Controversies in Osteoporosis Prevention and Management

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Learning Objectives

- Review the guidelines and controversies regarding screening and benefits and adverse effects of therapy
- Discuss the controversies regarding duration of therapy and monitoring of therapy

Epidemiology

- 1 in 2 postmenopausal women and 1 in 5 older men will have an osteoporosis-related fracture in their lifetimes!!
- Because of the aging of the U.S. population, the number of hip fractures in the U.S. is expected to double or triple by 2040.
- 53.6 million older US adults have osteoporosis or low bone mass at the femoral neck or lumbar spine.

(USPSTF, Ann Intern Med 3/1/2011; Schneider and Guralnik 1990, Wright et al JBMR 2014)

Definition

- Disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.

Screening Guidelines: Women

- Women 65 years or older (USPSTF 2011, NOF 2014)
- Postmenopausal women aged 50-64:
  - fracture during adulthood
  - condition (e.g., rheumatoid arthritis) or medication associated with low bone mass or bone loss (NOF)
  - Women <65 y/o whose 10-year risk of osteoporotic fracture is ≥ that of a 65-year-old white woman who has no additional risk factors (i.e., ≥ 9.3%) (USPSTF)


FRAX practical considerations: contd

- Not validated for spine bone mass
  - If normal hip bone mass with low spine bone mass, FRAX underestimates fracture risk
- Not validated for:
  - Patients treated with osteoporosis pharmacotherapy past 1-2 years
- Underestimates fracture risk in patients with:
  - Recent or multiple fractures
  - Those at increased risk for falling


Screening guidelines: men

- Current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.

Current diagnostic and treatment criteria rely on dual-energy x-ray absorptiometry (DXA) measurements of lumbar spine and hip ONLY.

T-scores from other technologies cannot be used according to the WHO diagnostic classification because they are not equivalent to T-scores derived from DXA.


Interpreting the DXA: World Health Organization Diagnostic class.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMD</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Within 1 SD of a young adult reference population</td>
<td>T-score at -1.0 and above</td>
</tr>
<tr>
<td>Low Bone Mass (Osteopenia)</td>
<td>Between 1.0 and 2.5 SD below that of a young-adult reference population</td>
<td>T-score between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2.5 SD or more below that of a young-adult reference population</td>
<td>T-score at or below -2.5</td>
</tr>
<tr>
<td>Severe or Established Osteoporosis</td>
<td>2.5 SD or more below that of a young-adult reference population</td>
<td>T-score at or below -2.5 with one or more fractures</td>
</tr>
</tbody>
</table>

New emphasis!

• Vertebral fractures detected incidentally by x-ray confer dx of osteoporosis. So….
• √ vertebral x-rays if any of the following:
  • T-score ≤ -1.5 if ≥ 65 y/o
  • (Even lower threshold T-score ≤ -1.0 in ♀ ≥ 70 y/o ♀ ≥ 80 y/o)
  • Height loss ≥ 1.5” vs. peak, 0.8” in clinic over time - √ yearly!
  • Low-trauma fx, recent/chronic prednisone use

**Whom to treat: NOF 2014**

- Postmenopausal women and men age ≥50 if:
  - Hip or vertebral (clinical or asymptomatic) fracture
  - T-score ≤ -2.5 femoral neck, total hip, or lumbar spine
  - Low bone mass (T-score between -1.0 and -2.5 at femoral neck, total hip, or spine) if:
    - 10-yr probability of hip fracture ≥3% or
    - 10-yr probability of major osteoporosis-related fracture ≥20% based on U.S. WHO FRAX.


**Vitamin D levels?**

- Evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency.
- Accuracy of serum vitamin D assays is unknown
- No clear consensus on threshold for deficiency.
- Treatment of patients with asymptomatic vitamin D deficiency does not improve outcomes:
  - Cancer
  - Type 2 diabetes
  - Fracture risk
  - Mortality


**Calcium and Vit. D: Institute of Medicine**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Calcium</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>51-70</td>
<td>1,200 mg/d</td>
<td>600 IU/d</td>
</tr>
<tr>
<td>Men</td>
<td>51-70</td>
<td>1,000 mg/d</td>
<td>600 IU/d</td>
</tr>
<tr>
<td>Women and Men</td>
<td>&gt;70 y/o</td>
<td>1,200 mg/d</td>
<td>800 IU/d</td>
</tr>
</tbody>
</table>


**Vitamin D levels?**

- KEY POINT:
  - Populations with bone diseases were excluded because vitamin D testing in these populations could be considered management of a condition rather than general screening
  - I check 25-OH Vit. D levels annually and aim for 20 or 30 ng/mL in pts with osteoporosis.
## Benefits of therapy: Systematic review

- High-strength evidence that the following drugs reduce fractures compared with placebo:
  - Bisphosphonates
  - Denosumab
  - Teriparatide
  - Risk reductions 40-64% for vertebral fractures, 20-40% for nonvertebral fractures
- Raloxifene reduces only vertebral fractures.
- Demonstrated hip fracture reduction: bisphosphonates, denosumab (Crandall et al Annals of Internal Medicine 2014)

## Adverse effects of therapy: Systematic review

- Mild upper GI symptoms:
  - Bisphosphonates
  - Denosumab
  - Teriparatide
- Influenza-like symptoms:
  - Zoledronic acid
- Serious infections:
  - Denosumab (cellulitis, infectious arthritis, endocarditis)
  - (Crandall et al Annals of Internal Medicine 2014)
- VTE, fatal stroke:
  - Raloxifene
- Atypical subtrochanteric fracture:
  - Bisphosphonates
- Osteonecrosis of the jaw:
  - Bisphosphonates
  - 0.03%-4.3% (pending new standardized case definitions)


- Reported in patients taking BPs, and in patients on denosumab
- Also occur in patients with no exposure to these drugs.
  - Probably associated with glucocorticoid use
- Absolute risk with BPs is low, 3.2 to 50 cases per 100,000 person-years.
- Long-term use may be associated with higher risk (~100 per 100,000 person-years)
- MRI: Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh (Shane et al JBMR 2013)

### Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus

- Vast majority of cases (>90%) have occurred in cancer patients receiving six-fold to 10-fold higher doses of BPs than those used to treat osteoporosis.
- Invasive oral surgery procedures are an important risk factor. Also glucocorticoids, DM, poor oral hygiene.
- Therefore, it is recommended by the Task Force that patients who undergo invasive oral surgery have their antiresorptive therapy withheld following the procedure until soft tissue healing has occurred.
  - (Khan et al JBMR 2015)

### Diagnosis and Management of Osteonecrosis of the Jaw: American Association of Oral and Maxillofacial Surgeons 2014

- Risk of ONJ among patients exposed to oral bisphosphonates following tooth extraction is 0.5%
- Antiangiogenic agents, when given with antiresorptive medications, are associated with an increased risk of ONJ
- There is currently no evidence that interrupting bisphosphonate therapy alters the risk of ONJ in patients following tooth extraction.

### Osteonecrosis of the jaw: American Association of Oral and Maxillofacial Surgeons 2014

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Osteonecrosis of the jaw: American Association of Oral and Maxillofacial Surgeons 2014

- Individuals receiving monthly intravenous bisphosphonates or denosumab for treatment of oncologic disease have an increased risk of developing ONJ following tooth extraction and thus these procedures should be avoided if possible.


Bisphosphonates and osteonecrosis of the jaw: American Association of Oral and Maxillofacial Surgeons 2014

- 3 scenarios:
  - Scenario 1: oral bisphosphonate for < 4 years and have no clinical risk factors
  - Scenario 2: oral bisphosphonate for < 4 years and corticosteroids or antiangiogenic meds concomitantly
  - Scenario 3: oral bisphosphonate > 4 years


Bisphosphonates and osteonecrosis of the jaw: American Association of Oral and Maxillofacial Surgeons 2014

- Scenario 1: Oral bisphosphonate for < 4 years and no clinical risk factors:
  - No alteration or delay in planned surgery is necessary.
  - This includes any and all procedures common to oral and maxillofacial surgeons, periodontists.
  - If dental implants are placed, give informed consent related to possible long-term implant failure and the low risk of developing osteonecrosis of the jaw if the patient continues to take an antiresorptive agent.


Bisphosphonates and osteonecrosis of the jaw: American Association of Oral and Maxillofacial Surgeons 2014

- Scenario 2: Oral bisphosphonate for < 4 years and corticosteroids or antiangiogenic meds concomitantly:
  - Prescribing provider should be contacted to consider discontinuation of oral bisphosphonate (drug holiday) for at least 2 months prior to oral surgery, if systemic conditions permit.
  - The antiresorptive should not be restarted until osseous healing has occurred.


Bisphosphonates and osteonecrosis of the jaw: American Association of Oral and Maxillofacial Surgeons 2014

- Scenario 3: Oral bisphosphonate > 4 years:
  - Prescribing provider should be contacted to consider discontinuation of the antiresorptive for two months prior to oral surgery, if systemic conditions permit.
  - The bisphosphonate should not be restarted until osseous healing has occurred.


Choice of therapy: What do I do?

- “The harms of bisphosphonates, the most commonly prescribed therapies, are no greater than small.” (USPSTF, Ann Intern Med 3/1/2011).

What do I do?

- Balance risk of serious AE’s with risk of fracture if untreated:
  - Likely benefits outweigh risks:
    - Preexisting vertebral or hip fracture
    - L-spine or hip BMD T-score ≤ -2.5
  - Unlikely benefits outweigh risks:
    - Absolute 10-year risk of fracture ≤ 3% at hip or ≤ 20% for major osteoporotic fracture
Monitoring: Serial testing

USPSTF

- Evidence is lacking about optimal intervals.
- Because of limitations in the precision of testing:
  - minimum of 2 years to reliably measure a change in BMD
  - longer intervals may be necessary to improve fracture prediction.


Monitoring: Untreated older women

Study of Osteoporotic Fractures postmenopausal women ≥65 y/o

<table>
<thead>
<tr>
<th>If baseline T-score is…</th>
<th>then the time period required for 10% of women to progress to osteoporosis BMD was:</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.01 to -1.49</td>
<td>15 years</td>
</tr>
<tr>
<td>-1.50 to -1.99</td>
<td>5 years</td>
</tr>
<tr>
<td>-2.00 to -2.49</td>
<td>1 year</td>
</tr>
</tbody>
</table>

(Gourlay et al. NEJM 2012)

Monitoring: Untreated younger postmenopausal women

- Women’s Health Initiative study
- In women without osteoporosis at baseline, the time for 1% of women to have hip or clinical vertebral fx was:
  - 12 years if 50-54 y/o
  - 7 years if 60-64 y/o
  - (Vs. 3 years in women with osteoporosis at baseline)

- Thus, women aged 50-64 years without osteoporosis on first BMD test are unlikely to benefit from frequent rescreening before age 65 yrs. (Gourlay et al Menopause 2014)

Monitoring: Untreated elderly

- Population-based Framingham Osteoporosis Study, men and women, mean age 75 years.
- Median follow-up of 9.6 years
- In untreated older persons, a 2nd BMD measure after 4 years did not meaningfully improve prediction of hip or major osteoporotic fracture. (Berry et al JAMA 2013)

Monitoring during treatment: Systematic review

- RCTs were not designed to show that monitoring BMD during therapy decreases hip fractures.
- For patients receiving antiresorptive therapy for whom serial BMD measurements have not shown an increase, or who have decreases in BMD, statistically significant benefits are still obtained in terms of fracture reduction.

- (Crandall et al Annals of Internal Medicine 2014)
Monitoring after treatment

- Prospective Fracture Intervention Trial Long-term Extension (FLEX) study
- Among women who discontinue alendronate after 4-5 years:
  - Age and hip BMD at discontinuation predict clinical fractures in the subsequent 5 years
  - DXA and bone turnover markers 1 year after discontinuation do not.

(Bauer et al JAMA Intern Med 2014)

Duration of treatment: Systematic review

- RCTs were not specifically designed to compare shorter with longer duration of therapy
  - post-hoc analyses only
- Optimal duration of therapy unknown.

(Crandall et al Annals of Internal Medicine 2014)

Duration of therapy: NOF Guidelines

- After the initial 3-5 year treatment check:
  - interval fractures, new chronic diseases/meds
  - BMD testing
  - Vertebral imaging if height loss during rx

- hx fx, BMD T-score remains ≤ -2.5 may benefit from continued rx:
  - FDA review Whitaker NEJM 2012 (post-hoc Black NEJM 2012 & JBMR 2012)

Newly-emerging risk factors

- Diabetes mellitus, despite being associated with increased BMD, is associated with increased fracture risk. (Leslie et al JBMR 2012)
- Trabecular bone score, obtained using DXA machine, predicts fracture risk independently of BMD. (Leslie et al JCEM 2013)
- Weight gain and weight loss, even intentional weight loss, is associated with increased risk of subsequent fracture (Crandall et al BMJ 2015)

New medication in 2014: TSEC

- Tissue-selective Estrogen Complex: Conjugated estrogens (0.45mg) + bazedoxifene (20mg) daily
  - Bazedoxifene is an estrogen agonist/antagonist
  - Only for postmenopausal women who still have uterus, osteoporosis prevention
  - (No fracture data available)


(A few…) Gaps in knowledge

- What is optimal:
  - Exercise type, intensity, duration, freq.?
  - Optimal duration, long-term AEs meds
  - Role of drug combinations/sequential meds?
  - Screening/treatment in men?
- How to:
  - Assess bone strength?
  - Incorporate lumbar BMD into FRAX?
  - Assess fracture risk during pharmacological rx?
Summary

- Women ≥ 65 y/o screen based on initial T-score:
  - T-score -1.0 to -1.9: wait 5 years
  - T-score -2.0 to -2.4: wait 1-2 years

- Women aged 50-64: screen based on FRAX score, secondary causes

- Men ?: consider screening if 10-year risk for osteoporotic fracture ≥ 9.3%, secondary causes.

- Measurement error of the machine!!!!
  - Changes in BMD of < 3-6% at hip and 2-4% at spine from test to test may be due to the precision error of the test itself!

Summary cont’d

- Measure height if height loss and/or low bone density (alters dx and rx decisions)
- Don’t ignore incidentally-detected vertebral fx
- Treat if hip or vertebral fracture or BMD T-score ≤ -2.5.
- Use FRAX to aid treatment decisions in persons over age 50 with low bone density (not in osteoporotic range)
- To decrease hip fracture, use bisphosphonates or denosumab. (I consider bisphosphonate 1st line).
- Counsel about low absolute risk of serious AEs with bisphosphonates, balance against fx risk if no therapy.
- Counsel to avoid excessive alcohol intake/smoking.

- Only 2 in 10 fractures are followed up with testing or treatment!

- After hip fracture:
  - Only 40% fully regain their pre-fracture level of independence.
  - Only 1 in 3 are treated within 12 months of d/c


References

