

OSTEOPOROSIS: PREVENTION AND MANAGEMENT

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OSTEOPOROSIS: OVERVIEW

- Definitions
- Key Risk factors
- Screening and Monitoring
- Treatment
 - Choices
 - How long
 - Alternatives

OSTEOPOROSIS: DEFINITIONS

- Normal: BMD no lower than 1 SD below mean for young adult women
 - ($T < 1$)
- 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 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

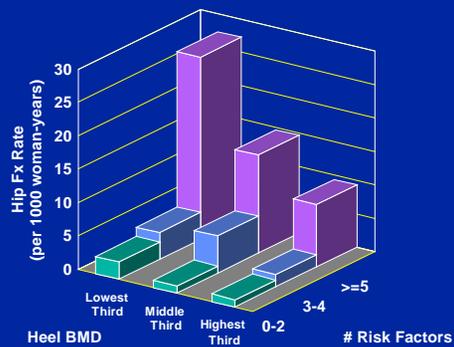
OSTEOPOROSIS RISK FACTORS

- Age
- Female Sex
- Previous fractures*
- Family History*
- Low body weight*
 - * <127 lbs
- Smoking*
- Steroid Use
- White or Asian race
- Premature Menopause
- Amenorrhea
- Hyperthyroidism
- Impaired vision
- Urge incontinence
- Homocysteine
- Low calcium intake
- Low physical activity
- Alcohol >2 drinks per day

KEY RISK FACTORS

- In addition to age, gender and race
 - Previous fracture
 - Family history of fractures
 - Low body weight
 - Current cigarette smoking
- BMD is an additive risk factor

BMD and Risk Factors



Cummings et al., NEJM 332(12):767-773, 1995

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

QUESTION

- Which of the following women should be screened for osteoporosis?
 - 66 year old healthy woman
 - 57 year old healthy woman who does not exercise
 - 55 year old woman whose mother had a hip fracture
 - 1 and 3
 - 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

OTHER MODES OF BMD SCREENING

- Peripheral DXA and Single X-ray Absorptiometry (SXA)
 - Forearm, hand and heel
- Quantitative Ultrasound
 - FDA approved for screening
- Quantitative CT
- Biochemical markers
 - Not presently useful for screening

OSTEOPOROSIS SCREENING

- Population based screening for osteoporosis is controversial
- Treating women with known osteoporosis can reduce the risk of hip fractures
- No study has shown that screening for osteoporosis reduces the risk of hip fracture

NATIONAL OSTEOPOROSIS FOUNDATION

- Evidence based guidelines for screening and prevention
 - Initially published in 1999 and updated in 2003
- Recommend screening and treatment alternatives

NATIONAL OSTEOPOROSIS FOUNDATION GUIDELINES

- 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
- Women at risk for Vitamin D deficiency should receive 400-800 IU of Vitamin D daily
- Fall prevention
 - Consider hip protectors for high risk women

WHO TO SCREEN

- All women >65
- Younger postmenopausal women with one or more risk factor
 - (other than being white, postmenopausal and female)
- Postmenopausal women who present with fracture
 - (to confirm diagnosis and assess disease severity)

USPSTF RECOMMENDATIONS

- Screen all women age 65 and older
 - Evidence for screening is indirect
- Screen women aged 60-64 who are at increased risk
 - Age
 - Low body weight
 - Non-use of HRT
- NIH argue that evidence is insufficient to recommend screening

When should BMD be repeated?

- Is the woman on treatment?
- Is the previous result near a treatment threshold?
- Should treatment response be monitored?
 - Potential goals would be increasing adherence to treatment regimens and determining treatment responses

Repeat bone density and fracture prediction

- Hillier TA et al. Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women. The Study of Osteoporotic Fractures. Arch Intern Med 2007; 167: 155-60.
- AIM: To determine whether a second BMD test contributes to the ability to predict fractures among older postmenopausal women.

METHODS

- Prospective cohort study
- 4124 women over 65 (mean age 72) followed prospectively after initial BMD
- Second BMD about 8 years later
- Outcomes: hip and non-spine fractures
- Association between BMD at each time point and non-spine fractures
 - Initial BMD
 - Change in BMD
 - Initial BMD plus change in BMD

RESULTS

- Initial BMD was predictive of fracture
- Change in BMD over 8 years was predictive of fracture
- For fracture prediction, repeat BMD did not add much to original BMD 8 years earlier
- Even in groups with high rates of bone loss, there was no additional benefits

IMPACT FOR PATIENT CARE

- For patients with normal or mildly reduced BMD, repeat testing 8 years later adds little to original testing
- Rates of bone loss were 0.5% (0.1 T score) per year
 - Rarely exceeds 2% per year
- Repeating bone density routinely may not be necessary
 - Every 4-10 years?

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 BMD is monitored, decreases should trigger questions about adherence

MONITORING TREATMENT?

- If most women will gain BMD with treatment and since resistance to raloxifene and alendronate has not been documented, there may not be value in monitoring BMD during treatment
- Will monitoring reinforce adherence?
 - Most adherence problems occur early
 - Bone densitometry is typically done later

IMPACT FOR INTERNAL MEDICINE

- With any diagnostic test, if the results will not change management, it may be best not to order it
- BMD is a very precise measurement, but random error can occur

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?
- Start Calcium and vitamin D
- Start raloxifene 60 mg per day
- Start alendronate 70 mg per week
- 1 and 3

NOF: WHO TO TREAT

- Women whose BMD falls below specified thresholds should consider treatment
 - Women without risk factors
 - » T score <2.5
 - Women with risk factors (thinness, history of fragility fracture since menopause or family history of hip fracture)
 - » T score <2.0-2.5
- Prior vertebral or hip fracture

TREATMENT GUIDELINES

- Fracture rates are highest in women with T score <-2.5 but fractures can occur in women with T scores of -1.0 to -2.5
 - In peripheral BMD screening study, 82% of the fractures in the following 12 months occurred in women with T scores greater than -2.5
- How to determine which of these women will benefit from treatment?

PREDICTORS OF SHORT TERM FRACTURE RISK

- Risk factor assessment may be useful in guiding treatment of osteopenic women
 - Previous fracture biggest risk regardless of T score
 - T score -1.8 or less
 - Self rated poor health status
 - Poor mobility

NON-PHARMACOLOGIC INTERVENTIONS

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

PHARMACOLOGIC THERAPIES

- Calcium
- Calcium plus Vitamin D
- Estrogen
- Bisphosphonates
- Calcitonin
- SERMs
- Parathyroid hormone
- Strontium ranelate
- Folate and Vitamin B₁₂

CALCIUM

- Calcium
 - One prospective study showed that 800 mg of calcium per day reduced the risk of hip fracture, but other studies have not confirmed this
 - Up to 2 grams of calcium is safe
 - All postmenopausal women should be encouraged to consume at least 1200 mg of calcium per day
- Calcium plus Vitamin D
 - Reduces risk of hip fracture in institutionalized elderly
 - Recommended for institutionalized and homebound elderly

CALCIUM PLUS VITAMIN D

- Jackson RD et al. Calcium plus vitamin D supplementation and the risk of fractures. NEJM 2006; 354: 669-83.
- AIM: to determine the effect of calcium and Vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women

METHODS

- Randomized clinical trial
- 36,282 women already enrolled in the WHI
 - 1000 mg calcium carbonate with 400 IU vitamin D daily vs placebo
- 7 year follow-up
- Outcomes
 - Fractures
 - BMD

RESULTS

- No overall difference in fractures
 - Hazard ratio 0.88 (95% C.I. 0.72, 1.08) for hip
 - Hazard ratio 0.90 (0.74, 1.10) for spine
- BMD 1.065 higher in treatment group
- Increased risk of renal calculi in treatment group
 - HR 1.17 (1.02, 1.34)

RESULTS

- Hip fracture was decreased among adherent women
 - 0.71 (0.52, 0.97)

CONCLUSION

- Among healthy postmenopausal women, calcium and Vitamin D resulted in a small increase in BMD, had no overall effect on fractures and increased the risk of kidney stones

IMPACT FOR CLINICAL PRACTICE

- Lower than expected hip fracture rate reduced study power
- Average baseline calcium intake was close to current national recommendations
- NNT
 - 5045 for a year to prevent one hip fracture
 - 1945 for a year to prevent one hip fracture for women aged 60 and over

IMPACT FOR INTERNAL MEDICINE

- Women should continue to 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 (eg anti-resorptive therapies) may also be necessary

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
- Recent meta-analysis found a 27% reduction in non-vertebral fractures
- Women's Health Initiative
 - Reduced hip fracture risk by 34%

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

- Three approved: alendronate, risedronate, ibandronate
- Bind to bone and inhibit osteoclastic resorption
- Increase BMD by 3% per year
- Have been shown to reduce the risk of fracture

BISPHOSPHONATES Fracture Intervention Trial (FIT)

- Results differed in women with and without vertebral fractures
- Women with vertebral fractures
 - Reduced risk of hip, wrist and vertebral fractures by 50%
- Women without pre-existing fractures
 - Vertebral fractures decreased 50%
 - Reduced fracture rate only in those with t score <2.5

FIT CONCLUSIONS

- Women with osteoporosis (T score <2.5 or vertebral fractures) benefit from 3-4 years of treatment with alendronate
- Women with higher BMD receive little or no benefit

EARLY POSTMENOPAUSAL BONE LOSS

- 1605 healthy women received alendronate (2.5 mg, 5 mg) or placebo for 6 years
- Women on alendronate had increases in hip and spine BMD
- Trend toward reduction in fractures in alendronate treated women
 - Not statistically significant

RISEDRONATE

- Newer bisphosphonate
 - 5 mg per day or 35 mg per week
- VERT Study
 - 41% reduction in new vertebral fractures over 3 years
 - Cumulative incidence of non-vertebral fractures was 39% lower in treated women
- Decrease in hip fractures in women with hip BMD T score <3.0
- Similar GI safety to placebo

RISEDRONATE

- HIP study
 - 5445 women aged 70-79 with low BMD
 - 386 women at least 80 years old with at least one non-skeletal risk factor
- Hip fracture reduced from 3.2% in placebo group to 1.9% in treatment group
 - RR 0.6
 - Most benefit in those who already had vertebral fractures
- No effect in older women

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

- Compliance with bisphosphonates is a challenge
- Once weekly bisphosphonates have improved compliance
- Ibandronate (Boniva) approved in March, 2005 for once monthly treatment
 - 150 mg a week
 - BMD outcomes: no studies with fracture endpoints
- Yearly zoledronate

Zoledronic Acid

- Black DM et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. NEJM 2007; 356: 1809-22
- AIM: to determine whether once a year infusion of zoledronic acid is associated with a reduction in fractures.

Zoledronic acid

- Very potent bisphosphonate
- 3 year prospective trial with 3889 patients
- IV zoledronate once a year vs placebo
- Outcome: BMD, bone turnover, fracture

• Black et al NEJM 2007

Zoledronic Acid : Outcomes HORIZON Trial

- 70% reduction in vertebral fracture
- 41% reduction in hip fracture
- Improved bone mineral density and markers of bone metabolism
- Increased rate of atrial fibrillation in the zoledronic acid group
 - 50 vs 20 patients: $p < 0.001$

BISPHOSPHONATES: ADVERSE EFFECTS

- **Atrial fibrillation**
 - Increased in zoledronic acid trial
 - Reanalysis of FIT showed nonsignificant trend with alendronate
- **Gastrointestinal side effects less with less frequent dosing**
- **Osteonecrosis of the jaw**

Osteonecrosis of the Jaw

- **More common with potent bisphosphonate use**
 - 94% treated with IV zoledronate or ibandronate
 - 4% of cases have osteoporosis; most have cancer
 - 60% caused by tooth extraction
- **Risk factors?**
 - Duration of treatment
 - Over-suppression of bone turnover?

Osteonecrosis of the Jaw

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

BISPHOSPHONATES: DURATION OF USE

- **Black DM et al. Effects of continuing or stopping alendronate after 5 years of treatment: the fracture intervention trial long term extension (FLEX) : A randomized trial. JAMA 2006; 296: 2927-2938.**
- **AIM: to determine the effects of discontinuing alendronate after 5 years vs continuing for 10 years**

METHODS

- 1,099 women who were previously randomized to alendronate in FIT were randomized to alendronate or placebo for an additional 5 years
- Outcomes were BMD or biochemical markers of bone remodeling

RESULTS

- Compared to continuing alendronate, those who discontinued 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
- Markers of bone turnover increased after discontinuation but again remained above pretreatment levels
- No difference in morphometric vertebral fractures
- Lower risk of clinically recognized vertebral fractures for those who continued

CONCLUSION

- 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?

Osteoporosis

- What is the evidence for other drug therapies?
- Most other therapies are probably less effective than bisphosphonates

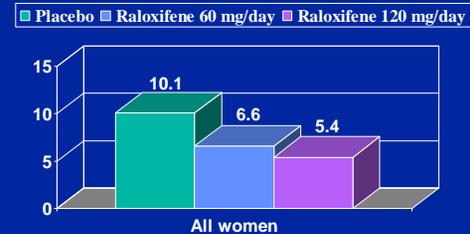
QUESTION

- 67 year old woman had 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 is the appropriate next step?
 - Start ibandronate monthly
 - Start raloxifene 60 mg per day
 - Start daily subcutaneous PTH
 - Start intranasal calcitonin

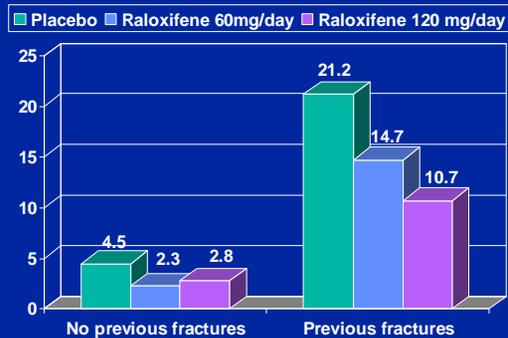
RALOXIFENE

- Selective Estrogen Receptor Modulators
- Ideally maximize bone and cardiovascular protective effects of estrogen, while minimizing negative effects (endometrial and breast cancers)
- Raloxifene increases bone mineral density
 - Effect on fractures?

New Vertebral Fractures



New Vertebral Fractures



RALOXIFENE

- Raloxifene reduces vertebral fractures, many of which were clinically silent
- No effect on nonvertebral fracture
 - RR 0.9 (0.8-1.1)
- Increased risk of thromboembolic events
 - RR, 3.1 (1.5-6.2)
- No effect on vaginal bleeding/uterine cancer

RALOXIFENE

- The increase in spine BMD is roughly half that previously observed with bisphosphonates or estrogen
- The reduction in vertebral fracture risk of 30% to 40% is comparable to the bisphosphonates

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

PARATHYROID HORMONE

- **Physiology**
 - Pulsatile vs constant effect is anabolic
- **Potential effect on bone formation and resorption**
- **Reduces vertebral and nonvertebral fractures**
- **How does it compare with other treatments?**
- **Daily subcutaneous injection**

ALENDRONATE PLUS PTH

Effects of alendronate, PTH or both on bone density

- **PTH alone had the biggest effect on bone density**
- **Alendronate may reduce the anabolic effects of PTH**
- **No fracture outcomes**

ALENDRONATE PLUS PTH: SEQUENTIAL TREATMENT

- **Recent study looked at sequential PTH then alendronate**
- **In year one, women randomized to PTH, alendronate or both and had similar increases in BMD**
- **In year two, those on PTH randomized to alendronate or placebo**
 - Spine BMD increased 8% in those who got alendronate
 - Study too small to look at fracture outcomes

ESTROGEN PLUS ALENDRONATE

- **No studies with fracture endpoints**
- **Study in younger women assessed the effect of estrogen and alendronate separately and combined on BMD and biochemical markers**
 - No significant difference in hip BMD
- **Study in elderly women compared alendronate, HRT and combination with placebo**
 - Any treatment better than placebo
 - Hip BMD higher with alendronate than with HRT
 - Combination had a greater effect on hip BMD than either alone

STRONTIUM RANELATE

- Oral agent which stimulates bone formation and decreases bone resorption
- 1649 women with vertebral fractures received strontium or placebo and were followed for 3 years
 - RR vertebral fracture 0.59 (95% C.I. 0.48, 0.73)
 - NNT=9
- Not available in U.S. for several years
- Strontium may be in complementary medicine preparations
 - Efficacy?

FOLATE AND VITAMIN B₁₂

- Elevated homocysteine has been shown to be a risk factor for fracture
- Double blind RCT in 628 women with stroke and hemiplegia
 - 5 mg folate and 1500 micrograms of mecobalamin or placebo
 - 2 year follow up
- Relative risk of hip fracture 0.20 (0.08-0.50) in treated group
 - NNT 14
- Generalizability?

CHOICE OF PHARMACOLOGIC THERAPIES

- Estrogen* and the bisphosphonates have been studied most extensively and should remain first line agents
- Consider the risks and benefits of HRT
 - * 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

CHOICE OF PHARMACOLOGIC THERAPIES

- Raloxifene, calcitonin and PTH should remain second line agents
 - Raloxifene may 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 unable to tolerate other treatments
- Strontium not currently available
- Folate and B₁₂ may be promising

OSTEOPOROSIS PREVENTION

- All women
 - Avoid or quit smoking
 - Regular weight bearing exercise
 - 1-1.5 g of calcium per day (with Vitamin D if necessary)
- Postmenopausal women <65 years old
 - Screening BMD if strong risk factor for fractures
 - Treat if BMD <2.0 or <1.5 with risk factors

OSTEOPOROSIS PREVENTION

- Women >65
 - Measure BMD if woman will consider treatment
 - Fall prevention (reduce or stop sedatives, visual impairment, strength and balance exercises for women with >2 falls or at high risk)
- Women with vertebral fractures or established osteoporosis
 - Look for any treatable risk factors
 - Ensure >1.2 g per day of calcium
 - Drug treatment

SUMMARY

- All women should be encouraged to adopt lifestyle modifications which reduce the risk of osteoporosis
- Fall prevention is important
- Screening for osteoporosis in all women >65 and women 50-64 with risk factors

SUMMARY

- Screening BMD should be repeated at some point if the result was near a treatment threshold
 - Women with high initial BMD have less benefit from repeat screening
- Bisphosphonates should remain first line treatments for osteoporosis