Evaluation and Treatment of Osteoporosis

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All of the following are risk factors for osteoporosis EXCEPT:
1. Low Calcium intake
2. Smoking
3. Alcohol Use
4. Rheumatoid Arthritis
5. Obesity
All of the following have been shown to decrease the risk of hip fractures EXCEPT:
1. Vitamin
2. Estrogen
3. Alendronate
4. Calcitonin
5. Denosumab
What is Osteoporosis?

“A systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.”

Normal Bone*

Osteoporotic Bone*


*Images used with permission of David Dempster, PhD. Copyright 2001.*
Bone density maximum at age 30 and it's all downhill after that!

Gender and ethnic factor important in maximum bone density and therefore density as a person ages

Susan Ott, MD
Osteoporosis is Common

• Most common bone disease
  ▪ 10 million Americans have osteoporosis and 33.6 million have low bone density at the hip.
  ▪ Over 200 million worldwide
• Approximately 50% of Caucasian women and 20% of men will experience an osteoporotic fracture

National Osteoporosis Foundation Clinician’s Guide 2008
www.iofbonehealth.org/health-professionals/about-osteoporosis/epidemiology
Osteoporotic Fractures Are More Common Than Sequelae of Other Chronic Diseases

1. Riggs BL and Melton LJ III, Bone. 1995;17(suppl.):505S-511S.
Hip Fractures have Serious Complications

- Up to 24-30% excess mortality with 1 year
- Nearly 65,000 women die from complications of hip fracture each year
- 50% of hip fractures survivors are permanently incapacitated
- 20% of hip fracture survivors require long term nursing home care
Spinal Fractures

- Back Pain
- Spinal Deformity
- Increased Fracture Risk
- Increased Lung Problems, Co-morbidities
- More Bone Loss
- Decreased Activity
- 23% Increased Mortality
- Sleeping Problems
- Loss of Appetite
- Decreased Lung Capacity
- Impaired Function
Common Secondary Causes

• Nutritional
  ▪ Vitamin D deficiency

• Diseases
  ▪ COPD
  ▪ Rheumatoid arthritis
  ▪ Crohn’s
  ▪ Malabsorption (Celiac disease, gastric bypass, etc)

• Endocrine
  ▪ Hypogonadism

• Medications
  ▪ Glucocorticoids
  ▪ Anticonvulsants
  ▪ Aromatase inhibitors or GnRH agonists
  ▪ Other: SSRIs, PPIs, TZDs?
What Testing Should be Done?

ASBMR Recommendations

Basic: CBC, chemistry panel, TSH, 25(OH)D, 24 hour urine calcium/creatinine.

Additional: E2, LH, FSH, prolactin, PTH, 1,25-OHD, 24 hour urine free cortisol, Iron/TIBC/ferritin, celiac testing, SPEP/UPEP, ESR/CRP, bone turnover markers, transiliac bone biopsy (if low trauma fracture and negative evaluation).

Cohen Adi, Shane E. Primer ASBMR 2009;289-293
Indications for DXA

• NOF guidelines 2008
  - All women ≥ 65, men ≥ 70 regardless of clinical risk factors
  - Younger postmenopausal women and men 50-69 with clinical risk factors (specific risk factors listed)
  - Women in the perimenopausal transition if there is a specific risk factor associated with increased fracture risk
  - Anyone being treated for osteoporosis, to monitor treatment effect

• USPTF recommendations for screening 2011
  - All women ≥ 65
  - Younger postmenopausal women whose fracture risk is equal to an average 65 y/o without risk factors
  - No recommendation for men “balance of evidence is insufficient to assess the balance of benefits and harms of the service”

www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteors.htm
**WHO Classification of Postmenopausal Osteoporosis**

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>T-score</th>
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<tr>
<td>Normal</td>
<td>Equal to -1.0 or higher</td>
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<tr>
<td>Low Bone Mass (Osteopenia)</td>
<td>Between -1.0 and -2.5</td>
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<tr>
<td>Osteoporosis</td>
<td>Equal to -2.5 or lower</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>Equal to -2.5 or lower with fracture</td>
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T-score Compares With Young Adult; Z-score with Age-Matched

\[
\text{T-score} = \frac{\text{Patients BMD} - \text{Young Normal Mean BMD}}{\text{SD of Young Normal}}
\]

\[
\text{Z-score} = \frac{\text{Patients BMD} - \text{Age Matched Mean BMD}}{\text{SD of Age Matched}}
\]
Using T and Z-scores

• T-scores
  ▪ Used for diagnosis
  ▪ Only applicable to postmenopausal women or men over 50

• Z-scores
  ▪ Used to compare to age-matched controls i.e. to determine if BMD is what you would expect at that age
  ▪ Appropriate for children and healthy adults under the age of 50
Do **NOT** Use T-scores in:

- Premenopausal Women
- Men Under Age 50
- Children

T-score use is inappropriate in these populations as a low value would imply increased fracture risk.

Even with low BMD, young healthy people are at low fracture risk (perhaps because they do not have the microarchitectural deterioration that occurs with age and menopause).
When Should Follow-up DXA be Performed?

- “It depends”
- Not more frequently than yearly
- Initiation of steroids is an exception (6 months)
- ISCD position; measure one year after initiation of Rx to document response (stability or increase)
- Medicare has defined monitoring interval as no more frequently than every 23 months

Remember that stable BMD on Rx = Success
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?

243 women with hip fractures in Study of Osteoporotic Fractures

- 54% T-score greater than -2.5
- 46% T-score -2.5 or less

Wainwright SA et al. J Clin Endocrinol Metab. 2005;90:2787-2793
**FRAX™: The WHO Fracture Risk Assessment Tool**

www.shef.ac.uk/FRAX/

- Assesses 10-year risk of hip fracture and all osteoporotic fractures
- Based on risk factors plus or minus femoral neck BMD
- Fracture probability calculated from 12 world-wide cohorts (59,232 individuals, 250K person-years), validated in 11 independent cohorts (>1 million person-years)
Risk Factors other than Age, Gender and Race

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Ratio</th>
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<tbody>
<tr>
<td>BMI (20 vs 25)</td>
<td>1.95</td>
<td>1.42</td>
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<tr>
<td>Parental hip fracture</td>
<td>2.27</td>
<td>2.28</td>
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<td>Glucocorticoids</td>
<td>2.31</td>
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<tr>
<td>Prior fragility fracture</td>
<td>1.85</td>
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<td>Current smoking</td>
<td>1.84</td>
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<td>High intake alcohol</td>
<td>1.68</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>1.95</td>
<td>1.73</td>
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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 all major osteoporosis-related fracture probability of ≥20%

www.nof.org
Non-Pharmacologic Therapy

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

NOF Recommendations

• Adequate intake of dietary calcium and vitamin D
  ▪ Calcium: at least 1200 mg/day
  ▪ Vitamin D: at least 800-1000 IU/day

• Regular weight-bearing and muscle-strengthening exercise

• Avoidance of smoking and excess alcohol

• Fall prevention
Vitamin D Deficiency (<20ng/ml) Common and Present in Fracture Patients

- **Children**
  - 52% blacks and hispanic
  - 48% white girls at the end of the winter in Maine
- **Young Adults**
  - 32% of medical students and residents in Boston
- **Adults >50 years**
  - 27% of men, 35% of women
- **Fracture Patients:**
  - Hospitalized patients with fragility fracture
    - 81%<20ng/ml
  - Women with Hip Fracture
    - 70%<12ng/ml
Musculoskeletal Consequences of Vitamin D Deficiency

• Impaired calcium absorption (<20ng/ml)
  ▪ Increased bone resorption
  ▪ Increased PTH
  ▪ Increased rate of bone loss
• Osteomalacia(<12ng/ml)
• Muscle weakness, poor balance and falls
Physical Therapy Basics for Osteoporosis

• Discourage
  ▪ Heavy lifting
  ▪ Back flexion

• Encourage
  ▪ Fall prevention
  ▪ Balance exercises
  ▪ Weight bearing exercise eg walking
  ▪ Back extension exercises
Assess Fall Risk

• ASK: Have you fallen in the last year?
• EVALUATE:
  ▪ Muscle strength
    ◊ Sit-to-stand without the use of arms
  ▪ Balance
    ◊ Heel-to-toe walking
    ◊ Stand on one foot (begin with holding your hand or counter)
Prevention of Falls

- Correct visual and hearing impairment
- Optimize medications
- Bathroom grab-bars and nonskid mats
- Avoid throw-rugs and slippery mats
- Keep electric and telephone cords away
- Reduce clutter from walking areas
- Nightlight in bedroom and bathroom
- Handrails on steps and stairs
- Walking aids, if needed
- Exercise for strength and balance (T’ai Chi)
Extension Exercises

Reproduced with permission, National Osteoporosis Foundation
Avoiding Flexion and Managing ADL’s

Reproduced with permission, National Osteoporosis Foundation
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

Sinaki *Osteoporos Int* 14:773-779, 2003
What Would You Recommend?
Pharmacologic Therapy

• Antiresorptive
  ▪ Block osteoclastic bone resorption
• Anabolic
  ▪ Promote osteoblastic bone formation
What is Bone?

- **Bone matrix**
  - 90% collagen
  - 10% other proteins (osteocalcin, osteonectin, osteopontin)

- **Bone mineral**
  - Hydroxyapatite (calcium and phosphorus)

- **Bone cells**
  - Osteoclasts, osteoblasts, osteocytes
Bone is Living Tissue that Models and Remodels

- **Modeling**
  - Change in size and shape of bone during growth in response to physical demands

- **Remodeling**
  - Replacement of old bone with new bone in response to stress damage, microfractures, and other factors
  - Important for bone repair and for maintaining metabolic balance (most remodeling occurs in response to metabolic needs)
Premenopause: Balanced Bone Formation and Bone Resorption

- **Activation**
  - Multinucleated osteoclasts
  - Sealed resorption cavity

- **Resting**
  - Lining cells

- **Formation**
  - Osteoblasts produce osteoid

- **Reversal**
  - Apoptotic osteoclasts
  - Active osteoblasts
Medications Work at Different Points of the Remodeling Cycle

- DMAB
- Resting Lining cells
- Activation Osteoclasts
- BP’s
- Reversal
- Formation Osteoblasts
- PTH

ISCD
Antiresorptive vs Anabolic Therapy

Osteoporotic Bone: resorptive cavities, loss of connectivity

Antiresorptive: fills in resorptive cavity, increases mineralization

Anabolic: produces osteoid, increases connectivity
How do Antiresorptive Agents Improve Bone Strength?

• Prevent bone loss
• Prevent microarchitectural deterioration
• Decrease stress risers
• Promote mineralization
Pharmacologic Therapy

• Antiresorptive
  ▪ Estrogen
  ▪ Calcitonin
  ▪ Raloxifene
  ▪ Bisphosphonates
  ▪ Denosumab
Osteoporosis is Treatable

Evidence that hip fractures are preventable:

- Calcium/Vitamin D$^1$ (France) ↓43%
- Estrogen$^2$ ↓34%
- Alendronate$^3$ ↓51%
- Risedronate$^4$ ↓39%
- Zoledronate$^5$ ↓41%
- Denosumab$^6$ ↓40%

NOTE: there are no head-to-head fracture studies so this data cannot be used to compare treatment efficacy

1 Chapuy NEJM 327:1637, 1992
2 WHI JAMA 288:321,2002
3 Black Lancet 348:1535,1996
4 McClung NEJM 344:333, 2001
5 Black NEJM 356:1809, 2007
6 Cummings NEJM 361:756-765, 2009
Estrogen

• BMD: preserves/increases BMD
• Fractures: reduces spine, hip, and forearm fractures by 35%, 33% and 29%
• Extraskeletal considerations
  ▪ Relieves symptoms of estrogen deficiency
  ▪ Increases risk of breast cancer, VTE, coronary disease, stroke
  ▪ Endometrial cancer risk in unprotected uterus
  ▪ Reduces risk of colon cancer

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

- SERM (selective estrogen receptor modulator) also known as EAA (estrogen agonist/antagonist)
- BMD: increases at spine and hip
- 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
  - AE’s: VTE risk, leg cramps

Bisphosphonates

- Alendronate: po daily or weekly
- Risedronate: po daily, weekly or monthly
- Ibandronate: po monthly or IV q 3 months
- Zoledronic acid: yearly IV
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, can recycle
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
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?
Atypical Femur Fractures

- 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
- prodromal pain in thigh or groin is common
- often on other drugs, especially steroids or estrogen

References:
**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

Schematic representation of the basic multicellular unit of the bone remodelling cycle

Figure 14. Summary of Fracture Efficacy in Treatment of PMO Fracture Study (20030216) (Primary and Secondary Efficacy Endpoints)

- Placebo (N = 3906)
- Denosumab (N = 3902)

13 August 2009 Advisory Committee for Reproductive Health Drugs Meeting Briefing Document
Time to First Nonvertebral Fracture

- Placebo (N = 3906)
- Denosumab (N = 3902)

HR = 0.80 (95% CI: 0.67, 0.95) p = 0.0106
Denosumab Safety

- Hypocalcemia (2% of cases)
- Cellulitis (serious in 0.4%)
- Eczema (10%)
- Osteonecrosis of the jaw (2% in higher dose)
- Back pain (35%), extremity pain (12%), bone pain (4%)
- Atypical fractures (Not reported – yet)
- Theoretical Risk - increased infection?
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

Black Box Warning

• In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton)
Contraindications

• Children and adolescents
• Patients who have had bone cancer
• Patients who have had radiation therapy
• Patients with Paget's disease
• Patients with hypercalcemia or hyperparathyroidism
• Women who are pregnant or nursing
• Patients with gout or high uric acid
Side effects

• Nausea in 8% (similar to placebo)
• Headache in 8%
• Dizziness in 9%
• Leg cramps in 3%
• Hypercalcemia in 11% (usually mild)
• Uric acid increased by 13%
## Summary: BMD Response

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<tr>
<th>Medication</th>
<th>Spine</th>
<th>Hip</th>
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<tbody>
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## Summary: Fracture Risk Reduction (PMO)

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# FDA-Approved Medications

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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?
What drugs can be used to treat osteoporosis?

- **1st line**: ALN, RIS, ZOL, DMAB
- **2nd line**: IBN, RAL
- **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
Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis

- **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 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
Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis

- How 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
Summary of Pharmacologic Rx

• Multiple medications now available for prevention and treatment of osteoporosis
  ▪ All have been shown to decrease spine fracture. Effect on non-vertebral and hip fractures variable
  ▪ All current medications except teriparatide are antiresorptive – block action of osteoclasts
  ▪ Teriparatide is the only current anabolic – increases activity of osteoblasts
• Bone resorption and bone formation are coupled
• Choosing appropriate therapy for an individual patient requires consideration of risk/benefit ratio
• Increasing knowledge of bone biology will lead to additional therapies in the future
New Advances and Future Therapies for Osteoporosis
Evolving Therapies

• Promising future breakthroughs
  ▪ *Cathepsin K*
  ▪ *Integrins*
  ▪ *Sclerostin*
  ▪ *Nitroglycerin*

• Medications that are probably effective
  ▪ *Thiazides*
  ▪ *Strontium ranelate*
Evolving Therapies

• Possibly effective drugs
  ▪ Bicarbonate, Vitamin K

• Conflicting data
  ▪ Statins, Growth Hormone, Vitamin D metabolites, Magnesium

• Not effective
  ▪ Fluoride, Progesterone, Phytoestrogens, Boron
Sclerosteosis

- Sotosomal recessive disease with thick bones, entrapment of cranial nerves leading to deafness and facial nerve palsy, increased intracranial pressure, and frequently syndactyly.
- Most patients are from South Africa and are homozygotic for a specific mutation in the SOST gene, which is mapped to 17q12-21.
- None of their 63 patients have ever had a fractured bone.
- Heterozygous gene carriers are resistant to fractures.
- Do not have degenerative osteoarthropathy.
SOST and Sclerostin

- SOST is expressed mainly in osteocytes. These cells form a network which senses mechanical strain. Osteocytes can alter the secretion of sclerostin to regulate bone formation.
- Sclerostin inhibits bone formation and enhances apoptosis of osteoblasts.
- Li X. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. J Bone Min Res 2008:23:860
Romosozumab
An Anti-Sclerostin Antibody

ROMOSOZUMAB IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

Romosozumab
An Anti-Sclerostin Antibody

A Lumbar Spine

B Total Hip

Percentage Change from Baseline

Study Month

Percentage Change from Baseline

Study Month
QUESTIONS????????