New Developments in Osteoporosis: Screening, Prevention and Treatment

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Osteoporosis: Overview

- Definitions
- Risk factors
- Screening and Monitoring
- Treatment

Background

- Hip and vertebral fractures are associated with premature mortality
- Any fracture is associated with an increased risk of 5-10 year mortality
- A subsequent fracture is associated with an increased mortality risk for 5 more years
  - Dubbo Osteoporosis Epidemiology Study

Osteoporosis: Definitions

- Normal: BMD no lower than 1 SD below mean for young adult women
- Osteopenia (Low bone mass): BMD 1.0-2.5 SD below the mean for young adults
  - (T=-1 to -2.5)
- Osteoporosis: BMD more than 2.5 SD below young adult mean
  - (T<-2.5)
Osteoporosis: Definitions

- T scores vs Z scores
  - T scores compare the patient with the average young adult female
  - Useful for treatment decisions
  - Z scores compare the patient with an age matched female
  - Useful for ruling out secondary causes of bone loss

Risk Factors

- Age
  - Risk of hip fracture increases with age
  - Older women have a much higher fracture rate than younger women with the same bone density

- Vertebral fractures: very high risk
  - Even if asymptomatic
  - 20% risk of new fracture in the year following a fracture

10-Year Fracture Probability
Age vs. Femoral Neck T-score

Adapted from JA Kanis et al, Osteoporos.Int. 2001;12:989-995
Risk Factors in the WHO Risk Factor Assessment Tool

- Age
- Gender
- Personal history of fracture
- Low body mass index
- Oral glucocorticoids
- Secondary osteoporosis
- Parental history of hip fracture
- Current smoking
- Alcohol intake of 3 or more drinks per day
- Femoral neck BMD

Drugs Associated with an Increased Risk of Osteoporosis

- Thyroid hormone (over replacement)
- Aromatase inhibitors
- SSRIs
- PPIs
- Androgen deprivation agents
- Thiazolidinediones
- Anticonvulsants

Question

Which of the following women would you screen for osteoporosis?

A. 66 year old healthy woman
B. 57 year old healthy woman who does not exercise
C. 55 year old woman whose mother had a hip fracture
D. A and C
E. A, B, and C
Screening for Osteoporosis

- Bone density is the single best predictor of future fracture
  - Hip BMD is best predictor of hip fracture
- Central dual x-ray absorptiometry (DXA) of spine, hip and body most commonly used and preferred when available

NOF 2014: BMD Screening

- Women age 65 and older, men >70 regardless of risk factors
- Adults who have a low trauma fracture after age 50
- In postmenopausal women age 50 to 64
  - Adults with a condition (e.g., RA) or taking a medication associated with low BMD or bone loss
    - $\geq 5$ mg prednisone QD or equivalent for $\geq 3$ months
  - Historical height loss of 1.5 inches or more (4 cm)
  - Prospective height loss of 0.8 inches or more (2 cm)


Case

- Bonnie Bony is a 68 year old woman who wants to know when she should have her next bone mineral density test. Her last BMD was 2 years ago and showed osteopenia with a t score of -1.8. What do you tell her?

Choices

A. Let’s schedule it now
B. We should do it in 2 years
C. We should do it in 3 years
D. We should do it in 5 years
E. I have no idea…when do you want to do it?

50% 15% 22% 5% 8%
**USPSTF Recommendations**

- Screen all women age 65 and older  
  - Evidence for screening is indirect
- Screen younger women whose fracture risk is equal to or greater than a 65 year old white woman who has no additional risk factors
- “Evidence is lacking about optimal intervals for repeated screening”  
  - A minimum of 2 years may be needed to reliably measure a change in BMD  
  - Longer intervals may be needed to improve fracture risk prediction  
  - USPSTF 2011

**BMD Testing**

- Medicare pays for BMD every two years regardless of baseline BMD
- Is repeat BMD useful?
- Does change in BMD provide additional information about fracture risk?

**The News**

- *Bone-density testing interval and transition to osteoporosis in older women.*  
  - Gourlay et al. NEJM 2012
- Aim: To determine how the BMD testing interval relates to the timing of the transition from normal BMD or osteopenia to the development of osteoporosis before a hip or vertebral fracture occurs

**Methods**

- 4,597 women from the Study of Osteoporotic Fractures (SOF)  
  - Aged 65 and older, population based  
  - Study examinations at year 2, 6, 8, 10 and 16
- Outcome: Estimated interval for 10% of individuals to make transition from normal BMD or osteopenia to osteoporosis before a hip or clinical vertebral fracture or treatment for osteoporosis
Results

- Within each t score range, a percentage of women developed osteoporosis over 15 years
  - Normal (-1.00 or higher) 0.8%
  - Mild osteopenia (-1.01 TO -1.49) 4.6%
  - Moderate osteopenia (-1.50 to -1.99) 20.9%
  - Advanced osteopenia (-2.00 to -2.49) 62.3%

Results/Competing Risk Analyses

- Adjusted interval between baseline testing and the development of osteoporosis in 10% of study participants
  - Normal BMD 16.8 (11.5-24.6) yrs
  - Mild osteopenia 17.3 (13.9-21.5) yrs
  - Moderate osteopenia 4.7 (4.2-5.2) yrs
  - Advanced osteopenia 1.1 (1.0-1.3) yrs

Conclusions

- Osteoporosis would develop in <10% of individuals during rescreening intervals of 15 years for women with normal BMD or mild osteopenia, 5 years for women with moderate osteopenia and 1 year for women with advanced osteopenia

- Future screening recommendations will probably be based on likelihood of osteoporosis progression based on initial BMD

Take Home Message

- Decisions about when to rescreen should be based on the results of initial screening
- Few women with normal BMD will develop osteoporosis at 15 year follow-up
- Back to Bonnie: Would probably wait at least 5 years from her prior BMD
Repeat BMD Screening: The News

• *Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture.*
• Aim: To determine whether BMD changes after 4 years provide additional information on fracture risk and to quantify the change in fracture risk classification after a second BMD measure.

Methods

• Framingham Osteoporosis Study population based cohort of 310 men and 492 women
  – Two BMD measures from 1987 to 1999
• Outcome: risk of hip or major osteoporotic fracture through 2009 or 12 years after second BMD measure
• Net Reclassification Index (NRI):
  – Quantifies change in risk classification after a second BMD measure
  – High risk: Risk of hip fracture 3% or greater or major osteoporotic fracture 20% or greater (vs low risk)

Results

• Mean age 74.8 years
• Mean BMD change -0.6% per year
• Median follow up 9.6 years
• NRI increased proportion classified as high risk by 3.9% and decreased the proportion defined as low risk by 2.2%
• Adding BMD change to a model that included baseline BMD did not improve performance of the ROC curve
  – AUC baseline 0.71 (0.65-0.67) vs 0.72 (0.66-0.79)

ROC Curves for Hip and Major Osteoporotic Fractures

Figure Legend:
Receiver Operating Characteristic Curves for Models Investigating Fracture in Older Adults From the Framingham Osteoporosis Study.BMD indicates bone mineral density. All models are adjusted for age, sex, body mass index, weight loss (per pound), and history of fracture measured at the time of the second BMD test. Models are defined in the Methods section.
Conclusion and Take Home Message

- In untreated men and women with a mean age of 75, a repeat BMD after 4 years did not meaningfully improve the prediction of major hip or osteoporotic fracture
- Repeating a BMD after 4 years to improve fracture risk prediction may not be necessary in adults of this age untreated for osteoporosis

Monitoring Guidelines

- All recommend follow-up monitoring but no consensus on site and frequency
- What is “treatment failure?”
  - ISCD: DEXA spine and hip when expected change in BMD exceeds LSC expected on bone densitometer
    - Every 1-2 years and less often when stable
  - AACE: DEXA spine and hip every 1-2 years until stability
  - NAMS: DEXA hip every 2 years
- Question: What are you going to do?

OSTEOPOROSIS

Absolute Risk Assessment

WHO Fracture Risk Algorithm

- FRAX
- Calculate the 10 year probability of a hip fracture and the 10 year probability of any osteoporotic fracture
- Includes femoral neck BMD and risk factors
- Can be used only in previously untreated patients
- Can be used with or without BMD
- Algorithm adapted for the U.S.
- Available as an I phone app

www.shef.ac.uk/FRAX
WHO Fracture Risk Algorithm

- Most useful in identifying individuals in the osteopenic range who are most likely to benefit from treatment
- Treat when there is a 10 year risk of hip fracture ≥3% or a 10 year risk of a major osteoporosis-related fracture that is ≥20% based on the U.S. adapted WHO algorithm
- In the future some BMD machines may be able to provide a report with absolute fracture risk
**Question**

Mrs. P is a 66 year old woman who has no previous fracture or other risk factors. Her hip BMD t score is -2.3. She is on no medications. What are your next steps?

A. Discuss Calcium and Vitamin D intake
B. Start raloxifene 60 mg per day
C. Start alendronate 70 mg per week
D. A and C

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**NOF 2014: Vertebral Imaging**

- Vertebral fractures indicate very high risk
- Consider in women age 70 and over and men aged 80 and over with BMD T score ≤-1.0
- Consider in women aged 65-69 and men aged 70-79 with BMD T score ≤-1.5
- Consider
  - Low trauma fracture during adulthood
  - Long term glucocorticoid use
  - Height loss
    - Historical ≥ 1.5 inch
    - Prospective ≥ 0.8 inch
- No evidence for treatment initiation based on these criteria

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**NOF 2014: Treatment Guidelines**

- Prior hip or vertebral fracture
- Other prior bone fracture, or
- Secondary medical condition, or
- Elevated 10 year fracture risk

**T-Score**

- No Risk Factors
- 0
- -1.0
- -1.5
- -2.0
- -2.5
- -3.0

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**NOF: Osteoporosis Prevention**

- Preventive measures for everyone:
  - Calcium: diet alone or with supplements
    - 1,000 to 1,200 mg a day
  - Vitamin D intake of 800-1,000 IU a day
  - Weight bearing and muscle strengthening exercise to improve agility, strength, posture and balance, increase bone density and avoid falls and fractures
  - Assess fall risk and appropriate modifications
  - Avoid tobacco and excessive alcohol
  - Hip protectors for some at risk?

2014 NOF Guidelines
Calcium/Vitamin D

- Women should ideally get RDA for calcium and Vitamin D from diet
- Previous studies have suggested that calcium/Vitamin D are necessary but not sufficient
  - Even if a woman is receiving adequate calcium and Vitamin D, she may still be at risk for fracture
  - Additional therapies (eg anti-resorptive therapies) may also be necessary

USPSTF Recommendations

- Evidence is insufficient to assess balance of benefits and harms
  - Vitamin D with or without calcium for cancer prevention
  - Vitamin D and calcium for primary prevention of fractures in postmenopausal women or men
  - Daily supplementation with >400 IU of Vitamin D3 and 1,000 mg of calcium for fracture prevention
- Recommends against daily supplementation with <400 IU of Vitamin D3 and 1,000 mg calcium for primary prevention of fractures in noninstitutionalized postmenopausal women

Vitamin D and Falls

- USPSTF concluded that Vitamin D supplementation is effective in preventing falls in community dwelling adults aged 65 and older who are at increased risk for falls
  - Ages 51-70: 600 IU daily
  - Older than aged 70: 800 IU daily

Screening for Vitamin D Deficiency

- Should we be screening for Vitamin D deficiency?
- USPSTF concludes that the evidence is insufficient to assess the balance of benefits and harms of screening for Vitamin D deficiency in asymptomatic adults
What do you most commonly use for treatment of osteoporosis?

A. Weekly bisphosphonate
B. Monthly bisphosphonate
C. Yearly bisphosphonate
D. Raloxifene
E. PTH
F. Denosumab

Pharmacologic Therapies

• Estrogen
• Bisphosphonates
• Calcitonin
• SERMs
• Parathyroid hormone
• Denosumab

Estrogen

• 50% reduction in hip and other non-spine fractures in observational studies
• Estrogen reduced the risk of new vertebral fractures by half in two RCTs
• Reduced hip fracture risk by 34% in WHI
  – No overall benefit even in women at high risk for osteoporosis
• USPSTF does not recommend the use of estrogen for the treatment of any chronic disease
  – Some women may be taking estrogen for other reasons

Bisphosphonates

• Four approved: alendronate, risedronate, ibandronate, zolendronate
• Increase BMD by 3% per year
• Reduce fracture risk
  – All reduce vertebral fracture
  – All but ibandronate reduced nonvertebral fracture (including hip fracture)
• Therapeutic effects with 10 year use of alendronate
• Gradual loss of effect with discontinuation of medication
Bisphosphonates: Adverse Effects

- Osteonecrosis of the jaw
- Femoral shaft fractures

Potential Long-term Side Effect of Bisphosphonates?

Osteonecrosis of the Jaw

- Associated with potent bisphosphonate use:
  - 94% treated with IV bisphosphonates
  - 4% of cases have OP, most have cancer
  - 60% caused by tooth extraction.
- Extremely rare
  - Estimated risk in those treated for osteoporosis
    - 1/10,000 to 1/100,000 person years
- Dental exam recommended before Rx, but no need to stop for dental procedures

Ann Intern Med, 2006
ADA Guidelines, 2011

Osteonecrosis of the Jaw

- 7332 patients receiving oral alendronate in Taiwan
  - 40 cases of ONJ
  - 22 had preceding invasive dental procedures
- Risk increased with longer duration of therapy
  - 0.23% to 0.92% as duration went from 2-10 years
- Risk factors: advanced age, diabetes, rheumatoid arthritis and duration of use
  - Chiu, J Clin Endocrinol Metab 2014
Atypical Femoral Fractures (AFF)

- Long-term BP users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
- ASBMR Task Force (2013)
  Stress fractures. Microdamage?
  Clinical studies: RR for BPs= 2-50
  Risk goes up with longer use and down 1 year after stopping

Re-analysis of Data in 3 RCTs

- 284 hip or femur fractures in 14,195 women
  - 12 were atypical
- Relative hazards
  - RH 1.03 (95% C.I. 0.06, 16.46) for alendronate in FIT
  - RH 1.50 (95% C.I. 0.25, 9.00) for zoledronic acid in HORIZON-PFT
  - RH 1.33 (95% C.I. 0.12, 14.67) for continued alendronate in FLEX
- Conclusions
  - Fracture of subtrochanteric or diaphyseal femur was rare even in women on bisphosphonates for up to 10 years
  - No significant increase in risk but wide confidence intervals

Impact for Practice

- Small risk of atypical fracture associated with bisphosphonate use must be weighed against the population benefits of overall reduction in hip fractures with bisphosphonates in women with osteoporosis

Case

- Bonnie Bony is a 76 year old woman who has been on alendronate for 5 years after having a hip T-score of -2.8. She also has diabetes and hypertension. Her best friend, Veronica Vertebrae, just stopped her bisphosphonate because she developed osteonecrosis of the jaw (ONJ). Bonnie wants to know if she should continue taking the alendronate or whether she should stop. What do you tell her?
What do you tell her?

A. Yes, everyone should stop after 5 years of treatment
B. No, you should continue the medication
C. We can stop it if you are having a dental procedure
D. Let’s repeat your bone density and decide
E. I’m not sure. What do you want to do?

FDA View of Long-term Bisphosphonate Use (Sept. 2011)

- Independent review of epidemiologic studies to date and all bisphosphonate trial data...
- FDA conclusions about atypical fractures
  - "conflicting results...causality uncertain"
  - "no agreement on effects of duration or cumulative dose"
- FDA conclusions about ONJ
  - "some evidence that risk increases after 4 yr."
  - "causality not established"

Bisphosphonates: Duration of Use

- “Bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains but no adequate clinical trials have yet delineated how long the drugs’ benefits are maintained after cessation.”
- New “Important Limitation of Use Statement”
  - Optimal duration of use has not been determined
  - Periodic re-evaluation of continued need

The News

- Objective:
  - To provide guidance on bisphosphonate therapy duration with a risk-benefit perspective
Background

- Fracture risk increases with age
- Does continued bisphosphonate therapy continue to confer benefit?
  - Long half life
- Rare but real side effects
  - Jaw osteonecrosis
  - Atypical femoral fractures
- How long should women remain on therapy?
  - Drug holidays?
- FDA “Limitation of Use Statement”
  - Optimal duration of use has not been determined
  - “All patients on bisphosphonates should have the need for continued therapy reevaluated on a periodic basis”

Methods

- Systematic literature reviews
  - Two RCTS (FLEX and HORIZON) provide evidence on long term use
- Evaluation of benefits and risks of bisphosphonates and alternatives

Recommendations

- After 5 years of oral bisphosphonates or 3 years of IV bisphosphonates, reassessment of risk should be considered
  - In women at high fracture risk, consider continuation of oral BP for 10 years or IV BP for 6 years
    - High risk based on age (>70 or 75), medication use, new dx of disorder associated with secondary osteoporosis
    - Clinician deemed high risk based on femoral neck T score, age or other risk factors
  - For women not at high fracture risk after 3-5 years of treatment, consider a drug holiday of 2-3 years
- For high risk women, risks of atypical femoral fracture and ONJ are outweighed by reduction in vertebral fracture

What is “high risk?”

- Older women (>70 or 75)
- Low hip T score or high fracture risk score (FRAX criteria)
- Previous osteoporotic major fracture
- Fracture on therapy
- Limitations
  - Limited evidence
  - White postmenopausal women
  - Vertebral fracture reduction only
**Impact for practice**

- Patients at “low risk” may safely have bisphosphonates discontinued
  - Younger, no fracture history, medication was started for osteopenia, BMD approaching normal?
- Patients at “increased risk” may benefit from continued therapy
  - Older, history of fracture, BMD remaining in osteoporotic range?
- Decisions about when to restart?
  - Role of BMD
  - Currently, no evidence to support use of bone turnover markers

**Bea Brittle**

- Bea Brittle is a 68 year old woman whom you started on alendronate two years ago for a hip BMD t score of -2.8. She keeps hearing bad things about the bisphosphonates and wonders if she should switch to a different drug. What do you tell her?

**Back to Bonnie**

- Bonnie is “high risk” based on her age
- Reasonable to continue for 10 years
- Consider BMD?

**What do you tell her?**

A. We should change to PTH  
B. We should change to denosumab  
C. We should change to raloxifene  
D. We should change to zolendronic acid  
E. We should continue the alendronate
**Raloxifene**

- Selective Estrogen Receptor Modulators
- Ideally maximize bone and cardiovascular protective effects of estrogen, while minimizing negative effects (endometrial and breast cancers)

**Calcitonin**

- Intranasal spray
- Increased BMD 10-15% in two years
- Fracture evidence limited and inconclusive
- Analgesic effect in acute osteoporotic fracture
- Oral calcitonin in studies
- Possible increased cancer risk
  - Basal cell and other cancers

**Parathyroid Hormone**

- Anabolic therapy
  - vs anti-resorpive
  - Reduces vertebral fractures by 65% and nonvertebral fractures by 53% after 18 months
- FDA approved for postmenopausal women at high risk for fracture
- Safety and efficacy has been shown for 2 years
  - Most BMD gains occur in first few months
- Daily subcutaneous injection

**Raloxifene**

- Raloxifene reduces vertebral fractures, but not hip fracture
- Increased risk of thromboembolic events
- Breast cancer prevention
  - Similar to tamoxifen
- No effect on vaginal bleeding/endometrial cancer
**PTH vs Bisphosphonates**

- They have not been compared head to head in a trial that evaluated fracture outcomes
- PTH increased BMD more than alendronate
- PTH is much more expensive
- Long term safety of PTH?

**Combination Treatment**

- **PTH plus bisphosphonates**
  - No additional benefit
  - Bisphosphonate may impair PTH stimulation of new bone formation
- **PTH plus SERMs**
  - No evidence that adding SERM is beneficial
- **PTH plus hormone therapy**
  - Small studies show an increase in BMD with combined therapy
- **PTH plus denosumab**
  - Increased BMD more than either agent alone and more than reported with other approved therapies
  - No fracture outcomes
- Not currently recommended

**PTH: Adverse Effects**

- Hypercalcemia and hypercalcuria
- Concern for osteosarcoma
  - Higher doses for longer duration increased risk in rats
  - Case reports of co-existing osteosarcoma in patients with primary hyperparathyroidism
  - Only one reported case in post-menopausal woman on PTH
- FDA currently recommends limiting PTH therapy to two years
  - Post-marketing surveillance is ongoing

**After PTH...**

- PTH is recommended for two years
- Some BMD decline after discontinuing PTH
- Some anti-resorptive therapy should be added after PTH discontinuation
  - Bisphosphonate
  - Raloxifene is an alternative

**After PTH...**

- PTH is recommended for two years
- Some BMD decline after discontinuing PTH
- Some anti-resorptive therapy should be added after PTH discontinuation
  - Bisphosphonate
  - Raloxifene is an alternative
**PTH Alternatives to Daily Injection**

- Intermittent PTH
  - 3 months on and 3 months off
- Weekly PTH injection?
- Transdermal patch with 1300 microneedles
  - Phase 2 trial
  - Results in PTH surge and pulsatile effect
  - Increase BMD

**Denosumab: FREEDOM Trial**

- Human monoclonal antibody against RANKL
  - RANKL is a cytokine essential to osteoclast function
  - Inhibits osteoclast mediated bone resorption
- 7,868 women with osteoporosis received denosumab 60 mg or placebo SQ every 6 months for 36 months
- Reduced fracture risk
  - Vertebral fractures (2.3% vs 7.2%)
  - Hip fracture (0.7% vs 1.2%)
  - Nonvertebral fracture (6.5% vs 8.0%)

  *Cummings SR et al.. NEJM 2009: 361: 756-65*

**PTH: Summary**

- Big impact on BMD
- Reduces spine and non-spine fractures compared with placebo
  - Hip fracture?
- Long term safety issues
- Daily injection of an expensive drug
- Consider use in severe osteoporosis when other agents have failed

**Denosumab**

- FDA approved for the following groups
  - High risk for fracture including androgen deprivation therapy for prostate cancer and aromatase inhibitor therapy for breast cancer
  - Treatment for osteoporosis in postmenopausal women at high risk for fracture
**On the Horizon**

- Sclerostin is an osteocyte-derived inhibitor of osteoblast activity
- Individuals with hereditary deficiency of sclerostin have high bone mass and resistance to fractures
- Monoclonal antibody romosozumab binds to sclerostin and increases bone formation
- In Phase 2 trial of 419 postmenopausal women, romosozumab increased BMD at multiple sites more than placebo, alendronate or PTH
  - No fracture outcomes yet
  - Stay tuned

  McClung, NEJM 2014

**Back to Bea……**

- There is currently no compelling reason for her to switch from a bisphosphonate to any other osteoporosis therapy

**Summary:**

**Osteoporosis Prevention**

- Avoid or quit smoking and avoid excess alcohol use
- Regular weight bearing and muscle strengthening exercise
- Calcium and vitamin D
- Fall prevention

**Summary**

- Measure bone mineral density in women aged 65 and older
- Consider risk factors in measuring BMD in younger postmenopausal women
- WHO FRAX tool is useful for absolute risk assessment especially in women with low bone mass
- BMD monitoring frequency should be based on initial BMD and impact on management
Choice of Pharmacologic Therapies

• The bisphosphonates have been studied most extensively and should remain first line agents
  – Consider stopping after 5 years in “low risk” patients
  – Guidelines about when or whether to stop bisphosphonates remain in evolution

• Raloxifene, calcitonin and PTH should remain second line agents
  – Raloxifene reduces breast cancer risk

Choice of Pharmacologic Therapies

• Calcitonin may be an option for women who decline or cannot tolerate other options or who desire analgesic effect

• PTH may be an option for women who have failed other treatments
  – Treatment for 2 years should be followed by an antiresorptive therapy

• Denosumab for women with breast cancer on AIs and for high risk postmenopausal women with osteoporosis

Let’s ask the dog.....
Thank you!

Questions?