Update on Treatment of Osteoporosis

Disclosure

• No direct compensation from potentially conflicting entities
• Employed by New Mexico Clinical Research & Osteoporosis Center, which has received the following in the past one year:
  – Research grant support from Amgen, Radius, Mereo
  – Consulting and scientific advisory board fees from Amgen, Radius, Alexion, Sandoz
  – Honoraria for service with speakers’ bureaus of Alexion, Radius
  – Support for project development with University of New Mexico
• Board positions with the ISCD, NOF, OFNM
• Guideline committees with ISCD, NOF, AACE

Objectives

• Define indications for pharmacologic treatment of osteoporosis
• Describe mechanism of action for different drug classes for treating osteoporosis
• Determine strategies for selecting initial therapeutic agents and changing therapy
• Apply methods for understanding and explaining to patients the balance of benefits and risks with treatment
Osteoporosis

- A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture
- Bone strength reflects the integration of two main features: bone density and bone quality (e.g., architecture, turnover, damage accumulation, mineralization)


DXA Measures Bone Density

DXA = Dual-energy X-ray Absorptiometry

WHO Classification of BMD

<table>
<thead>
<tr>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
</tr>
<tr>
<td>-1.0 or higher</td>
</tr>
<tr>
<td><strong>Osteopenia</strong></td>
</tr>
<tr>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
</tr>
<tr>
<td>-2.5 or lower</td>
</tr>
<tr>
<td><strong>Severe Osteoporosis</strong></td>
</tr>
<tr>
<td>-2.5 or lower + fragility fracture</td>
</tr>
</tbody>
</table>

Applies to peri- and postmenopausal women, and men age 50 and older. Cannot be used in premenopausal women and men under age 50. Should never be used in children (under age 20). T-score ≤ -2.5 is not always osteoporosis. A patient may have osteoporosis with a T-score > -2.5.
More About T-scores

- T-score ≤ -2.5 is not always osteoporosis
  - Osteomalacia
  - Invalid measurement (e.g., laminectomy)
- T-score > -2.5 may be osteoporosis
  - Fracture
    - High fracture probability (FRAX)
- Many risk factors for fracture other than T-score
  - Especially advancing age and previous fracture
  - Also family history, smoking, glucocorticoids, RA, AI, ADT, etc.
- Correlation between T-score and fracture risk is a gradient, not a threshold

DXA Measures Bone Quality (TBS)

TBS = Trabecular Bone Score

TBS = 0.872
Bone Quality
Bone Density

Experimental
Bone Density
Bone Quality

TBS = 1.495

TBS = 1.241

TBS = Trabecular Bone Score
Osteoporosis: Good News

- Improving awareness
- Excellent diagnostic tools
- Fracture risk assessment algorithms
- Effective and safe treatments
- Inexpensive generic drugs
- Better understanding of pathogenesis
- Federal initiatives to improve care

Osteoporosis: Bad News

- Underdiagnosis and undertreatment
- Poor adherence to therapy
- Poor understanding of risk/benefit ratio
- Restrictions on coverage of BMD testing, drugs, vitamin D testing, bone turnover markers
- Severely diminished drug pipeline
- DXA quality concerns
- Medicare cuts in DXA reimbursement

Treatment Gap Getting Worse

Review of US insurance claims data (commercial + Medicare) in 99,687 patients hospitalized with hip fracture, 2002-2011

Reduced Bisphosphonate Prescription Rates Starting in 2008


Who should be treated, how should they be treated, and how can we do it better?
Ann is a 55 year-old woman who feels well. She has had no known fracture. She smokes ½ pack per day and has a mother with hip fracture at age 78. She asks you if she should have a bone density test.

Your answer is …
A. Yes
B. No
C. Maybe
D. You need more information
You order a DXA for Ann. The report states:
Lumbar spine T-score = -2.8, osteoporosis, fracture risk is high
Femoral neck T-score = -2.1, osteopenia, fracture risk is moderate
33% radius T-score = -0.9, normal, fracture risk is low

The correct diagnosis is ...
A. Osteoporosis
B. Osteopenia
C. Normal
D. All of the above

Fracture risk is ...
A. High
B. Moderate
C. Low
D. All of the above

3 Ways to Diagnose Osteoporosis

• BMD testing (WHO, ISCD)
  — T-score ≤ -2.5 at LS, TH, FN, or 33%R
• Fragility fracture (NBHA)
  — Low trauma hip fracture regardless of BMD
  — Low trauma vertebral, proximal humerus, pelvis or some distal forearm fractures with T-score between -1.0 and -2.5
• FRAX (NBHA, USA only)
  — MOF risk ≥ 20% or HF risk ≥ 3%


In the Office

Focused history
• Prior fractures
• Family history of fractures
• Childhood development
• Falls
• Medications, supplements
• Osteoporosis treatments
• Historical max. height
• Lifestyle
• Surgery
• Diet
• Review of systems
• More

Physical exam
• Height (stadiometer)
• Falls risk assessment
• Gait
• Scoliosis
• Kyphosis
• Rib-pelvis space
• Skeletal deformity
• Rash
• Tremor
• Hepatomegaly
• Flexibility
• More
Measure Height with Wall-mounted Stadiometer

Spine imaging if historical height loss > 1.5 inches

Laboratory Evaluation

Almost everyone
• CBC
• Blood chemistries
  – Creatinine
  – Calcium
  – Phosphorus
  – Albumin
  – Alkaline phosphatase
  – Liver enzymes
• 25-OH-vitamin D
• 24-hour urine for calcium, sodium

Selected patients
• TSH
• Celiac antibodies
• Bone turnover markers
• Urinalysis
• sIFE, kappa/lambda light chain ratio
• Intact PTH
• Overnight dexamethasone suppression

Most Women with Hip Fracture have T-score > -2.5

NOF Treatment Guidelines
For postmenopausal women and men age 50 and older, after appropriate evaluation for secondary causes

Osteoporosis by T-score
• T-score -2.5 or less at FN, TH, or LS, or . . .

Clinical Osteoporosis
• Hip or vertebral (clinical or morphometric) fracture, or . . .

Low BMD + High Fx Risk
• T-score between -1.0 and -2.5 at FN, TH, or LS, and . . .
• FRAX 10-year probability of hip fracture ≥ 3% or major osteoporotic fracture ≥ 20%

Universal Recommendations
• Regular weight-bearing and muscle-strengthening physical activity
• Falls prevention
• Avoid tobacco use and excess alcohol
• Identification and treatment of risk factors for fracture
• Calcium 1000-1200 mg/day, ideally from diet
• Vitamin D 800-1000 IU/day, target ≥ 30 ng/mL

Pharmacological Therapy

<table>
<thead>
<tr>
<th>Inhibit Bone Resorption (Antiresorptives)</th>
<th>Stimulate Bone Formation (Anabolic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax, generic)</td>
<td>Teriparatide (Forteo)</td>
</tr>
<tr>
<td>Risedronate (Actonel, Atelvia, generic)</td>
<td>Abaloparatide (Tymlos)</td>
</tr>
<tr>
<td>Ibandronate (Boniva, generic)</td>
<td></td>
</tr>
<tr>
<td>Zoledronate (Reclast, generic)</td>
<td></td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista, generic)</td>
<td></td>
</tr>
<tr>
<td>Salmon Calcitonin (Miacalcin, generic)</td>
<td></td>
</tr>
<tr>
<td>Estrogen (various)</td>
<td></td>
</tr>
<tr>
<td>CE/Bazedoxifene (Duavee)</td>
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</tr>
</tbody>
</table>

All of these can increase BMD, improve bone strength, and reduce fracture risk. Only anabolic agents can build new bone and restore degraded bone structure. Anabolic agents are superior to antiresorptives for high risk patients.

Bone Remodeling

Activation → Resorption
Resting Phase → Formation
Reversal Phase

Osteoclast

Zaidi and Chambers, 1987
**Progression of Osteoporosis**

- Normal
- Bad
- Very Bad

Anabolic vs. Antiresorptive Therapy

Courtesy Dr. A. Boyle

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**Treatment Sequence Matters**

- Anabolic therapy superior to antiresorptive for fracture risk reduction in high risk patients:
- Potent antiresorptive therapy before anabolic may attenuate or delay onset of effect (hip BMD decrease with teriparatide after denosumab)
- Antiresorptive therapy after anabolic is essential to consolidate or enhance therapeutic effect


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**Sequence of Osteoporosis Therapy**

- Antiresorptive → Anabolic
  - Delay or attenuation of anabolic effect; decreased BMD with TPT after Dmab
- Anabolic → Antiresorptive
  - Antiresorptive is essential after anabolic; initial therapy with anabolic is best choice for high risk patients
- Anabolic → Anabolic
  - Probably neutral
- Antiresorptive → Antiresorptive
  - Greater BMD effect with more robust antiresorptive, especially Dmab after BP
Individualizing Initial Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Oral bisphosphonates</td>
<td>Pro: inexpensive, work well in many patients</td>
</tr>
<tr>
<td></td>
<td>Con: GI distress, avoid with low GFR, bad rep in lay press</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Pro: very long dosing interval, post-hip fracture data</td>
</tr>
<tr>
<td></td>
<td>Con: acute phase reaction, avoid with low GFR, IV</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Pro: long dosing interval, greatest BMD increase, SC</td>
</tr>
<tr>
<td></td>
<td>Con: FDA list of &quot;side effects&quot; (Back pain, high cholesterol, etc.)</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Pro: not a BP, decreases breast cancer risk</td>
</tr>
<tr>
<td></td>
<td>Con: VTE, hot flashes, no proven hip fracture decrease</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Pro: anabolic (SEQUENCE MATTERS)</td>
</tr>
<tr>
<td></td>
<td>Con: high cost, daily injection, refrigeration, rat osteosarcoma</td>
</tr>
<tr>
<td>Abaloratide</td>
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Personal opinion.

Treat-to-Target

- Initiate therapy with medication that has high likelihood of achieving an acceptable level of fracture risk
- Response to therapy is essential but not necessarily sufficient
- Patient may respond well but remain at high risk of fracture
- For patient started on treatment because of T-score ≤ -2.5, consider target > 2.0
- Greater increase in BMD are associated with greater reduction in fracture risk


Osteoporosis Wheel of Fear

Consider “Drug Holiday” for Postmenopausal Women Treated with Oral BP ≥ 5 Years or IV BP ≥ 3 Years

- Low fracture risk: hip T-score > -2.5 and no hip, spine, or multiple osteoporotic fracture before or during therapy
  - Consider drug holiday of 2-3 years

- High fracture risk: hip T-score ≤ -2.5 or hip, spine, or multiple osteoporotic fracture before or during therapy
  - Consider continuing oral BP up to 10 years and IV BP up to 6 years


Annals of Internal Medicine

Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology

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No Holiday with Other Osteoporosis Medications

Stopping non-bisphosphonate (estrogen, raloxifene, denosumab, teriparatide, abaloparatide) is followed by rapid loss of effect.

Fracture Liaison Service (FLS)

- Secondary fracture prevention by systematic identification and management of fracture patients
- Objectives
  - Gerald Champion Regional Medical Center
  - Christus St. Vincent Regional Medical Center
  - UNMH
  - In development: Presbyterian
- Key person: FLS coordinator - USP or discharge planner
- Technology: patient registry, task tracker, quality measures, etc.

When to Refer to an Osteoporosis Specialist

- Low trauma fracture with normal BMD
- Recurrent fractures or continuing bone loss despite treatment
- Unexpectedly severe osteoporosis (e.g., very low BMD in young patient)
- Uncommon features (e.g., low alk phos, low P)
- Uncommon secondary causes (e.g., bariatric surgery, celiac disease)
- Complicating conditions (e.g., CKD, hyperpara)

Adapted from AACE Guidelines. Endocr Pract. 2016;22 (Suppl.4).
Bone Health
Register at www.ofnm.org

Average Number of Participants Per Bone Health TeleECHO Session

<table>
<thead>
<tr>
<th>Year</th>
<th>Participants</th>
</tr>
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<tbody>
<tr>
<td>2015</td>
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</tr>
<tr>
<td>2016</td>
<td>19</td>
</tr>
<tr>
<td>2017</td>
<td>32</td>
</tr>
<tr>
<td>2018</td>
<td>42</td>
</tr>
</tbody>
</table>
UNM Bone Health TeleECHO

Participants in:
- Canada
- Mexico
- Chile
- Brazil
- Trinidad and Tobago
- Iceland
- England
- Denmark
- Russia
- Ukraine
- Armenia
- United Arab Emirates

Self-Efficacy Outcomes Measures

Before ECHO

After ECHO


Register at www.ofnm.org
Summary

• Osteoporosis is a common disease with serious consequences due to fractures

• Effective and safe medications to reduce fracture risk are available

• Osteoporosis is a lifelong disease that deserves lifelong attention

Contact me for more information: mlewiecki@gmail.com