A Bone to Pick: Osteoporosis Risk Assessment
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Objectives
- Review osteoporosis risk assessment:
  - Guidelines
  - Controversies

The Situation
- 1 in 2 postmenopausal women 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.

Direct medical care costs of osteoporotic fractures = $17 billion/yr U.S.

(USPSTF 2011, Blume & Curtis OI 2011)
Definition

- Disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.


Clinical diagnosis is by either....

- Adult hood hip or vertebral fracture in the absence of major trauma (such as motor vehicle accident of multiple story fall)—regardless of BMD value!! or
- BMD T-score ≤ -2.5 at lumbar spine or hip by dual-energy x-ray absorptiometry (DXA)


<table>
<thead>
<tr>
<th>World Health Organization Diagnostic class.</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>


Which test?

- 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.

Which women to screen

- Women 65 years or older (USPSTF 2011, NOF 2014)
- Postmenopausal women aged 50-64:
  - fracture during adulthood, or
  - condition (e.g. rheumatoid arthritis) or medication associated with low bone mass or bone loss (NOF 2014)
- 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. ≥ 0.3%) (USPSTF)


FRAX practical considerations

- 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

Controversy 1: Screening young postmenopausal women

- United States Preventive Services Task Force (USPSTF)
  - Women 65 years or older
    - Women 65+ who do not have a history of major osteoporotic fracture
      in a 10 year or whose 10 year risk of major osteoporotic fracture
      is ≥9.3% (65 year old white woman no other osteoporosis risk factors)

(USPSTF, Ann Intern Med 3/1/2011)

Prior to advent of FRAX

- Osteoporosis Self-Assessment Tool (OST)
- Simple Calculated Osteoporosis Risk Estimation Tool (SCORE):
  - weight
  - age
  - race
  - rheumatoid arthritis
  - non-traumatic hip, wrist, or rib fracture after age 45 years
  - prior estrogen therapy (Lydick 1998)

Objective

- To compare, among postmenopausal U.S. women aged 50-64 years, the ability of the current USPSTF FRAX-based screening strategy with that of SCORE and OST to discriminate between women who did and did not experience incident major osteoporotic fractures over 10 years of f/u.

- No published studies had done this.
Summary

- Among women aged 50-64:
  - The USPSTF strategy only identified about one-quarter of women who went on to experience incident fracture during 10-year follow-up.
  - The low sensitivity was especially apparent for the youngest women (ages 50-54 sensitivity 4.7%, specificity 97%).
  - None of the 3 strategies performed better than chance alone in discriminating between women who did and did not have a subsequent fracture.
- (Crandall et al. J CEM 2014)

Varying cutpoints to obtain sensitivity of ≥ 80%

<table>
<thead>
<tr>
<th>FRAX</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>PPV (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4.81</td>
<td>90.1 (88.4-91.7)</td>
<td>89.8-92.1</td>
<td>8.8 (8.5-9.2)</td>
<td>0.56 (0.54-0.58)</td>
</tr>
<tr>
<td>≥ 4.33</td>
<td>85.2 (84.2-86.1)</td>
<td>84.9-86.4</td>
<td>8.8 (8.5-9.1)</td>
<td>0.56 (0.54-0.58)</td>
</tr>
<tr>
<td>≥ 3.75</td>
<td>84.4 (83.3-85.4)</td>
<td>83.9-84.9</td>
<td>8.8 (8.5-8.6)</td>
<td>0.56 (0.54-0.58)</td>
</tr>
<tr>
<td>≥ 2.98</td>
<td>85.0 (84.4-85.6)</td>
<td>84.1-85.7</td>
<td>8.8 (8.5-8.5)</td>
<td>0.56 (0.54-0.58)</td>
</tr>
<tr>
<td>≥ 1.79</td>
<td>95.0 (94.8-95.2)</td>
<td>94.6-95.4</td>
<td>8.8 (8.5-8.6)</td>
<td>0.56 (0.54-0.58)</td>
</tr>
</tbody>
</table>

(Varying cutpoints to obtain sensitivity ≥ 80%)

Sensitivity, specificity, and AUC values for identifying major osteoporotic fracture (10 years of follow-up), stratified by age

<table>
<thead>
<tr>
<th>Aged ≥64 (n=6879)</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF (FRAX ≥8.9)</td>
<td>7.7 (7.5-8.1)</td>
<td>97.0 (96.6-97.3)</td>
<td>0.54 (0.52-0.55)</td>
</tr>
<tr>
<td>SCORE (≥7)</td>
<td>18.5 (18.2-18.8)</td>
<td>79.7 (78.4-81.0)</td>
<td>0.54 (0.52-0.55)</td>
</tr>
<tr>
<td>ØST (≥2)</td>
<td>22.0 (21.8-22.3)</td>
<td>74.5 (72.8-76.0)</td>
<td>0.54 (0.52-0.55)</td>
</tr>
</tbody>
</table>

(Varying cutpoints to obtain sensitivity ≥ 80%)

<table>
<thead>
<tr>
<th>Aged 50-64 (n=2346)</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>PPV (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF (FRAX ≥8.9)</td>
<td>20.5 (19.8-21.1)</td>
<td>89.5 (88.7-90.3)</td>
<td>8.8 (8.6-8.9)</td>
<td>0.55 (0.53-0.57)</td>
</tr>
<tr>
<td>SCORE (≥7)</td>
<td>22.1 (21.7-22.5)</td>
<td>81.8 (81.2-82.3)</td>
<td>9.0 (8.8-9.3)</td>
<td>0.55 (0.53-0.57)</td>
</tr>
<tr>
<td>ØST (≥2)</td>
<td>36.7 (35.8-37.6)</td>
<td>85.3 (84.7-85.8)</td>
<td>9.3 (9.1-9.6)</td>
<td>0.55 (0.53-0.57)</td>
</tr>
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Among women aged 50-64:

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- The low sensitivity was especially apparent for the youngest women (ages 50-54 sensitivity 4.7%, specificity 97%).
- None of the 3 strategies performed better than chance alone in discriminating between women who did and did not have a subsequent fracture.
- (Crandall et al. J CEM 2014)
Same situation for detecting T-score ≤ -2.5

Osteoporosis Screening in Postmenopausal Women 50 to 64 Years Old: Comparison of US Preventive Services Task Force Strategy and Two Traditional Strategies in the Women’s Health Initiative


Conclusion

- Our findings suggest that fracture risk prediction in young postmenopausal women requires assessment of risk factors not included in currently available strategies.

Bone Mineral Density as a Predictor of Subsequent Wrist Fractures: Findings From the Women’s Health Initiative

Conclusions: The FRAX threshold recommended to identify screening candidates did not identify the majority of women who subsequently experienced wrist fracture.

(J Clin Endocrinol Metab 100: 4315–4324, 2015)
Height loss

- Vertebral fractures detected incidentally by x-ray confer dx of osteoporosis. So….

- √ vertebral imaging (x-ray or on DXA) if any of following:
  - T-score
    - ≤ -1.5 in ♀ ≥ 65-69 y/o, ♂ ≥ 70-79 y/o
    - ≤ -1.0 in ♀ ≥ 70 y/o ♂ ≥ 80 y/o
  - Height loss ≥ 1.5” vs. peak, 0.8” in clinic over time √ yearly!
  - Low-trauma adult fx, recent/chronic prednisone use

(‘National Osteoporosis Foundation Clinician’s Guide to Prevention and Treatment of Osteoporosis 2014’)

Whom to screen

← [Monitoring] → Whom to treat

Monitoring: Measurement error

- 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!


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.

(Am Intern Med 3/1/2011)
Monitoring: Untreated older women
Study of Osteoporotic Fractures postmenopausal women ≥65 y/o without prior fracture

<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 (before having a fracture) was:</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.01 to -1.49</td>
<td>17 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>

(Courtesy of NEJM 2012)

Monitoring: Untreated younger postmenopausal women
Women’s Health Initiative study

If no osteoporosis at baseline then the time period required for 1% of women to experience hip or clinical vertebral fracture was:

<table>
<thead>
<tr>
<th>50-54 years-old</th>
<th>12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59 years-old</td>
<td>11 years</td>
</tr>
<tr>
<td>60-64 years-old</td>
<td>7 years</td>
</tr>
</tbody>
</table>

(vs. osteoporosis at baseline all ages) (3 years)

Women 50-64 y/o without osteoporosis on 1st BMD test are unlikely to benefit from frequent rescreening before age 65. (Gourlay, Overman, Fine, Ensrud, Crandall et al Menopause 2014)

Whom to screen

Monitoring

Whom to treat: NOF 2014

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

Controversy 2: The Wrist Fracture

- Should wrist fractures be an indication for pharmacotherapy too?
- Most common fracture type in perimenopausal women.

- No longitudinal U.S. studies had examined fracture types following wrist fracture in postmenopausal women.
- First step.

Objective

- To determine among postmenopausal women the associations between wrist fracture and subsequent fracture incidence, according to anatomic site and age.

(Crandall et al JCMR 2015)

<table>
<thead>
<tr>
<th>Wrist Fracture</th>
<th>No</th>
<th>Yes</th>
<th>Total N Event</th>
<th>Adj. HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any non-wrist</td>
<td>136,017</td>
<td>28,790</td>
<td>1 (ref)</td>
<td>1.37 (1.29-1.46)</td>
</tr>
<tr>
<td>Spine Fracture</td>
<td>136,017</td>
<td>4,544</td>
<td>1 (ref)</td>
<td>1.46 (1.29-1.65)</td>
</tr>
<tr>
<td>Humerus</td>
<td>136,017</td>
<td>3,676</td>
<td>1 (ref)</td>
<td>1.67 (1.46-1.92)</td>
</tr>
<tr>
<td>Upper extr. (non-wrist)</td>
<td>136,017</td>
<td>6,184</td>
<td>1 (ref)</td>
<td>1.80 (1.62-2.01)</td>
</tr>
<tr>
<td>Lower extr. (non-hip)</td>
<td>136,017</td>
<td>12,718</td>
<td>1 (ref)</td>
<td>1.30 (1.19-1.43)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>136,017</td>
<td>3,186</td>
<td>1 (ref)</td>
<td>1.48 (1.26-1.71)</td>
</tr>
</tbody>
</table>

Mean f/u 11 yrs, adj. falls +. (Crandall et al JBMR, 2015, 30 (11): 2086-2095)
Time to any non-wrist fracture in the presence and absence of initial wrist fracture during the WHI follow-up

(unadjusted cumulative incidence with vs. without prior wrist fracture) (Crandall et al., JBMR, 2015, 30 (11): 2086–2095)

Summary

- Nearly 1 in 5 women with initial wrist fracture went on to experience a subsequent non-wrist fracture over 11 years of follow-up.

- Our results suggest substantial missed opportunity for intervention in the large number of women who present with wrist fractures to prevent subsequent fractures.

Case

- 67 year-old healthy woman (no fracture) baseline screening DXA:
  - femoral neck T-score of -1.7
  - lumbar spine T-score of -1.9.

- The most appropriate next step is:
  1. No further evaluation
  2. FRAX assessment
  3. Prescribe bisphosphonate
  4. Prescribe raloxifene
Case

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  - femoral neck T-score of -1.7
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  1. No further evaluation
  2. FRAX assessment
  3. Prescribe bisphosphonate
  4. Prescribe raloxifene

Future

- Garvan risk calculator
  - Includes falls
  - No longitudinal large U.S. studies vs. FRAX
- FRAX doesn’t work well with DM (numerous studies by Leslie et al)
- FRAX may include falls in future

Ok, so what to do in clinic??

- Women ≥65 y/o:
  - Screen, rescreen based on initial T-score:
    - T-score -1.0 to -1.9: I wait 5 years
    - T-score -2.0 to -2.4: I wait 1-2 years
  - Women aged 50-64:
    - Screen based on FRAX score? Definitely secondary causes!
  - Don’t ignore incidentally-detected vertebral fx
  - Treat women ≥50 y/o if: Hip or vertebral fracture or BMD T-score ≤ -2.5.
  - Treat BMD T-score between -1 and -2.5 selectively based on presence of other fracture risk factors.

- Only 3 in 10 fractures in U.S. 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.
