Osteoporosis Diagnosis: BMD, FRAX and Assessment of Secondary Osteoporosis

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Disclosures
I have nothing to disclose

Pathogenesis of Osteoporosis

AGING
MENOPAUSE
OTHER RISK FACTORS
RESORPTION > FORMATION
Bone Loss
POOR BONE QUALITY
LOW BONE DENSITY
FRACTURES
FALLS

BMD: A Continuum of Risk

Relative Risk of Fracture

-5 -4 -3 -2 -1 0 1 2
Osteoporosis Low Bone Mass Normal


**WHO Bone Density Criteria**

<table>
<thead>
<tr>
<th>Diagnostic criteria*</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T is above or equal to -1</td>
<td>Normal</td>
</tr>
<tr>
<td>T is between -1 and -2.5</td>
<td>Osteopenia (low bone mass)</td>
</tr>
<tr>
<td>T is -2.5 or lower</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>T 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.

http://www.nof.org

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**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>


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**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>
<tr>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Age & BMD

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

FRAX Model: Caveats

- The model is based on femoral neck BMD only—not spine BMD
- Limited to 4 ethnicities in US (Caucasian, Black, Hispanic, Asian)
- Dichotomous input for continuous variables such as previous fracture, steroid use and smoking
- It is not clear what margin of error is present in the fracture risk estimates
- The model does not fully account for the fracture risk associated with falling
- It is not obvious that all risk factors carry equal weight in predicting the response to pharmacologic treatment
**2008 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, FN or Total Hip)
- Other Fractures after Age 50 (Excluding Fingers, Toes and Face)
- 10-year Probability of Hip Fracture >3% or Probability of All Major Fractures >20%
- Secondary Causes with High Fracture Risk*

*such as glucocorticoid use or total immobilization

http://www.nof.org

**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 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>Phenothiazine</td>
<td>Osteogenesis imperfecta</td>
<td>COPD</td>
</tr>
<tr>
<td>Ponphoria</td>
<td>Calcium deficiency</td>
<td>Phenobarbital</td>
<td>Homocystinuria</td>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Glycopenia</td>
<td>Alcoholism</td>
<td>Depo-Provera Aromatase inhibitors</td>
<td>Ehlers - Danlos syndrome</td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Hypercalciuria</td>
<td>Aromatase inhibitors</td>
<td>Marfan syndrome</td>
<td>Thalassemia</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 Aromatase inhibitors</td>
</tr>
<tr>
<td>Myeloma</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%
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:
    - >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)
- “Persistent” additional testing is appropriate if there is a statistically significant BMD decrease on therapy

References:
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>Serum chemistry</td>
<td>malabsorption; malnutrition</td>
</tr>
<tr>
<td>Albumin</td>
<td>myeloma</td>
</tr>
<tr>
<td>Globulin</td>
<td>malignancy, cirrhosis, vitamin D deficiency</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>hyperparathyroidism, malabsorption</td>
</tr>
<tr>
<td>Calcium (high or low)</td>
<td>malnutrition, osteomalacia</td>
</tr>
<tr>
<td>Phosphate</td>
<td>renal disease</td>
</tr>
<tr>
<td>BUN, creatinine</td>
<td>vitamin D deficiency</td>
</tr>
</tbody>
</table>

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

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