Disclosures

• Grant Support
  – National Institute of Health
  – Department of Defence
  – Radius Health
  – Fund for Henry Ford Hospital

• No direct conflict of interest for today’s talk
Objectives

• Approach to the patient with low BMD/OP/Fx
• Scope & magnitude of osteoporosis problem
  – i.e., Fracture Epidemiology & Disease burden
• Therapy selection based on the type of Fx risk assessment
  – Hip versus Spine
• Determinants of therapeutic efficacy
• Monitoring Rx: BMD Vs. Biomarkers & How Often?
• How long should we treat & how safe are anti-Fx therapies?
• Vitamin D: How much is enough & how much is too much?
• Controversy about Ca supplements
• Concluding remarks
78y Black woman
Low BMD
Spontaneous multiple vertebral fractures
Pelvic fracture with trivial trauma
Rheumatoid arthritis
Long term prednisone therapy; currently on 10mg/day
LH-78y Black woman

LUMBAR SPINE [L1 - L4] -- Scan mode: F

Bone Mineral Density: 0.83g/cm²
T-score: -3.7
Z-score: -2.0
WHO Classification: Osteoporosis

LEFT HIP [FEMORAL NECK] -- Scan mode: F

Bone Mineral Density: 0.595g/cm²
T-score: -3.7
Z-score: -2.1
WHO Classification: Osteoporosis
How many risk factors does she have?
Some Ground Rules

• My remarks & presentation are
  – Mostly *evidence* based
  – Partly *eminence* based (The Rao’s principles!)

• What we measure & follow are
  – Largely surrogate measurements
    • BMD, BTMs, X-rays etc (Just like HgA1c, LDL, BP, etc)
  – …not the events we intend to prevent-fragility Fxs (MI, Stroke, CRF)

• Trial results are
  – Selected population group based
  – May not necessarily applicable to the individual patient in the clinic
    • Value judgment/value imposition
Scope & Magnitude of OP Problem

Fracture Epidemiology
&
Disease Burden
Osteoporotic fractures are more common in women than heart attacks, strokes & breast cancers combined

2. Heart and Stroke Facts: 2007 Statistical Supplement, American Heart Ass’n
3. Cancer Facts & Figure: 2006, American Cancer Society

* 2005 annual incidence all ages
** 2004 estimate
† 2004 estimate, new and recurrent
‡ 2006 new cases, women all ages
Interesting Facts About Fractures

- Bone remodeling occurs every 15 seconds!
- Fxs occur every 3 seconds somewhere in world
- Each Fx increases the risk of another fracture
  - 1=3 fold; 2=5 fold; 3=9 fold!
- 2/3rds of vertebral Fx are asymptomatic
- Wrist Fx is a harbinger of future Fx esp. of the hip
- Both vert & hip Fxs carry morbidity & mortality
- A previous Fx implies “poor” architecture
Osteoporosis Definition

“A systemic disorder characterized by decreased bone mass micro-architectural deterioration and increased susceptibility to fractures in the absence of other recognizable causes.”
<table>
<thead>
<tr>
<th>Condition</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>$\geq -1.0$</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>$-1$ to $-2.5$</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>$\leq -2.5$</td>
</tr>
<tr>
<td>‘Established’ osteoporosis</td>
<td>$\leq -2.5$ + presence of one or more fractures</td>
</tr>
</tbody>
</table>
Pathogenesis of Osteoporosis & Fracture

![Graph showing the relationship between bone mineral density (BMD) and age](image)

- BMD (g/cm²)
- Age (years)

**Lumbar Spine**

- BMD increases with age, reaching a peak around 30 years, then decreases.

**Proximal Femur**

- BMD increases with age, reaching a peak around 40 years, then decreases.
Osteoporosis

Normal

Severe Osteoporosis

Osteoporosis

Severe Osteoporosis

Courtesy Dr. A. Boyde
Minimal Evaluation of a Patient

- Detailed H & P
  - Risk factor assessment
  - Personal history of fragility fractures after age 25y
  - Parenteral history of hip fractures
  - Accurate height measurement & assessment
  - Costo-pelvic interval (Rao Index!)

- Diagnostic Evaluation
  - BMD and VFA ± X-ray spine
  - Lab tests as appropriate or dictated by H & P
    - Biochemical profile, 25-OHD, & 24h urine Ca, Na, Cr
    - PTH, TSH

- Application of FRAX for therapeutic decision
  - https://www.sheffield.ac.uk/FRAX/
Risk Factors for Osteoporosis

• **Primary (Non-modifiable)**
  - Aging
  - Female gender
  - Low peak adult bone mass
  - Caucasian, Asian,
  - Estrogen deficiency
  - Family history of osteoporosis
  - Thin and/or small frame (?)
  - Use of certain medications
    (corticosteroids, Depo-provera, aromatase inhibitors, anticonvulsants)

• **Secondary (Modifiable)**
  - Cigarette smoking
  - Excessive use of alcohol
  - Lack of physical activity
  - **Vitamin D deficiency**
  - **Inadequate lifetime calcium intake**
  - Dietary deficiencies or excesses (protein, sodium, caffeine)
The Big 3!

1. *Age* of the patient

2. *Personal history* of fracture after age 25y
   
   Fractures of skull, clavicle(?), fingers & toes don’t count!

3. *Parental* history of *hip* fracture

   - BMD is a distant fourth!

   - Contributes about 35-40% to a fracture
Classification of Osteoporosis

1. **Primary**
   - Type I (Postmenopausal): Accelerated bone loss
   - Type II (Age-related): Constant slow bone loss
   - Type III (?Senile): Unclear?

2. **Secondary Osteoporosis**
   - A large number of conditions & disorders
     - Corticosteroid Rx is the most common

3. **Others**
   - Drugs: aromatase inhibitors; anticonvulsants etc
   - Transplant bone disease
   - Idiopathic osteoporosis (?male osteoporosis)
Relationship of BMD To Future Fx Risk

Relationship of Prevalent VF to Future Fx Risk

Nevitt M.C. Bone 1999
Fracture Probability According to Age & BMD

Add Age
Assessing the Risk for Hip Fracture

STRENGTH OF BONE
- Bone Turnover
- Bone Mass
- Bone Quality

Fall-Related Trauma
- Risk of Fall
- Neuromuscular Function
- Environmental Hazards
- Time Spent at Risk

Force of Impact
- Type of Fall
- Protective Responses
- Energy Absorption
FDA Approved Therapies for Osteoporosis Prevention & Treatment

Prevention (Antiresorptive)
• Estrogens*
• Calcitonin*
• Bisphosphonates
  – Alendronate
  – Risedronate
  – Ibandronate (oral & IV)
• SERMS (Raloxifene)

Treatment (Antiresorptive & Anabolic)
• Calcitonin*
• Bisphosphonates
  – Alendronate (daily/weekly)
  – Risedronate (daily/weekly/monthly)
  – Ibandronate (oral monthly & IV 3m)
  – Zolidronate (IV-yearly or less often)
  – Denosumab (Prolia) SC-6 monthly
• SERMS (Raloxifene)*
• Teriparatide (Anabolic)*
• Abaloparatide (Anabolic)*
• Romosozumab (?mixed action)
Each was evaluated in well designed RCT

- Very few head to head trials
- In general: ERT/HRT, CT, SERM are “weaker” with respect to BMD change
  - However, vertebral Fx reduction is “comparable”
  - CT trial is probably the weakest of all trials
  - BP trials are the strongest as is the denosumab trial
- BPs have long “skeletal residence half time”
  - So, concern about atypical femur fractures (AFF) & osteonecrosis of jaw (ONJ)
  - How long & how safe?
- Denosumab is a bit unique and different from BPs
  - “non-accumulating”
- Teriparatide & Abaloparatide are the only anabolics currently available
  - Slightly faster & more robust increase in BMD, but no data for hip Fx reduction
- Romosozumab is a new kid on the block
  - A bit unique in action and different from all others.
**Baseline Characteristics, Changes in BMD & Reductions in Incident Vertebral Fractures**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Spine BMD</th>
<th>Reduction in Vert Fx</th>
<th>Spine T-score</th>
<th>Baseline Vert Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN-FITII</td>
<td>7.9%</td>
<td>47%</td>
<td>-2.5</td>
<td>90%</td>
</tr>
<tr>
<td>RIS-US</td>
<td>5.4%</td>
<td>41%</td>
<td>-2.4</td>
<td>&gt;100%</td>
</tr>
<tr>
<td>ZOL</td>
<td>7.5</td>
<td>65%</td>
<td>-2.8</td>
<td>50%</td>
</tr>
<tr>
<td>Ralox</td>
<td>2.6%</td>
<td>40%</td>
<td>-2.6</td>
<td>37%</td>
</tr>
<tr>
<td>CT</td>
<td>1.2%</td>
<td>36%</td>
<td>&lt;=-2.0</td>
<td>75%</td>
</tr>
<tr>
<td>TPTD</td>
<td>15%</td>
<td>65%</td>
<td>-2.6</td>
<td>90%</td>
</tr>
<tr>
<td>Deno</td>
<td>8.8%</td>
<td>68%</td>
<td>-2.8</td>
<td>23%</td>
</tr>
</tbody>
</table>
Currently Available Tools to Monitor Therapy

• Height measurement
  – Easy to measure, pitfalls & advantages, cost effective
• Bone Mineral Density (BMD)
  – Definition, methods, precision, accuracy, interpretation etc
• Bone Turnover Markers (BTMs)
  – Easy to measure, but large variability in individual response
• X-ray procedures
  – Which ones & when?
• Bone Biopsy for histomorphometry
  – What, when, & why?
# Monitoring Frequency for BMD

<table>
<thead>
<tr>
<th></th>
<th>AACE</th>
<th>NAMS</th>
<th>ISCD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Site</strong></td>
<td>Spine &amp; Hip</td>
<td>Hip ± Spine</td>
<td>Spine &amp; Hip</td>
</tr>
<tr>
<td><strong>Instrument</strong></td>
<td>DEXA</td>
<td>DEXA</td>
<td>DEXA</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Normal Baseline BMD: every 3-5y</td>
<td>Untreated: every 5y</td>
<td>On Rx: Yearly till therapeutic effect</td>
</tr>
<tr>
<td></td>
<td>Prevention: 1-2y till stable; then 2-3y</td>
<td>Treated: every 2y</td>
<td>Loner intervals</td>
</tr>
<tr>
<td></td>
<td>On Rx: yearly till stable; then q 2 y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BTMs are also “validated” in RCTs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Formation</th>
<th>Resorption</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>BSAP, P1NP, P1CP &amp; OC</td>
<td>uNTX, sCTX, DPD</td>
<td>Fracture &amp; BMD</td>
</tr>
<tr>
<td>Risedronate</td>
<td></td>
<td>uNTX, uCTX, uDPD</td>
<td>Fracture &amp; BMD</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>BSAP, P1NP, OC</td>
<td>uCTX</td>
<td>Fracture</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>BSAP, P1NP, P1CP</td>
<td>uNTX, sCTX, DPD</td>
<td>Fracture &amp; BMD</td>
</tr>
</tbody>
</table>
BTMs: What do they mean/reflect?

• Whole body bone turnover
  – By contrast BMD is site specific
• Diurnal variation
• Biologic variation
• Measurement variations
• Short term response
How to Identify Non-responders? 
Real vs. Apparent

- **Apparent**
  - Positioning, Instrument, & other technical issues
  - Artifacts and surgeries
    - Laminectomy, hip replacement etc
  - Age related changes at the sites of measurement
  - Regression to mean

- **Real**
  - Adherence to therapy
  - *Problems in taking Rx*
  - Intercurrent illnesses and/or therapy
    - **Steroid therapy**
    - **Inadequate vitamin D & Ca intake/supplements**
  - Occult malabsorption
What are our concerns, constrains & questions?

• How do we define efficacy?

• What constitutes a “non-response”?
  – Densitometric?
  – Biochemical?
  – Clinical?

• Fracture assessment during therapy
  – Reduction versus elimination
  – “Usual” versus “Unusual” fractures

• Treatment Failure
  – Decline in BMD on “optimal” therapy during follow-up
  – An incident fracture on therapy ≠ treatment failure?
The Last Word!

• Monitoring chronic diseases, such as OP, that require long-term Rx is critical, because adherence to Rx is often inadequate.

• Serial BMD, BTM, VFA (& accurate height measurements to be sure) allow physicians to monitor efficacy of therapy, improve adherence, & as a result, the intended outcomes.

• Discussions between physicians & patients about patient progress enhances adherence.

• Proper use of monitoring tools provides feedback to patients; if not, the management of OP therapy will simply be a guesswork.

• To be useful, however, these tools require strict quality control and proper interpretation, which is sorely lacking at present.
What is required to make monitoring worthwhile?

- Test should reliably categorise change within an appropriate timescale

- *Test should predict clinical outcome*

- Result of test should influence physician management and/or modify patient behaviour

- Use of test for monitoring should be cost-effective
Role of Calcium & Vitamin D Nutrition in Osteoporosis
Non-pharmacologic fracture prevention strategies

• All RTCs of Osteoporosis
  – Calcium Supplementation 500-1000 mg/day
  – Vitamin D 200-400 IU/day

• \textit{Ca: 1500-2000 mg/d & Vitamin D: 800-1000 IU/d}
  – Rao DS., J Clin Densitometry, December 1999
  – Guardia…Rao et., al Osteoporosis Int 2008

• Fall prevention and its monitoring
• Hip protectors in selected patients
Assessing the Risk for Hip Fracture

- **STRENGTH OF BONE**
  - Bone Turnover
  - Bone Mass
  - Bone Quality

- **Fall-Related Trauma**
  - Risk of Fall
  - Neuromuscular Function
  - Environmental Hazards
  - Time Spent at Risk

- **Force of Impact**
  - Type of Fall
  - Protective Responses
  - Energy Absorption

- **Adequate Calcium & Vitamin D Nutrition**
Ca Supplements & CV Events

**Myocardial infarction**
Hazard ratio 1.26, (95% CI 1.07 to 1.47), P=0.005

**Stroke**
Hazard ratio 1.19, (95% CI 1.02 to 1.39), P=0.03
The Bottom Line

• A wide variety of drugs are now available for prevention & treatment of both low bone density and fractures; many are in pipe line
  – *Ale Carte or smorgasbord*

• For good bone balance…target the peak bone mass
  – *Osteoporosis is really a pediatric disease*

• *Bone balance is better than bank balance!*
Osteoporosis Therapy Options
Postmenopausal Women

STAGE
- At Risk/Osteopenia
- Osteoporosis
- Severe Osteoporosis

BMD
- Higher
- T-Score -2.5
- Lower

AGE
- Increasing risk of fracture with age

During
Hot Flashes

Past Vasomotor Symptoms
Before fracture

After Fracture

HRT

Raloxifene

Bisphosphonates

Teriparatide

Calcitonin

*Increasing risk of fracture with age
LH-36932007

78y Black woman
Low BMD
Spontaneous multiple vertebral fractures
Pelvic fracture with trivial trauma
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Long term prednisone therapy; currently on 10mg/day
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WHO Classification: Osteoporosis

LEFT HIP [FEMORAL NECK] -- Scan mode: F

Bone Mineral Density: 0.595g/cm²
T-score: -3.7
Z-score: -2.1
WHO Classification: Osteoporosis
How many risk factors does she have?

- Older age
- Menopause without HRT
- Rheumatoid arthritis
- Long term prednisone therapy
- Low BMD
- Multiple fractures
Natural History of Osteoporosis
“People with osteoporosis do not just die; they slowly break apart.” — Linda Johnson
The paradox of Evidence Based Medicine

- It’s not what the data say, it’s what you say about the data
- Statistics mean you never have to say you’re certain
Continuing Medical Education

“Education is not the filling of a pail, but the lighting of a fire”

...William Butler Yeats (1865-1939)

www.quotesandsayings.com

Source: BMJ 332:518, 4 March 2006
D. Sudhaker Rao, M.B;B.S., FACP, FACE
Section Head, Bone & Mineral Metabolism
Director, B & M Research Laboratory

Tel:313-916-2369; Cell:313-971-4984
Fax:313-916-8343; srao1@hfhs.org
Osteoporotic Fractures Are More Common In Women Than Heart Attack, Stroke & Breast Cancer Combined

A. True
B. False
Having a fragility fracture after age 25 does not increase the risk of future fragility fractures?

A. True  
B. False
Bone mineral density measurement is the best available diagnostic tool both to screen & monitor OP therapy?

A. True
B. False
Although all are important risk factors for future fractures, which of the following is the most important?

A. Bone density
B. Parental history of hip fracture
C. Personal history of a fragility fracture
D. Age
E. Ethnicity/Race
Which of the following FDA approved drugs is not used for prevention of osteoporosis?

A. Alendronate
B. Risedronate
C. Ibandronate
D. Estrogen/Reloxifene
E. Zoledronic acid (iv)
Which of the following drugs is the most common cause of secondary osteoporosis?

A. Estrogen
B. Long term corticosteroids
C. Depo-provera
D. Anticonvulsants
E. Aromatase inhibitor therapy for breast cancer
How frequently BMD test should be repeated while on treatment for osteoporosis?

A. Every 6 months
B. Every 12 months
C. Every 2-3 years
D. Not needed if patient is already on treatment