Disclosures

Research, advisory panel and/or speakers bureau:
Lilly, Pfizer, BMS, Roche, GSK, AMGEN, Merck, Novartis, UCB, HGS, TEVA, CSL, Astra-Zeneca, Centocor
Hip Fracture: Devastating Event

- Mortality rate same as breast cancer
- 20% excess mortality in the first year
- 50% incapacitation
- 20% of females need assisted living or nursing home
- 80% of 75 yo preferred death to hip fx & nsg hm

• The Osteoporotic Event: Hip Fracture

- Fall (impact at hip) *
- Failure of protective response *
- Insufficient soft tissue energy dissipation *
- Intrinsic bony fragility
- Low bone mass *
- Osteomalacia *
- Long hip axis
- Unrepaired fatigue damage
Normal Bone Remodeling: A Coupled Homeostatic Process

Bone Remodeling

Red = Osteoclasts
Blue = Osteoblasts
AGENDA
Top 10 issues in Osteoporosis 2013

1. DXA & FRAX
2. Calcium & Vit D
3. ONJ
4. Duration of treatment
5. Esophageal cancer
6. Atypical fractures
7. Denosumab
8. PPI
9. Transplantation
10. Organ Specific Issues
#1: Questions about Osteoporosis

When should Bone Density Measurement be performed?
As BMD Decreases  Fracture Risk Increases

• Remember: Only ~1/3 of spine fractures are acutely painful


Osteoporosis
World Health Organization Criteria
Postmenopausal Caucasian with DXA measure

T-score

Normal
≥ -1

Osteopenia
< -1 and > -2.5

Osteoporosis
≤ -2.5

Severe
≤ -2.5 with Fracture

Osteoporosis

• WHO Study Group  JBMR  1994
Bone Mass Measurement Act

Federal Register 1997 for HCFA/CMS
Medicare Osteoporosis Measurement Act 2003

1. Women with estrogen deficiency
2. Spine x-ray evidence of fracture or OP
3. Glucocorticoid therapy (3mos, 5 mg/d)
4. Primary Hyper-PTH
5. Follow-up treatment (23 months unless medical reason for sooner e.g. steroids)
now open at TIBA

with first Mammography Test or first Bone Density/Osteoporosis Tests offering
1/2 hour massage & 1/2 hour manicure
$50.00
or
1/2 hour beauty flash facial & 1/2 hour manicure
$50.00
USPSTF 2010 Recommendations: Screening for Osteoporosis

- BMD testing for women 65 & older
- BMD in 60-64 yo if ↑ fx risk
  - Use WHO FRAX® risk tool
- If clinical based fracture risk of 9.3% then order bone density measurement

Nelson et al Ann Int Med July 2010
WHO Fracture Risk Prediction

FRAX
WHO Fracture Risk Assessment Tool

Calculation Tool

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

Country: US (Caucasian)  Name/ID:  

Questionnaire:
1. Age (between 40-90 years) or Date of birth
   Age: 72  Date of birth:  
2. Sex  Male  Female
3. Weight (kg)  65.77
4. Height (cm)  165.1
5. Previous fracture  No  Yes
6. Parent fractured hip  No  Yes
7. Current smoking  No  Yes
8. Glucocorticoids  No  Yes
9. Rheumatoid arthritis  No  Yes
10. Secondary osteoporosis  No  Yes
11. Alcohol 3 or more units per day  No  Yes
12. Femoral neck BMD (g/cm²)  T-Score -2.2

Weight Conversion
Pounds → Kgs
145  Convert

Height Conversion
Inches → Cms
65  Convert

BMI 24.1
The ten year probability of fracture (%) with BMD
- Major osteoporotic 22
- Hip fracture 9.2
Example of Applying the FRAX Tool

Which Woman is at Higher Fracture Risk?

54 year old smoker with a T-score of -2.0
- 10 year risk of hip fracture = 2.5%; major osteoporotic fracture = 10%

81 year old with no prior fracture with a T-score of -1.4
- 10 year risk of hip fracture = 3.2%; major osteoporotic fracture = 26%
2013 FRAX update (& shortcomings)

1. Current version is 3.8

2. Reduced hip fracture rates due to trends

3. Deliberate exclusion of risk factors & ”dose”:
   - Vitamin D deficiency, falls, dementia, bone turnover, other drugs
   - Number & severity of fractures, dose of ETOH/Tobacco

4. Low spine BMD not included but can compensate for it: Leslie WD, Osteoporos Int (2011) 22:839–847

5. “Untreated” defined:
   - In past year: no ET/HT, SERM, calcitonin, PTH, denosumab
   - No bisphosphonate for the past two years (or oral for <2 months)
   - Calcium & Vit D are not “treatment”

Ettinger et al Osteoporosis Int.2010 (21)25-33
www.shef.ac.uk/FRAX;
www.iscd.org/visitors/resources/fractureriskmodels.cfm
Medicare Payment Rate for DXA Scan 2006-2013

- National Average Medicare Physician Fee Schedule
- Patient Protection and Affordable Care Act
- Temporary Payroll Tax Cut Continuation Act of 2011 (Jan-Feb 2012 Only)
Patient Protection and Affordable Care Act

• Signed by the President March 23, 2010

• Section 3111 set a floor for DXA and VFA at 70% of the 2006 national average for two years

  • For DXA: $98

  • For VFA: $25

• These rates expired in March of 2012
#2: Questions about Osteoporosis

Are calcium & Vitamin D supplements needed?
Calcium

• Essential for prevention and treatment regimens

• Institute of Medicine of the National Academy of Sciences
Recommendations:

  – Over age 50  1200 mg daily

  *Institute of Medicine. 1997. Washington, DC, Academy Press*

• Fracture reduction in some but not all studies
But are calcium supplements safe?

Meta analysis*

- 11 trials, RDBPCT, ≥ 500mg/d elem. Ca, Avg age >40, >1 yr duration
- Excluded if given with Vitamin D (assoc with decreased mortality**)

Conclusion: 30% increased MI risk

- No sig increase in mortality or stroke
- Independent of age, sex, type of ca. suppl.
- Caveats: Not 1° outcome, not diet Ca, no VitD

Calcium: What Is the Right Dose?

- A longitudinal and prospective cohort study, (Swedish Mammography Cohort)
- 61,433 women (born between 1914 and 1948) were followed up for 19 years. 5022 of these women participated in the subcohort.

Conclusions:

- Dietary calcium < 700 mg/day = increased risk of hip fracture, any fracture, and of osteoporosis
- The highest reported calcium intake did not further reduce the risk of fractures of any type, or of osteoporosis, but was associated with a higher rate of hip fracture

Warensjö E et al. BMJ 2011;342:bmj.d1473
Multivariable adjusted spline curve for relation between cumulative average intake of dietary calcium and time to first hip fracture.

Warensjö E et al. BMJ 2011;342:bmj.d1473
What about Vitamin D?

Optimal level: bone health $\geq 32\text{ng/ml}$

IOM: for general pop $=20\text{ng/ml}$

Deficiency: falls, $3.4 \times$ CHF death

Possibly cancer, DM, autoimmune disease, etc., remember Vit E?

Supplements: assoc with decreased mortality

1000 IU daily increase level $\sim 10\text{ng/ml}$

Too much at once? 500,000 IU and falls

Toxicity?

Liu et al, Heart Failure Society of America San Diego Sept 2010
Binkley et al, Endocrinol Metab Clin N Am 2010
Bischoff-Ferrari H. et al. JAMA. 2005;293(18):2257-2264
Vit D: Not everyone responds equally

7 adults age 66-88 given 1600 IU daily

Binkley et al JBMR 2008
2012 Questions about Osteoporosis

Are Bisphosphonates safe?

3. ONJ
4. Treatment duration
5. Esophageal cancer
6. Atypical fractures
### FDA Approved Osteoporosis Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Post Menopausal OP</th>
<th>Steroid OP</th>
<th>Male OP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevention</td>
<td>Treatment</td>
<td>Prevention</td>
</tr>
<tr>
<td>Alendronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Estrogen</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Calcitonin</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
3. What is the Clinical Presentation of ONJ?

• Signs & Symptoms:¹
  – Asymptomatic or
  – Facial pain, jaw pain
  – Soft-tissue swelling, drainage
  – Exposed, necrotic bone
• Cultures: actinomyces²
• Risk factors
  – Cancer & concomitant therapies
  – Poor oral hygiene
  – Smoking
  – Pre-existing dental disease, anemia, coagulopathy, and infection
• Management
  – Povidone-iodine & 0.12% chlorhexidine mouthwash
  – Oral antibiotics and anti-inflammatory drugs
  – Conservative debridement for necrotic tissue

¹ Expert Panel Recommendations for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaws: June 2004
Bisphosphonate-associated Osteonecrois (BON) & American Dental Association

- Oral bisphosphonate users: very low risk for developing BON. Actual incidence unknown; estimates 0 to 1 in 2,260
- Low risk for BON may be minimized but not eliminated.
- Oral health program: sound oral hygiene practices, regular dental care, ... optimal approach to lower risk for BON.
- No validated diagnostic technique for BON risk.
- Discontinuing bisphosphonate therapy may not eliminate any risk for developing BON.

ADA Expert Panel Recommendations 2008
ONJ Comparative Risks

- Any Fragility Fracture (1): 2,668
- Hip Fracture (1): 387
- Anaphylaxis from Penicillin Shot: 32
- Death by MVA: 11
- Death by Murder: 6
- ONJ-Osteoporosis Patient: 0.7
- Death by Lightning Strike: 0.6
- Risk per 100,000 People per Year

(1) Women age 65-69 (from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.)

#4. How long should a patient stay on bisphosphonate treatment?
Cumulative Incidence of Clinical Vertebral Fractures With 10 yrs. Alendronate

**Cumulative Incidence, %**

**Years of Treatment Since FIT**

- **ALN/Placebo**: N: 437, 436, 428, 425, 419, 412, 404, 398, 392, 387
- **ALN/ALN (Pooled)**: N: 662, 660, 651, 646, 638, 631, 626, 615, 606

**Risk Reduction**

1. **55%**
2. **5.4%**
3. **2.5%**
4. **P = 0.013**
5. **ARR 2.9%**

ARR = absolute risk reduction.

2. Data available on request from Merck & Co., Inc. Please specify 20650700(1)–FOS.
What about a bisphosphonate “holiday”?  

• Reasonable to stop bisphosphonates at 5 years & follow Bone Turnover Markers  
• Consider switch to teriparatide for drug holiday from bisphosphonates  
• FDA advisory committee, 9/9/11  
  “… no clear evidence of benefit or harm in continuing the drugs beyond 3-5 years.”

Ott  Clev Clin J Med 2011  
Laster, Tanner  Rheum Dis Clin of NA  2011  
www.fda.gov
#5. Can Bisphosphonates Cause Esophageal Cancer?

Doubled risk to 2/100,000 per 5 yrs if:
10 or more Rx, 3 years or more; Nested case control study, 2,954 cases, 77K controls; 1995-2005 UK GPRD, 7.5 years, not seen for stomach or colon ca

Pros: adequate sample size, control group, and adjustment for covariates (age; sex; smoking status; alcohol drinking; body mass index; diagnosis of osteoporosis; previous fracture; upper gastrointestinal disease; and prescription of non-steroidal anti-inflammatory drugs, corticosteroids, or acid suppressants)

Cons: Did not validate diagnoses by medical records nor provide information on whether drugs were taken according to directions. Previous shorter studies negative.

Green et al BMJ 2010; Wysowski BMJ 2010
Can Bisphosphonates Cause Atypical Femoral Fractures?

September 14, 2010
ASBMR Task Force report to FDA:

1. Change Bisphosphonate Labeling:
   Indicate risk of atypical fractures
   50% have premonitory thigh or hip pain
   25% bilateral involvement

2. Need new codes for research and tracking

3. International registry for tracking

JBMR 2010
Sub Trochanteric Fractures

- 250,000 hip fractures /year US
- 25-80,000 subtrochanteric femoral shaft fractures (SFSF)
- Atypical SFSF, rare

Black et al NEJM 2010
Girgis et al NEJM 2010
Swedish Data Base

- population-based nationwide analyses
- “reassuring for patients who receive bisphosphonates”
- high prevalence of current bisphosphonate use among patients with atypical fractures
- But the absolute risk was small
- Increase in absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7)

Schilcher et al NEJM 2011
Features of Atypical Femoral Fractures

- Rare
- Low energy or spontaneous
- Subtrochanteric, arbitrarily 5cm below lesser trochanter
- Thickened lateral cortex (often bilat.)
- Transverse or spiral fracture
- “beak” associated with stress fracture
- Thigh pain before fracture
- Often 5-10 years of bisphosphonate use

Bisphosphonates & Atypical Femoral Fractures

Mechanism:

• Loss of bone turnover? *Whyte JBMR 2009*
• No link with over suppression *Black NEJM 2010*
• Similar appearance to hypophosphatasia or sclerosing bone disorders (osteopetrosis, pycnodysostosis) *Bukata ISCD Ann Mtg 2010*

*Is this result of a bone condition that has erroneously been diagnosed and treated as osteoporosis or a side effect of the medication?*
Atypical Femoral Fractures: What to do?

- X-ray both femurs
- ?tetracycline labeled bone biopsy
- √ labs: Vit D level, phos, other metabolic bone parameters
- Prophylactic nail?
- Consider teriparatide treatment
What about the newest treatment: denosumab for osteoporosis?
Monoclonal antibody for Osteoporosis: RANKL-Inhibition

OPG  RANKL  RANK

Denosumab

CFU-M

Prefusion osteoclast

Multinucleated osteoclast

Active Osteoclast

Stromal cells

Osteoblast

BONE

Adapted from Boyle et al. Nature. 2003;423:337.
Denosumab sub Q inj. q6mo: Effect on Lumbar Spine BMD

Denosumab 60 mg q 6 months Decreased Incidence of New Vertebral, Nonvertebral, & Hip Fractures

65% reduction new spine fractures

20% reduction new Non-spine fractures

40% reduction new hip fractures
Densoumab

• Indicated for postmenopausal osteoporosis with high fracture risk or failed, or intolerant of other therapies

• Has been given to renal impairment pts. (including ESRD) single dose, without affecting pharmacodynamics or pharmokinetics of the drug; no safety signals

Block et al National Kidney Foundation Mtg, Orlando, FL; April 13-17, 2010
### ‘Adverse Events’

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>New primary malignancy</td>
<td>2.2% (84)</td>
<td>2.4% (93)</td>
</tr>
<tr>
<td>Infections (AEs)</td>
<td>54.4%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Infections (SAEs)</td>
<td>3.4% (133)</td>
<td>4.1% (159)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4% (54)</td>
<td>1.4% (56)</td>
</tr>
<tr>
<td>Coronary heart disease events</td>
<td>1.0% (39)</td>
<td>1.2% (47)</td>
</tr>
<tr>
<td>Atrial fibrillation (SAE)</td>
<td>0.7% (29)</td>
<td>0.7% (29)</td>
</tr>
<tr>
<td>Delayed fracture healing</td>
<td>0.1% (3)</td>
<td>0.1% (2)</td>
</tr>
<tr>
<td>ONJ</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

*No significant reactions to the injection*

RANKL: Immunology & Inflammation

• Overproduction of RANKL seen in Rheumatoid Arthritis and Psoriatic Arthritis

• RANKL in the immune system:
  – Produced by activated T helper cells
  – Maturation & Survival factor for Dendritic cells
  – Regulation of T cell-dependent immune response.
  – Activates antiapoptotic kinase thus regulation of cell apoptosis.
  – May have a role in vascular calcification
  – RANKL deficient mice exhibited defects in early differentiation of T & B lymphocytes, and failed to form lobulo-alveolar mammary structures during pregnancy.

Yeung RSM J Rheumatology 2005 (32) 11: 2072-74
#8: Questions about Osteoporosis

Why the warning about Proton Pump Inhibitors?
2010 FDA Warning: Proton Pump Inhibitors and Increased Fracture Risk

• Revised warning for PPI: possible increased risk of hip, wrist, & spine fractures.
• Based on 7 epidemiologic studies & claims data base analysis (no randomized trials)
• Increased risk after 1-7 years of treatment
  – (note: OTC label for 14 days treatment)
• Risk include age >50, “high dose”, longer duration
• 3 studies: no relation to BMD and PPI use
• 1 study: no fracture risk if pts. have no other risk factors
• WHI: spine but not hip risk, no effect on BMD
• Calcium carbonate absorption? Magnesium? Other?
Transplantation-Induced Osteoporosis (TIOP)

- 3-11% bone loss 1st yr. post transplant
- 14-36% increase incidence of fragility fxs.
- Most fracture occur at relatively normal Bone Mineral Density: Bone Quality?
- Pre-transplant: chronic disease & GCS
- Post-transplant: GCS & calcineurin inhib.
- Controversy: cyclosporine A & tacrolimus
  - tacrolimus better?, may allow less GCS

Carbonare et al Transplantation 2011
Kidney

Bone loss: greatest in 1st 6-18 months, 4-9%
Assoc. with low estradiol & testosterone, not always gender, age, GCS, rjxn, PTH

Fractures: higher in diabetics, more in hips, long bones, feet than spine & ribs. Post transplant 34% increase in hip fractures compared to continued dialysis pts.

Treatment: increase BMD, reduce fx, adjust bisph dose, consider Dmab
#10: TIOP : Organ Specific Issues

Lung -
37% osteoporosis at txp

Bone loss: 2-5% in first year

Fractures: 18-37% in first year, fractures occur at T-score of -1.5; pre txp low BMD & GCS = more fx
#10: TIOP : Organ Specific Issues

Heart-
Bone loss: 3-11% in first year

Fractures: 14-36% in first year, 22-35% longterm, fractures occur at T-score of -1.5;

Treatment: 92% vitamin D deficient
Liver-
Bone loss: 3.5-24% in first year, worse in older pt, post menopause, & less time since txp

Fractures: Highest in 1st 6-12 months, 24-65%, Ribs and spine most common, pre txp vert fx predict increased risk post txp
#10: TIOP : Organ Specific Issues

Bone Marrow –
Usually younger, shorter time from dz onset to txp, less bed rest vs. solid organ txp

Bone loss: 2-9% 1st year, recovers after 12 mos, baseline at 48 mos., GVHD and GCS contributes to loss

Vitamin D: marked decline pots txp, ? Low sun exposure to avoid GVHD
Future Drug Developments

• Anabolics drugs
  – Antibodies or small molecules inhibit Sclerostin or DKK-1

• Cathepsin kinase inhibitors

• Modulation of LRP5 and Wnt pathway
Learn More About Osteoporosis Management

Know How to Read DXA Scans
Know What is Really Happening with Your Patients

The International Society for Clinical Densitometry

www.ISCD.org