Directions in Osteoporosis

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Objectives
► Appreciate Osteoporosis impact & prevalence on society
► Understand components of "Bone Strength"
► Know secondary causes & at-risk populations
► Implement primary screening tactics
► Look for & Recognize Vertebral Fractures
► Understand available treatment modalities & become familiar with risks & limitations

What is Osteoporosis?

Normal Bone

Osteoporotic Bone
Teamwork

- Osteoporosis Screening & Management
  - Subspecialist NOT Required!
  - Primary Care Physicians Take the Lead!
  - 80% of Family Docs wanted to be better informed about DXA & Tx
  - PCP ideal for EARLY recognition

Osteoporosis Prevalence & Social Impact

- 44 Million in US with decreased bone density
  - 10 Million in US with Osteoporosis
  - 8 Million >50 years old with Osteoporosis
- 14 Million Osteoporotic Women by 2020
- Osteoporosis leads to increased disability & death from Hip, Spine, & Wrist Fx
- Could cost $20 Billion per year in US
  - Hip Fx accounting for >1/3 expenditure
What’s A T-score?

► Osteopenia
  ▪ T-score of -1 to -2.5

► Osteoporosis
  ▪ T-score below (more negative than) -2.5

► Bone Quality - remodeling, trabecular connectivity, damage accumulation, and mineralization of the matrix.

• BMD is easy to obtain through a DXA test.
• Common determinants of bone quality are difficult to measure.
  A bone biopsy is the best way to obtain information on bone quality, but it is not routinely done.
• Two additional factors to consider are age and spine fracture status.

Bone Quality

► Trabecular Connectedness
► Remodelling
  ▪ Estrogen
  ▪ RANK
  ▪ Disease
  ▪ Nutritional
► Damage accumulation
► Mineralization of the matrix
Secondary Causes of Osteoporosis
- Diabetes Type I  ➔ HgA1c, Fasting glucose
- Chronic Inflammatory Dz  ➔ RF, CCP, ESR, plasma cortisol, ESR, CRP
- Hyperparathyroidism  ➔ PTH-intact, Ca+
- Hypogonadism  ➔ Testosterone, FSH, LH
- Malabsorption Syndromes  ➔ Alb, D25-OH, Celiac Ab panel
- Multiple Myeloma  ➔ SPEP, UPEP
- Hyperthyroidism  ➔ TSH, Free T4, T3
- Vitamin D Deficiency  ➔ D25-OH

Prevention
- Adequate calcium (at least 1,200 mg per day)
- Get a Vitamin D25-OH level tested
- Vitamin D (800-1,000 IU per day)
- Regular weight-bearing & muscle-strengthening exercise
- Reduce the risk of falls and fractures
- Avoid tobacco & excessive alcohol intake
- Proper calorie intake & weight maintained
- FEED KIDS MILK INSTEAD OF POP!!

Endocrine Society Practice Guidelines for D
- Recommends levels between 40 and 60 ng/mL
- Screen at risk population
  - Obese, blacks, pregnant/lactating, malabsorption
  - Very common in all age groups
- Test 25-hydroxy vitamin D (25(OH)D), NOT 1,25(OH)2D
- Deficiency defined as < 20ng/mL
- Supplement at least minimum amount
  - Infants-1 year 400 IU/day (1000-1500 – supervision)
  - Children at least 600 IU/day (may need at least 1000)
  - Adults 19-70 at least 600 IU/day, but may need 2000 IU/day
  - Adults 70 yrs+ require at least 800 IU/day
Osteoporosis Physical Exam

- Assess possible signs and symptoms of fracture, including acute back pain
- Measure height using a stadiometer
  - Accurate and reproducible
  - Inexpensive
- Compare present height to historical “tallest height”
- Clinically significant height loss includes
  - Historical height loss of 2 to 4 cm (0.8 to 1.6 in)
  - Prospective, documented height loss >2 cm (0.8 in)

Incidence of Osteoporotic Fractures Increases with Age

- Vertebral
- Hip
- Wrist

- Asymptomatic vertebral fractures were present in ~18% of the study population.
- Between 26% and 40% of women needing treatment could be missed using BMD alone.
Vertebral Fractures Increase with Age

- Approximately 15% of patients aged 60-69 years have a fracture.
- Approximately 32% of patients aged 70-79 years have a fracture.

Let's Take off our Blinders!

Many Ways to Look for Fracture

- Lateral thoracic and lumbar spine x-ray
- Vertebral fracture assessment (VFA)
- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- Lateral chest radiograph

*Look for vertebral fracture even if imaging study is ordered for other reasons.*
**One View Is BEST View!**

- Anterior-posterior (AP) views and an oblique view may not be needed to diagnose a vertebral fracture.
- Lateral thoracic and lateral lumbar spine x-rays require 2 films only.
- Instructions should be given to radiologists to specifically look for vertebral fractures.

**Vertebral Compression Fracture Grades**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Anterior</th>
<th>Middle</th>
<th>Posterior</th>
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</thead>
<tbody>
<tr>
<td>0- Normal</td>
<td><img src="Image1" alt="Image" /></td>
<td><img src="Image2" alt="Image" /></td>
<td><img src="Image3" alt="Image" /></td>
</tr>
<tr>
<td>1- Mild</td>
<td><img src="Image4" alt="Image" /></td>
<td><img src="Image5" alt="Image" /></td>
<td><img src="Image6" alt="Image" /></td>
</tr>
<tr>
<td>2- Moderate</td>
<td><img src="Image7" alt="Image" /></td>
<td><img src="Image8" alt="Image" /></td>
<td><img src="Image9" alt="Image" /></td>
</tr>
<tr>
<td>3- Severe</td>
<td><img src="Image10" alt="Image" /></td>
<td><img src="Image11" alt="Image" /></td>
<td><img src="Image12" alt="Image" /></td>
</tr>
</tbody>
</table>

Obtained at same time as BMD

**VFA – Vertebral Fracture Assessment**

- GE
- Hologic

Radiation from VFA is less than standard spine X-Rays
Who Should Have DXAs?
► In women age 65 and older and men age 70 and older
  • 4% Bone Density Loss/Yr x 10 years post Menopause
► In postmenopausal women and men age 50-69 if several risk factors
► Previous fracture
► Patients on current osteoporosis therapy
► Patients taking daily steroids long-term

Medicare Requirements for DXA
► 5 Criteria
  • Woman who is estrogen deficient and also has osteoporosis risk factors
  • Radiographic abnormalities indicating osteoporosis, osteopenia, or vertebral fx
  • Receiving or expected to receive >3 months of ≥ 5mg daily corticosteroid tx
  • Primary Hyperparathyroidism
  • On medication for osteoporosis

Fracture Risk Assessment Tool (FRAX)
► The FRAX® tool developed by WHO to evaluate fracture risk of patients.
► Based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at femoral neck.
► 10-year probability of hip fracture & 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).
► www.sheffield.ac.uk/FRAX/
FRAX Questions

<table>
<thead>
<tr>
<th>AGE</th>
<th>Ages between 40 &amp; 90</th>
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<tbody>
<tr>
<td>SEX</td>
<td>Male or Female</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>In Kg</td>
</tr>
<tr>
<td>HEIGHT</td>
<td>In cm</td>
</tr>
<tr>
<td>PRIOR FX</td>
<td>Spontaneous or Atypical Traumatic</td>
</tr>
<tr>
<td>Parent Hip Fx</td>
<td>Hip fracture in patient's Mom or Dad</td>
</tr>
<tr>
<td>Smoker</td>
<td>Yes or No CURRENTLY</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>5mg/D x 3 mos = 450mg total!</td>
</tr>
<tr>
<td>RA</td>
<td>Yes or No</td>
</tr>
<tr>
<td>2° Osteoporosis</td>
<td>untreated hyperthyroidism, hypogonadism or premature menopause (&lt;45 years), malabsorption &amp; chronic liver dz, DM I, chronic malnutrition, osteogenesis imperfecta</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3/D (Beer, Whiskey oz, 120cc Wine, 60cc Liqueur</td>
</tr>
<tr>
<td>BMD</td>
<td>Femoral Neck BMD in g/cm². Leave blank if N/A</td>
</tr>
</tbody>
</table>

Calculation Tool

U.S. Preventive Service Task Force
Screening Intervals

- Lack of evidence exists about optimal repeat screening intervals
- Testing Precision Limitations
  - 2+ yr minimum may be needed to reliably measure change
  - Fx risk prediction improved with longer intervals
- True BMD changes vs DXA method/machine
  - BMD 1% change per year
  - DXA 1-6% variation between scans
When to Consider Treatment

► Postmenopausal women and men aged 50 years and older, based on the following:
  ▪ A hip or vertebral (clinical or morphometric) fracture
  ▪ T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
  ▪ T-score between -1.0 and -2.5 at the femoral neck or spine AND:
    ▪ FRAX 10-year probability of a hip fracture ≥ 3%
    ▪ FRAX 10-year probability of a major osteoporosis-related fracture ≥ 20%
  ▪ Clinician's judgment and/or patient preferences

Treatment Modalities

► Anabolic
  ▪ Parathyroid Hormone
    ► teriparatide – Forteo – 20mcg daily x 2 yrs
    ► PTH 1-84-Preos - Not Approved

► Antiresorptive
  ▪ Bisphosphonates
  ▪ Selective Estrogen Receptor Modulators (SERMs)
  ▪ Estrogen
  ▪ Calcitonin
  ▪ Strontium ranelate
    680mg strontium
  ▪ RANKL Ab
    ► denosumab - Prolia

Antiresorptive Modalities

► Bisphosphonates
  ▪ inactivate osteoclasts & increase bone mineral density preventing fractures
  ▪ long-term treatment produced microdamage accumulation and increased susceptibility to fractures in dogs
    ► Has not been reported in patients with osteoporosis but could occur as a consequence of inhibition of bone formation rate
    ► remains a concern
  ▪ Renal limitations
  ▪ GI disturbances
Bisphosphonates continued

Biochemical markers of both bone resorption (N-telopeptide) & bone formation (bone-specific alkaline phosphatase) show dramatic decreases with bisphosphonates.

► Fosamax (alendronate)
  • Released in 1995
  • 70mg po q wk
► Actonel (risedronate)
  • Now monthly
► Boniva (ibandronate)
  • 3mg IV q 3 months
  • 150mg PO monthly
► Reclast (zoledronic acid)
  • Injection q 1-2 yrs x 3
  • 5mg/100mL
  • Hydration important
  • Vitamin D repletion

Antiresorptives continued

► Calcitonin
  • Inhibits osteoclastic bone resorption, an effect mediated by calcitonin receptors
  • Calcitonin downregulates calcitonin receptors, and this may reduce its effectiveness over time
► Prolia (made by Amgen)
  • Immune system suppression with skin rash & serious systemic infection
  • Injection provided in Dr’s office
  • 2 injections per year, $825/injection

What is RANKL?

► Attaches to Osteoclast RANK receptor
► Prolongs Osteoclast lifespan by apoptosis inhibition
► Secreted by Osteoblasts
► Cytokines IL-1, IL-6, & TNFα enhance production of M-CSF and RANKL
► Up-regulated by glucocorticoids, down-regulated by estrogen
► Osteoprotegrin inhibits/blocks RANKL
  • OPG-deficient mice ➔ Osteoclastogenesis ➔ Osteoporosis
► Prolia is a RANKL Antibody
Antiresorptives continued

► Raloxifene (Evista)
  - SERM which prevents bone loss and fractures in postmenopausal women
  - Inhibits the growth of uterine tissue and reduces the incidence of breast cancer
  - Increases the incidence of thromboembolic phenomena

► Estrogen
  - Reduces fractures and colorectal cancer
  - Increases the incidence of coronary artery disease, stroke, breast cancer, and thromboembolic events

Questions You’ll Be Asked

► Osteonecrosis of the jaw?
  - 95% are CA pt on Aredia (pamidronate) or Zometa (zoledronate)
  - Stop 6 mos to 1 year prior to planned invasive dental procedure
  - Of 500,000 CA pts on IV form – 1%-10% may develop problem
  - 2009 - 208 pts at USC School of Dentistry in LA
    - 9 (4%) – 4 cases after tooth extractions
    - All women
    - Aged 63-80
    - Usage range from 12 to 120 months
    - Oral Fosamax
Post-menopausal Fxs with Lateral Femur Biopsies

► 12 on Bisphosphonates x 8.5 yrs
  • heterogeneities of the mineral/matrix ratio were reduced in the bisphosphonate group by 28%
  • crystallinity of the bone was significantly reduced by 33% (p < 0.05)
  • Long-term alendronate may inhibit microdamage normal repair arising from Severe Suppression of Bone Turnover (SSBT)
  • Microdamage accumulation would lead to brittle bone and unexpected stress fractures, characteristically at the subtrochanter of femur

► 9 without Bisphosphonates

Fracture Intervention Trial Long-term Extension (FLEX)

► Postmenopausal women with 5 years alendronate therapy, then:
  • Group with alendronate for five additional years
  • Placebo Group

► Findings & Recommendations
  • effect of bisphosphonate therapy was maintained after discontinuation of therapy
  • Drug holiday for women treated with bisphosphonates after 5 years

New Frontiers

► Investigational Drugs
  • αvβ3 integrin Inhibitors
  • An adhesion receptor that mediates attachment of osteoclasts to bone surface
  • Osteoprotegerin (OPG)
    • inhibits both differentiation and activation of osteoclasts
    • shown to profoundly inhibit bone resorption in postmenopausal women and in patients with multiple myeloma or skeletal metastases caused by breast cancer.
References

12. ISCD 2010 Official Positions on FRAX. [PubMed] [Google Scholar]