Current and Emerging Approaches for Osteoporosis

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No Disclosures

What’s New in Osteoporosis

- Risk identification and stratification
- Under recognition and poor compliance
- New potential concerns about treatments
- When to start and stop drug therapy
What Would You Do? Mrs. C...

• Semi-retired 68 WF new patient
• Healthy, no meds. No fractures, sister had breast cancer. Has 2-3 drinks/d, avoids dairy. Exam normal.
• About 5’7” and weighs 130
• Femoral neck BMD T-score -2.2
• No contraindication to treatment but little tolerance for mistakes…

What Would You Do?

1) Start daily calcium 1000 mg + vitamin D 800iu
2) Start alendronate 70 mg or risedronate 35 mg per week
3) Start raloxifene 60 mg/d
4) Both 1) and 2)
5) Both 1) and 3)
What is Osteoporosis?

“A disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk.” WHO, 1993

Traditional Risk Factors for Fracture

- The Big Three: older age, postmenopausal female, and Caucasian/Asian
- Other important risk factors
  - Family history of fracture (hip)
  - Low body weight (<127 in women)
  - Smoker, 3 or more drinks/d
  - Certain drugs (steroids, Als) and diseases (RA, sprue)
  - Previous fracture (especially hip or spine)
- Measurement of bone mineral density (BMD) strongly predicts fracture
Interpretation of Bone Density: The Basics

- Absolute mineral (calcium) content using x-rays
- Relative to a healthy reference population
- T-score is the number of standard deviations above or below average 30 year old female
  - T greater than -1.0 = “normal”
  - T between -1.0 and -2.5 = “low bone mass” (previously “osteopenia”)
  - T less than -2.5 = “osteoporosis”
- Z-score is number of SDs above or below others of the same age (use in those <50)

Hip BMD and Fracture Risk at Age 70

<table>
<thead>
<tr>
<th>T-score</th>
<th>5 year</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; -1</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>-1 to -2</td>
<td>1%</td>
<td>8%</td>
</tr>
<tr>
<td>-2 to -3</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>&lt; -3</td>
<td>9%</td>
<td>29%</td>
</tr>
</tbody>
</table>
BMD and Risk Factors

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

Hip Fx Rate (per 1000 woman-years)

Heel BMD

Lowest Third

Middle Third

Highest Third

0-2

3-4

>=5

# Risk Factors

0

5

10

15

20

25

30

Calculating Absolute Fracture Risk: FRAX

http://www.shef.ac.uk/FRAX/tool.jsp

FRAX™ WHO Fracture Risk Assessment Tool

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

1. Age (between 40-99 years) or date of birth
   - [ ] Male
   - [ ] Female

2. Weight (kg)
   - [ ] 50

3. Height (cm)
   - [ ] 160

4. Previous fracture
   - [ ] No
   - [ ] Yes

5. Parental history of hip fracture
   - [ ] No
   - [ ] Yes

6. Current smoking
   - [ ] No
   - [ ] Yes

7. Glucocorticoids
   - [ ] No
   - [ ] Yes

8. Rheumatoid arthritis
   - [ ] No
   - [ ] Yes

9. Osteoporosis
   - [ ] No
   - [ ] Yes

10. Secondary osteoporosis
    - [ ] No
    - [ ] Yes

11. Alcohol 3 more units per day
    - [ ] No
    - [ ] Yes

12. Femoral neck BMD
    - [ ] T-score
    - [ ] Z-score
    - [ ] -2.0

Calculation Tool

FRAX 21.8
The ten year probability of fracture (%) with BMD

- Major osteoporotic fracture: 7.8%
- Hip fracture: 1.2%
Who Should Be Tested and Treated? US Practice Guidelines*

- Preventive measures for everyone: adequate calcium/vitamin D, exercise, avoid bad habits
- Hip BMD: women >65 (or >50 with risk factors), men >70, anyone >50 after fracture
- Consider vertebral fracture assessment >70?
- US pharmacologic treatment thresholds:
  - Anyone with hip or spine fracture
  - T-score (any site) < -2.5
  - “Low bone mass” and FRAX 10 year hip fracture risk >3% or OP-related fracture risk >20%

*Revised 2013 NOF Guidelines
### Repeat Screening: Risk at Age 65 of Developing Osteoporosis Over Next 15 Years

<table>
<thead>
<tr>
<th>BMD Result Femoral Neck</th>
<th>15 Yr Risk for Osteoporosis</th>
<th>Time to 10% BMD &lt;-2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &gt; -1.0</td>
<td>0.8%</td>
<td>16.8 y</td>
</tr>
<tr>
<td>T = -1.01 to -1.49</td>
<td>4.6%</td>
<td>17.3 y</td>
</tr>
<tr>
<td>T = -1.50 to -1.99</td>
<td>20.9%</td>
<td>4.7 y</td>
</tr>
<tr>
<td>T = -2.00 to -2.49</td>
<td>62.3%</td>
<td>1.1 y</td>
</tr>
</tbody>
</table>

Gourlay, NEJM 2012

### Implications for Follow-up Testing

- BMD results higher than –1.5 at age 65 can safely defer repeat screening until age 80
- BMD between –1.5 and –2 at age 65 merits repeat screening BMD at 5 years
- BMD results –2 to –2.5 merits rescreening at 2 years
- Caveat: applies to untreated US white women >65 at average risk

Gourlay, NEJM 2012
Under Recognition of Osteoporosis

- Among women with fracture or BMD<-2.5 about a third are evaluated and treated!
- 12 months after hip: 2% had DXA, 15% treated with appropriate drug
- Ask about fracture history, note vertebral fractures, use chart reminders for DXA

Soloman, Mayo Clin Proc, 2005
Shibli-Rahhal, Osteo Internat, 2011

Medical Work-up

- Very little data, lots of opinions
- A reasonable start:
  - Vitamin D (25-OH, not 1,25-OH)
  - Serum calcium, Cr, TSH
- Additional tests that may be helpful:
  - Sprue serology, SPEP, UEP
- Unlikely to be helpful:
  - PTH, urine calcium

Jamal et al, Osteo Inter, 2005
What Else Can Be Done To Prevent Osteoporosis?

Non-pharmacologic Interventions

- Little new data
- Smoking cessation, avoid alcohol abuse
- Physical activity: modest transient effect on BMD but reduced fracture risk
- Fall prevention: targeted PT, home eval.
- Conflicting data on hip protector pads (compliance is big issue)
**Calcium and Vitamin D**

- **Chapuy, 1992**
  - Elderly women in long-term care
  - 30% decrease in hip fracture
- **Porthouse, 2005:**
  - Women >70 with 1+ risk factor
  - No benefit on hip, nonspine (RR=1.01, CI: 0.71, 1.43)
- USPSTF meta-analysis: 11% fewer fractures (together not alone)

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**Can Your Calcium Pills Kill You?**

- Meta-analysis of 15 calcium RCTs: CHD increased 30%
  - Not 1st endpoint, trials with vitamin D (WHI) excluded
- Add calcium+D trials? Results similar after excluding those taking personal calcium supplements in WHI. No harm if everyone included...
- Little supporting mechanistic data
  - No effect on surrogates (coronary calcium, IMT)
  - Dietary calcium not implicated
- ASBMR Task Force: “evidence is insufficient to conclude that calcium supplements cause adverse CV events…”

*Bolland, BMJ, 2011  Bockman, JCD, 2011*
How Much Is Enough? The IOM Report

- Calcium (elemental)
  - 1200 mg/d for women >50 and men >70; no more than 2500 mg/d
  - Dietary sources preferred (estimate intake using 300 mg/d plus 300-400 per dairy serving)

- Vitamin D (non-skeletal benefits not established)
  - 600-800 IU/d (maximum 4,000/d)
  - Recommends serum levels 20-50 ng/ml

Institute of Medicine Report, 2010

What About the US Preventive Task Force? Widely Misunderstood...

- “Insufficient evidence to assess risks/benefits for daily routine supplementation with calcium >1000 mg/d and vitamin D3 >400 IU”

- “Recommend against routine supplements with calcium 1000 mg or less and vitamin D 400 IU or less…”

  Not applicable if inadequate intake!

- Vitamin D supplements effective for fall prevention ≥ 65 yr at high risk

Bisphosphonates

- Four approved agents in US: alendronate, risedronate, ibandronate, and zoledronic acid
  - No head-to-head fracture studies
- What we know: fracture risk reduced 30-50% if
  - Existing vertebral fracture OR
  - Low hip BMD (T-score < -2.5)
- What about those with low bone mass (“osteopenia”)?
  Multiple risk factors resulting in increased absolute risk?

Effect of Alendronate on Non-spine Fracture Depends on Baseline BMD

<table>
<thead>
<tr>
<th>Baseline hip BMD</th>
<th>Relative Hazard (± 95% CI)</th>
</tr>
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<tbody>
<tr>
<td>T -1.5 – -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T -2.0 – -2.5</td>
<td>0.97 (0.72, 1.29)</td>
</tr>
<tr>
<td>T &lt; -2.5</td>
<td>0.69 (0.53, 0.88)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.86 (0.73, 1.01)</td>
</tr>
</tbody>
</table>

Cummings, Jama, 1998
Risedronate HIP Study: Two Groups

Group 1
- 5445 age <80; hip BMD T-score < -3.0
- 39% decreased hip fracture risk

Group 2
- 3886 age >80; risk factors for hip fx
- No significant effect on hip fracture risk

McClung, NEJM, 2001

More Bad News: Compliance with Bisphosphonates is Poor

- 50-60% persistence after one year
  - Multiple practice settings (similar to other preventive treatments)
- Reasons for non-compliance
  - Burdensome oral administration (fasting, remain upright for 30 minutes)
  - Upset stomach and heartburn can occur
  - Asymptomatic until fracture
- Trials show clinician interest (but not tests) can improve compliance

Clowes, JCEM, 2004
RCT of Nurse Visits to Discuss Medication Compliance

Nurse visits q3 mo. improved adherence by 59%

Does Dosing Interval Matter?

- Poor quality data:
  - Daily to weekly may improve compliance
  - Weekly to monthly may not

- Yearly dosing available: zolendronic acid
  - Extremely potent IV bisphosphonate
  - Fracture reduction with 3 annual injections: hip 40%, spine 60%, non-spine 25%
  - Precautions: acute phase reaction, renal insufficiency

- Don’t forget to discuss potential side effects...

Black et al, NEJM, 2007
A New Side Effect of Potent Bisphosphonates?

- Associated with potent bisphosphonate use:
  - 94% treated with IV bisphosphonates
  - 4% of cases have OP, most have cancer
  - 60% caused by tooth extraction. Other risk factors unknown. Infection?

- Key points: extremely rare, early identification, conservative tx

- Dental exam recommended before Rx, but no need to stop for dental procedures

[References]
Woo et al; Ann Intern Med, 2006
ADA Guidelines, 2011
Other Things to Worry About

- Atrial fibrillation (zolendronate and alendronate RCTs)
  - No association in other trials
  - Likely spurious

- Esophageal cancer
  - Case series (FDA author) and two conflicting cohorts,
  - Might be spurious

- Subtrochantic fracture (with atypical features)
  - Likely real...

Atypical Femoral Fractures (AFF)

- Thousands of reports in long-term bisphosphonate users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
What Would You Do Now?

- Mrs. C. felt strongly about therapy, and has now been on Ca/D and weekly alendronate for 5 years
- Misses her weekly dose about 8-10 times per year
- No new fractures
- Repeat hip BMD: T-score –2.4 (was -2.2)
- How would you advise her?

What Would You Do Now?

1) Urge better compliance and continue current oral bisphosphonate
2) Switch to IV bisphosphonate
3) Switch to denosumab q 6 mo
4) Stop bisphosphonate, continue Ca/D
How Long to Treat with Bisphosphonates?

- Long half-life also suggests that life-long treatment may not be necessary
- Ongoing concerns about excessive suppression of bone resorption
- FIT Long-term Extension (FLEX) study
  - 1099 ALN-treated FIT subjects
  - Randomized to ALN or PBO for 5 yr.

Black, Jama, 2006

FLEX Change in Femoral Neck BMD: % Change from FIT Baseline

Mean Percent Change

- Placebo
- ALN (Pooled 5 mg and 10 mg groups)

P<0.001 ALN vs PBO
Cumulative Incidence of Fractures During FLEX

<table>
<thead>
<tr>
<th></th>
<th>PBO (N = 437)</th>
<th>ALN (N = 662)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-spine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>20%</td>
<td>19%</td>
<td>1.0 (0.8, 1.4)</td>
</tr>
<tr>
<td>Hip</td>
<td>3%</td>
<td>3%</td>
<td>1.1 (0.5, 2.3)</td>
</tr>
<tr>
<td><strong>Vertebral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphometric</td>
<td>11%</td>
<td>10%</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>Clinical</td>
<td>5%</td>
<td>2%</td>
<td>0.5 (0.2, 0.8)</td>
</tr>
</tbody>
</table>

ASBMR Task Force on Long-Term Bisphosphonate Use, JBMR 2015
2015 Update: Who Should Be Treated and When to Stop?

- US (NOF) treatment thresholds:
  - Existing hip or vertebral fracture? Yes!
  - T-score < -2.5? Yes!
  - “Low bone mass” + FRAX score that exceeds absolute threshold? Probably not

- Drug holiday after 5 yr of bisphosphonate? Maybe
  - No hip/vertebral fracture; no fracture on therapy
  - BMD T-score > -2.5 before stopping
  - How long? Monitor? Risk stratify after 3-5 yr

Other Anti-resorptive Agents

- Less effective than bisphosphonates
  - Calcitonin (poor quality studies)
  - Raloxifene (prevents vertebral fractures only; use for breast cancer?)

- Hormone replacement

- Denosumab (antibody to RANKL)
  - SQ q 6 months, not cleared by kidneys
  - Effective but expensive, less long-term data
**Multiple Outcomes of Raloxifene Evaluation (MORE)**

**Design:**
7705 women >55 with low BMD or fracture
Raloxifene (60 or 120 mg) vs. placebo for 3 yr.

**Primary Endpoints:**
- New spine fracture: RR = 0.65 (0.53, 0.79)
- Non-spine fracture: RR = 0.94 (0.79, 1.12)

**Other Endpoints:**
- Breast cancer: RR = 0.24 (0.13, 0.44)

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**Women’s Health Initiative**

- RCT of ERT, PERT or PBO among women age 50-79, 10,739 with hysterectomy. Primary prevention
- PERT, ERT arms stopped after 5-7 years
  - Follow-up 93% complete
- Endpoints: ERT vs. PBO
  - Hip RR = 0.61 (0.41, 0.91)
  - Non-spine RR = 0.70 (0.63, 0.79)
  - CVD RR = 1.12 (1.01, 1.24)

WHI Writing Group, Jama, 2004
**Rank Ligand Inhibition: Denosumab**

- Human monoclonal antibody against RANKL
- Extremely potent inhibition of osteoclast activity
- Preclinical studies: increased trabecular, cortical bone mass and increased strength
- Rapid inhibition for months following a single injection, rapid resolution when stopped

**Denosumab Vs. Placebo: Fracture Risk (The FREEDOM Trial)**

- Multicenter study funded by Amgen
- 7808 postmenopausal women with OP
- Denosumab, 60 mg SC every 6 months (n=3902) or placebo (n=3906)
- 3 years of follow-up (83% completed study)
- Primary outcome: new vertebral fracture
- Secondary outcomes: BMD, markers, non-spine fracture, hip fracture

Cummings et al, NEJM 2009
### SQ Denosumab Vs. Placebo Every 6 Months for 3 Years (FREEDOM)

<table>
<thead>
<tr>
<th>Fracture Outcome</th>
<th>Dmb vs. PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>0.32 (0.26-0.41)</td>
</tr>
<tr>
<td>Hip</td>
<td>0.60 (0.37-0.97)</td>
</tr>
<tr>
<td>Any Non-spine</td>
<td>0.80 (0.77-0.95)</td>
</tr>
</tbody>
</table>

Cummings et al, NEJM 2009

### The Future: Anabolic Agents

- Most treatments inhibit bone resorption (and formation)
- Anabolic agents (anabolic steroids, fluoride, intermittent PTH) stimulate formation (and resorption)
- Daily SQ PTH (1-34) for 18 mo. reduces vertebral and non-spine fracture. No hip fracture data
- After teraparatide use bisphosphonate
- Expensive, daily self-administered injections...
  - Use with severe OP, when other agents have failed?

Neer, NEJM, 2001
Daily SQ PTH (1-34) for 18 months

- Big effects on BMD
  - Spine increased 9-13%
  - Hip increased 3-6%
  - Wrist decreased 1-3%
- Big effects on fracture
  - Vertebral decreased 65%
  - Non-spine decreased 54%
- Well tolerated

Conclusions

- Absolute risk estimates help clinicians and patients
- Aggressive screening and treatment = fewer fractures
  - Identify those who have already have the disease!
- Bisphosphonates: treatment of choice
  - Use when spine/hip fracture or T<-2.5
  - Adherence counseling. Consider yearly dosing
  - Duration of therapy: 3-5 years then off for many
- Denosumab and PTH effective but less clear when to use, and others (odoncatib, sclerostin antibody) on the way...