BMD and Fracture Risk for Osteoporosis Diagnosis

Dennis M. Black, PhD
Dept. of Epidemiology and Biostatistics
University of California, San Francisco

Outline

• Types and sites of bone mass measurement
• Relationship of “BMD” to fracture risk and use of T-scores
• FRAX: Diagnosis: The Next Generation
• A bit about clinical utility of bone quality and markers for diagnosis

Central Bone Mineral Density (BMD) Measurements

• Dual Energy X-ray Absorptiometry (DXA)
  – Measures multiple skeletal sites
    • spine
    • proximal femur
  – Office based
  – Low radiation

Peripheral Measurements

• Self contained X-ray systems
  – Portable
  – Measurement sites
    • heel, forearm, hand
  – Lower cost, less radiation
• Ultrasound
  – Heel, other sites
• But less reliable: Use central DXA whenever possible
Bone Mineral Density (BMD) and Fracture Risk

- We now know that BMD predicts fracture
- Are all BMD measurements the same or are some sites/techniques preferred?
- Are some types of fracture better predicted?

BMD is a very good predictor of fracture risk

Approximate RR per SD decrease in BMD (age adj.)

<table>
<thead>
<tr>
<th>BMD Site</th>
<th>Wrist Fracture</th>
<th>Spine Fracture</th>
<th>Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Spine</td>
<td>1.6</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Hip (FN)</td>
<td>1.6</td>
<td>1.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Sources:
2. Black, 2002  

from JA Kanis et al, Osteoporos Int. 2001;12:989-995
**Clinical Use of BMD**

- T-scores developed to use BMD in clinical setting
- What is a T-score?
  - For a patient’s BMD value, the number of standard deviations below peak adult BMD

**Mean Bone Density (hip) by Age**

**Mean Hip BMD In Population by Age**

**Example T-score:**
Woman with BMD = 0.69 gm/cm²
**Example T-score:**

Woman with BMD = 0.69 g/cm²

- Peak BMD (0.89 g/cm²)
  - (SD at peak 0.10 g/cm²)

- BMD = 0.69 g/cm², 2 SD's below peak
  - T = -2.0

**Categorize Patients Based on T-scores:**

**WHO 1992**

<table>
<thead>
<tr>
<th>WHO Category</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Above T-score of -1</td>
</tr>
<tr>
<td>Osteopenic</td>
<td>Between -1 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Below -2.5</td>
</tr>
</tbody>
</table>

**Diagnosis based on BMD**

- Treatment thresholds based on T-score (1991 – Recent)

**Rationale for Use of -2.5 (1992)**

- 25% of post-menopausal women have a history of fracture (Mayo)
- Pick BMD value such that 25% of P-M women are below it
- No more arbitrary than other thresholds
- Current guidelines use T-score thresholds other than -2.5 and now risk

Adapted from JA Kanis et al, Osteoporos Int. 2001;12:989-995
Can T-scores be used for any device?

- Potentially provides means of standardizing across multiple BMD sites/devices
- T-scores from central DXA have been calibrated vs. each other. Not true for peripheral BMD.
- Beware of T-scores from other than hip and spine

Who Should Be Screened with Bone Densitometry

- All women over age 65 years
- Women age 60-64 years with risk factors
- US Preventive Services Task Force—as above
- National Osteoporosis Foundation: above +
  - All postmenopausal women with risk factors
    - History of p-m fracture, mom’s history of fracture, very low body weight, steroid use, etc.
- International Society for Clinical Densitometry: above +
  - Men aged 70 and older
  - Anyone being treated, to monitor treatment effect

Role of BMD in Primary Care Setting

- Other predictors of chronic disease
  - Blood pressure
  - Lipids
- Osteoporosis: chronic inferiority complex about BMD and fracture risk
  - (my risk factor is bigger than yours)
- Freudian-esque term: **Lipid-envy**

Risk of CHD Death in Young Men: Chicago Heart Association

11,017 Men Aged 18 to 39 at Baseline; 25-Year Follow-up

<table>
<thead>
<tr>
<th>Baseline Cholesterol Level</th>
<th>Age-Adjusted Death Rate/1000 Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160</td>
<td>5.5</td>
</tr>
<tr>
<td>160-199</td>
<td>12.4</td>
</tr>
<tr>
<td>200-239</td>
<td>24</td>
</tr>
<tr>
<td>240-279</td>
<td>47.8</td>
</tr>
<tr>
<td>&gt;280</td>
<td>84</td>
</tr>
</tbody>
</table>

**Cholesterol Predicting Heart Disease (CHD) vs. BMD Predicting Hip Fracture**

- **Relative Incidence**
  - I: Cholesterol/CHD
  - II: Hip BMD/ Fracture
  - III: Increasing Cholesterol
  - IV: Increasing BMD

- **Conclusions**
  - Lipid testing/treatment is accepted as integral part of primary medical care
  - BMD testing/treatment is at least as justified

---

**Risk Factors for Osteoporosis (independent of BMD)**

- Age, gender
- Low body weight
- History of postmenopausal fracture (including vertebral fracture)
- Family history of fracture
- Smoking
- Inactivity / bed rest

---

**Combining BMD with Clinical Risk Factors**

- **Hip Fracture Rate (per 1000 woman-years)**
  - Lowest Third
  - Middle Third
  - Highest Third
  - 0-2
  - 3-4
  - >5

**How can BMD and risk factors be put together (ala heart disease)?**

WHO Risk Model: Overview

- Begun in about 1999
- Headed by John Kanis and Olof Johnell (deceased)
- Base system on 10 year risk of fracture
- Define a set of robust risk factors by meta-analysis of epidemiological studies
- Build models with and without BMD
- Make country-specific risk-based diagnostic and treatment thresholds based on local cost effectiveness models

Calculating Fracture Risk: FRAX (online March 2008)

- Can calculate 10 year fracture risk online
- Risk of major osteoporotic fractures (4) or hip fractures
- Two options on how to use:
  - 1. Input individual values for risk factors and find 10 year risk using risk calculator
  - 2. Use charts of website by counting risk factors
- URL: http://www.shef.ac.uk/FRAX/index.htm
Fracture Risk Charts on FRAX website

- Country-specific
- Gender and age specific
- With and without BMD
- Count the number of risk factors

Use of risk charts: Count number of clinical risk factors (CRF's)

<table>
<thead>
<tr>
<th>Age &gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
</tr>
<tr>
<td>3.0</td>
</tr>
</tbody>
</table>

Risk is the estimated risk
Range is the range of risks—not a confidence interval.
- Higher for more potent risk factors (e.g. history of fracture)
- Lower for less potent risk factors (e.g. smoking)
**Treatment Threshold Concept**

- 10-Year Fracture Probability (%)
- BMD T-score
- 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

**More on FRAX**

- Can calculate 10 year risk for women or men
- U.S.: Caucasians, African American, Hispanic or Asian
- New recalculation for U.S. about to be launched
- Used as part of new treatment algorithm by National Osteoporosis Foundation (more tomorrow)

**More on FRAX**

- Some skeletons in FRAX closet
  - Not universal agreement that FRAX includes best/most parsimonious predictors
  - Calibration for each country not yet perfect nor non-whites
  - How to use for clinical decision-making?
  - Concerns that those with high risk (without low BMD) may not benefit from treatment
- But generally a strong infrastructure to help physicians

**Bone Quality for Fracture Prediction**

- Bone quality an important component of fracture risk
- But...our interest in bone quality is beyond our ability to measure it
- Some proposed measurements proposed as measures of bone quality:
  - QCT measurements of trabecular or cortical bone or bone geometry
  - HSA (hip structure analysis)...structure using DXA
  - Finite Element Modeling (FEM) from QCT
Bone Quality for Fracture Prediction: Results

- Few measures have been evaluated prospectively
- Ultrasound (heel) had been hoped to measure quality of bone but predictive ability disappointing
- QCT: Can be used to assess bone density and structure (trabecular and cortical) in spine and hip
  - Recent results: QCT parameters predicted hip fracture (Black, JBMR, 2008)
    - But prediction was not significant after adjustment for DXA
- Conclusion- DXA is a fortuitous combination of density and structure: no imaging yet found to improve on DXA

Biochemical Markers of Bone Turnover (aka “BTM’s”) for Diagnosis

- Measures of levels of bone turnover
  - Resorption and formation
    - From urine or serum
- Have been developing over last few years
- Increasing precision and ease of assay (automated platform)

Potential Advantages of Biochemical Markers as Predictors

- Integrated, dynamic assessment of skeletal metabolism
  - Metabolism not assessed with BMD
- Rapid and large changes with therapy
- Automated assays widely available, less expensive than DXA
- No DXA machine required

Potential Disadvantages of BTM’s

- High day-to-day variability (biologic)
  - Time of collection, fasting status
- Between laboratory variability (QC) unknown
- Scant and conflicting normative data
  - Reference ranges differ. eg for NTX
    - Quest: 10-110 mM BCE/mmol Cr
    - LabCorp: 5-65 mM BCE/mmol Cr
If BMD Known, Does Marker Help?

- Combination of tests best assessed by AUC in ROC analyses
- Only one study (EPIDOS)* has reported ROC for fracture prediction:
  - AUC with high uCTX = 0.58
  - AUC with low BMD = 0.63
  - AUC with both = 0.66
- Suggests little benefit from marker if BMD known
- Currently: little role for markers in diagnosis—
- Use for monitoring to be discussed tomorrow

*Garnero et al. Osteo Int 1998;8:563-569

Summary: Fracture Risk Prediction and Osteoporosis Diagnosis

- BMD very strong predictor
  - BMD at the hip especially useful
- Risk factors are very useful
  - eg. Age, Gender, BMI, Hx. Of fracture, family hx
- FRAX:
  - New web-based tool to combine risk factors with BMD for better prediction of fracture risk
  - Infrastructure now in place. Refinements on-going.
- Bone markers and BQ measures not (yet) clinically useful