NEW DEVELOPMENTS IN OSTEOPOROSIS: SCREENING, PREVENTION AND TREATMENT

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OSTEOPOROSIS: OVERVIEW

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

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?

1. She has no increased risk of future fracture
2. She has an increased risk of future fracture but no increased risk of mortality
3. She has an increased risk of future fracture as well as an increased mortality risk for 5-10 years
BACKGROUND

• Osteoporotic fractures are increasing as the population ages
• Hip and vertebral fractures are associated with premature mortality
• More recent evidence shows that 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 indicate very high risk
  – Even if asymptomatic
  – 20% risk of new fracture in the year following a fracture
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

Screening and Monitoring

QUESTION

- Which of the following women would you screen for osteoporosis?
  1. 66 year old healthy woman
  2. 57 year old healthy woman who does not exercise
  3. 55 year old woman whose mother had a hip fracture
  4. 1 and 3
  5. 1, 2 and 3

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 D₃ 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

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**

1. Let's schedule it now
2. We should do it in 2 years
3. We should do it in 5 years
4. I have no idea... when do you want to do it?

**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*

**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 0.8%
  - Mild osteopenia 4.6%
  - Moderate osteopenia 20.9%
  - Advanced osteopenia 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
BMD FOR 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 or change your management?

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

OSTEOPOROSIS

TREATMENT

QUESTION

- 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?
  1. Discuss Calcium and Vitamin D intake
  2. Start raloxifene 60 mg per day
  3. Start alendronate 70 mg per week
  4. 1 and 3
**NOF: WHO TO TREAT**

- Postmenopausal women and men age 50 and older
  - Hip or vertebral fracture
  - Other prior fractures and low bone mass (T score between -1.0 and -2.5)
  - T score <-2.5 after excluding secondary causes
  - Low bone mass (T score between -1.0 and -2.5) and secondary causes associated with a high risk of fracture
  - Low bone mass (T score between -1.0 and -2.5) and 10 year probability of hip fracture ≥3% or a 10 year probability of any major osteoporosis related fracture ≥20%

**ACP: WHO TO TREAT**

- Treat men and women with known osteoporosis and those who have had fragility fractures
- Consider pharmacologic treatment in men and women at risk for osteoporosis
- Choice of therapy should include risks, benefits and adverse effects of drug options for each individual

**NON-PHARMACOLOGIC INTERVENTIONS**

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

**Calcium/Vitamin D**

- Women should ideally get RDA for calcium and Vitamin D from diet
- Previous studies 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 (e.g., anti-resorptive therapies) may also be necessary
USPSTF Draft Recommendations June 2012

- 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 previously 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

What do you most commonly use for treatment of osteoporosis?

1. Weekly bisphosphonate
2. Monthly bisphosphonate
3. Annual bisphosphonate
4. Selective estrogen receptor modulator
5. 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

- Less frequent administration of bisphosphonates has improved compliance
  - Ibandronate or risedronate once a month
  - Ibandronate IV every 3 months
  - Yearly zolendronate
- Therapeutic effects with 10 year use of alendronate
- Gradual loss of effect with discontinuation of medication
BISPHOSPHONATES: ADVERSE EFFECTS

- Atrial fibrillation
  - Some studies have showed increases and others have not
- Osteonecrosis of the jaw
- 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
  - 60% 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)
  - Cartsos VM. JADA 2008: 139: 23-30
  - Grbic et al. JADA 2008: 139: 32-40

Osteonecrosis of the Jaw

- Goals:
  - Early identification
  - Conservative treatment
- Estimated risk in those treated for osteoporosis
  - 1/10,000 to 1/100,000 patient years

Atypical femur fractures

- Several case series have described an increased risk of atypical femoral shaft fractures in bisphosphonate users
  - Subtrochanteric fracture makes 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
- Re-analysis of data from 3 bisphosphonate trials
  - Black DM et al. 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

**Atypical Fractures**

- Case-control study of all fractures in a single hospital
- 39 patients with atypical fractures and 438 patients with classic fractures
  - OR 66.9 (27.2-165.1) for treatment with bisphosphonates and atypical fracture
  - OR 0.5 (0.3-0.9) for treatment with bisphosphonate and classic fracture
  - Higher risk atypical fracture with longer duration of treatment
- Absolute risk of atypical fracture
  - 32 cases per million person years

**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
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 affective
• Best evidence of any osteoporosis treatment
• After 5 years, some may stop
  – Who?
  – How to monitor?
  – How long?

Bisphosphonates: Duration of Use

• FDA Meeting September 9, 2011
  – Re-evaluate the efficacy of continuing bisphosphonates for more than 3-5 years
• “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

Impact for practice

• Patients at “low risk” may safely have bisphosphonates discontinued
  – Younger, no fracture history, med 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 and bone marker turnovers
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?
  1. Start ibandronate monthly
  2. Start raloxifene 60 mg per day
  3. Start daily subcutaneous PTH
  4. 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

- 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

  * Cummings et al. NEJM 2010: 362: 686-696

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

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: 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

### 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

### 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

- 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; C.I 0.67 to 0.95)
- Increased risk of cellulitis in denosumab group
  - No significant differences in overall infection or cancer
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

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
  - Women with 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

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
- 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 FDA approved for women with breast cancer on AIs and for postmenopausal women with osteoporosis
- Guidelines about when or whether to stop bisphosphonates in evolution

Questions?

Thank you!