Understanding the Development of Osteoporosis and Preventing Fractures: “WHO” Do We Treat Now?

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Past President, American Association of Clinical Endocrinologists (AACE)
President-Elect, American College of Endocrinology
Endocrine and Bone Densitometry Consultant – NASA: Johnson Space Center

Learning Objectives

1. Apply the 2008 recommendations from the National Osteoporosis Foundation (NOF) for bone density testing;
2. Understand the limitations and appropriate use of bone densitometry according to the 2007 positions of the International Society for Clinical Densitometry (ISCD);
3. Identify factors, as established by the World Health Organization (WHO) in 2008, that contribute to the risk of fracture, and determine absolute fracture risk;
4. Identify appropriate candidates for therapy according to the 2008 NOF recommendations.

Roadmap

1. The Stone Age
2. The Industrial Revolution
3. The Information Age
Modern Stone Age Equivalent: Case 1

67-year-old white woman with a history of two recent, minimal trauma, painful grade-2 vertebral fractures at T10 and T11 by vertebral fracture assessment (VFA).
- Dual-energy X-ray absorptiometry (DXA) results show a L1-L4 T-score of -1.9 with little variability between vertebral bodies and the lowest hip site at the left femoral neck at a T-score of -1.7. The technical quality of the study was good.

What is her diagnosis?
- A. Low bone density (osteopenia)
- B. Osteoporosis
- C. Severe Osteoporosis
- D. None of the above

Case 1 – Correct Answer

67-year-old white woman with a history of two recent, minimal trauma, painful grade-2 vertebral fractures at T10 and T11 by vertebral fracture assessment (VFA).
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Case 1: Lessons to be Learned...

We are still in the stone age as far as recognizing and treating the “low-hanging fruit”

Fracture Patients!

For more information: see ISCD VFA Course: www.iscd.org
Roadmap

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Case 2

- 42-year-old pre-menopausal woman with radiographic osteopenia;
- Risk factors: family history, low body weight;
- Referred for significant decrease in bone density;
- Two studies – 8 months apart. Studies done on same machine: Hologic® Delphi

Question Case 2

For which of the following patients is bone densitometry NOT appropriate according to the National Osteoporosis Foundation (NOF)?

1. Man, age 72, without risk factors
2. Post-menopausal woman, age 66, without risk factors
3. 42-year-old pre-menopausal woman with a family history of osteoporosis
4. 40-year-old pre-menopausal woman who has been taking glucocorticoids, 5 mg to 10 mg daily, for asthma the past 6 months
5. 51-year-old man who recently broke his wrist in a fall while walking
Question Case 2 – Correct Answer

For which of the following patients is bone densitometry NOT appropriate according to the National Osteoporosis Foundation (NOF)?

1. Man, age 72, without risk factors
2. Post-menopausal woman, age 66, without risk factors
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5. 51-year-old man who recently broke his wrist in a fall while walking


- Women (65 and older) and men (70 and older) regardless of clinical risk factors
- Younger postmenopausal women and men (aged 50 to 70 years) about whom you have concern based on the clinical risk factor profile
- Women who are in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture, or high-risk medication
- Adults who have a fracture after age 50

Bone Densitometry, cont.

- Adults who have a condition (e.g., rheumatoid arthritis) or who are taking a medication (e.g., glucocorticoids ≥ 5 mg per day for ≥ 3 months) that is associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone being treated for osteoporosis, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
- Postmenopausal women discontinuing estrogen
Case 3 – DXA of 12/6/2005

Spine T-score of -3.0

Case 3 - DXA 6 months earlier (4/29/2005)

Spine T-score of -2.2

Case 3 - Comparison

Spine (Total): 0.818  -3.0  71  3.7  73
Case 3 Question

For serial follow-up scan comparison, which of the following is FALSE?

1. You should compare T-scores to determine whether there has been a change.
2. You should not compare values on different machines of the same manufacturer unless a cross-calibration study has been done.
3. You should not compare values from machines made by different manufacturers.
4. A standard Caucasian reference database should be used for T-score determination regardless of the ethnicity of the patient.

---

Case 3 Question – Correct Answer

For serial follow-up scan comparison, which of the following is FALSE?

1. You should compare T-scores to determine whether there has been a change.
2. You should not compare values on different machines of the same manufacturer unless a cross-calibration study has been done.
3. You should not compare values from machines made by different manufacturers.
4. A standard Caucasian reference database should be used for T-score determination regardless of the ethnicity of the patient.

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Case 3 - Comparison

<table>
<thead>
<tr>
<th>Scan Information:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: April 29, 2005</td>
</tr>
<tr>
<td>Height: 164 cm</td>
</tr>
<tr>
<td>Weight: 61.3 kg</td>
</tr>
<tr>
<td>Age: 55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L4</th>
<th>14.16</th>
<th>11.97</th>
<th>0.845</th>
<th>-2.5</th>
<th>-2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>49.33</td>
<td>39.90</td>
<td>0.809</td>
<td>-2.5</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scan Information:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: December 06, 2005</td>
</tr>
<tr>
<td>Height: 164 cm</td>
</tr>
<tr>
<td>Weight: 61.3 kg</td>
</tr>
</tbody>
</table>

| Scan (Total) | 0.818 | -3.0 | 71 | 2.9 | 71 |
Case 3 - Lessons Learned

1. Compare BMD values, NOT T-scores
3. ISCD recommends using the standard ethnic reference population for T-scores and ethnic databases for Z-scores... for now
4. Know indications for performing a DXA!

Case 4

60-year-old woman with DXA study showing a bone density of 0.806 g/cm² at the L1-L4 spine in 2004 and 0.795 g/cm² in 2006. The DXA lab did not do a precision study. Her T-score in 2006 was -3.2.

Is this a significant change?
1. Yes
2. No

See: www.iscd.org
Understanding the Guidelines for Fracture Prevention

- Background
- Risk Factor Assessment
- Screening

Case 5

50-year-old African-American woman with menopause 6 months ago with:
- a T-score of -2.5 at the spine and -2.5 at the hip;
- no other risk factors

80-year-old white woman with:
- a T-score of -2.4 at the spine and -2.4 at the hip;
- prior spine fragility fractures;
- positive family history;
- smoker;
- body weight 120 pounds

Which is the BEST answer?
1. The patients have the same diagnosis.
2. The patients have the same fracture risk.
3. 1 & 2 are both true.
4. 1 & 2 are both false.
WHO Report: 1994

“If all you have is a hammer, then everything starts to look like a nail.”

Fracture Prediction by BMD

Some Treatment Guidelines Used in the United States
Problems...

Fracture Rates, Population T-Score Distribution, and Number of Fractures in National Osteoporosis Risk Assessment (NORA)

Fracture Probability at Hip by Age and BMD

Combined Effect of Bone Density and Prevalent Fractures

Roadmap

1. The Stone Age
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WHO Report on Fracture Risk Reporting
Scientific Meeting: Brussels, Belgium, May 5-7, 2004

Studies Included in the "Mega-Analysis"

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Fracture Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVOS/EPOS</td>
<td>Hiroshima</td>
<td>Any fracture = 5444</td>
</tr>
<tr>
<td>Rochester</td>
<td>Sheffield</td>
<td>Osteoporotic fractures = 3495</td>
</tr>
<tr>
<td>Kuopio</td>
<td>Gothenburg I</td>
<td>Hip fractures = 957</td>
</tr>
<tr>
<td>EPIDOS</td>
<td>Dubbo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OFELY</td>
<td></td>
</tr>
</tbody>
</table>
WHO Risk Factors NOF (February 21, 2008)

- Current age
- Use of oral glucocorticoid therapy
- Gender
- Secondary osteoporosis (e.g., rheumatoid arthritis)
- Personal history of a fracture
- Parental history of hip fracture (not history of osteoporosis)
- Femoral neck bone mineral density (BMD)
- Current smoking
- Low body mass index (kg/m²)
- 3 or more alcoholic drinks per day

Use of the WHO Algorithm – the FRAX Model

- **Pertains only to previously untreated patients.**
- FRAX is used to calculate the 10-yr probability of a hip fracture and 10-yr probability of any major osteoporotic fracture (vertebral, hip, forearm, or humerus fracture) using femoral neck BMD and clinical risk factors. Total hip BMD may be substituted.
- Use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated.
- FRAX -- available online @ http://www.shef.ac.uk/FRAX/
- Patch for men T-scores on www.nof.org website

Current Treatment Model

Based on 7693 post-menopausal women with average age of 67

![Graph showing osteoporotic fracture risk by age and BMD T-Score](image-url)
WHO should be treated (NOF 2/21/2008)?

Post-menopausal women and men aged 50 years and older who present with the following:

- A hip or vertebral fracture (clinical or morphometric);
- T-score < -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes.

WHO should be treated (NOF 2/21/2008)?

- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and 10-yr probability of hip fracture ≥3% or a 10-yr probability of any major osteoporosis-related fracture ≥20% based on the U.S.-adapted WHO algorithm.

NOF Treatment Model (2/21/2008)

Using a 10-year any fracture risk threshold of 20% and -2.5 cut-point

Implications of WHO 2008 Model

- ISCD Position Development Conferences (PDC) 2005: Diagnostic classification of osteoporosis will not change.
- Distinguishes between diagnostic threshold and intervention threshold.
- “Osteopenia” will no longer be relevant – we’ll be able to calculate absolute fracture risk.
- Fewer younger patients who are at low risk will be treated and more older patients who are at higher risk will be treated.

Limitations of the WHO Model

- Limited as to reference site for BMD
- Does not apply to secondary osteoporosis
- Does not determine which interventions will be effective at lowering the fracture risk
  - Medications
  - Non-pharmacologic interventions
  - Nothing?

Case 6: 59-year-old white male

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD (g/cm²)</th>
<th>Z-Score</th>
<th>T-Score</th>
<th>AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>0.784</td>
<td>-2.03</td>
<td>-3.27</td>
<td>-3.00</td>
</tr>
<tr>
<td>L2</td>
<td>0.741</td>
<td>-2.51</td>
<td>-4.04</td>
<td>-2.00</td>
</tr>
<tr>
<td>L3</td>
<td>0.746</td>
<td>-2.13</td>
<td>-3.60</td>
<td>-2.60</td>
</tr>
<tr>
<td>L4</td>
<td>0.728</td>
<td>-1.70</td>
<td>-2.81</td>
<td>-1.40</td>
</tr>
<tr>
<td>L1/L2</td>
<td>0.824</td>
<td>-2.31</td>
<td>-3.70</td>
<td>-2.80</td>
</tr>
<tr>
<td>L2/L3</td>
<td>0.841</td>
<td>-2.41</td>
<td>-3.80</td>
<td>-2.10</td>
</tr>
</tbody>
</table>
Case 6: 59-year-old white male

- 2001 - Status post biliopancreatic bypass with duodenal switch
- Weight decreased from 325 lbs to about 200 lbs
- Injury playing golf – imaging negative for fracture but noted radiographic osteopenia
- Normal testosterone, thyroid studies
- Started on bisphosphonate therapy
Case 6: 59-year-old white male
- 2001 - Status post biliopancreatic bypass with duodenal switch
- Weight decreased from 325 lbs to about 200 lbs
- Injury playing golf – imaging negative for fracture but noted radiographic osteopenia
- Normal testosterone, thyroid studies
- Started on bisphosphonate therapy
- Six weeks later – presented in emergency room with seizures

Case 6
- 2001 - Status post biliopancreatic bypass with duodenal switch
- Weight decreased from 325 lbs to about 200 lbs
- Injury playing golf – imaging negative for fracture but noted radiographic osteopenia
- Normal testosterone, thyroid studies
- Calcium: 8.3 mg/dL (8.5-10.2); iPTH: 450 pg/mL (7-53); low urine calcium of 30 mg/24 hours; 25-OH vitamin D of 10 ng/mL (optimal 30 ng/mL or more); high bone turnover markers

Case #6 Question
Which of the following is the BEST answer?
1. The patient has primary osteoporosis.
2. The patient has secondary osteoporosis.
3. The patient has osteomalacia.
4. The patient has primary hyperparathyroidism.
**Case #6 Question**

Which of the following is the BEST answer?

1. The patient has primary osteoporosis.
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---

### Some of the Secondary Causes of Low Bone Mass in Adults

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Chronic Diseases &amp; Other</th>
<th>Nutritional Conditions</th>
<th>Endocrine Diseases or Metabolic Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Rheumatoid arthritis</td>
<td>Vitamin D Deficiency</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Myeloma and cancer</td>
<td>Malabsorption</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Alkalai inhibitors</td>
<td>COPD</td>
<td>Hyperparathyroidism</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Depo-Provera</td>
<td>Organ Transplantation</td>
<td>Hypercalciuria</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Phenylalanin</td>
<td>Renal tubular acidosis</td>
<td>Calcium deficiency</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Excess thyroid</td>
<td>Malignant hypercalcemia</td>
<td>Alcoholism</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Heparin</td>
<td>Thalassemia</td>
<td>Gastric obesity surgery</td>
<td>Hypophosphatasia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Immobilization</td>
<td>Chronic liver disease</td>
<td>Type I DM</td>
</tr>
<tr>
<td>Lithium</td>
<td>HIV</td>
<td>Malnutrition</td>
<td>Acromegaly</td>
</tr>
</tbody>
</table>

---

### Common “Occult” Causes of Low Bone Density

<table>
<thead>
<tr>
<th>Disorder</th>
<th>% (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency (20 ng/ml)*</td>
<td>21%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>10%</td>
</tr>
<tr>
<td>GI malabsorption (includes celiac sprue)</td>
<td>8%</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>7%</td>
</tr>
<tr>
<td>Exogenous hyperthyroidism</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
<tr>
<td>Patients with at least 1 new diagnosis</td>
<td>49%</td>
</tr>
</tbody>
</table>

*An additional 34% of patients had Vitamin D levels ≤ 32ng/ml

Tannenbaum C. JCEM 2002;87:4431; Luckey M. JCEM 2003; 88:1405
### Secondary Causes Of Osteoporosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h urine calcium for all</td>
<td>39/173</td>
</tr>
<tr>
<td>Serum calcium for all</td>
<td>3/173</td>
</tr>
<tr>
<td>Serum PTH for all</td>
<td>27/173</td>
</tr>
<tr>
<td>Serum 25-OH vitamin D for all</td>
<td>9/173 (+25)</td>
</tr>
<tr>
<td>Serum TSH for all on replacement</td>
<td>4/25</td>
</tr>
</tbody>
</table>

**Conclusion:** This strategy identifies 98% of cases, costs $116 per patient screened, costs $366 per case found.


### Further Diagnostic Evaluation of Low Bone Mass

- phosphorus, alkaline phosphatase, creatinine
- Thyroid Stimulating Hormone (TSH) on all
- Testosterone (males)
- Serum protein electrophoresis (SPEP), UPEP
- Bone marrow biopsy with tetracycline labeling

Bone Turnover Markers?

### Celiac Disease and Osteoporosis

**Celiac Prevalence**
- 3.4% among patients who have osteoporosis
- 0.2% among those who don’t

**Anti-TTG and Anti-EMA**
- Good sensitivity and specificity
- Levels correlated with severity of osteoporosis
- Preclude need for biopsy in some cases

Gluten-free diet improves BMD

Routine screening for celiac disease is expensive.
Cost to prevent 1 fracture in a patient who has celiac disease and osteoporosis ~ $43K

Clinical Practice Recommendation

Practice Recommendation:
All postmenopausal women should be evaluated for risk factors of osteoporosis, which include increasing age, white race, low weight or weight loss, nonuse of estrogen therapy, history of previous fracture, family history of fracture, history of falls, and low scores on one or more measures of physical activity or function.

Evidence-based Source:
AHRQ: http://www.ahrq.gov/clinic/3rduspstf/osteoporosis/ostecorr.html#clinical

Strength of Evidence:
A systematic review of 530 articles about risk factors, 123 about bone measurement tools, 23 about bone density monitoring, 277 about biochemical markers, and 53 about cost. An additional 242 studies were retrieved after reviewing reference lists of studies and by suggestion of the expert panel or leading researchers in the field.

Clinical Practice Recommendation

Practice Recommendation:
Consider postmenopausal women with vertebral or hip fractures candidates for osteoporosis treatment. The bisphosphonates (alendronate, etidronate, and risedronate), as well as calcitonin, estrogens and/or hormone therapy, parathyroid hormone (PTH 1-34), and raloxifene are recommended as treatment options for the secondary prevention of osteoporotic fragility fractures.

Evidence-Based Source:
National Guideline Clearinghouse @

Strength of Evidence:
The recommendations are based primarily on the available evidence from randomized controlled trials.

Summary

- When appropriate, include DXA along with assessment of clinical risk factors, in the evaluation of patients who are at risk for osteoporosis.
- For patients who are at significant risk of fracture, knowing the absolute fracture risk is likely to enable more effective interventions.
- When assessing patients for pharmacologic therapy, consider secondary causes of low bone density. Some laboratory evaluation may be necessary.
References

- ISCD VFA Course @ [http://www.iscd.org/Visitors/certification/VFACourse.cfm](http://www.iscd.org/Visitors/certification/VFACourse.cfm)
- FRAX. The World Health Organization's Fracture Risk Assessment Tool. Available online @ [http://www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/)