NEW DEVELOPMENTS IN OSTEOPOROSIS: SCREENING, PREVENTION AND TREATMENT

Judith Walsh, MD, MPH
Departments of Medicine and Epidemiology and Biostatistics
UCSF

OSTEOPOROSIS: OVERVIEW

• Definitions
• Risk factors
• Screening and Monitoring
• Treatment
• Emerging Issues

BACKGROUND

• Osteoporotic fractures are increasing as the population ages
• Hip and vertebral fractures are associated with premature mortality

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
  – $(T=-1 \text{ to } -2.5)$
• 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 IN THE WHO FRACTURE RISK ASSESSMENT TOOL

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

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

FRACTURE AND SUBSEQUENT RISK

- Frances Fragile is a 74 year old woman who trips over a suitcase in the hallway and fractures her wrist. She comes in to see you to start an osteoporosis medication and also wants to know whether there are any additional future consequences of her fracture. What do you tell her?
**What do you tell her?**

A. She has no increased risk of future fracture  
B. She has an increased risk of future fracture but no increased risk of mortality  
C. She has an increased risk of future fracture as well as an increased mortality risk for 5-10 years

**CLINICAL QUESTIONS**

- What is the mortality risk following an osteoporotic fracture?  
- Does degree of trauma matter?  
- Does subsequent fracture affect that risk?

**RESULTS IN WOMEN**

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>SMR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>89</td>
<td>509</td>
<td>2.53 (2.04-3.13)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>93</td>
<td>994</td>
<td>1.76 (1.43-2.17)</td>
</tr>
<tr>
<td>Major</td>
<td>48</td>
<td>591</td>
<td>1.60 (1.20-2.13)</td>
</tr>
<tr>
<td>Minor</td>
<td>76</td>
<td>1349</td>
<td>1.38 (1.10-1.74)</td>
</tr>
</tbody>
</table>

**Fracture and Mortality**

- Prospective cohort study from Dubbo Osteoporosis Epidemiology Study  
- Individuals who had a fracture between 1989 and 2007  
- Age and sex specific standardized mortality ratios compared with general population for hip, vertebral, major and minor fractures  
  - Bliuc et al. JAMA 2009
SUBSEQUENT FRACTURE AND MORTALITY

- Having another fracture was associated with an increased risk of mortality in women
  - HR 1.53 (1.15, 2.04)

IMPACT FOR PRACTICE

- 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
- We should pay more attention to non-hip, non-vertebral fractures

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. 1 and 3
E. 1, 2 and 3

OSTEOPOROSIS: OVERVIEW

- Definitions
- Risk factors
- Screening and Monitoring
- Treatment
- Emerging Issues
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 is preferred when available

NATIONAL OSTEOPOROSIS FOUNDATION 2010

• Evidence based guidelines for screening and prevention
• Recommend screening and treatment alternatives

NOF GUIDELINES 2010

• All postmenopausal women should receive at least 1,200 mg calcium per day, should engage in regular weight bearing exercise and should avoid smoking and excessive alcohol intake
• Adults over age 50 should receive 800 IU of Vitamin D$_3$ per day
• Fall prevention
  – Consider hip protectors for high risk women

NOF: WHO TO SCREEN

• All women >65 and men >70
• Younger postmenopausal women and men aged 50-70 about whom there is concern based on their clinical risk factor profile
• Women in menopausal transition if there is a specific risk factor
• Adults with a fracture after age 50
• Adults with a condition associated with low bone mass
• Postmenopausal women discontinuing estrogen should be considered
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

When should BMD be repeated?

- Is the woman on treatment?
- Is the previous result near a treatment threshold?
- Should treatment response be monitored?
  - No consensus on monitoring
  - Potential goals would be increasing adherence to treatment regimens and determining treatment responses
- There is some normal variation in the precision of BMD measurements
- Will it change management?

MONITORING TREATMENT

- Analysis of data from the FIT study
- Over 3 year follow-up, comparison of between person variation (treatment) with within person variation (measurement)
- Within person variation was greater than between person variation
- 97.5% of individuals gained BMD with alendronate treatment
- Routine monitoring in the first 3 years of bisphosphonate treatment is unnecessary
  - BMJ 2009

MONITORING TREATMENT?

- Treatment should be continued in patients who lose BMD initially
- Patients who have the largest increases during the first year are more likely to lose or have modest gains during the second year
- If most women will gain BMD with treatment and since resistance to osteoporosis drugs has not been documented, there may not be value in monitoring BMD during treatment
- Will monitoring reinforce adherence?
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.

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
Mrs. P is a 66 year old woman who has no previous fracture or other risk factors. Her hip BMD t score is -1.9. She is on no medications. What are your next steps?

A. Start Calcium and vitamin D
B. Start raloxifene 60 mg per day
C. Start alendronate 70 mg per week
D. 1 and 3
NON-PHARMACOLOGIC INTERVENTIONS

• Smoking cessation
• Avoid ETOH abuse
• Exercise has transient effect
• Avoid thyroid over-replacement
• Hip protectors (compliance)

CALCIUM

• Women should get RDA for calcium from diet, supplements or both
• Calcium/Vitamin D is 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 (e.g., anti-resorptive therapies) may also be necessary

What do you most commonly use for treatment of osteoporosis?

A. Weekly bisphosphonate
B. Monthly bisphosphonate
C. Annual bisphosphonate
D. Selective estrogen receptor modulator
E. PTH

FDA APPROVED PHARMACOLOGIC THERAPIES

• Estrogen
• Bisphosphonates
• Calcitonin
• SERMs
• Parathyroid hormone
ESTROGEN

50% reduction in hip and other non-spine fractures in observational studies
- In two RCTs of women with vertebral fractures, estrogen reduced the risk of new vertebral fractures by half
- Women’s Health Initiative
  - Reduced hip fracture risk by 34%
- Approved non-estrogen treatments should first be carefully considered

ESTROGEN

- 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
  - No head to head fracture studies
- Bind to bone and inhibit osteoclastic resorption
- Increase BMD by 3% per year
- Have been shown to reduce the risk of fracture
  - All reduce vertebral fracture
  - All but ibadronate reduced nonvertebral fracture (including hip fracture)

BISPHOSPHONATES

- Poorly absorbed
  - Take with tap water in the morning on an empty stomach
  - Stay upright at least one half hour to minimize esophageal lodging and irritation
  - Alendronate 70 mg a week has similar effects with less GI effects
- Continued therapeutic effects with 10 year use of alendronate
  - Well tolerated
  - Gradual loss of effect with discontinuation of medication
BISPHOSPHONATES: OTHER REGIMENS

- Less frequent administration of bisphosphonates has improved compliance
- Ibandronate or risedronate once a month
- Ibandronate IV every 3 months
- Yearly zolendronate

BISPHOSPHONATES: ADVERSE EFFECTS

- Atrial fibrillation
  - Increased in zoledronic acid trial
  - Reanalysis of FIT showed nonsignificant trend with alendronate
  - One recent population based case-control study also suggested increased risk with alendronate, but another did not
- Osteonecrosis of the jaw
- Increased risk of femoral shaft fractures?

Osteonecrosis of the Jaw

- More common with potent bisphosphonate use
  - 94% treated with IV zolendronate or ibandronate
  - 4% of cases have osteoporosis; most have cancer
  - 66% caused by tooth extraction
- Risk factors
  - Meds: chemotherapy, steroids
  - Dental extractions, periodontal disease, dental trauma, use of dentures

  - Pazianas M. Clinical Therapeutics 2007: 29 (2)
  - Godwin MH. JADA 2008: 139: 23-30
  - Grbic et al. JADA 2008: 139: 32-40

Osteonecrosis of the Jaw

- Goals:
  - Early identification
  - Conservative treatment
- Risk in those treated for osteoporosis
  - Probably < 1/100,000 patient years
Atypical fractures

- Several case series have described an increased risk of atypical femoral shaft fractures in bisphosphonate users
  - Subtrochanteric fractures make up 2-4% of all hip fractures
  - No estimate of population prevalence
- In population based registries, fracture rates higher in alendronate users
  - Increased alendronate use in high risk individuals
- Recent re-analysis of data from 3 bisphosphonate trials
  - Black DM et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. NEJM 2010;362:1761-71

RESULTS

- 284 hip or femur fractures in 14,195 women in 3 randomized trials
  - 12 were subtrochanteric or diaphyseal
- Relative hazards
  - RH 1.03 (95% C.I. 0.06, 16.46) for alendronate use in FIT
  - RH 1.50 (95% C.I. 0.25, 9.00) for zoledronic acid use in HORIZON-PFT
  - RH 1.33 (95% C.I. 0.12, 14.67) for continued alendronate use in FLEX

CONCLUSIONS

- Fracture of subtrochanteric or diaphyseal femur was very rare even in women on bisphosphonates for up to 10 years
- There was no significant increase in risk but confidence intervals were wide
  - Small number of events

Impact for Practice

- Even if there is a small risk of atypical fracture associated with bisphosphonate use, this must be weighed against the population benefits associated with an overall reduction in hip fractures with bisphosphonates in women with osteoporosis
BISPHOSPHONATE: DURATION OF USE

- Women who discontinued alendronate for 5 years had a decrease in BMD of 2.4% at hip and 3.7% at the spine but levels remained above pretreatment levels from 10 years earlier
- Lower risk of clinically recognized vertebral fractures for those who continued
- For many women, discontinuing alendronate after 5 years may not increase fracture risk
- Those at high risk for clinical vertebral fractures may benefit from continuing more than 5 years

BISPHOSPHONATES: SUMMARY

- Bisphosphonates reduce risk of vertebral and hip fracture in women with vertebral fracture or low BMD (T score <2.5)
- May not reduce fracture risk in women without osteoporosis
- Intermittent dosing appears to be effective
- Best evidence of any osteoporosis treatment
- After 5 years, some may stop
  - Who?
  - How to monitor?
  - How long?

QUESTION: CHOICE OF DRUGS

Bea Brittle is a 67 year old woman with a hip BMD with a t score of -2.8. She has severe GI side effects with weekly bisphosphonates. She is otherwise healthy, but had a DVT at the age of 33 when she was on birth control pills. What would you choose as the next step?

A. Start ibandronate monthly  
B. Start raloxifene 60 mg per day  
C. Start daily subcutaneous PTH  
D. Start intranasal calcitonin

RALOXIFENE

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

• Raloxifene reduces vertebral fractures, but has not been shown to reduce the risk of hip fracture
• Increased risk of thromboembolic events
• Effect similar to tamoxifen in preventing breast cancer
• No effect on vaginal bleeding/endometrial cancer

Lasofoxifene

• Cummings SE et al. Lasofoxifene in postmenopausal women with osteoporosis. NEJM 2010:362; 686-696.
• AIM: To determine the impact of lasofoxifene on fractures, breast cancers and cardiovascular disease in postmenopausal women with osteoporosis

Lasofoxifene: 5 year results

• Lasofoxifene (0.5 mg per day) reduced risk of vertebral and nonvertebral fractures
• 85% reduction in ER-positive breast cancer
• Reduced CHD and stroke
• Increased DVT
• Increased leg cramps, hot flushes, uterine polyps, endometrial hypertrophy, vaginal candidiasis and arthralgias with lasofoxifene
• 38% increase in all cause mortality with lasofoxifene
  0.25 mg; no increase with 0.5 mg dose

CALCITONIN

• FDA approved for women who are at least 5 years postmenopausal
• Intranasal spray
• Increased BMD 10-15% in two years
• 35% reduction in vertebral fractures
• Analgesic effect
• Oral calcitonin FDA approved and in studies
PARATHYROID HORMONE

• Pulsatile vs constant effect
  – Anabolic vs anti-resorptive
• PTH 1-34 and PTH 1-84
• 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

PARATHYROID HORMONE

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?

PTH vs Bisphosphonates

COMBINATION TREATMENT

• PTH plus bisphosphonates
  – No additional benefit
  – Bisphosphonate may impair PTH stimulation of new bone formation
• PTH plus SERMs
  – Does not suppress BMD response to PTH
  – No evidence that adding SERM is beneficial
• PTH plus hormone therapy
  – Small studies show an increase in BMD with combined therapy

COMBINATION TREATMENT

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

PTH: Adverse Effects
AFTER PTH...

• PTH is recommended to be used 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: 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

• Cummings SR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. NEJM 2009: 361: 756-65
• AIM: To determine the effect of denosumab on fracture risk in postmenopausal women with osteoporosis

Denosumab: Background

• Human monoclonal antibody against RANKL
• RANKL is a cytokine essential to osteoclast function
• Inhibits osteoclast mediated bone resorption
**Denosumab: FREEDOM trial**

- 7,868 women received denosumab 60 mg or placebo subcutaneously every 6 months for 36 months
- Endpoints were new vertebral fractures at 6 months and time to first hip and nonvertebral fractures

**Denosumab: FREEDOM Trial**

- Reduced risk of vertebral fractures
  - 2.3% in denosumab group vs 7.2% in placebo group
  - (Risk ratio: 0.32; 95% C.I. 0.26 to 0.41)
- Reduced risk of hip fracture
  - 0.7% in denosumab group vs 1.2% in placebo group
  - (Hazard ratio 0.60; 95% C.I. 0.37, 0.97)
- Reduced risk of nonvertebral fracture
  - 6.5% vs 8.0% in placebo group
  - (Hazard ratio 0.80; CI 0.67 to 0.95)
- Increased risk of cellulitis in denosumab group
  - No significant differences in overall infection or cancer

**Osteoporosis Management Guidelines**

- Management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society
  - Menopause 2010; 17:25-54
- Highlights
  - Periodic review of calcium, Vitamin D and lifestyle
  - Assess fall risk annually and when physical/mental status changes

**NAMS Highlights**

- Pharmacologic treatment:
  - women with fractures or osteoporosis
  - osteopenia who have a 10 year fracture risk of at least 20% and a 10 year hip fracture risk of at least 3%
- Drug choices
  - Bisphosphonates are first line
  - Consider PTH for women with osteoporosis at high risk
- Fracture risk after discontinuing therapy has not been adequately evaluated
EMERGING ISSUES

• Other effects of osteoporosis drugs
• Effects of other drugs on osteoporosis risk

Key Articles

• Bisphosphonates were associated with a lower risk of breast cancer in two observational studies
• Proton pump inhibitors were not associated with hip fractures but were associated with clinical spine, forearm and wrist fractures
  • Gray et al. Arch Intern Med 2010; 170; 765-771

SUMMARY: OSTEOPOROSIS PREVENTION

• Avoid or quit smoking
• Regular weight bearing 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
• Any fracture increases the risk of subsequent fracture and mortality
• WHO FRAX tool is useful for absolute risk assessment especially in women with low bone mass
CHOICE OF PHARMACOLOGIC THERAPIES

• The bisphosphonates and estrogen* have been studied most extensively and should remain first line agents

• Consider the risks and benefits of HT
  - * It is not recommended to start estrogen for chronic disease prevention, but if the woman is taking it for other reasons it is useful for osteoporosis prevention

• Raloxifene, calcitonin and PTH should remain second line agents

• Raloxifene can reduce breast cancer risk

• 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 anti-resorptive therapy

• Denosumab recently FDA approved