
<td>GnRH agonists</td>
<td>Multiple myeloma</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Vitamin D deficiency</td>
<td>Phosphonates</td>
<td>Aromatase inhibitors</td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Calcium deficiency</td>
<td>Phenoxybenzamine</td>
<td></td>
<td>|</td>
</tr>
<tr>
<td>Hypophosphatemia, in adults</td>
<td>Alcoholism</td>
<td>Depo-Provera</td>
<td></td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 1</td>
<td>Hypocalciuria</td>
<td>Aromatase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Acromegaly</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>Hypercalciuria</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>
</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%
Hypercalciuria 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: 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 disorder1
- 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

5. Eichler MS et al. Osteoporosis Int. 2008;19:591
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 tests and looking for

<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

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

References:
**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