Update on Osteoporosis
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Clinical Questions

• Who should be screened for osteoporosis?
• What is the appropriate interval for screening?
• What is FRAX and how should it be used?
• Who should be treated for osteoporosis?
Clinical Questions

- How long should bisphosphonates be given? How to monitor?
- How common are serious side effects with bisphosphonates?
- Who should receive denosumab?
- Who should receive teriparatide therapy?
- What is the optimal level of Vitamin D?
Osteoporosis Prevalence

• Lifetime risk hip fx: 1 in 6 for women.
• Osteoporosis affects 200 million women worldwide
  – 1/3 of women age 60-70
  – 2/3 of women >80
• Over 1.5 million fxs occur in US per/yr

Adapted from IOF Slide, www.nof.org
Prevalence

• In 2005, osteoporosis-related fractures responsible for estimated $19 billion in costs (25% costs -men)
• After hip fracture, 50% pts with some long term loss of mobility; 25% require long term care
• Rate of death from any cause increased >5 times in 1st 3 mos following hip fx
Osteoporotic fractures increase mortality

Cauley JA et al. Osteop Int 2000;11:556
Post Fracture: Inadequate Treatment

• Most patients who have had fractures are not receiving treatment

• Community based study women > 65 with hip fracture, 13% receiving adequate treatment.\(^1\)

• Nursing home patients with recent hip, wrist or humeral fracture:\(^2\)
  – 4430 patients eligible, 11.5% received medication.

Pathogenesis of Fracture

- Low peak bone mass
- Post menopausal bone loss
- Age-related bone loss
- Other risk factors

Low bone mass → FRACTURE → Propensity to fall → Bone quality

Adapted from Melton LJ and Riggs BL. Osteoporosis: Etiology, Diagnosis and Management, Raven Press 1988, pp155-179.
Risk factors for Fractures

• Low Bone Density
  – Age
  – Gender
  – Estrogen deficiency
  – Ethnicity
  – Family history of fracture
  – Cigarette smoking
  – Low body weight
  – Low calcium intake (lifetime)
  – Excessive alcohol/caffeine
  – Reduced physical activity

• Falls
  – Cognitive impairment
  – Medications
  – Visual/proprioception
  – Obstacles

• History of Prior Fractures

• Secondary Causes
Age affects fracture risk independently of bone mineral density

![Graph showing the relationship between bone mineral density T score and 10-year probability of hip fracture for different age groups.](image-url)
Secondary Causes

- Anorexia nervosa
- Hypogonadism
- Hyperparathyroidism
- Rheumatoid Arthritis
- Alcoholism
- Meds: Glucocorticoids, anti-seizure, cancer chemotherapy, cyclosporine
- Malabsorption (sprue, post surgical)
- Hyperthyroidism
- Cushing’s Disease
Who Should Be Screened for Osteoporosis With BMD?

- ISCD position
  - Women 65 and older
  - Post menopausal women under 65 with risk factors
  - Men 70 and older
  - Adult with fragility fracture
  - Anyone being treated to monitor
  - Anyone considering treatment
  - Anyone with a condition or taking a medication associated with bone loss or low bone mass
Bone Density Testing

- **DEXA testing**
  - Most widely used
  - Can be used with FRAX
  - For each SD decrease in bone density, OR of 2.1 for vertebral fracture

- **Peripheral Bone testing**
  - Technical differences
  - Variations in definitions of bone areas being measured
  - Lack of reference values to calculate T scores/Can’t use with FRAX
  - Portable
  - Changes in peripheral bone sites too slow to use to monitor Rx

- **Quantitative Ultrasound (QUS)**
  - Portable, cheap and no radiation
  - Good prediction of fracture risk
  - Does not reliably exclude or confirm DEXA confirmed osteoporosis
  - Can’t use with FRAX
Case # 1

- 59 y/o Asian female comes in for a physical. Her weight is 105 lbs and she is 5’3” tall. She smokes ½ ppd. Family history is positive for her mother who had a hip fracture at age 74. DEXA scan shows a T-score of -1.5 in the femoral neck. She is taking calcium and vitamin D. What do you do?
FRAX

- Web based decision making tool
  [http://www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/)
- Estimates 10 yr probability of hip fracture
- Estimates 10 yr probability of major osteoporotic fracture
- Validated by country using cost-effectiveness data
- Can also use without BMD data
WHO Absolute Fracture Risk

Treat when probability of:

- Hip Fracture $\geq 3\%$
- Major Osteoporosis Fracture $\geq 20\%$

www.shef.ac.uk/FRAX
FRAX

- Not validated to assess patients on treatment
- No clinical trials to assess treatment based on absolute fracture risk versus BMD
- Not valid in premenopausal women
- Not valid for men < 40 yrs of age
- May be less useful in early PMP women

(JBMR, 2010)
NOF Guidelines

T-Score*

High Risk: Treat All

Moderate Risk: Treat
a) Prior fracture
b) 2° cause of bone loss
c) FRAX ≥ 3% hip fracture
≥ 20% major fracture

Low Risk: Recheck in 1-2 years

* Based on DXA Spine, Hip or FN

Case # 1

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Case # 1

- FRAX used – select for USA and Asian
- 10 yr risk of major osteoporotic fracture: 7.1%
- 10 yr risk of hip fracture 0.5%
- No Rx needed other than calcium/D, exercise, quitting smoking
- What if this lady was 72?  
  - FRAX hip risk: 4.2% → Treat
How Often to Screen?

- Limited data
- Ongoing risk factors: every 2 yrs
- High risk women: q2 yrs (at least during 1st 5 years of menopause)
- No risk factors: ? interval
Testing –Intervals

NEJM January 2012

• 4957 women, ≥67 years of age with normal BMD or osteopenia (no h/o hip or vertebral fracture)

• Followed prospectively for up to 15 yrs

• BMD testing interval defined as estimated time for 10% women to make the transition to osteoporosis before having a hip or clinical vertebral fracture
Stratified into 4 groups according to T-score at femoral neck and total hip
- Normal (T score > -1.00)
- Mild osteopenia (T score -1.00 to -1.49)
- Moderate osteopenia (T score -1.50 to 1.99)
- Advanced osteopenia (T score -2.00 to -2.49)

Risk factors evaluated were estrogen use at baseline, any fx after 50 yrs of age, current smoking, current or past use of glucocorticoids, and self reported RA
NEJM – Jan 2012

• Estimated BMD testing interval was 16.8 yrs for women with normal BMD
• 17.3 yrs for women with mild osteopenia
• 4.7 yrs for women with mod osteopenia
• 1.1 yrs for women with advanced osteopenia
2.4% had hip or clinical vertebral fx before transition to osteoporosis

Adjusted estimated time for 2% of women to have a hip or clinical vertebral fx was > 15 yrs with normal BMD or mild osteopenia and 5 years for mod-advanced osteopenia
Within a given T-score range, transition from osteopenia to osteoporosis was longer with younger age and for women taking estrogen at baseline.

For women with mild osteopenia, testing intervals were > 14 yrs for all BMI values.

For women with advanced osteopenia, all estimated intervals were close to 1 yr (0.8-1.3).
Response from ISCD

- PMP women > 67
- FRAX not utilized
- Evaluated only clinical vertebral fractures.
- Common for osteopenic patients to have undiagnosed vertebral fractures (14-30%).
- Doesn’t address BMD testing frequency intervals in younger PMP pts or men
- Screening rates very low in Medicare population
Case # 2

- 54 y/o male with newly diagnosed RA. He was just started on MTX and is on 5 mg Prednisone per day. Rheum thinks he will be on this dose for at least 3 months. He weighs 175 lbs and is 5’6” tall. He has no family hx of hip fracture and no personal h/o fx. He doesn’t smoke and drinks 3 beers/day. DEXA with T-score 1.0.
Steroids and Bones

- Increase bone resorption and inhibit bone formation
- Effect most pronounced in 1st few months
- Chronic use: major effect is on bone formation
- Increase fracture risk: for same bone density, more fractures
- Induce negative calcium balance
Steroid dose and fracture risk

Adjusted Relative Rate of Fracture (and 95% CIs)

Average Daily Glucorticoid Dosage (mg)
Chronic Steroids – ACR Recs

• Use FRAX for PMP women & men >50 to divide into Low, Medium, High Risk (<10%, 10-20%, >20%)

• Low: <7.5 mg/day → No Rx; ≥7.5 mg/day >3 mos → Rx with Bisphosphonate

• Medium: ≥7.5 mg for > 3 months, Rx with bisphosphonate

• High: Treat all patients. If > 1 month of Rx use bisphosphonates or teriparatide

Arthritis Care & Research
Vol. 62, No. 11, November 2010, pp 1515–1526
Steroids and Bones

- All pts to be on steroids >3 mos, regardless of dose: 1200 Calcium and 800 units Vitamin D
- Different guidelines for premenopausal women and men < 50 yrs of age
Case # 2

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Case # 2

- FRAX: Risk of major fracture: 6.4%
- 6.4% = Low risk group
- < 7.5 mg/day of Prednisone
- No Rx needed
What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?
Benefits of Exercise

• Recommendations: 30 minutes at least three times per week
• High or low intensity OK
• Meta-analysis of 18 RCT of exercise and BMD reported that aerobics, weight bearing, and resistance exercises all increased spine BMD while walking increased BMD at spine & hip (Cochrane Data Base Review 2002)
Calcium and Vitamin D

“Mary, you haven't been taking your calcium pills, have you?”
Calcium and Vitamin D

- Have a positive effect on bone mineral density in postmenopausal women
- Reduce rates of bone loss and also fracture rates in the elderly
- Reduce hip fracture rates in institutionalized elderly women
Vitamin D Deficiency Common Among Those at Risk

- 52% of post menopausal women receiving therapy for osteoporosis had Vitamin D levels of < 30ng/dl.¹

- 97% of patient hospitalized for non traumatic fractures had Vitamin D levels of <30mg/dl.²

¹ Holick MF et al JCEM 2005
² Simonelli C et al J Bone Min Res 2004
Adult Recommendations

- **National Osteoporosis Foundation**
  - Adults < 50: 400-800 (IU) of Vitamin D daily plus 1000 mg Calcium (from all sources)
  - Adults > 50: 800-1,000 IU of Vitamin D daily plus 1200 mg Calcium (from all sources)

- **Institute of Medicine**
  - Adults < 50: 600 IU Vitamin D plus 1000 mg Calcium
  - Adults 50-70: 600 IU Vitamin D plus 1200 mg Calcium
  - Adults > 70: 800 IU Vitamin D plus 1200 mg Calcium
Vitamin D Levels

- Controversy over levels: high levels of Vitamin D found to be harmful
- Institute of Medicine: $> 20$ ng/dl
- NOF, AGS, IOF: $> 30$ ng/dl
- All agree than lower than 20 is bad for skeletal health
Treatment Options

Antiresorptive agents
- *Bisphosphonates*
- Raloxifine
- Calcitonin
- Estrogens
- Denosumab

Anabolic Agents
- *Teriparatide*
Bisphosphonates - Evidence

- **Fracture Intervention Trial**
  - Vertebral Fracture Arm:
    - Increased femoral neck and spine BMD by 4.1 and 6.2 %
    - Reduced risk of vertebral fracture by ~50%
    - Reduced risk of hip & wrist fractures by ~ 30%
  - Clinical Fracture Arm
    - Reduced risk of vertebral fractures by 44% but not hip fractures
    - In subgroup with osteoporosis, decreased risk of hip and all clinical fx by 56 and 36%
Bisphosphonates

- Anti-resorptive agents; slow bone turnover
- Oral agents: Aledronate, Risendronate, ibandronate
  - Must be taken on empty stomach in am
  - Don’t take calcium supplements for at least 1 hour post taking
  - GI issues (very low)
  - Do not use with creatine clearance < 35 ml/min
- IV agents: Zoledronic acid, ibandronate
  - SE: Flu-like symptoms, hypocalcemia, ARF
- Replete Vitamin D prior to giving
Evidence

• Meta-analysis of 11 trials of Aledronate
  – RR of vertebral fxs on 10 mg dose: 0.55
  – RR of non-vertebral fxs on 10 mg dose: 0.84

Cochrane Database Syst Rev. 2008
Case # 3

• 67 year old comes in for physical. She has been on Fosamax 70 mg weekly for the past 6 years. She has a history of a clinical vertebral fracture 4 years ago but none since. Her last DEXA was 2 years ago and her T-score was -3.2. Baseline DEXA prior to starting meds was -3.5. She is walking 20 minutes per day. Can you stop her Fosamax?
FLEX Trial

- After completion of FIT, 1099 post-menopausal women who had completed 5 years of Aledronate randomized to placebo or another 5 yrs of Aledronate
- Average age 73
- 34 % with vertebral fractures
- 60% with history of clinical fractures since menopause
- Baseline: hip BMD -1.9, FN -2.2, LS -1.3
Flex Trial
Survival Curve for Time to First Nonvertebral Fracture and Time to First Clinical Vertebral Fracture (FIT)
FLEX Trial

– Rate of nonvertebral fracture not significantly different but many FLEX participants without osteoporosis
– Lower risk of clinical vertebral fractures in Aledronate group: RR 0.45 (absolute rate reduction 2.9%)
– No difference in adverse events (no ON of jaw seen)
– Excluded women with T-score < -3.5
FLEX Trial – Use in Practice

• Lower risk woman: T-score > -2.5, no fx: Consider stopping after 5 years
• High risk woman: T-score < -3.5, history of clinical vertebral fracture, elderly, high fall risk: Continue up to 10 years
• Drug Holidays: 1-5 yrs typically
• Need to monitor with DEXA or bone turnover markers
Case # 3

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Case #3

- No absolute correct answer
- Given h/o compression fractures and low BMD, would lean towards continuing Fosamax for 10 years
Bisphosphonates – Adverse Effects

- Musculoskeletal pain
- Renal impairment with IV
- Atypical femur fractures
- Osteonecrosis of Jaw
Atypical Femur Fractures

In contrast to a typical osteoporotic fracture of the femur (shown at left) with multiple fragments and apparent thinning of bone, an atypical subtrochanteric fracture (shown at right) in a patient who took bisphosphonates for 7 years is a cleaner break in apparently thick bone that occurred with minimal trauma.

(Photo credit: Andrew Neviaser, MD)
Atypical Femur Fracture

- Secondary analysis of data from 3 large RCT of bisphosphonates; looked at the characteristics of 284 hip or femur fractures among 14,195 women.
- 12 atypical fxs occurred in 10 women; rate of 2.3 fx per 10,000 patient years.
- Bisphosphonate use not associated with statistically significant higher risk in any of the trials
- Because fractures so rare, benefits of bisphosphonates for osteoporosis far outweigh the risks
- Consider atypical femur fracture in women at risk for osteoporotic fractures who present with thigh or groin pain

Black et al, NEJM 2010
Osteonecrosis of the Jaw
Non-healing exposed bone in oral cavity for > 8 weeks

FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr. Jay Neugarten, New Hyde Park, NY.)
Osteonecrosis of Jaw - Risks

- IV bisphosphonates
- Cancer and anti-cancer therapy
- Duration of exposure
- Dental extractions, dental implants, poorly fitting dentures
- Glucocorticoids
- Pre-existing dental disease
Osteonecrosis of Jaw

- Risk: 1 in 10,000 to 1 in 100,000 in pts taking oral bisphosphonates for osteoporosis
- ACOMFS recommends for those pts on bisphosphonates < 3 yrs, proceed with dental alveolar surgery while on meds.
- If > 3 yrs, stop bisphophonates for 3 months prior to surgery and don’t restart until bone has healed
Case #4

• A 84 year old woman comes in for follow up of osteoporosis. She has been on Fosamax for 7 years. She was recently in the hospital after breaking her hip. X-rays also showed multiple old vertebral fractures but new in the past 3 years. She is on adequate Calcium and Vit D supplementation. What would you do?
Teriparatide

- Targets osteoblasts to enhance bone remodeling
- Net increase in bone formation over bone resorption
- Affects trabecular bone more than cortical bone so mainly increases lumbar BMD
Teriparatide Effects on Bone Matrix
Micro CT Studies: Baseline and After 20 Months

Before Teriparatide Treatment

After Teriparatide Treatment

Jiang et al, J Bone Miner Res. 2002;17(Suppl 1):S135
Teriparatide Indications

- Men or postmenopausal women with severe osteoporosis (T score $\leq -3.5$ or $\leq -2.5$ + fragility fracture)
- Pts with osteoporosis who can’t take bisphosphonates
- Pts with treatment failure
Before Starting Teriparatide

- DEXA
- Baseline uric acid, creatinine, alkaline phosphatase, albumin, serum calcium, 25-OH Vitamin D
- 24 hr urine calcium, creatinine
Before Starting Teriparatide

• Replete Vitamin D prior to Rx
• If baseline hypercalciuria or hypercalcemia present, work up for hyperparathyroidism
• Don’t give to patients at increased risk for osteosarcoma (Paget’s, unexplained alk phos)
Fracture Prevention Trial of PTH 1-34

- 1637 PMP women with h/o vertebral fx s randomized to PTH (20 or 40 mcg/day SQ) vs placebo
- 20 mcg group: 9/3 % increase in lumbar/femoral neck BMD
- 40 mcg group: 13/6 % increase
FPT Trial – Fracture Risk

- RR for vertebral fractures 0.35 for both 20 and 40 mcg groups
- RR 0.47 for non-vertebral fractures
- Too few hip fractures to make conclusions
PTH – Adverse Effects

SHORT TERM
• Hypercalcemia
• Hypercalcuria
• Increase serum uric acid
• Nausea
• Headache

LONG TERM: ? risk of osteosarcoma
Teriparatide Dosing

• 20 mcg SQ daily X 24 months (max)
• Intermittent (being investigated)
• Weekly (being investigated)
• Transdermal (being investigated)
Monitoring

• Calcium: baseline, 1, 6 and 12 months
• Uric acid: baseline and 6 months
Combo therapy?

- No difference between PTH alone and PTH plus alendronate when used as initial therapy
- Alendronate appears to block PTH stimulation of new bone formation
- Can use PTH after bisphosphonates but somewhat blunted response
- Can start PTH right after D/C bisphosphonates
- Restart bisphosphonate after PTH therapy!
- If can’t use bisphosphonates, can use Raloxifene
Mean changes (percent) in volumetric trabecular spine BMD as measured by quantitative CT over 24 months of treatment in PTH placebo group (in blue) and PTH followed by alendronate group (in red).

Case #5

• 92 year old woman presents for f/u of chronic pain since a pelvic fracture 2 years ago. Was on Fosamax for many years but was stopped several months ago due to a GFR of 31. Last DEXA with a T-score of -3.1. Scared of needles and does not want a daily injection. What would you do?
RANKL (expressed by osteoblasts) binds RANK receptor on osteoclast precursors to stimulate their differentiation. OPG (osteoprotegerin) is the endogenous receptor that acts as a decoy to inhibit this bone resorption. Denosumab is a human monoclonal antibody with specificity toward RANK.
Denosumab

- Human monoclonal antibody to RANKL
- Inhibits osteoclast formation
- Decreases bone resorption
- Increases bone mineral density
- Reduces risk of fracture
- 60 mg subQ injection once every 6 months
- No dosing adjustments for CKD needed
Primary outcome was risk of vertebral fracture—was reduced by 68% at 3 y 2.3% in the denosumab group, versus 7.2% in the placebo group. Hip fracture (secondary) was reduced by 40%, other non-vert fx reduced by 20%.
Denosumab vs Aledronate

- 1189 PMP women with T score ≤ -2.0 randomized to Aledronate 70 mg weekly plus SQ placebo injections vs denosumab 60 mg SQ q 6 mos plus oral placebo
- After 1 year, BMD gains at total hip, femoral neck and lumbar spine were slightly but significantly greater with denosumab

*J Bone Miner Res 2009*
Denosumab

- Effective in PMP women who were previously treated with bisphosphonates
- Effective for prevention
- Effective in reducing rate of vertebral fx in men on androgen deprivation therapy for prostate cancer
- Effective in breast cancer pts with bony mets or on aromatase inhibitor therapy
Denosumab- Possible Indications

- PMP women at high risk for fracture who have failed or intolerant of other available osteoporosis therapies
- Men receiving androgen deprivation Rx
- Women undergoing breast cancer Rx
- Not recommended for prevention at this time
Denosumab – Adverse Effects

- ? Immune effects: some trials with increased # infections requiring hospitalization
- No osteonecrosis of jaw seen (although theoretically possible)
- No symptomatic hypocalcemia in women with normal renal function (all women supplemented with calcium/vit D)
# Osteoporosis Treatment Decisions

## Non-Fracture Patient

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<tr>
<th>Condition</th>
<th>T-score</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1.0</td>
<td>Calcium, Vitamin D, Exercise</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>-2.5</td>
<td>Bisphosphonates, Raloxifene</td>
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</table>

- **Calcium**
- **Vitamin D**
- **Exercise**

2º cause of bone loss, or FRAX ≥ 3% hip fx, or ≥ 20% major fx

## Fracture Patients

- **Bisphosphonates**
- **Teriparatide**
- **Denosumab**