Osteoporosis in Men
Update Ohio State: November 2011
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Disclosures

- Research Support
  - Novartis
  - Genentech
  - Eli Lilly
  - Amgen
  - Merck
Objectives - Participants should be able to:

- Outline the etiology and risk factors
- Discuss use of fracture risk calculators and other means to identify men at risk
- Describe current Rx and the challenges of using surrogates for patient outcomes in chronic disease studies
OP in Men Evaluation

- Pathophysiology and Classification
  - Primary osteoporosis
  - Secondary osteoporosis
- Choosing men for evaluation
- Laboratory Evaluation
- DXA
Primary Osteoporosis: Type I

- Ages 51-75
- Women >> Men (6:1)
- Trabecular bone lost
- Vertebral and distal radius fractures
- Associated with menopause in women
- ?Cause in men
Type I OP in Men: Potential Causes

- Increased urinary calcium excretion
  - Long term negative calcium balance
  - Often have a history of kidney stones
- Decreased IGF-I with normal GH
- Low free estradiol
- ?Low free 25 (OH) Vitamin D
- Mastocytosis in marrow only
- Cryptic secondary causes
Primary Osteoporosis: Type II

- Age > 70
- Women > Men (2:1)
- Trabecular and Cortical Bone
- Hip and vertebral fractures
- Age-related, other factors
Fx Risk Increases With Advancing Age

Secondary OP: Short List

- GIOP (Glucocorticoid-induced)
- Hyperthyroidism
- Malabsorption
- Alcohol Excess
- Hypercalciuria
- Hyperparathyroidism
- Hypogonadism
Causes of Secondary OP

- Hypogonadism
  - Primary and secondary (organic)
  - Cancer chemotherapy (cyclophosphamide)
  - Androgen withdrawal for prostate cancer
  - ?Testosterone decline with aging

- Chronic diseases, EtOH

- Medications: examples
  - Anti-seizure meds → OP & osteomalacia
  - Neuroleptics (↑ Prolactin), PPIs, TZDs,
  - Anti-depressants?
Hypogonadism & OP

- Organic hypogonadism causes OP
- Testosterone replacement increases bmd
- No Fracture data
- Does the milder decline in testosterone with aging lead to osteoporosis?
Declining Testosterone in Aging

- Common but mild decrease
- Total T not correlated with bone density
- Better correlation of bioavail E₂ & BMD
- Newer studies find some relation with T: data from MrOS suggest men with lower bioavail T may at higher risk for fracture (but were also the men with lowest bioavail E₂ and highest SHBG)

## Secondary Factors in 1571 Older Men (MrOS)

<table>
<thead>
<tr>
<th>Factor</th>
<th>OP %</th>
<th>Non-OP %</th>
<th>aOR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low T</td>
<td>15.2</td>
<td>13.6</td>
<td>1.5 (0.9-2.3)</td>
</tr>
<tr>
<td>Vitamin D deficient</td>
<td>30.7</td>
<td>24.8</td>
<td>1.5 (1.02-2.1)</td>
</tr>
<tr>
<td>eGFR &lt; 60</td>
<td>17.1</td>
<td>17.9</td>
<td>0.8 (0.5-1.4)</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>17.3</td>
<td>12.5</td>
<td>1.5 (0.9-2.3)</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>11.7</td>
<td>9.5</td>
<td>1.2 (0.7-2.0)</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>2.5</td>
<td>2.0</td>
<td>1.4 (0.5-4.0)</td>
</tr>
<tr>
<td>Low E</td>
<td>28.9</td>
<td>18.2</td>
<td>1.8 (1.3-2.7)</td>
</tr>
<tr>
<td>Hyperparathyroid</td>
<td>6.2</td>
<td>3.4</td>
<td>1.9 (0.9-4.0)</td>
</tr>
</tbody>
</table>

HA Fink, ASBMR 2011
Comparative Effects: T & E

- Healthy men ages 20-50
- All received GnRH analog → hypogonadism
- Group A: Different doses of T gel
- Group B: T gel doses + anastrozole
- Serum CTX change determined

J Finkelstein et al, ASBMR 2011
Effect of T/E vs T only

- T/E (i.e. T gel) → ↓CTX with ↑ T gel dose

- T only (i.e. T gel + anastrozole) → slight ↓ CTX (but dose response present)

Conclusions:
- T & E both affect bone turnover in men
- E more important

J Finkelstein et al, ASBMR 2011
$E_2$ may be important, but...

- Assays for estradiol are problematic in the low male range
- What is the reference range?
- Treat men with $E_2$?
- Treat men with SERMs?
- Testosterone Rx as a pro-hormone and hormone?
75 men with mildly low T (ages 64-83)
Received T or placebo for 3 years
One group received T + finasteride
BMD Response to T

Amory et al JCEM 89:503, 2004
T-Rx: 3 Year Study

- Improvement in BMD, muscle mass
- Decreased LDL cholesterol
- No change in HDL cholesterol
- No change in \( \Delta PSA \) or prostate volume
Effects of Testosterone and Metabolites in Men

- Testosterone
  - Dihydrotestosterone
    - Facial & Body Hair
      - Acne
      - Scalp Hair Loss
    - Prostate Growth
  - Muscle Mass
  - Skeletal Growth
  - Spermatogenesis
  - Sexual Function
- Estradiol
  - Bone Formation
  - Breast Tissue
OP in men: Etiology Summary

- Idiopathic OP in middle aged men: Spine
- Aging-associated OP: ↑ “old old” : Hip
- Secondary causes important in men
- Testosterone for organic hypogonadism
- ?T for men with the mildly ↓ T of aging
- Most older men with osteoporosis have normal testosterone level for age – Rx other than T probably indicated
Evaluation other than DXA

- History and physical exam
- Modest laboratory evaluation
  - Serum chemistries
  - 25-OH Vitamin D
  - 24 hour urine calcium
  - CBC, occasional SPEP, UPEP
  - Sometimes: TSH, PTH, Testosterone (+ LH, FSH, prolactin), celiac antibodies
OP and Vitamin D

N=206 men

- Sufficient
- Insufficient
- Deficient

C Ryan, Osteoporos Int 22:1845, 2011
Men referred for Osteoporosis

- About $\frac{3}{4}$ had a secondary cause of osteoporosis
- Many patients had multiple risk factors such as low Vitamin D, smoking, poor calcium intake
- Even those with known secondary OP often had other diagnoses, risk factors identified

CS Ryan, Osteoporos Int 22:1845, 2011
Diagnosis Summary

- Identify high risk men
- History & PE for secondary causes
- Limited lab tests
  - CBC, Chemistries, ?PTH, ?TSH
  - 25 (OH) vitamin D levels
  - Urinary calcium excretion
  - T/LH/FSH
- Find underlying disorders requiring specific treatment
Osteoporosis in Men

- Diagnosis before fracture!
  - Best test still DXA of spine, hip, and often forearm
  - Spine DXA often not helpful
  - Forearm BMD predicts fx well in men
  - Who should get a DXA?
DXA Testing in Men

- What age?
- ACP Guidelines: Men > 70 years old, younger if risk factors present
- NOF: DXA at 70, earlier with risk factors
- USPSTF: Not enough evidence to screen men at age 70
- Case finding: Age an important risk factor
WHO: Validated Risk Factors

- BMD of femoral neck
- BMI (can substitute for BMD??)
- Age
- Prior Fragility Fracture
- Glucocorticoid Exposure
- Parental history of Hip Fracture
- Current Smoking
- Excess Alcohol Intake
- Secondary Causes (e.g. Rheumatoid Arthritis)

www.shef.ac.uk/FRAX/
www.fractureriskcalculator.com
Please answer the questions below to calculate the ten year probability of fracture with BMD.

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: [ ]
   - Date of birth: [ ]

2. Sex
   - Male
   - Female

3. Weight (kg)
   - [ ]

4. Height (cm)
   - [ ]

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 more units per day
    - No
    - Yes

12. Femoral neck BMD
    - Select
    - [ ]

[Calculate]
FRAX® vs. Garvan Calculator

- 81 yo man, 66.2Kg, 168.3cm tall, no other risk factors
  - BMD 0.736 g/cm²
  - 10 yr hip fx risk: 2.4%
  - 10 yr OP fx risk: 6.8%
  - Generally would not treat (U.S.)

- 81 yo man, no falls or fractures
  - BMD 0.736 g/cm²
  - 10 yr hip fx risk: 5.1%
  - 10 yr OP fx risk: 25.3%
  - Treat!
  - Based on Australian population

SK Sandhu, Osteoporos Int
21:863, 2010
Garvan vs. FRAX in Men
% Probability of Fx

SK Sandhu, OI 21:863, 2010
FRAX vs. Garvan

- Why are there such differences?
- Why does Garvan identify more men?
  - Garvan includes falls
  - FRAX includes glucocorticoid use
  - Both rely on femoral neck BMD
Femoral Neck BMD ± OA

BMD

No OA  Mod OA  Severe OA

RK Chaganti OI 21:1307, 2010
DXA in Older Men

- Spine BMD often spuriously high
- Hip BMD also affected by arthritis
- Forearm BMD identifies osteoporosis
  - Hyperparathyroidism
  - Androgen deprivation therapy
  - ?Decrease of T/E_2 with aging?

JM Bruder, Urology 67:152, 2006
Men on ADT: DXA vs FRAX®

- 115 Men sent from GU clinic
- 58% African-American
- Age 77 ± 8 (51-91)
- BMI 28.8 ± 4.9 (17.6-42.4)
- Duration of ADT 3.6 ± 3.3 (0.1-11)
- DXA of spine, hip, forearm

RA Adler, Osteoporos Int 21:647, 2010
Men on ADT: DXA vs FRAX®

- Current Smoking 14.8%
- History of adult fracture 8.7%
- Parental hip fracture 0.9%
- Rheumatoid Arthritis 0%
- Prednisone use 2.6%
FRAX® vs. T-score

- Rx by FRAX w/o BMD
- Rx by FRAX w/ BMD
- Rx by T-score < -2.5
- Rx by T-score < -2.0
- Rx by T-score < -1.5

Percent
BMD vs FRAX Score

Adler RA, Osteoporos Int 21:647, 2010
Screening, diagnosis, evaluation, and treatment of male osteoporosis

Indications present?

yes

Re-assess in 2 years*

no

Central DXA (spine & hip♦)

T-score ≤-2.5 in spine or hip+

Hx, PE & Basic Labs (25OHD, 24 hr U Ca/Cr, SCa/albumin/Cr)
Consider PTH, PO4, TSH, Testosterone, CBC, ESR, AP

GC/ADT/Other 2° causes
Consider evaluation and Rx
Repeat BMD 12 months

Low trauma Fx
Evaluate & consider treatment

No 2° Causes or Fx
Re-evaluate in 2 years
Lifestyle Counseling
Ensure adequate Ca/D

T-score >-2.5 but <-1

T-score ≥-1 in spine or hip

No Osteoporosis
Lifestyle Counseling
Ensure adequate Ca/D

Abnormal

Rx Abnormalities** and/or refer pt

Re-evaluate for Rx of Osteoporosis

Treatment
1. Ensure adequate Ca: 1200 mg/d
2. Ensure adequate Vit D: 800+ IU/d
3. non-pharmacologic interventions to reduce fracture risk
4. Oral bisphosphonates

Refer to metabolic bone specialist if Bisphosphonates are contraindicated, or pt intolerant or not responsive

Glucocorticoid therapy (5 mg/d x > 3 mos)
Low trauma fx after age 45 yrs
Radiographic evidence of vertebral osteopenia or Fx
Androgen deprivation therapy (ADT)/ hypogonadism
Anticonvulsant therapy (>2 yrs)
Gastrectomy/ malabsorption/celiac/bariatric surgery
Excess alcohol consumption
Other conditions/medications*

* See FAQs for explanation
** see FAQs for Rx of low vitamin D
+ for T-score ≤ -2.5 & multiple Fx or T-score ≤ -3.5, consider referral to a metabolic bone specialist
♦ Do a forearm BMD if spine can not be interpreted
VA Algorithm

- DXA in men with following risk factors:
  - Oral glucocorticoid Rx (≥ 5 mg pred X 3 mos)
  - Low trauma fx or fx on spine x-ray
  - ADT/hypogonadism
  - Anti-convulsant Rx
  - Gastrx, malabsorption, bariatric surgery
  - Current smoking, excess EtOH

- VA prefers case finding but age is not considered an indication (yet)
Recommendations for men

- Use FRAX® with caution
- Consider Garvan nomogram for men
- Evaluate high risk men for osteoporosis
- Treat those with osteoporosis based on male database
- Consider treatment in men with osteopenia and other risk factors – clinical judgment still important

www.fractureriskcalculator.com
FDA Approved Rx for Men

- Alendronate
- Risedronate
- Zoledronic Acid
- Denosumab (Men on ADT)
- Teriparatide

Rx studies: T < -2.5 by the male database or T ≤ -2 plus a fragility fracture
ALN increases BMD in Men

Orwoll NEJM 343:604, 2000
ALN Decreases Vert Fx (X-ray)

Fx Incidence

Placebo
ALN

Orwoll NEJM 343:604, 2000
Risedronate ↑ BMD in Men

1 Year % Change in Spine BMD

Placebo

Risedronate
Risedronate ↓ Hip Fx after CVA

- Metacarpal BMD increased more in risedronate men, on both normal and hemiplegic sides
- 10 hip fractures in placebo group, 2 in risedronate group
- RR 0.19 [0.04-0.89]
- NNT 16 [9-32]

Y Sato, Arch Intern Med
165:1743, 2005
IV Zoledronic Acid

- FDA-approved to increase BMD in men and after hip fracture
- Once yearly intravenous infusion
- Good choice for patients with esophageal motility disorders, Barrett’s, GERD not under control
- Potential improvement in adherence to Rx
Response to ZA in men

-1% 0% 1% 2% 3% 4% 5%

Spine | Total Hip | Total Forearm | 1/3 Distal Radius

Overall | Per Year

DA Johnson, Endocr Pract
16:960, 2010
Effect of PTH 1-34 in Men

![Graph showing the effect of PTH 1-34 in men. The graph compares the percent change (mean±SE) over months for different treatment groups: PLACEBO, TPTD20, and TPTD40. The graph indicates that TPTD20 and TPTD40 show a significant increase compared to PLACEBO at all timepoints after baseline, with P<0.001.](image)
Denosumab in Men on ADT

- 3 year study of 734 men on Denosumab vs. 734 men on placebo (All: Cal/D)
- Denosumab increased BMD at:
  - Spine
  - Hip
  - Distal 1/3 radius
- Denosumab decreased vertebral fx (x-ray)
- Denosumab FDA-approved: men on ADT

MR Smith, NEJM 361:745, 2009
OP Rx in Men

- Most p.o. bisphosphonate studies used daily dosing
- Some studies: ↓vertebral fx on x-ray
- Same Δ bone markers as in women
- No studies show ↓clinical fractures
- Thus, all Rx based on “bridging” studies and surrogates for fracture!
Choosing Rx in Men-1

- Problems with calcium & vitamin D
  - Calcium → Constipation
  - Getting enough Vitamin D

- Problems with bisphosphonate adherence
  - No difference in how patient feels
  - Special method of oral Rx

- Rx based on surrogates for fracture
  - How to choose a bisphosphonate?
Choosing Rx in Men - 2

- **Teriparatide Contraindications**
  - H/o radiation to bone
  - Potential for osteoblastic metastases – thus not for patients with prostate cancer
  - Previous/concurrent bisphosphonate Rx may blunt or delay response to PTH

- **Use PTH in drug-naïve patients with severely low bone mass/high fracture risk**
Risk of Fracture in Older Men

- Age 50: Lifetime risk about 13%
- Lifetime atraumatic fracture risk (Dubbo)
  - Age 60: 25.6%
% Patients Who Died at 1 yr (Age 75-84)

Block, Calcif Tissue Int 61:84, 1997

Bar chart showing the percentage of patients who died at 1 year for women and men, categorized by cause (All Cause and Hip Fracture)
Hip Fracture & Mortality

- Women have twice the risk of hip fracture
- Men with hip fracture have twice the risk of dying from a hip fracture
- Thus, the overall mortality rate from hip fracture is about the same in men and women!
Osteoporosis in Men - Summary

- Secondary OP important in men
- Modest evaluation → Dx, risk factors
- Large holes in knowledge base
- Role of testosterone still unclear
- FRAX®/Garvan nomogram may help
- Treatment options increasing
- Need to find those men at highest risk
Men Fracture Too!
Conclusion

- Osteoporosis is not just a disorder of postmenopausal women
- Men with osteoporosis need to be identified
  - This is a silent disorder with fatal consequences
- Finding cases, diagnosing and treating OP in men will save lives and money

F. Borgstrom et al, Bone 34:1064, 2004