Osteoporosis-No Bones About It

Keith A. Reich DO, FACOI, FACR, RhMSUS

Assistant Professor of Medicine
Midwestern University
Fellowship Director
Rheumatology/ St. James Healthcare
DISCLOSURES

- Genentech
- Abbvie
- Exagen
- Crescendo
- Sonosite
One in 3 or 4 women and one in 5 or 6 men, will suffer from an osteoporotic fracture.

Morbidity and mortality associated with hip fractures has considerable medical, social and financial implications.

Fragility fractures are to some extent preventable.
1994 - Development of a diagnostic classification of osteoporosis based on bone density.

WHO-BMD of 2.5 standard deviations or more below the mean peak bone mass as measured by dual X ray absorptiometry
2015 paradigm shift- Focus now is on preventing fragility fractures and their negative consequences rather than treating a low BMD.

BMD now viewed as only one of several risk factors for fragility fracture.
WHY?
If a test has a predictive sensitivity of <5% should we use that test?
US Preventive Services Task Force:

- Osteoporosis screening for women younger than 65 years old whose 10 year predicted risk of major osteoporotic fracture is >9.3%

Crandall CJ. J Bone Miner Res. 2014 Jul;29(7):1661-6
<table>
<thead>
<tr>
<th>FRAX RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Weight/Height</td>
</tr>
<tr>
<td>Previous Fracture</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>Secondary Osteoporosis</td>
</tr>
<tr>
<td>ETOH &gt; 3</td>
</tr>
<tr>
<td>Femoral Neck BMD</td>
</tr>
</tbody>
</table>
WHI OBSERVATIONAL STUDY AND CLINICAL TRIAL

- 62,492 PMW 50-64
  - Sensitivity of only 25.8% for identifying women with MOFs

Women 50-54

sensitivity of only 4.7%!
AGES 50-54

- Osteoporosis Self Assessment Tool - 18.5%
- Simple Calculated Osteoporosis Risk Estimation (SCORE) tool - 22.9%
All 3 of these tools are no better than flipping a coin in identifying younger women for MOF
Osteoporosis a common disease with significant morbidity and mortality and without screening many high-risk patients would go undetected.

A number of effective therapies are available to reduce fracture risk in patients who are diagnosed with osteoporosis.

IN FAVOR OF BMD SCREENING
The risk for most fractures is inversely proportional to BMD.

Overall the specificity was high for all women:
- 83.3% for US TK Force,
- 65.8% for SCORE
- 66.7% for OST
ROMEO: NAY, THAT’S NOT SO
(Act 1 Scene 4)

- Reasons against
  - Only one randomized study did not show benefit (design problems)
  - No discrete value for BMD that discriminates clearly between patients who will fracture and those who will not
  - Single measurement indicates only current BMD, not the anticipated rate of bone loss
  - FRAX contains most known fracture risk factors—does not capture falls—(vigorous?) Does not look at nutrition
Risk analyses of data from 4,957 women, 67 years of age or older, who did not have osteoporosis at baseline and who were followed longitudinally for up to 15 years.

Study of Osteoporotic Fractures (NIH)
How often should one be screened?
SCREENING INTERVAL DEFINITION

- Time for 10% of subjects in each category of osteopenia severity to make the transition from normal BMD, or osteopenia, to osteoporosis before fractures occurred and before treatment for osteoporosis was initiated.
Interval was found to be

- 5 years for moderate osteopenia, and 1 year for advanced osteopenia
- **15 years for normal BMD/mild osteopenia!**

Look carefully at risk factors
Do not be a slave to every two years must get a BMD
Look at the actual numbers, not just average
Treatment Issues
2005- 9 cases of atypical femur fractures while receiving bisphosphonates

Observational studies show a small increase in risk of atypical fracture with bisphosphonate use

CONCERN- “FROZEN BONE”

- BPs affinity for mineralized tissue

- Bind strongly to calcium crystals inducing a cellular effect on the osteoclasts during bone resorption.

- Long half-life, thus affecting osteoclast activity for several months

- By reducing bone turnover, BPs treatment leads to increased bone micro-damage- decreased bone toughness -higher risk of micro-cracks and fractures
Biopsies performed on the iliac crest or at the fracture site showed *low bone turnover* in the majority of patients.

Caution should be used when interpreting a biopsy at the fracture site because the fracture itself speeds up the remodeling processes.

- Shane et. al Bone Miner Res. 2010 Nov;25(11):2267–94
HOW COMMON IS IT REALLY?

- US data: 33,851 patients treated with BPs, only 104 sustained an AFF, with an estimated occurrence of **1.46 per 1,000** treated patients per year.

Compared 39,567 alendronate from 1996 to 2005 with 158,268 untreated control
Subtrochanteric and diaphyseal fractures occurred at a rate of 13 per 10,000 patient/year in untreated women
31 per 10,000 patient/year in women receiving alendronate

International Task Force by the American Society of Bone and Mineral Research on atypical diaphyseal and subtrochanteric femoral fractures 2010, updated in 2013
Long-term use (median 7 yrs.) increases the RR of atypical fractures

Absolute risk is low (3.2 to 50 cases per 100,000 person-years)

Risk may rise with duration of bisphosphonate exposure (100 per 100,000 person-years)
SO WHAT TO DO

- Usually evolve over time and prodromal symptoms may be present
- May be cortical thickening on plan X rays
- Evaluate new onset of groin or mid thigh pain
- Limit Reclast to 5 years
- Limit oral bisphosphonates to <7 years
High risk patient - no clear consensus

- Continue bisphosphonates
- Switch to teriparatide
- Denusomab – few case reports of AF
- Conflicting data on whether to add Teriparatide (Forteo) either to speed healing or to replace a BP

- Shane et al. J Bone Miner Res. 2014;29(1):1
IF ONE DRUG IS GOOD HOW ABOUT TWO?

- PTH plus alendronate - no benefit on BMD
- Risdronate or alendronate 2B
- **Ibandronate** (Boniva) may be more convenient for patients, a reduction in hip fracture risk has not been established.
Bone constantly remodeled/ first broken down then rebuilt

Formation tightly coupled to resorption-to prevent changes in bone mass

Bone disease occurs when formation and resorption is uncoupled
BONE MARKERS

- Helpful in clinical trials to understand mechanism of action of therapeutic agents
- Has not been well established in care of individuals
- Significant variability between labs
- Some indication about future risk for bone loss and efficacy of antiresorptive agents in populations
Rapid Bone Loss and Bone Markers

BONE FORMATION MARKERS

- Bone specific alkaline phosphatase (BALP)
- Osteocalcin
- N-terminal propeptide of type 1 procollagen (P1NP)
BONE RESORPTION MARKERS

- Urinary hydroxyproline
- N-telopeptide of type 1 collagen (NTX)
- C-terminal telopeptide of type 1 collagen (CTX)
- Pyridinoline cross links (PYD and DPD)
LSC defined as a change that is 2.8 times the precision error for the assay

For urinary excretion of NTX, 50% decline is predictive of BMD improvement and fracture risk

CTX, P1NP and ALP, 30% decline
### Bone turnover markers

<table>
<thead>
<tr>
<th>Formation</th>
<th>Assay</th>
<th>Circadian rhythm</th>
<th>LSC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>S*</td>
<td>Y</td>
<td>21 percent</td>
<td>Lack of standardization, rapidly degraded in serum, requires collection on ice</td>
</tr>
<tr>
<td>BALP</td>
<td>S*</td>
<td>N</td>
<td>28 percent</td>
<td>Cross-reactivity with liver isoform (15 to 20 percent)</td>
</tr>
<tr>
<td>P1NP/P1CP</td>
<td>S*</td>
<td>Y</td>
<td>21 percent/24 percent</td>
<td></td>
</tr>
</tbody>
</table>

#### Resorption

| NTX       | U*, S | Y    | 35 percent (S), 70 percent (U) |                                                                 |
| CTX       | U*, S*| Y    | 30 percent (S), 80 percent (U) |                                                                 |
| D-PYR     | U     | Y    | 26 percent                     |                                                                 |
| PYD       | U*    | Y    | 36 percent                     |                                                                 |
| HYP       | U     |      |                                | Reflects bone resorption and dietary intake                      |
| TRACP5b   | S     | Y    | 17 percent                     |                                                                 |

Data from:


Interaction of low bone mineral density and increased bone turnover in predicting fracture risk

In women over age 75 years followed prospectively, the odds ratio for hip fracture was increased 2.7-fold in those with a 1 standard deviation reduction in hip BMD but normal markers for bone turnover (first column), approximately twofold in those with normal BMD but a value for urinary CTX excretion or free D-Pyr excretion above the premenopausal range (second and third columns), and 4.5-fold when both risk factors were present (last two columns).

BMD: bone mineral density; CTX: C-terminal telopeptide of type 1 collagen; D-Pyr: deoxypyridinoline.

<table>
<thead>
<tr>
<th>Population</th>
<th>Odds Ratio (95% CI)</th>
<th>Likelihood Ratio</th>
<th>Probability of Fracture Over 5 y, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women (N = 435)</td>
<td>...</td>
<td>...</td>
<td>12.6</td>
</tr>
<tr>
<td>Women with low femoral neck BMD (T score &lt;=-2.5)</td>
<td>2.8 (1.4-5.6)</td>
<td>2.80</td>
<td>39</td>
</tr>
<tr>
<td>Women with high serum CTX (T score &gt;2)</td>
<td>2.1 (1.2-3.8)</td>
<td>1.70</td>
<td>25</td>
</tr>
<tr>
<td>Women with high urine DPD (T score &gt;2)</td>
<td>1.8 (1.0-3.4)</td>
<td>1.68</td>
<td>24</td>
</tr>
<tr>
<td>Women with low BMD + high CTX</td>
<td>3.8 (1.9-7.3)</td>
<td>3.70</td>
<td>54</td>
</tr>
<tr>
<td>Women with low BMD + high free DPD</td>
<td>2.1 (0.7-6.2)</td>
<td>3.04</td>
<td>45</td>
</tr>
</tbody>
</table>

Markers can also be useful in selected cases to improve the assessment of individual fracture risk when bone mineral density (BMD) measurement by itself does not provide a clear answer.

- Following discontinuation of resorptive treatment
- Compliance
IF USING BTM

- Automated technology
- Same Lab
- Fasting labs, second fasting am urine
- Small variability P1NP, CTD, NTX
- BSALP if no liver disease
Doc, my dentist will not take out my tooth what do I do?
Proposal using serum CTX to assess risk for those on bisphosphonates requiring invasive dental procedures

Recommended withholding procedure when CTX below a certain threshold

Derived from 17 patients who develop ONJ while taking bisphosphonates

Did not measure CTX in a control group of unaffected treated individuals

Bisphosphonates suppress bone resorption (why they work)-BTM (CTX) are reduced

The vast majority do not get ONJ

Impossible to identify a particular CTX level which increases risk of ONJ without a large study

We do not advocate this approach

American Association of Oral and Maxillofacial Surgeons:
Medication-Related Osteonecrosis of the Jaw – 2014 Update
Simov et alVolume 2013 (2013), Article ID 535319, International Journal of Case Reports in Medicine,
FRACTURE PREVENTION TRIAL (FPT)

- 1637 PMW with osteoporotic lumbar fractures
- Forteo 20 & 40 ug vs. placebo for 19 months
- BTM 1, 3, 6, 12 months
Fracture Prevention Trial

Increases in bone formation markers occurred first followed by increases in bone resorption.

Correlation between baseline bone turnover status and Lumbar BMD (20 ug).

1 month PICP and 3 month PINP correlated most with lumbar BMD at 18 months.

PINP to evaluate Forteo treatment

PINP at baseline and after 1-3 months of therapy (Fracture Prevention, Forteo-Alendronate Comparator and Anabolic After Antiresorptive trials)

>10ug/L should continue drug

If less check for compliance etc.

Hey doc, my patient just had a spinal surgery and her spine felt like mush.
Would it help to start Forteo?
- Teriparatide Vs. Calcitonin Vs Placebo
- Rabbits
- Posterolaeral L5-6 intertransverse arthodesis with autologous iliac crest bone graft
FUSION RATES

- Teriparatde - 86.7%
- Calcitonin - 62.5%
- Saline - 50%

■ 57 women
■ Teriparatide and risedronate
■ 2 months prior and 8 months after surgery
■ Posterior lateral fusion with bone graft
- Teriparatide  bone union 82%
- Bisphosponate 0 68%

- Daily teriparatide was superior in promoting bone union

Ohtori et al. Spine; 2012 (37) 23; E1464
44 year old women, active

3rd metatarsal fracture in 2 years. Only one on fifth digit

BMD is normal

No vitamin deficiencies, malabsorption or other risk factors

Do you treat this patient?
- Similar patient 74 years old with foot fracture and no other secondary risk factors
- BMD is normal
- Do you treat this patient?
9704 elderly, Multicenter Study of Osteoporotic Fractures

Women who sustained a foot fracture had a lower bone mineral density in the distal part of the radius and a lower calcaneal bone mineral density.

Conclusions:
- less likely to be physically active
- more likely to have had a previous fracture after the age of fifty

Overall, foot fractures appeared to be typical osteoporotic fractures, whereas ankle fractures occurred in younger women with a relatively high body mass index.
- Retrospective analysis of 68 PMW with metatarsal fractures using heel BMD
- Conclusion: no indication of osteoporosis

CONCLUSION

- Look again at risk fractures
- Also, look at foot structure- abnormal stresses?
Women using proton pump inhibitors (PPI) and women with a previous fracture after the age of 40 had increased risk for attaining new fractures during follow-up.

MALE OSTEOPOOROSIS

- Routine BMD – > age 70 or less with risk factors
- BMD
- Testosterone – Yes
- Low BMD despite testosterone-???

- Endocrine Society Clinical Guidelines
STRONTIUM

- Consists of two atoms of strontium and an organic moiety (ranelic acid)
- Modest effect on bone resorption and little on formation
- Has some increase in BMD