The Diagnostic Evaluation of Patients with Low Bone Mass

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UW Osteoporosis Clinical & Research Program
Investigate

Look for underlying diseases causing or contributing to low bone mass
The Pathogenesis of Idiopathic Postmenopausal Osteoporosis

Before Menopause: “less than optimal peak bone mass”
- Heredity accounts for 50-70% of peak bone mass
- Diet
- Exercise
- Other factors

Increasing Age: 1% bone loss per year after age 30-35 years

Following Menopause: estrogen deficiency results in bone resorption and decreased bone formation

Diagnostic Caveats

T-score -2.5 or less does not always mean osteoporosis

– Example: 65 year old woman with compression fracture and T-score –2.8
Diagnostic Caveats

Low T-score does not identify the cause of osteoporosis

– Example: 55 year old woman with itchy rash, iron deficiency and low vitamin D levels
Why Evaluate for Secondary Causes?

- Remedial diseases are not missed
- Appropriate therapy is chosen based on the underlying etiology of bone loss
Laboratory Menu

- CBC
- Creatinine
- AST
- Alkaline phosphatase
- Calcium
- Phosphorus
- Intact PTH
- 25(OH)D
- TSH
- 24 hour urine calcium

Other selected tests:
- Celiac sprue panel
- Sacroiliac films
- Cortisol levels
- Markers of bone turnover
- Others
Primary Hyperparathyroidism

- 121 subjects with 1° Hyperparathyroidism, half undergo surgery and half do not

- Surgical correction of the condition improves bone mass within one year

- In those undergoing surgery,
  - Lumbar Spine bone mass + 8%
  - Femoral Neck bone mass + 6%

Possible Flags Prompting a Work Up for Secondary Osteoporosis in Postmenopausal Women

- Z-score < -1
- Z-score < -2
- T-score < -3
- Cortical > trabecular bone loss
- Osteoporosis with > 1 fracture
- Failure of antiresorptive therapy to improve bone mass or prevent a fracture
- All women

There is no consensus on the appropriate work up for secondary causes of osteoporosis in older women.
What is in the Literature?

- How often do patients have an identifiable cause of bone loss?
- What is the basic laboratory evaluation for a person with bone loss?

A recent review article states that 20% of women have a secondary cause of osteoporosis

(Fitzpatrick, Mayo Clinic Proceedings)
• Retrospective study of women referred to the Brigham and Women’s OP Clinic
• 237 women, ~200 postmenopausal
• Mean age 56 (±13.8) years
• Mean Lumbar T score –2.35, Z –1.34
• Mean Femoral Neck T score –3.25, Z –1.28
• Labs: Intact PTH, 25(OH)D, TSH, 24 hour urine calcium, serum and urine electrophoresis

Haden, Calcif Tissue Int 1999;64:275-279
By History Alone, 54% Had A Cause of Bone Loss other than Menopause

Haden, Calcif Tissue Int 1999;64:275-279
38% with Secondary Cause of Osteoporosis by Laboratory Testing

- 16% had vitamin D Deficiency \([25(OH)D < 15 \text{ ng}]\)
- 15% had high urine calcium
- 12% had 1\(^o\) or 2\(^o\) Hyperparathyroidism
- 4% had hyperthyroidism
- one patient with myeloma
Summary of Brigham Experience

- 54 % have historical cause of osteoporosis
- 38 % have laboratory cause of osteoporosis

Steroids
Thyroid Disease
Menopause before Age 40
Low Vitamin D Levels
Mount Sinai Hospital, 1992-1996

- Cross sectional chart review study
- 508 women referred to OP Clinic for evaluation of newly discovered OP

Tannenbaum, J Clin Endocrinol Metab 2002;87:4431-4437
Women in the Study

Study Synopsis

Eligible Subjects
- Complete labs available
- n=173

Ineligible Subjects
- Incomplete labs
- n=136

Perimenopausal or postmenopausal women over age 45
- BMD T Score < -2.5
- n=664

No previous known contributors to osteoporosis based on interview
- n=309

A history of diseases and medications affecting bone metabolism
- n=335

Tannenbaum, J Clin Endocrinol Metab 2002;87:4431-4437
Cause of Osteoporosis by History: 53%

- 27% Steroids
- 16% Early Menopause
- 14% Alchol/Liver
- 10% Chemo/Seizure
- 9% Miscellaneous
- 9% Thyroid/Parathyroid
- 8% Malnutrition
- 7% Immobility

Tannenbaum, J Clin Endocrinol Metab 2002;87:4431-4437
173 Subjects Underwent Laboratory Testing

- Subjects with known causes of bone loss by history were excluded
- CBC, chemistry profile, 24 hour urine calcium, 25OHD, PTH

Tannenbaum, J Clin Endocrinol Metab 2002;87:4431-4437
46% with Metabolic Condition

- Vitamin D Insufficiency: 34%
- Vitamin D Deficiency: 16%
- Hypercalciuria: 12%
- Malabsorption: 5%
- HPT: 5%
- Hyperthyroidism: 20%
- Miscellaneous: 8%
Predictors of Metabolic Disease

- No relationship with...
  - T score
  - Z score
  - Age
  - Weight
  - History of nephrolithiasis, hypertension, family and personal fragility fracture

Tannenbaum, J Clin Endocrinol Metab 2002;87:4431-4437
Evaluation for Secondary Causes of Bone Loss in Kansas

• 180 women with osteoporosis
• Detailed interview and examination
• Laboratories: CBC, TSH, 25(OH)D, urinalysis, and 24 hour urine calcium

Johnson, Arch Intern Med 1989;149:1069-1072
Underlying Cause in 46%
Osteoporosis is often Multifactorial

- Single cause in 47 of 83 women
- Two causes in 29 women
- Three causes in 7 women

Johnson, Arch Intern Med 1989;149:1069-1072
## Summary of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>% with Cause</th>
<th>Top Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigham Boston</td>
<td>237</td>
<td>54%</td>
<td>Steroids, Hyperthyroid, Premature Ovarian Failure</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>664</td>
<td>62%</td>
<td>Steroids, Premature ovarian failure, Vitamin D, Hypercalciuria</td>
</tr>
<tr>
<td>New York City</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kansas</td>
<td>180</td>
<td>46%</td>
<td>Steroids, Premature Menopause</td>
</tr>
</tbody>
</table>
About 50% of Women Have a Specific Cause of OP

Steroids: 24%
Premature menopause: 21%
Hyperthyroidism: 6%
Inadequate Vitamin D: 9%
Hypercarniuria: 9%
The Cost Effective Strategy

Urine and serum calcium, PTH and TSH (*among women on replacement*) diagnosed 85% of women with secondary causes

**Cost**

$75 per patient screened

*JCEM 2002;87:4431-4437*
# Treatment of Common Causes of Osteoporosis in Women

<table>
<thead>
<tr>
<th>Cause</th>
<th>How Many?</th>
<th>Therapy?</th>
<th>BMD Increase?</th>
<th>Fracture Decrease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>~21 %</td>
<td>Alendronate, Risedronate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Early Menopause</td>
<td>~21%</td>
<td>Bisphosphonates, SERMS, teriparatide</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>~6%</td>
<td>Treat thyroid disease</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>~9%</td>
<td>Vitamin D</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>9%</td>
<td>HCTZ 25 mg bid</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>
men AND osteoporosis
Misconceptions about Male Osteoporosis

- Male osteoporosis is uncommon
- Men do not require osteoporosis screening

- One in four men aged 50 will experience a fragility fracture in remaining life
- The ISCD recommends a screening bone density study for all men at age 70
Osteoporosis is a woman's disease.

[Image of a woman with a saxophone, suggesting the connection between music and bone health.]
Osteoporosis in Men
University of Pennsylvania

- 47 men with low trauma fracture (91%) or radiographic osteopenia (9%)
- All men: interview, radiographs, DXA, bone biopsy, and labs
- Fasting blood for CBC, SPEP, calcium, phosphorus, albumin, creatinine, alk phos, electrolytes, liver and thyroid tests, vitamin D, intact PTH, testosterone
- Fasting urine calcium, phosphorus, creatinine, free cortisol

64% of Men had Specific Cause of Bone Loss

- Steroid Use: 17%
- Hypogonadism: 15%
- Alcohol: 15%
- Miscellaneous Causes: 17%
- Primary Osteoporosis: 36%
Miscellaneous Causes

- Osteomalacia (4)
- Hyperthyroidism (2)
- Anticonvulsants (1)
- Multiple Myeloma (1)
Barcelona, Spain

- 81 men with osteoporosis, defined by low bone mass or low trauma compression fracture
- All patients: interview plus CBC, chemistry profile, 24-hour urine calcium
- Selected patients without obvious cause: testosterone, PTH, cortisol, 25(OH)D, thyroid tests

Brit J Rheumatol 1995;34:936-941
Spain: 88% had Secondary Osteoporosis

- Hypogonadism: 10%
- Steroids: 12%
- Alcoholism: 12%
- Multiple Causes: 12%
- Miscellaneous: 12%
- Primary Osteoporosis: 27%
- Hypercalciuria: 15%
<table>
<thead>
<tr>
<th>Spain: Miscellaneous Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorption</td>
</tr>
<tr>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Cushings syndrome</td>
</tr>
<tr>
<td>Addison’s Disease</td>
</tr>
<tr>
<td>Neurologic Disorders</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>OI</td>
</tr>
<tr>
<td>Hematologic Disorder</td>
</tr>
</tbody>
</table>
Symptoms of Osteoporosis

- 85% of men reported back pain
- 69% had vertebral crush fractures
- Mean 25(OH)D was 18.2 ng in those with secondary causes, 13.3 ng in those with “idiopathic” osteoporosis, without an increase in PTH
- Men with hypogonadism did not volunteer symptoms of it
Men with Osteoporosis

Three Most Likely Causes

Steroid Therapy (12-17%)
Hypogonadism (15%)
Alcohol Use (12-15%)
Work Up of Osteoporosis in Men

• Ask men about use of steroids, alcohol
• Ask men about symptoms of hypogonadism
• If no obvious cause by history, a first morning testosterone level might be the most appropriate single test

Additional tests if history and serum testosterone are normal
Questions for Hypogonadism

1. Do you have a decrease in libido?
2. Do you have a lack of energy?
3. Do you have a decrease in strength or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

“Yes” to questions 1 or 7, or to three of the above, are highly sensitive and specific for low testosterone levels.
• Both women and men often have a specific cause of osteoporosis that can be identified
• If a secondary cause is identified, this can be directly addressed, leading to
  – More effective increases in bone mass
  – Different therapeutic options or…
  – A combination of therapies that best serves the patient
# Most Common Causes of Osteoporosis

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Steroids</td>
</tr>
<tr>
<td>Premature menopause</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Vitamin D</td>
</tr>
</tbody>
</table>
Chronic Kidney Disease (CKD)
Monitoring for Renal Osteodystrophy at Various Stages of CKD

- Monitor PTH
- Check Vit D Status
- Pi Restriction
- Pi Binders

- Treat Acidosis
- Avoid Al (Vit D Sterols)

Consider:
- Vit D Sterols
- Dialysate Ca
- Monitor Al
- Bone Bx
- PTX
- Dialysis regime
- Calcimimetics

Target for Intact PTH

Target for PTH 1-84

Slide courtesy of Kevin Martin
K/DOQI Guideline 1
Evaluation of Calcium and Phosphorus Metabolism and Bone Disease

The target plasma intact PTH in the various stages of CKD are:

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (ml/min/1.73 m²)</th>
<th>Target “intact” PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30–59</td>
<td>35-70 pg/ml (OPINION)</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>70-110 pg/ml (OPINION)</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
<td>150-300 pg/ml (EVIDENCE)</td>
</tr>
</tbody>
</table>
Renal Osteodystrophy

**Low Turnover**
- Osteomalacia
- Aluminum related bone disease
- Adynamic bone disease

**High Turnover**
- Secondary Hyperparathyroidism (osteitis fibrosa)

Normal bone
Mild or Mixed Lesion
Renal Osteodystrophy

Calcium, Vitamin D, Aluminum

- Adynamic
- Normal
- Mild
- Osteomalacia
- Mixed Lesion: Osteomalacia + HPT
- Osteitis Fibrosa

PTH
Treatment in CKD

• Oral 1,25(OH)D therapy (e.g. calcitriol) is recommended for
  – patients with stage 3-4 CKD and
  – 25(OH)D > 30 ng/ml and
  – iPTH above goal
Investigate

Identify major risk factors for fracture

Note- some of these risk factors are well established for postmenopausal women, but not necessarily for pre-menopausal women or for men
5 Major Risk Factors for Osteoporosis and Fracture

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
5 Major Risk Factors for Osteoporosis and Fracture

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
Prior Fragility Fracture

- anterior-posterior view: adult
- acetabulum
- femoral head
- fracture
- femur
Prevalent Vertebral Fracture Predicts Risk of Future Hip Fracture

Physical Exam Findings Suggesting Compression Fracture

- Rib-pelvis distance < 2-3 finger breadths
- Tooth count < 20
- Wall-occiput distance: inability to touch occiput to wall when standing with back and heels against the wall
- Height Loss
Risk of Another Vertebral Fracture is Higher in the Year Following a New Fracture

* p<0.05, vs. patients with no prevalent vertebral fractures (12-Fold Increased Risk)

Lindsay, et. al., JAMA 2001; 285: 320-23
Identifying Patients with Prior Spine Fractures

• Vertebral compression fractures are the most common form of osteoporotic fracture
• Two in three vertebral fractures are painless
• If my patient experiences a painless vertebral fracture, how can I tell?
Signs of Silent Osteoporotic Compression Fractures

• Height Loss: each complete compression fracture causes ~1 cm loss in height
• Dorsal kyphosis
• Ribs rest on pelvis
• Abdominal distention

## Height Loss and Odds Ratio for Compression Fracture

<table>
<thead>
<tr>
<th>Height loss, cm</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>1.8</td>
<td>1.1-3.1</td>
</tr>
<tr>
<td>1-2</td>
<td>5.1</td>
<td>3.0-8.7</td>
</tr>
<tr>
<td>2-3</td>
<td>13.5</td>
<td>6.9-26.3</td>
</tr>
<tr>
<td>3-4</td>
<td>19.1</td>
<td>8.1-45.0</td>
</tr>
<tr>
<td>&gt;4</td>
<td>20.6</td>
<td>9.3-45.8</td>
</tr>
</tbody>
</table>
Height Loss
L4 Compression Fracture
5 Major Risk Factors for Osteoporosis and Fracture

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
Family History of Fracture

- Family history of wrist fracture increased a woman’s risk of wrist fracture
  - Maternal wrist fracture = 1.52 fold risk
  - Paternal wrist fracture = 2.41 fold risk

- Family history of hip fracture increased a woman’s risk of hip fracture
  - Maternal hip fracture = 1.48 fold risk
  - Sister’s hip fracture = 1.83 fold risk
  - Brother’s hip fracture = 2.26 fold risk

Fox, Osteoporosis Int 1998;8:557-562
Family History of Fracture

- Family history of osteoporotic fracture at the wrist, hip or spine was associated with a **2-fold** higher risk of osteoporotic fracture among 1,003 Caucasian women aged 45-64 years.

- A positive family history of wrist fracture increased a woman’s own risk of wrist fracture by over **4-fold**

Family History of Fracture
Summary of Two Studies

• The higher risk of fracture based on family history remained true and unchanged, after controlling for bone density
• A site-specific risk of fracture was noted
• A male relative with fragility fracture also increased a woman’s risk of fragility fracture
• The overall risk of fracture was about two fold higher when a family member had experienced fragility fracture
Family History of Fragility Fracture

- Did any person in your family break a hip or wrist?
- Did any of your relatives have a “widow’s hump” or break a spine bone?
5 Major Risk Factors for Osteoporosis and Fracture

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
Low Body Weight
Low Body Weight

Low body weight is one of the best single predictors of low bone mass and future fracture.

The full mechanism by which low body weight increases risk of osteoporosis and fracture is unknown.

The cut off for “low” body weight differs among published guidelines:
- Weight < 154 pounds  USPTF
- Weight < 127 pounds  NOF
Low Body Weight as a Risk Factor for Hip Fracture in Women

• Women aged > 50 with hip fracture were identified among six centers in Europe
• Two control women of the same age were selected for each woman with hip fracture
• A structured interview recorded various risk factors for osteoporosis and fracture
• The study identified ≈ 2,000 with hip fracture and 3500 controls

Johnell, J Bone Miner Res 1995;10:1802-1815
Relative Risk of Hip Fracture According to Weight

Risk plateaus beyond 155#

It doesn't help to weigh more than ~155#
5 Major Risk Factors for Osteoporosis and Fracture

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
Tobacco and Bone Density

• Meta-analysis of 29 studies on smoking
• Smoking has no material effect on bone density in pre-menopausal women
• Bone density was lower in postmenopausal women who smoked, compared to nonsmokers
• For every 10 years increase in age, bone density of smokers fell by about 2%

Law, BMJ 1997;315:841-846
Tobacco and Fracture

• A meta-analysis of 19 studies reporting fracture showed a higher risk of hip fracture in smokers compared to nonsmokers that was
  –  17 % higher at age 60
  –  41 % higher at age 70
  –  71 % higher at age 80
  – 108 % higher at age 90
Tobacco and Fracture

• The higher risk of fracture in smokers was independent of
  – body mass index
  – exercise
  – use of estrogens

• There was a dose-response relationship with higher risk of fracture in heavier smokers

• One in 8 hip fractures could be directly attributed to smoking, after control for other risk factors
5 Major Risk Factors for Osteoporosis and Fracture

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
Fracture Risk with Steroids

- Retrospective cohort study using UK General Practice Research Database
- Controls matched to steroid users for age, gender
- 244,235 steroid users and 244,235 controls
- Mean age 57 years, 59% female
- Most frequent indication for steroids: respiratory disease (40%)

Van Staa TP, JBMR 2000;15:993-1000
Fracture Risk During Steroid Therapy

<table>
<thead>
<tr>
<th>Fractures</th>
<th>&lt; 2.5 mg</th>
<th>2.5-7.5 mg</th>
<th>&gt; 7.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>0.99</td>
<td>1.77</td>
<td>2.27</td>
</tr>
<tr>
<td>Vertebral</td>
<td>1.55</td>
<td>2.59</td>
<td>5.18</td>
</tr>
</tbody>
</table>

Van Staa TP, JBMR 2000;15:993-1000
Relative Risk of Fracture after Cessation of Steroids

Suggests osteoblast recovery
Fractures Occur at Lower T-scores when Taking Steroids

Correct Causes of Bone Loss and Fracture Risk Factors

- Stop steroids or minimize dose
- Stop use of tobacco products
- Minimize falls
- Correct any underlying conditions
  - Hyperparathyroidism
  - Vitamin D deficiency
  - Hypercalciuria
5 Major Risk Factors for Osteoporosis/Fracture: Women

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
5 Major Risk Factors for Osteoporosis/Fracture in Men

1. Adult fracture
2. Fragility fracture in 1st degree relative
3. Weight <127#
4. Current smoking
5. Oral steroids > 3 months
Thank you for your attention

Questions?