When Calcium and Vitamin D Aren’t Enough: Treatment of Osteoporosis
HopeArgenziano MD

Patient AM: 84 y/o female with hip fracture
- 84 y/o home bound patient admitted with a hip fracture after falling out of bed
- Mild Alzheimer’s
- 3 falls last year, 10lb weight loss
- CBC, CMP normal, Vit D 15
- Surgery: hip pinned

Recommendations?
- If Crcl 25?

Who Do We Treat?

Problem: Most Women with Hip Fractures Do Not have Osteoporotic T-scores

Who Should Be Treated?

Problem: Most Women with Hip Fractures Do Not have Osteoporotic T-scores

Challenge
How can we identify those with high risk of fracture who could benefit from pharmacological therapy?

Wainwright SA et al. J Clin Endocrinol Metab. 2005;90:2787-2793

2014 update available on-line at www.NOF.org

2014 NOF Guide

- Practical clinical guide that includes recommendations on
  - When to do DXA
  - How to treat
  - Secondary causes to consider
  - Treatment options

NOF Guidelines
Who Should Be Treated?

- Fragility fracture hip or spine
- T-score ≤ -2.5
- T-score -1.0 to -2.5 (osteopenia) and 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability of ≥20%

www.nof.org
Basic Guide to Management

- Evaluation
  - History and Physical
  - Labs
  - Imaging
    - DXA
    - Spine imaging
- Non Pharmacologic therapy
- Pharmacologic Therapy

Non-Pharmacologic Therapy

- Nutrition
  - General
  - Calcium
  - Vitamin D
- Exercise
  - Physical therapy
- Fracture management
  - Physical Therapy
  - Surgery

Universal Recommendations for Prevention: NOF Recommendations 2014
Apply to postmenopausal women and men age 50 and older

- Counsel on the risk of osteoporosis and related fractures
- Advise on a diet rich in fruits and vegetables and that includes adequate amounts of total calcium intake
  - 1,000 mg per day for men 50-70
  - 1,200 mg per day for women 51 and older and men 71 and older

Is Calcium Supplementation Needed in All Patients?

**STEP 1: Estimate calcium intake from calcium-rich foods**

<table>
<thead>
<tr>
<th>Product</th>
<th># of Servings</th>
<th>Estimated calcium/ serving in mg</th>
<th>Calcium in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (8 oz.)</td>
<td>X 300</td>
<td></td>
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</tr>
<tr>
<td>Yogurt (6 oz.)</td>
<td>X 200</td>
<td></td>
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</tr>
<tr>
<td>Cheese (1 oz. or 1 cubic in.)</td>
<td>X 200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortified foods or juices</td>
<td>X 80 to 1,000**</td>
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</tr>
</tbody>
</table>

Subtotal**

**STEP 2: Total from above + 250 mg for non-dairy sources**

- total dietary calcium
- TOTAL Calcium, in mg =

*About 75 to 80 percent of the calcium consumed in American diets is from dairy products.
**Calcium content of fortified foods varies.
**Physical Therapy Basics for Osteoporosis**

Discourage
- Heavy lifting
- Back flexion

Encourage
- Fall prevention
- Balance exercises
- Weight bearing exercise eg walking
- Back extension exercises

**Extension Exercises**

**Avoiding Flexion and Managing ADL’s**

**Use of Back Braces**

- Acute fracture
  - Rigid braces used after back surgery are difficult for patients with osteoporosis to tolerate
  - Thoracolumbar corsets can decrease pain and increase mobility
  - Discontinue when acute pain subsides to avoid muscle atrophy

- Chronic back pain
  - Posture training support
  - Promotes extension

- 1 to 3 # weights in posterior pouch

**Pharmacologic Therapy**

- Antiresorptive
  - Block osteoclastic bone resorption

- Anabolic
  - Promote osteoblastic bone formation

**Premenopause: Balanced Bone Formation and Bone Resorption**

- Activation
  - Multinucleated osteoclasts
  - Sealed resorption cavity

- Resting
  - Lining cells

- Osteoid mineralized

- Formation
  - Osteoblasts produce osteoid

- Reversal
  - Apoptotic osteoclasts
  - Active osteoblasts
How do Antiresorptive Agents Improve Bone Strength?

- Prevent bone loss
- Prevent microarchitectural deterioration
- Promote mineralization

Pharmacologic Therapy

- Antiresorptive
  - Estrogen
  - Calcitonin
  - Raloxifene
  - Bisphosphonates
  - Denosumab

Estrogen

- Approved only for prevention
- Women’s health initiative documented a decrease in spine fractures by 35%, hip by 33% and forearm by 29%

- Extraskeletal considerations
  - Relieves symptoms of estrogen deficiency
  - Increases risk of breast cancer, VTE, coronary disease, stroke
  - Endometrial cancer risk in unprotected uterus

Nasal Calcitonin Reduces Spine Fractures

PROOF Trial: Prevent Recurrence of Osteoporotic Fractures

5-year study of 1255 women, average age 68, with 1-5 prevalent vertebral fractures

No significant reduction in non-vertebral fractures or hip fractures
No change in BMD from placebo

Raloxifene (Evista)

- SERM (selective estrogen receptor modulator) also known as EAA (estrogen agonist/antagonist)
- Fractures: reduces risk of vertebral fractures 30-50%
  - no proven benefit for hip or nonvertebral fractures
- Extraskeletal:
  - reduces risk of breast cancer (approved for prevention of breast cancer), does not reduce hot flashes
  - VTE risk, leg cramps
  - PMO: prevention and Tx 60mg daily. Caution advised with hepatic or renal impairment

Bisphosphonates

- Alendronate (Fosamax): po daily or weekly
  - PMO Prevention: 5mg daily, 35mg weekly
  - PMO TX: 10mg daily, 70mg weekly
- Risedronate (Actonel): po daily, weekly, or monthly
  - PMO Prevention and Tx: 5mg OD, 35mg weekly, 150mg monthly. Men 35mg weekly
- Ibandonrate (Boniva): po daily, monthly, IV q3 months
  - PMO Prevention and TX: PO 2.5mg daily, 150mg monthly
  - PMO TX only: 3mg IV every 3 months
- Zoledronic acid (Reclast): IV only
  - PMO Prevention 5mg IV Q 24 months
  - PMO TX 5mg IV Q 12 months
  - Men: 5mg IV Q 12 months
Bisphosphonate Characteristics

- Poorly absorbed
- Not metabolized
- ~50% excreted by kidney
- ~50% binds to bone
- High affinity to bone – Binds preferentially at resorptive surfaces
- Induces osteoclast dysfunction
- Long skeletal half-life

Fracture Risk Reduction with Bisphosphonates in RCTs

- Pivotal fracture trials
  - Alendronate: FIT 1, FIT 2
  - Risedronate: VERT, HIP
  - Ibandronate: BONE
  - Zoledronic acid: HORIZON
- Results
  - Spine fractures reduced ~50% in all
  - Hip fractures reduced ~40% with alendronate, risedronate and zoledronic acid

Atypical Femur Fractures

- Key characteristics:
  - Fractures of femoral diaphysis or in subtrochanteric region
  - Transverse rather than spiral
  - May begin with stress reaction or stress fracture of lateral femoral cortex which may be bilateral
  - Proximal pain in thigh or groin is common
  - Often on other drugs, especially steroids or estrogen

Medications Work at Different Points of the Remodeling Cycle

Bisphosphonate Safety

- Possible GI intolerance with oral agents
- Not recommended for GFR < 30-35 ml/min
- Acute phase reaction with IV
- Hypocalcemia
- Chronic muscle/joint pain?
- Oversuppression of bone turnover?
- Osteonecrosis of the jaw (ONJ)?
- Atypical femoral fractures

Denosumab

- Antiresorptive, fully human monoclonal antibody, binds and inhibits RANKL (RANKL triggers activation of osteoclasts)
- BMD: increases at spine and hip
- Fracture: decreases spine, hip and nonvertebral fracture by 68%, 40%, 20%
- Injection SQ every 6 months
- Safety: increased infection risk?
Lining cells

DMAB

Activation
Osteoclasts

BP's

Resting

Lining cells

Formation
Osteoblasts

Antiresorptive vs Anabolic Therapy

Osteoporotic Bone: resorptive cavities, loss of connectivity

Antiresorptive: fills in resorptive cavity, increases mineralization

Anabolic: produces osteoid, increases connectivity

Teriparatide: rhPTH(1-34)

• Class: anabolic, hormone
• BMD: increases at spine and hip
• Bone turnover markers: increased (different from anti-resorptives, which decrease bone turnover markers)
• Fractures: decreases spine and nonvertebral fractures by 65% and 53%, no proven benefit for hip in RCT
• Extra-skeletal considerations:
  • Osteosarcoma in rats, daily subcutaneous injection, refrigeration, hypercalcemia, leg cramps, dizziness, high cost, limit of 2 years of therapy

FDA-Approved Medications

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<th>Drug</th>
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<th>GIO</th>
<th>Men</th>
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<td></td>
<td>Preventio n</td>
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<tr>
<td>Estrogen</td>
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Summary: Fracture Risk Reduction (PMO)

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We now have multiple choices for prevention and treatment of osteoporosis

• How do we choose appropriate therapy for an individual patient?
Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis

- What drugs can be used to treat osteoporosis?
  ◊ 1st line: Alendronate, Risedronate, Zoledronic acid, DMAB
  ◊ 2nd line: Ibandronate, Raloxifene
  ◊ Other:
    - Calcitonin: last line of therapy
    - Teriparatide: for patients with very high fracture risk
    - Advise against the use of combination therapy

Watts et al. Endoc Pract 2010;16(6):1016-9

What is successful treatment?
- BMD stable or increasing, no fractures
- For antiresorptive agents, bone turnover markers at or below the median value for premenopausal women
- One fracture not necessarily evidence of failure

Watts et al. Endoc Pract 16(6):1016-9, 2010

How is treatment monitored?
- Baseline DXA spine or total hip, repeat every 1-2 years until stable
- Follow-up scans should be in the same facility, with the same machine, and, if possible, with the same technician

What long should patients be treated?
- For bisphosphonates, if osteoporosis is mild, consider a "drug holiday" after 4 to 5 years of stability
- If fracture risk is high, consider a drug holiday of 1 to 2 years after 10 years of treatment
- Follow BMD and bone turnover markers during a drug holiday period and reinitiate therapy if bone density declines substantially, bone turnover markers increase, or a fracture occurs

Watts et al. Endoc Pract 16(6):1016-9, 2010

What to Do with the Patient Who Does not Respond
- Review the actual DXA scan including the image to ensure there is a true loss
- Mistakes in interpretation can occur
- Must know the least significant change at that center to determine if a true loss has occurred
- Assess compliance and persistence
- Are they taking adequate calcium and vitamin D?
- Evaluate for missed secondary causes
- If there is a true loss in a compliant patient and no secondary causes are found, consider a change in therapy e.g. oral bisphosphonate to IV or to an agent with a different mechanism of action i.e. denosumab or teriparatide

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Patient AM: 84 y/o female with hip fracture teaching points
- Calcium, Vit D replacement. PT/OT
- Although patients with hip fractures are at high risk of more fractures, they are often not treated
- Denosumab is a good choice for non compliant patients
- Denosumab and Teriparatide are a good choice in renal insufficiency
Patient MD: Elderly male with low bone mass

- 82 y/o male, routine DXA
- T score
  - LS -1.2
  - FN -2.2
- Severe GERD
- Parkinson's
- WTD?

Teaching Points

- Pharmacologic Therapy
  - He meets NOF guidelines for intervention by FRAX calculation but there is limited evidence that Pharm therapy prevents future fractures in males with osteopenia and no fractures
- Non-Pharm therapy
  - Main goal is to prevent fractures
  - Prevent falls
    - PT/OT, muscle strengthening, balance exercises, cane
    - Hip protectors???
  - FRAX should be used as a guideline for decisions, not a mandate

Bone turnover markers: most common use

Bone turnover markers commonly used to asses efficacy of anti-resorptive therapy:
1. NTX (Urinary Collagen Type 1 cross-linked N-telopeptide)
2. CTX (Urinary or Serum collagen Type 1 cross-linked C-telopeptide)
   - Bone turnover markers will show decreased levels during efficacious anti-resorptive therapy
   - NTX is cost efficient and covered by medicare. Shortage of the assay
   - CTX not covered by medicare or private insurance

Bone turnover markers: most common use

Bone turnover marker commonly used to asses anabolic effect of therapy:
1. P1NP (Serum Type 1 procollagen C terminal/N terminal)
   - Used to assess bone formation. Forteo
   - Level increases
   - Covered by medicare