Osteoporosis and Metabolic Bone Disease

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Intensive Review of Internal Medicine, July 18, 2012

Disclosures

- Stock Ownership: GE, Amgen
- Eli Lilly: research placebo and medication for DOD grant

“Fractures due to bone disease are common, costly, and often become a chronic burden on individuals and society”

Objectives

To review and understand:
- Factors that contribute to the development of and diagnostic evaluation and treatment of:
  - Osteoporosis
  - Osteomalacia
  - Paget’s Disease

Fractures Increase with Age

Incidence/100,000 person-year

- Hip
- Vertebrae
- Colles’

Cooper et al. JBMR; 1992
Cooper et al. Osteo Int 1992

Osteoporosis Is a Silent Disease Until There is a Fracture

- Increased Osteoclastic Bone Resorption?
- Decreased Osteoblastic Bone Formation?
Osteocytes, Osteoclasts

Who Should Have A Bone Density Test?

**Women and Men: 2008**

- Age 50-70 with concern regarding risk factors
- Women: age ≥ 65 without risk factors
- Men: age ≥ 70 and older
- Women or men with known risk factor

**Medicare Coverage 1998**

- Vertebral deformity / fracture
- Hyperparathyroidism
- Glucocorticoid therapy (≥ 5.0 mg/d for ≥3 months)
- Monitor response to therapy
- Medical necessity

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**World Health Organization Bone Density Criteria-1994**

- **T-score**
  - Osteopenia (Low Bone Mass): -1.0 to -2.5 SD
  - Osteoporosis: ≤ -2.5 SD

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**Fracture Risk Assessment (FRAX®)**

- Developed by WHO integrates Risk Factors and Femoral Neck BMD

  - Country Code (Ethnicity): __________
  - Name/ID: __________

  - Questionnaire:
    1. Age (between 40 and 90) or Date of Birth
    2. Sex: Male: ___ Female: ___
    3. Weight (KG): ___
    4. Height: ___
    5. Previous Fracture: No: ___ Yes: ___
    6. Parent Fractured Hip: No: ___ Yes: ___
    7. Currently Smoking: No: ___ Yes: ___
    8. Glucocorticoids: No: ___ Yes: ___
    9. Rheumatoid arthritis: No: ___ Yes: ___
    10. Secondary Osteoporosis: No: ___ Yes: ___
    11. Alcohol >3 units per day: No: ___ Yes: ___
    12. Femoral neck BMD:___

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**World Health Organization**

- 50% of Fractures Occur in Non-Osteoporotic Women: Assessment of Risk Factors are Important (NORA DATA)

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**Hip Bone Density by DXA**

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**Matsuo, Koichi. IBMS BoneKEy 9, 2012 Article number: 39**
Perspective: FRAX® Facts

- FRAX® has greatly enhanced treatment of women and men with osteopenia and at risk for fractures
- Secondary causes of osteoporosis included in FRAX® are: Type 1 diabetes, osteogenesis imperfecta, longstanding hyperthyroidism, hypogonadism, premature menopause, chronic malnutrition, malabsorption or liver disease
- If the femoral neck BMD or T-score is entered into the algorithm, secondary causes of osteoporosis are not accounted for in fracture risk estimates
- Spine BMD and a number of other clinical risk factors are not included in the algorithm

Who Should Have FRAX Calculation?

- Postmenopausal (not premenopausal) women age 40 years and older and men age 50 years and older with osteopenia to estimate fracture probabilities.
- FRAX® has not been validated for use on patients currently or formerly treated with pharmacotherapy for osteoporosis

Evaluation of Secondary Causes of Osteoporoses Important

Secondary osteoporoses can lead to:
- Skeletal changes that may be reversible
- Reduced acquisition of peak bone mass, a determinant of osteoporosis later in life
- Increased bone loss and elevated fracture risk

Medical Disorders or Medications Associated With Low Bone Mass and/or Osteoporosis.

- Endocrinological abnormalities
  - Vitamin D deficiency, glucocorticoid excess, thyroid excess, hypogonadism, anorexia, athletic triad, prolactinomas, hyperparathyroidism (primary or secondary), hypercalcemia
- Process affecting the marrow
  - Multiple myeloma, mastocytosis, leukemia, Gaucher’s disease
- Chronic Kidney Disease (CKD)
  - Osteoporosis And Other Metabolic Bone Diseases
- Connective tissue disorders
  - Osteogenesis imperfecta, homocystinuria, Ehlers-Danlos syndrome

One Third of The Population Deficient Vitamin D Levels:

High Risk Individuals:
- Elderly
- Hip Fracture Patients
- Obese
- Black/African American

Vitamin D Deficiency and Hip Fractures: BWH and Baltimore

<table>
<thead>
<tr>
<th>25 Hydroxyvitamin D Levels (ng/ml)</th>
<th>&lt;20 deficiency</th>
<th>&lt;32 insuff</th>
<th>&gt;32 suff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston 1999</td>
<td>77%</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Baltimore</td>
<td>89%</td>
<td>99%</td>
<td>1%</td>
</tr>
</tbody>
</table>

LeBoff MS, Kohlmeier L, Weight J, Glowacki J, JAMA 1999

Oral Glucocorticoids Increase Fracture Risk

Oral Glucocorticoids

Increase Fracture Risk

Daily Oral Glucocorticoid Use

Relative Risk


Systemic Mastocytosis: 26 Year-Old Student with Skin Lesions and Low Bone Density

Chronic Kidney Disease and Fractures

- Secondary Hyperparathyroidism: fracture
- Osteomalacia: fracture
- Mixed Renal Bone Disease: fracture
- Aluminum Bone Disease: may fracture
- Adynamic Bone Disease: small fracture risk
- Osteoporosis: fracture

Miller PD. Current Osteoporosis Reports 2005

Medical Disorders or Medications Associated With Bone Loss and Osteoporosis

Gastrointestinal diseases
- Gastrectomy, primary biliary cirrhosis, celiac disease

Rheumatologic disorders
- Ankylosing spondylitis, rheumatoid arthritis, osteoarthritis

Medications
- Aromatase inhibitors, heparin Anticonvulsants, methotrexate, cytotoxan and GnRH agonists (hypogonadism), lithium, cyclosporine, premenopausal tamoxifen, serotonin reuptake inhibitors, proton pump inhibitors

Gastrointestinal Disorders and Metabolic Bone Disease

- Inflammatory Bowel Disease: Ulcerative Colitis, Crohn’s Disease
- Celiac Disease (Sprue)
- Postgastrectomy
- Weight Loss, Bariatric Surgery

CN Bernstein, WD Leslie, MS LeBoff. Gastroenterology 2003; 124:795
Summary: Yearly Bone Loss Associated with Breast and Prostate Cancer Therapies

<table>
<thead>
<tr>
<th>Cancer treatment-Associated bone loss</th>
<th>Normal Men</th>
<th>Late menopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menopausal women</td>
<td>2% (range 1-3%)</td>
<td>2-2.6%</td>
</tr>
<tr>
<td>Androgen-Deprivation Therapy in Prostate</td>
<td>4.6%</td>
<td>Andrographin/Anatomize inhibitor (AI) therapy</td>
</tr>
<tr>
<td>Ovarian failure secondary to chemotherapy</td>
<td>7.9%</td>
<td>Aromatase inhibitor (AI) therapy</td>
</tr>
<tr>
<td>Ovarian failure from Oophorectomy (premenopausal)</td>
<td>10.7%</td>
<td>2% (range 1-3%) Early menopausal women</td>
</tr>
<tr>
<td>Lumbar spine BMD loss at 1 year (%)</td>
<td></td>
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</tr>
</tbody>
</table>

Evaluation of Secondary Osteoporosis

- Detailed history, calculated calcium intake, and physical examination
- Family History
- Bone Density testing
- Laboratory Tests

Cost of Potential Screening

- Serum calcium, 25-hydroxyvitamin D, 24-hour urine calcium, PTH, and TSH for adults on thyroid hormone identified 98% of the cases of secondary osteoporoses at low cost ($116, 1999 Medicare reimbursement)

Osteoporosis Evaluation (Including a Low Z-score = -1.5 or -2.0)

**Laboratory Tests:**
- Calcium
- Phosphorus
- Creatinine
- alkaline phosphatase
- liver tests
- CBC
- 25-hydroxyvitamin D
- 24-hour urinary calcium
- =TSH
- PTH (if calcium high)
- serum testosterone (men)

**Selected cases:**
- More definitive tests for endocrine (Cushing’s), infiltrative (tryptase for mastocytosis), neoplastic (serum protein electrophoresis), gastrointestinal (tissue transglutaminase and IGA for celiac disease), and genetic disorders
- Markers of bone turnovers

Who Should Be Treated?

Postmenopausal woman or man 50 or older and:

- Osteoporosis with T-score ≤ -2.5
- Fragility fracture at the hip or spine (clinical or morphogenic)
- Osteopenia and a 10-year risk for hip fracture of ≥3% or 10-year risk for major osteoporotic fracture of ≥20% (clinical spine, forearm, hip or shoulder fracture)
- Clinical judgment is important for treatment decisions
Calcium and Vitamin D and Skeletal Health: Institute of Medicine 2011

Recommendations for Adults
- Calcium: ideal intake from diet, supplement if necessary
- Vitamin D 600 IU to 1,000 IU daily
  - More needed in high risk individuals (2,000 IU/d being investigated in the VITAL trial)
- Regular weight-bearing and muscle-strengthening exercise, fall prevention/intervention and balance training

FDA-Approved Osteoporosis Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose &amp; Administration</th>
<th>Fracture Risk Reduction</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>70 mg PO once weekly</td>
<td>Vertebral, non-vertebral, hip</td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>5 mg PO once daily</td>
<td>Vertebral, non-vertebral, hip</td>
<td></td>
</tr>
<tr>
<td>Zoledronic Acid (ZA)</td>
<td>5 mg IV once yearly</td>
<td>Vertebral, non-vertebral, hip</td>
<td></td>
</tr>
<tr>
<td>SERMs (Selective Estrogen Receptor Modulators)</td>
<td>45 mg PO once daily</td>
<td>Vertebral</td>
<td>Hot flashes, deep vein thrombosis (rare)</td>
</tr>
<tr>
<td>PTH (Parathyroid Hormone)</td>
<td>39 mcg SC daily (for maximum of 2 years)</td>
<td>Vertebral, non-vertebral, hip</td>
<td>Nausea, hypercalcemia, hyperuricemia, hypocalcemia (rare), osteonecrosis (rare)</td>
</tr>
<tr>
<td>RANKL inhibitor Denosumab</td>
<td>60 mg SC every 6 months</td>
<td>Vertebral, non-vertebral, hip</td>
<td>Skin infections, nausea, extravasation of the jaw (rare)</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>100-200 IU nasally or subcutaneously once daily</td>
<td>Vertebral</td>
<td>nasal congestion</td>
</tr>
</tbody>
</table>

Bisphosphonates: Inhibit Bone Turnover
- Reduce fractures
- Accumulate in bone and at sites of bone turnover; ~50% excreted by the kidneys; long skeletal retention, but affinity for bone varies with different bisphosphonates
- Side effects: gastrointestinal, musculoskeletal pain, ocular pain (rare), 2005 precaution osteonecrosis of the jaw (uncommon), atypical femur fractures <0.1% or absolute risk 5 cases/10,000 patient treatment years

Meta-Analysis of Alendronate and Risedronate - Effects on Fractures

<table>
<thead>
<tr>
<th>Fracture Sites</th>
<th>Alendronate RR (95% CI)</th>
<th>Risedronate RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>0.55 (0.45-0.67)</td>
<td>0.63 (0.50-0.76)</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>0.84 (0.74-0.94)</td>
<td>0.80 (0.72-0.90)</td>
</tr>
<tr>
<td>Hip</td>
<td>0.61 (0.40-0.92)</td>
<td>0.74 (0.59-0.94)</td>
</tr>
<tr>
<td>Wrist</td>
<td>0.68 (0.34-1.37)</td>
<td>0.67 (0.42-1.07)</td>
</tr>
</tbody>
</table>

Zoledronic Acid (5mg/yr) Reduced Risk of Morphometric Vertebral Fractures and Hip Fractures: FDA-approved 2007

Meta-Analysis of Alendronate and Risedronate - Effects on Fractures

http://handbook.partners.org/docs/CDP_BisphosphonateReview.pdf

Zoledronic Acid (5mg/yr) Reduced Risk of Morphometric Vertebral Fractures and Hip Fractures: FDA-approved 2007

http://handbook.partners.org/docs/CDP_BisphosphonateReview.pdf
**Atypical Femur Fracture:rare**

- Transverse or oblique fracture, medial beaking and cortical thickening with minimal or no trauma
- Prodromal pain: Ask patient about groin or femur pain
- Increased risk with longer use

**U.S. Food and Drug Administration (FDA) Advisory Committee: Management Strategies 2012**

- Bisphosphonates have robust effects on fracture reduction. There are concerns about the long-term use.
- FDA: There is no global regulatory restriction on duration of use. Post-hoc analyses indicate that bisphosphonates may be discontinued in patients at low risk of fracture.
- There may be subgroups of patients who may benefit from continued therapy
- Evaluate benefit and risk in each patient.

**Denosumab: FDA Approved June 2010**

- Inhibits the Cellular Mechanisms Underlying Bone Resorption
- Indication: Treatment of Postmenopausal Women with Osteoporosis at high fracture risk; or patients intolerant to other osteoporosis treatments
- Administered: 60 mg SC every 6 months
- Adverse Effects: Hypocalcemia, musculoskeletal pain, serious skin infections, rare osteonecrosis of the jaw

**Receptor activator of nuclear factor-kappa B ligand (RANKL) Stimulates Bone Resorption**

RANK Ligand Is Essential for Osteoclast Formation, Function, and Survival

**Mechanism of Action for Denosumab**

**Denosumab: Effect on Incidence of New Vertebral, Nonvertebral, and Hip Fractures**

Anabolic Therapy: Teriparatide (1-34 PTH): FDA-Approved

- Stimulates new bone formation greater than bone resorption; increases BMD-effect attenuated by alendronate
- Side effects: headache and nausea, mild transient hypercalcemia, osteosarcoma (rodents)-therapy limited to 2 years
- Consolidate anabolic effect after 2 years-start a bisphosphonate

Teriparatide (1-34 PTH) Therapy: Who is a candidate for?

- Adult-motivated to take daily injection
- Osteoporosis, fractures
- Do not use in patients with: hypercalcemia, XRT, bone cancers, elevated alkaline phosphatase, Paget's Disease, kidney stones?

Quality Measures: Bone Density Test and Treatment

- Bone Density Test
- Treatment:
  - Oral Bisphosphonate: generic alendronate most cost effective
  - Zoledronic Acid: once yearly therapy for osteoporosis
  -Raloxifene
  -Denosumab
  -Teriparatide

Osteomalacia

Delayed Mineralization of Bone
Osteomalacia: Clinical Signs

- Generalized bone pain
- Bony Deformity
- Kyphoscoliosis
- Bowed legs
- Proximal muscle weakness
- Pseudofractures (arrow) also called Looser’s zones

Causes of Osteomalacia and Rickets

Vitamin D deficiency or dysfunction
- Reduced availability
  - Nutritional deficit
  - Reduced exposure to ultraviolet light
  - Malabsorption (celiac disease, Crohn’s disease, gastrectomy, jejunoileal bypass, cholestyramine, primary biliary cirrhosis, biliary atresia)

Causes of Osteomalacia and Rickets, cont’d

Alteration in the metabolism of vitamin D
- Reduced 25-hydroxyvitamin D – severe liver disease, nephrotic syndrome, anticonvulsant drugs
- Reduced 1,25-dihydroxyvitamin D or altered action on target tissues – Chronic Kidney Disease
- 1α-hydroxylase deficiency - Vitamin D-dependent rickets type I
- Vitamin D Resistance due to an abnormal Receptor - Vitamin D-dependent rickets type II

Causes of Osteomalacia and Rickets, cont’d

Phosphate deficiency
- Decreased availability
  - Dietary deficiency, phosphate-binding antacid
  - Impaired intestinal phosphate absorption
    - Pancreatic insufficiency, intrinsic bowel disease, short bowel syndromes
  - Decreased renal tubular phosphate reabsorption
    - Familial: Hypophosphatemic rickets/osteomalacia
    - Acquired: Hypophosphatemic osteomalacia, oncogenic osteomalacia
    - Generalized renal tubular disorders

Oncogenic Osteomalacia

- Hypophosphatemia, reduced renal phosphate tubular reabsorption, inappropriately low 1,25-dihydroxyvitamin D levels, bone pain, marked muscle weakness, fractures
- High FGF23 levels (expressed by tumors) - regulator of phosphate homeostasis: high levels associated with low phosphate levels
- Often small mesenchymal tumors such as hemangiomas, giant cell tumors located in bone, skin, oral cavity, sinuses. Usually benign; rare cancers (prostate, small cell carcinoma)
- Tumors difficult to locate on physical exam or imaging, but resection results in resolution of clinical symptoms

Circulating Levels of FGF-23 in Oncogenic Osteomalacia and X-linked Hypophosphatemia

Causes of Osteomalacia and Rickets, cont’d

**Acidosis**
- Renal tubular acidosis, ureterosigmoidoscopy, carbonic anhydrase inhibitors (acetazolamide)

**Miscellaneous mineralization defects**
- Inhibitors of mineralization
  - Fluoride, Aluminum antacids (e.g. TPN, CRF)
- Hypophosphatasia

Biochemical Parameters in Osteomalacia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal or slightly decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
<td>Increased or Normal</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
<td>Hypophosphatemic osteomalacia</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>Increased</td>
</tr>
<tr>
<td>FGF23</td>
<td>Increased in Tumor-Induced Osteomalacia and Hypophosphatemic Osteomalacia and Rickets</td>
</tr>
</tbody>
</table>

Workup For Osteomalacia

- Calcium, phosphorus, alkaline phosphatase, urinary calcium
- 25-hydroxyvitamin D and intact PTH levels
- Specialized tests: 1,25-dihydroxvitamin D, tubular reabsorption of phosphate and select imaging procedures

Treatment of Osteomalacia

**Vitamin D deficiency:**
- Oral Vitamin D (high doses for severe malabsorption)
- Treatment of underlying gastrointestinal process (e.g., gluten-free diet for sprue)

**Altered Vitamin D metabolism:** 1,25-dihydroxyvitamin D or other vitamin D analogues for renal disease

**Phosphate deficiency:** phosphate therapy and 1,25-dihydroxyvitamin D

Paget’s Disease of Bone—Second Most Common Metabolic Bone Disease

- Affects 2% of the population over age 55
- 15%-30% positive family history (more common patients of Northern European descent)
- Marked increase number and size of osteoclasts
- Most common sites (axial skeleton): skull, spine, pelvis, femur or tibia
- May be localized or involve several bones
Paget’s Disease: Clinical Signs

- Bone pain
- Skeletal deformities
- Osteoarthritis of adjacent joints
- Pathologic fractures
- Nerve compression and hearing loss
- High output failure (rare)
- Osteogenic sarcoma (<1%)

Many patients are asymptomatic

Pathophysiology of Paget’s Disease

- Etiology—possibly viral etiology (i.e., myxovirus)
- Genetics: mutations of sequestosome 1/p62 gene; linkage to 5q31, 18q21-22 and others
- More data needed

Biochemical and Radiological Indices

- Calcium and Phosphorus: usually normal, (hypercalcemia may develop with immobilization)
- Alkaline Phosphatase elevated (common initial presentation)
- Urinary Collagen Crosslinks: elevated

Bone Scans: assess the activity of Paget’s disease (sensitive but not specific)

X-rays: Characteristic radiological findings
- Enlarged thickened bones, Disorganized bone with Lytic (“blade of grass”), blastic, and/or sclerotic changes
- Cortical thickening

Treatment of Paget’s Disease

- Bisphosphonates—standard therapy
  Etidronate, Pamidronate, Alendronate*, Tiludronate, and Risedronate*, Zolendronic Acid*
- Injectable calcitonin, salmon (rarely used)
- Nonsteroidal anti-inflammatory drugs or analgesics to alleviate associated joint pain

*Potent bisphosphonates may produce sustained "remissions"
Indications for Treatment of Paget’s Disease

- Pain
- Hypercalcemia (immobilization)
- Fractures
- High output failure (rare)
- Neurological compromise

Other Possible Indications:
Prevention of Progression of Paget’s Disease Involving:

- Vertebral body
- Skull
- Weight bearing bones (e.g., femur, tibia)
- Disease adjacent to major articular region

Lowering of Serum Alkaline Phosphatase (over days) with Risedronate (oral) or Zoledronic Acid (IV) in Paget’s Disease (mean ± SEM)

Case I

- 80 y.o. woman admitted with a femoral neck fracture. She states she lost 4 inches in height; wrist fracture age 60
- Medications: hydrochlorothizide, calcium
- Laboratory tests: eGFR 48, calcium= 8.6, 25OHD level 13 ng/ml

How should you evaluate and treat her?

Case I: How Should You Evaluate and Treat Her?

a) Fall prevention intervention
b) Evaluation for secondary causes of her osteoporosis
c) Bone Density test and treatment of her osteoporosis
d) Treat her vitamin D deficiency
e) All of the above

Case 2

- 50 y.o male with progressive pain on ambulation
- Physical exam: bowing increased warmth
- Lytic changes on the X-ray of his tibia

What do his tests show?
Case 2

a) Elevated alkaline phosphatase
b) High serum phosphate
c) Low serum calcium
d) High FGF23
e) Delayed mineralization on double tetracycline label