Osteoporosis Diagnosis: BMD, FRAX and Assessment of Secondary Osteoporosis

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Disclosure and Conflicts of Interest
Steven T Harris MD 2014-2015

• Advisory Board/Consulting:
  – Alexion Pharmaceuticals, Amgen, Eli Lilly & Co, Gilead Sciences, Merck, Primus Pharmaceuticals, Radius Health

• Speaking/Teaching:
  – Eli Lilly & Co, Gilead Sciences
Pathogenesis of Osteoporosis

- Aging
- Menopause
- Other Risk Factors

Resorption > Formation

Bone Loss

- Poor Bone Quality
- Low Bone Density
- Low Peak Bone Mass
- Fractures

Falls


BMD: A Continuum of Risk

### 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

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### Treatment Threshold Concept

**10-Year Fracture Probability (%)**

**Current treatment threshold based on T-score**

**Treatment threshold concept based on WHO Absolute Fracture Risk**

Adapted from JA Kanis et al, Osteoporos Int. 2001;12:989-995
Risk Factors for Fracture: Beyond Age + T-score

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


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

| Prior fracture | Relative risk of future fracture |
|---|---|---|
| Wrist | Vertebra | Hip |
| Wrist | 3.3 | 1.7 | 1.9 |
| Vertebra | 1.4 | 4.4 | 2.3 |
| Hip | NA | 2.5 | 2.3 |

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>Age &amp; BMD</th>
<th>Age &amp; BMD Smoking</th>
<th>Age &amp; BMD Smoking Parental Hip Fx</th>
<th>Age &amp; BMD Smoking ParentalHip Fx Wrist Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>6.1</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>0.8</td>
<td>1.4</td>
<td>1.5</td>
<td>3.0</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)

Gnudi S et al. J Bone Miner Res 2001;16:2102-08
**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%

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**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

[http://www.nof.org](http://www.nof.org)
### 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 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>Marfan syndrome</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Vitamin D deficiency</td>
<td>Phenytoin</td>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Calcium deficiency</td>
<td>Phenobarbital</td>
<td></td>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Hypophosphatasia, in adults</td>
<td>Alcoholism</td>
<td>Depo-Provera</td>
<td></td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 1</td>
<td>Hypercalciuria</td>
<td>Aromatase inhibitors</td>
<td></td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Acromegaly</td>
<td>Hyperparathyroidism</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

Osteoporotic Women With New Diagnoses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency (25-OH D &lt;20 ng/mL)</td>
<td>20%</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>10%</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>7%</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>3%</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>3%</td>
</tr>
<tr>
<td>Primary</td>
<td>1%</td>
</tr>
<tr>
<td>Secondary</td>
<td>5%</td>
</tr>
<tr>
<td>Over-replacement with T4 (4)</td>
<td>2%</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
</tbody>
</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)
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
Evaluation Of The Patient With Osteoporosis

- Careful history and examination
- Laboratory testing
  - Chemistry
  - CBC
  - 24 hour urine calcium (and creatinine)
  - 25-OH vitamin D
  - *Thyroid function tests (TFTs) if symptoms warrant or the patient is on thyroid replacement therapy*

Identified 92% of new diagnoses at modest cost

<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><strong>Serum chemistry</strong></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</td>
<td>hypercalciuria, malabsorption</td>
</tr>
<tr>
<td>creatinine)</td>
<td></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
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

Importance of 24-hour Urine Calcium

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

Low T-score  ➔  Treatment