Battling Metabolic Bone Disease

26th Annual Oley Foundation Consumer-Clinician Conference

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DISCLOSURE

Relevant Financial Relationship(s)
None

Off Label Usage
None
OBJECTIVES

- Discuss factors as to future fracture risk
  - Age, previous fracture(s), bone mineral density (BMD)
  - FRAX® WHO fracture risk assessment tool
  - Biochemical markers (BCM) of bone turnover

- Review FDA approved drug treatments
  - Calcium and vitamin D
  - Anti-resorptive therapy
  - Anabolic therapy

- Monitoring therapy
More Than 1.5 Million Fractures Yearly

Vertebral
46%
(700,000)

Wrist
16%
(250,000)

Hip
19%
(300,000)

Other
19%
(300,000)

NIH/ORBD National Resource Center, October 2000
Pathogenesis of Fractures

- Aging
- Menopause
- Sporadic factors
  - Genetics
  - Calcium
  - Vitamin D
  - Tobacco smoking
  - Alcohol excess
  - Gonadal dysfunction
  - Steroids
  - Malnutrition

Inadequate peak bone mass
Increased bone loss
Low bone density
Low bone quality
Propensity to fall
Fall mechanics
Excess load or Trauma
Skeletal fragility
Fracture

Melton LJ, Osteoporosis Int 1999
Assessing Fracture Risk
Central (Hip-Spine) Dual-Energy-Xray-Absorptiometry (DXA) Measurement

- OP clinical ‘surrogate’ in absence of fracture
- DXA bone density considered the clinical standard
- Measures multiple skeletal sites
  - Spine, hip, forearm, and total body
The WHO criteria were established for use in postmenopausal women.
Age and BMD are Independent Risk Factors for Hip Fracture

Kanis, OI 2002;12:989

3% 10-year Hip Fx Risk

T-score

Age (yrs)

10 Yr Hip Fx Probability (%)

80
70
60
50

0
10
20

-3
-2
-1
0
1

Age and BMD are Independent Risk Factors for Hip Fracture
Osteoporotic Fracture Rates, Numbers and BMD Distribution

Fracture Rate (Fx’s/1,000 person-yrs)

- Fracture rate
- BMD distribution
- Women with fractures

Women with fractures (no.)

Siris: Surgeon General’s Workshop on Osteoporosis and Bone Health, December 2002
10-Yr Probability of Major OP Fx

Men and women aged 65 yrs and BMI 25 kg/m²; Fx risk according to T score and number of clinical risk factors

Please answer the questions below to calculate the ten year probability of fracture.
Country: US (Caucasian)  Name / ID: 

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 69
   Date of birth: [Y: __  M: __  D: ___]

2. Sex
   Male  Female

3. Weight (kg)  55.9

4. Height (cm)  162.9

5. Previous fracture
   No  Yes

6. Parent fractured hip
   No  Yes

7. Current smoking
   No  Yes

8. Glucocorticoids
   No  Yes

9. Rheumatoid arthritis
   No  Yes

10. Secondary osteoporosis
    No  Yes

11. Alcohol 3 or more units per day
    No  Yes

12. Femoral neck BMD (g/cm²)
    GE-Lunar  0.781  T-score: -1.8
Limitations of WHO FRAX*

- Fracture risk may be over-estimated
  - Without the inclusion of DXA BMD
- Fracture risk may be under-estimated
  - If >1 prevalent vertebral Fx present
  - If bone turnover increased
  - With high-dose steroid use
  - For vertebral fracture (VFx) risk, as FRAX uses only hip DXA BMD to assess 10-yr hip fracture and all skeletal fracture
- Only for postmenopausal women, and men >50 yrs
  - WHO BMD criteria should not be applied in children, premenopausal women, men <50 yr

*World Health Organization Fracture Risk Assessment tool*
Calcium and Vitamin D
## National Academy of Sciences
Institute of Medicine (IOM) 2011 Guidelines

<table>
<thead>
<tr>
<th>Life Stage Group (age and gender)</th>
<th>Calcium RDA (mg/d)</th>
<th>Calcium Upper Limit (UL) (mg/d)</th>
<th>Vitamin D RDA (IU/d)*</th>
<th>Vitamin D Upper Limit (UL) (IU/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo (M+F)</td>
<td>200&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>400&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6-12 mo (M+F)</td>
<td>260&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>400&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1500&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1-3yr (M+F)</td>
<td>700</td>
<td>2500</td>
<td>600</td>
<td>2500</td>
</tr>
<tr>
<td>4-8yr (M+F)</td>
<td>1000</td>
<td>2500</td>
<td>600</td>
<td>3000</td>
</tr>
<tr>
<td>9-13yr (M+F)</td>
<td>1300</td>
<td>3000</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>14-18yr (M+F)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1300</td>
<td>3000</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>19-30yr (M+F)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1000</td>
<td>2500</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>31-50 yr (M+F)</td>
<td>1000</td>
<td>2500</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>51-70 yr (M)</td>
<td>1000</td>
<td>2000</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>51-70yr (F)</td>
<td>1200</td>
<td>2000</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>71+yr (M+F)</td>
<td>1200</td>
<td>2000</td>
<td>800</td>
<td>4000</td>
</tr>
</tbody>
</table>

<sup>a</sup> RDA = intake that covers needs of 97.5% of the healthy normal population.
<sup>b</sup> Reflects Adequate Intake (AI) reference value rather than RDA. RDAs have not been established for infants due to insufficient data.
<sup>c</sup> Calcium and vitamin D RDAs are the same for pregnant or lactating females in these age groups.
Is There an Optimal Vit-D Level?  
Who is at risk?

"deficiency"
"insufficiency"
"optimal-normal"

*modified after RP Heaney  (10 ng/mL = 25 nmol/L)
Bone Loss, Vitamin D and 2°HPT

Ambulatory EVOS* Subjects (Spain, latitude 43°N, n=268, mean age 68 years). Prevalence 2° HPT: F 24.1%, M 18.5%

*European Vertebral Osteoporosis Study, Kidney International. 2003;63(S85):S44
# When To Consider Vit-D Deficiency

## Clinical Setting
- Decreased sun exposure
- Poor vitamin D intake
- Malabsorption
  - Gastric bypass, Celiac sprue, short bowel
- Chronic illness
  - Pain, weakness, falls
  - CKD, seizure Rx
  - Underweight-malnourished
- Bone loss or fracture

## Laboratory
- ↓ 24-hr urine calcium
- ↑ Total or bone alk phos
- ↑ Parathyroid hormone
- ↑ Creatinine (GFR < 60)

## Radiographs
- Radiographic bone loss
- Low bone mineral density
- Skeletal fracture
- Skeletal pseudofracture
Vit D, Calcium Absorption, and PTH

Fasting PTH

Calcium Absorption (p<0.001)

Mean serum 25(OH)D level, nmol/L

No pre-treatment with vitamin D or 25(OH)Vit
50.2 nmol/L = 20.1 ng/mL

Pre-dosed with 25(OH)Vit D for 3 weeks prior to study
86.5 nmol/L = 34.6 ng/mL

Vit D Deficiency and Osteoporosis
Treatment Effect On BMD and Fx at 18 Mo

Ave. age 84 years, n = 3270

Chapuy, NEJM 1992; 327:1637

Calcium 1200 mg + Vitamin D 800 IU
HPN

- **Calcium**
  - 1 gram IV calcium gluconate; provides 4.7 mEq calcium, or 9% (90 mg) elemental calcium
    - Oral calcium may be poorly absorbed
    - Normal urine calcium excretion ≤ 275-300 mg/day; may be increased by sodium/salt intake

- **Vitamin D**
  - MVI (multivitamin injectable); provides 200 I.U. (international units) vitamin D3 (cholecalciferol)
    - Oral intake may need to be in large doses
    - IM source limited; uVB sunlight exposure if needed
  - Blood measurement desirable
Anti-resorptive Therapy
Bone “Remodeling” Activity

- Remodeling Too Low
  - Poor growth
  - Poorly-mineralized
  - Ex. Osteo-malacia

- Normal Bone

- Remodeling Too High
  - ↓ Bone mass/structure
  - Stress risers
  - Ex. Osteo-porosis
Normal Bone “Remodeling” Activity
A Coupled Homeostatic Process

- Resting Stage
- Activation Phase: Resorption
- Reversal Phase
- Bone Formation
- Remodeling Complete

2-3 wks
3-4 months

Lining cells
Osteoclast precursors
Osteoclasts
Osteoblasts
Lining cells

Bone remodeling unit
Postmenopausal Osteoporosis
Trabecular Micro-architectural Change

Normal

Dempster, 2000

Osteoporosis

Horizontal Perforations
Micro-callous
Bone Remodeling Unit

Lining cell

Quiescence

Bone

Activation

Osteoclast
(N-Telopeptide)
(C-Telopeptide)

Anti-Resorptive

Resorption

Osteoblast
(Bone Alk Phos)
(P1NP)

Anabolic

Formation

Mineralization
Biochemical Bone Turnover Marker Response to Therapy

Anti-resorptive Rx (Alendronate-Fosamax)

Anabolic Rx (Teriparatide-Forteo)

McClung, et al, ASBMR 2003
Denosumab (Prolia)

• A fully human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANK-L)
  • Blocks RANK-L binding to RANK, inhibiting osteoclast recruitment and activity

Denosumab 60 mg q6mo (Cummings et al. NEJM 2009;361:756)
  • 7868 women with PMO (T scores <-2.5)
  • Significant ↓ (p<0.001) in bone markers (CTX, P1NP); n=160

Denosumab 60 mg q6mo (Cummings et al. NEJM 2009;361:756)
  • 7868 women with PMO (T scores <-2.5)
    ✓ 441 subset of patients with BMD
  • Significant 9.2% ↑ in L-spine BMD vs PBO at 36 mo
  • Significant 6.0% ↑ in total hip BMD vs PBO at 36 mo
Denosumab
A monoclonal antibody to RANKL

*NEJM* 2009;361:756

7868 women with PMO, mean age 72 yrs

60 mg SQ q6mo X3 yrs
Calcium 1000 mg/d
Vit-D 400-800 IU/d

Vertebral fractures
AR 2.3% vs 7.2%
RR 68% ↓

Hip fractures
AR 0.7% vs 1.2%
RR 40% ↓
# FDA Approved Anti-resorptive Rx

## RCT’s of 3-5 Years Duration (*parenteral form available)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Pt.No.</th>
<th>VFx RR↓</th>
<th>Hip Fx RR↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹Calcitonin*</td>
<td>PROOF</td>
<td>1255</td>
<td>36%</td>
<td>ns</td>
</tr>
<tr>
<td>²Evista</td>
<td>MORE</td>
<td>7704</td>
<td>30-55%</td>
<td>ns</td>
</tr>
<tr>
<td>³HRT/ERT*</td>
<td>WHI</td>
<td>16608</td>
<td>34%</td>
<td>34%-39%</td>
</tr>
<tr>
<td>⁴Alendronate</td>
<td>FIT-1</td>
<td>2027</td>
<td>47%</td>
<td>51%</td>
</tr>
<tr>
<td>⁵Risedronate</td>
<td>VERT</td>
<td>2458</td>
<td>41-49%</td>
<td>(na)</td>
</tr>
<tr>
<td>⁶Risedronate</td>
<td>HIP-OP</td>
<td>5445</td>
<td>(na)</td>
<td>40%</td>
</tr>
<tr>
<td>⁷Ibandronate*</td>
<td>BONE</td>
<td>2946</td>
<td>52%</td>
<td>ns</td>
</tr>
<tr>
<td>⁸Zoledronate*</td>
<td>HORIZON</td>
<td>7765</td>
<td>70%</td>
<td>41%</td>
</tr>
<tr>
<td>⁹Denosumab*</td>
<td>FREEDOM</td>
<td>7868</td>
<td>68%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Monitoring Therapy
Monitoring Anti-resorptive Therapy

**Left:** Given a 1-1.5% precision error of BMD, a 2-yr Rx is likely to be needed to observe a significant change.  **Right:** With 10-15% precision error of BCM-BTO, the effect of Rx will likely be seen at 3 mo, especially for resorption markers.

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Delmas PD. *Osteoporos Int* 2000;11(18):S66-76  
Tx: treatment, Pl: placebo
Anti-resorptive Effects on BMD and Bone Turnover During & After 2-Yr Rx

Bauer DC. JBMR 2011;26(2):239
Anabolic Therapy
3D-CT reconstruction of paired iliac crest bone biopsy before (left) and after (right) 20 mcg/day SQ teriparatide (rhPTH 1-24). Note: increased cortical thickness, trabecular bone volume, and trabecular connectivity. 68 yo woman, 21 mo therapy.


Teriparatide (Forteo®) Effect on Vertebral Fracture Risk

**p <0.001 vs. Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=448)</th>
<th>rhPTH 20 (n=444)</th>
<th>rhPTH 40 (n=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women who had ≥ 1 vertebral fracture</td>
<td>64</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>% of Women</td>
<td>100%</td>
<td>75%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Neer, NEJM 2001; 344:1434
Teriparatide (Forteo®) Effect on Non-vertebral Fracture Risk

No. of women who had ≥ 1 non-vertebral fragility fracture

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=544)</th>
<th>rhPTH 20 (n=541)</th>
<th>rhPTH 40 (n=552)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Women</td>
<td>30</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>* p = 0.02 vs. Placebo</td>
<td>** p = 0.01 vs. Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neer, NEJM 2001; 344:1434
Bisphosphonate Preserves BMD Gain after PTH

Months After PTH Withdrawal

Lumbar Spine

BMD (% change)

-6
-4
-2
0
2
4
6

Bisphosphonate (n=12)

None (n=7)

***
**
*

Bisphosphonate (n=12)

None (n=7)
SUMMARY

Etiology of fractures is multi-faceted

- Aging
  - Inadequate peak bone mass
- Menopause
  - Increased bone loss
- Sporadic factors
  - Low bone density
  - Low bone quality
  - Propensity to fall
  - Fall mechanics
  - Excess load or Trauma
  - Skeletal fragility
  - Fracture
SUMMARY

HPN Treatment:
- Calcium
- Vitamin D
- Anti-resorptive therapy
  - No oral bisphosphonates
  - IV bisphosphonates
  - SQ denosumab (Prolia)
- Anabolic therapy
  - SQ teriparatide (Forteo)
  - Hormone therapy: topical estrogen/testosterone

Assessing therapy:
- FRAX®
  - WHO 10-yr hip fracture risk
- Skeletal x-rays
  - Thoracic and lumbar spine
- Bone mineral density
- Labs/blood tests
  - Bone alkaline phosphatase
  - C-telopeptide
  - 24-hour urine calcium
  - 25-hydroxyvitamin D
Thank you!

hurley.daniel@mayo.edu
REFERENCES

- “Clinician’s Guide to Prevention and Treatment of Osteoporosis”

  www.nof.org web site for the National Osteoporosis Foundation (NOF) and clinical guidelines

  www.shef.ac.uk/FRAX web site for the World Health Organization (WHO) Fracture Risk Assessment tool (FRAX)