Managing Osteoporosis 2013
Susan L. Greenspan, MD

I. Scope of the Problem
A. 1.3 million fractures per year; -50% spine, -25% hip
B. After age 50, 1 of 2 postmenopausal women will an osteoporotic fracture
C. By age 90, 1 of 3 postmenopausal women will develop a hip fracture (still 20% mortality)
D. Annual cost $19 billion
E. In US, 10 million have osteoporosis, 34 million have low bone mass (osteopenia)

II. Types of Bone
A. Trabecular bone
   1. More metabolically active
   2. 15-20% of skeleton
   3. Found in lumbar spine, trochanter, calcaneus, femur
B. Cortical bone
   1. Less metabolically active, less likely to see changes with therapy
   2. Found in proximal forearm, skull, phalanges
   3. 80-85% of skeleton
   4. Greater loss of cortical bone with hyperthyroidism and hyperparathyroidism
C. Adult peak bone mass
   1. Achieved at about age 30 in women, age 35 in men
   2. Diet, exercise, lifestyle, genetics, gonadal status important factors to maximize peak adult bone mass
   3. Used in classification of osteoporosis
      a. T-score: SD from adult peak bone mass
      b. Z-score: SD from age/gender matched bone mass
         (i) Used to help determine if secondary causes are present
         (ii) If Z-score = -2 SD or lower, secondary causes of bone loss likely

III. Fracture Risk Prediction
A. Risk factors for low bone mass: female, postmenopausal or amenorrheic, family history, race (Caucasian, Asian), thin, low dietary calcium/vitamin D
intake, inactivity, smoking, alcohol, medication

B. Risk factors for hip fracture in elderly women: maternal history of hip fracture, previous fracture, height, poor health, previous hyperthyroidism, caffeine, inactivity, inability to rise from chair without using arms, poor depth perception, poor contrast sensitivity, tachycardia, low bone density

C. Risk factors in men: hypogonadism, glucocorticoids, alcoholism, androgen deprivation therapy for prostate cancer

IV. Secondary Causes of Osteoporosis

A. Exclude drugs and diseases: secondary osteoporosis

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Nutritional</th>
<th>Endocrine</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteogenesis imperfect</td>
<td>Malabsorption syndromes</td>
<td>Hypogonadism</td>
<td>Steroids, Phenobarbital, Dilantin, L-thyroxin excess</td>
<td>Multiple myeloma, Rheumatoid arthritis, Acromegaly, Mastocytosis, Immobilization</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Chronic liver disease</td>
<td>Thyrotoxicosis</td>
<td>Hyperparathyroidism, Androgen deprivation therapy, Aromatase Inhibitors, Depo Provera</td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Alcoholism</td>
<td>Hypercorticism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium deficiency</td>
<td>Hyperparathyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin D deficiency</td>
<td>Anorexia nervosa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Drugs: steroids, anticonvulsants, excess thyroid hormone, androgen deprivation therapy, aromatase inhibitors, Depo provera
2. Diseases
   a. Affecting vitamin D metabolism (absorption, renal activation)
   b. Affecting bone turnover/lysis
      i. Endocrinopathies: hyperthyroidism, hyperparathyroidism, Cushing’s
      ii. Malignancy: carcinoma, myeloma

B. Selective tests
   1. Ruling out secondary causes of osteopenia: 25 hydroxy vitamin D (important cause of secondary osteoporosis), calcium/albumin, , CBC, BUN/creatinine, alkaline phosphatase, TSH, 24 hour urinary calcium
   2. Requiring clinical judgment
      a. PTH with calcium determination
      b. Bone biopsy rarely indicated

C. Glucocorticoid induced bone loss
   1. Trabecular bone preferentially affected
   2. Pathophysiology
      a. Decreased GI calcium
      b. Increased urinary calcium excretion
      c. Decreased osteoblastic bone formation
d. Increased bone resorption
e. Decreased sex hormones

V. Bone Mineral Densitometry and Screening

A. Screening/classification of osteoporosis
   1. X-rays: insensitive for bone loss but excludes other conditions and evaluates for fracture
      a. Vertebral radiographic changes c/w osteoporosis
         i. Anterior wedging
         ii. More than one vertebrae involved
         iii. Below T6

B. Types of bone mineral densitometry

<table>
<thead>
<tr>
<th>Technique</th>
<th>Site</th>
<th>Radiation</th>
<th>Time (mins.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual-energy X-ray Absorptiometry (DXA) - Gold Standard</td>
<td>Spine (PA/lateral)</td>
<td>Negligible</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wrist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Photon Absorptiometry (SPA)</td>
<td>Wrist</td>
<td>Negligible</td>
<td>15</td>
</tr>
<tr>
<td>Quantitative Computed Tomography (QCT)</td>
<td>Spine Hip</td>
<td>5-10 CXR</td>
<td>10-20</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Heel</td>
<td>None</td>
<td>5</td>
</tr>
</tbody>
</table>

C. World Health Organization's criteria for classification of osteoporosis by bone mineral densitometry

1. Normal: T-score ≥ -1.0 SD
2. Low Bone Mass (osteopenia): T-score between -1.0 SD and -2.5 SD
3. Osteoporosis: T-score ≤ -2.5 SD

D. Indications for bone mineral densitometry

   a. Postmenopausal women <65 years old if one or more risk factors (family history, low body weight, smoking, diseases or medication that increase risk)
   b. All women >65 years and men > 70 years old regardless of risk factors
   c. Patients ≥50 years with fractures (confirm diagnosis and severity)

   a. All women >65 years
b. Women < 65 years whose 10 year fracture risk is ≥ that of 65 year old woman without additional risk factors

c. Men: No recommendation


   a. Estrogen-deficient women at risk for osteoporosis
   b. Individuals with vertebral abnormalities
   c. Individuals on long-term glucocorticoids
   d. Individuals with primary hyperparathyroidism
   e. Individuals monitored to assess response to therapy

4. Follow-up DXA testing (if not on therapy, transition to osteoporosis)

   a. normal: T= >-1.0, ~15 years
   b. mild osteopenia: T= -1.01 to -1.49, ~ 15 years
   c. moderate osteopenia: T= -1.5 to -1.99, ~ 5 years
   d. advanced osteopenia: T= -2.0 to -2.49, ~1 year
   e. medicare coverage: greater than 23 months (~2 years)

VI. Biochemical Markers of Bone Resorption

A. N-telopeptide cross-linked of collagen type 1 (NTX)- morning urine collection

B. C-telopeptide cross-linked of collagen type 1 (CTX)- morning serum

C. These tests DO NOT replace bone density, they complement bone density

D. Utility - assess relative rate of bone loss: premenopausal vs. postmenopausal

VII. Prevention and Treatment of Osteoporosis

A. General preventive measures

1. Calcium: most studies suggest benefit, but some equivocal

   a. Efficacy
   b. Recommended Dietary Allowance (mg/d)- Institute of Medicine (Nov 2011)
      i. 1300 mg/d for ages 9-18
      ii. 1000 mg/d for ages 19-50
      iii. 1200 mg/d for ages 51 and over, women
      iv. 2000 mg/d upper level intake for adults
   c. Types of supplements
      i. Calcium carbonate: taken with meals
      ii. Calcium citrate: taken with or without meals
      iii. Preparations to avoid: dolomite, bone meal (may contain lead)
   d. Bioavailability: vinegar test - calcium tablet in 4 ounces white wine vinegar should disintegrate in 30 minutes
   e. Diet
      i. Dairy products roughly 300 mg/cup
      ii. Calcium-fortified orange juice approximately 350 mg/cup
      iii. If no dairy, average calcium intake approximately 250 mg/day
   f. Association with cardiovascular disease under debate and
2. Vitamin D
   a. 40% of patients in EW have low vitamin D levels
   b. Skin synthesizes vitamin D, synthesis blocked by sun block
   c. Efficacy: vitamin D + calcium resulted in 40% reduction in hip fractures in frail, older women
   d. Recommended Dietary Allowance “healthy” IU/d (IOM)
      i. 600 IU/d: ages 9-70
      ii. 800 IU/d: ages 71+
      iii. NOF- for bone health/osteoporosis/low bone mass:
           Up to 1000 IU/d
      iv. Upper level intake: 4000 IU/d
   e. USPSTF (2013) concluded for primary prevention in postmenopausal women (healthy women, without osteoporosis), insufficient evidence to assess
      > 400 IU vitamin D plus 1000 mg calcium, recommends against < 400 IU/day plus 1000 mg calcium daily
   f. Dietary sources: milk 100 IU/8 oz., yogurt, orange juice
   g. Supplements
      i. D₃ (cholecalciferol) preferred over D₂ (ergocalciferol)
      ii. Multivitamin has 400-1000 IU
      iii. Pure vitamin D supplement of 400 to 2000 IU
      iv. Calcium supplements may contain 200-500 IU/tablet

3. Antigravity exercise
   a. Efficacy
   b. Types
      i. Walking: 30 minutes 3 times per week
      ii. Treadmill
      iii. Step aerobics
      iv. High intensity strength training: 45 minutes two times per week

4. Fall reduction (important in elderly)
   a. Multifactorial interventions
      i. Medication adjustments
         (a) Long-acting benzodiazepines
         (b) Antipsychotics
      ii. Behavioral modification: physical therapy (back strengthening exercise, posture training, soft support, gait assessment), occupational therapy (evaluation to examine house for "fall safety")
      iii. Exercise
   b. Hip protectors: initial studies suggested reduction in hip fracture with hip protectors, but compliance poor and recent studies do not demonstrate efficacy

B. Indications for therapy

1. NOF Treatment Guidelines: 2008
   a. BMD T-score ≤ -2.5 spine, femoral neck, total hip after
secondary evaluation
b. Adult fragility fracture
c. BMD T-score between -1 and -2.5 with:
   i. Other prior fracture
   ii. Secondary causes (glucocorticoids, immobilization)
   iii. 10 year probability hip fracture ≥ 3% by FRAX®
       10 year probability any major osteoporotic fracture
       ≥ 20% using FRAX®
2. FRAX® - WHO algorithm
   a. calculates:
       i. 10 year probability of hip fracture
       ii. 10 year probability of any major osteoporotic fracture
   b. uses:
       i. BMD (g/cm²) femoral neck, age, height, weight,
       ii. smoking, glucocorticoids, previous adult fracture,
       iii. family history of fracture, rheumatoid arthritis
   c. designed for women and men age 40-90 years, no previous treatment

C. Therapeutic options (Tables 1 & 2)

<table>
<thead>
<tr>
<th>FDA-Approved Medications for Osteoporosis Prevention and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-menopausal osteoporosis</td>
</tr>
<tr>
<td>Prevention</td>
</tr>
<tr>
<td>Antiresorptive agent</td>
</tr>
<tr>
<td>Alendronate PO</td>
</tr>
<tr>
<td>Ibandronate PO</td>
</tr>
<tr>
<td>Ibandronate IV</td>
</tr>
<tr>
<td>Risedronate PO</td>
</tr>
<tr>
<td>Zoledronic acid IV</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Raloxifene</td>
</tr>
<tr>
<td>Calcitonin</td>
</tr>
<tr>
<td>Denosumab</td>
</tr>
<tr>
<td>Anabolic agent</td>
</tr>
<tr>
<td>Teriparatide [PTH(1-34)]</td>
</tr>
</tbody>
</table>


Documented Fracture reduction

No head-to-head trials comparing fracture outcomes

<table>
<thead>
<tr>
<th>Spine</th>
<th>Nonvertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIRESORPTIVE AGENTS (Bisphosphonates)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Risedronate</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>OTHER ANTIRESORPTIVE AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td>X</td>
<td>X (all fractures)</td>
</tr>
</tbody>
</table>
1. Calcium and vitamin D supplementation needed with all therapies

2. Calcium and vitamin D supplementation alone can still result in bone loss and fractures

3. Hormone replacement therapy - approved for prevention and management of postmenopausal osteoporosis, but generally not used for osteoporosis
   a. Efficacy: Improvement in bone density of hip and spine in clinical trials, 34% reduction in hip and vertebral fractures after 5.2 years in Women’s Health Initiative
   b. Risks: Women’s Health Initiative with combined conjugated estrogen and medroxyprogesterone after 5.2 years - increased risk of CHD, breast cancer, stroke, DVT
   c. Dose:
      i. Conjugated estrogen 0.625 mg/d - standard dose needed to maintain bone density
      ii. 0.3 mg/d or 0.45 mg/d plus calcium may also maintain bone mass
      iii. Generally only suggested for postmenopausal symptoms, short duration, lowest dose
   d. Progesterone for intact uterus
   e. Schedule: cyclic or combined continuous estrogen/progesterone

4. Raloxifene (Evista®) – estrogen agonist/antagonist
   a. Efficacy
      1. Increases hip, spine, total body BMD
      2. 50% reduction in vertebral fractures, no decrease in nonvertebral fractures
      3. Decreases total/LDL cholesterol
   b. Approved for 1) osteoporosis prevention and treatment, 2) prevention of invasive breast cancer in postmenopausal women with osteoporosis
   c. Dose: 60 mg/d
   d. Side effects: possible increase in hot flashes, leg cramps, slight increase in DVT/PE (similar to estrogen)

5. Bisphosphonates - mainstay of prevention and treatment
   a. Alendronate (Fosamax®) - approved for prevention and treatment of osteoporosis in postmenopausal women and men
      i. Bisphosphonate: antiresorptive agent
      ii. Efficacy
         a) Prevents bone loss
         b) Increases bone density at spine and hip
         c) Decreases spine, hip, and wrist fractures by 50%
Susan L. Greenspan, M.D.

over 3 years, but can see decrease in clinical vertebral fractures in 12 months and hip fractures in 18 months

d) Prevents glucocorticoid induced bone loss

iii. Dose: take 30 minutes before breakfast on empty stomach with full glass of water and remain upright

a) 70 mg once/wk or 10 mg/d for treatment of postmenopausal osteoporosis, male osteoporosis and glucocorticoid induced osteoporosis

b) 35 mg once/wk or 5 mg/d for prevention of postmenopausal osteoporosis

c) Available as an oral solution 70 mg in 75 ml

d) Available with vitamin D_{3} as alendronate 70mg plus 2800 units vit D_{3} or 70 mg plus 5600 units vit D_{3} once a week

e) Generic alendronate 70 mg once a week

iv. Side effects

a) GI symptomatology

b) Arthralgias/myalgias

v. Duration: efficacy sustained up to 10 years

b. Risedronate (Actonel®) - approved for prevention and treatment of postmenopausal and male osteoporosis

i. Efficacy

a) Prevents bone loss

b) Increases bone density at spine and hip

c) Decreases vertebral fractures by 40% over 3 years, can see benefit as early as 12 months

d) Decreases nonvertebral fractures by 39% over 3 years

e) 40% hip fracture reduction in 3 years in postmenopausal women with very low bone mass and risk factors

f) Prevents and treats glucocorticoid induced bone loss

ii. Dose: 150 mg once a month, 35 mg once a week or 5 mg daily for prevention and treatment of postmenopausal osteoporosis and glucocorticoid induced osteoporosis; must take 30 minutes before breakfast on empty stomach with full glass of water and remain upright

iii. Side effects: GI symptomatology

iv. Atelvia® risedronate 35 mg once weekly can be taken after breakfast

c. Ibandronate (Boniva®) – approved for treatment of postmenopausal osteoporosis

i. Efficacy

a) Increases spine and hip bone density

b) Reduces vertebral fractures by 62% in 3 years

ii. Dose

a) Oral: 150 mg po once monthly; must take 60
minutes before breakfast on an empty stomach with full glass of water and remain upright
b) Intravenous: 3 mg intravenous every 3 months
d. Zoledronic acid (Reclast®) – approved for prevention and treatment of postmenopausal osteoporosis and male osteoporosis
i. Efficacy
   a) Increases spine and hip bone density
   b) Reduces vertebral fractures by 70%, nonvertebral fractures by 25%, and hip fractures by 41% over 3 years
ii. Dose: Intravenous only; 5 mg IV once a year for treatment; 5 mg IV every 24 months for prevention
iii. Adverse Events
   a) Flu-like syndrome for 24-48 hours after IV dose
   b) Increase in serious AEs for atrial fibrillation (1.3% Reclast®, 0.5% placebo)
iv. Contraindication: Creatinine clearance <35mL/min
e. Osteonecrosis of the jaw - rare side effect in patients treated for osteoporosis
i. Pathophysiology-etiology unclear
ii. American Dental Association (ADA) suggests good dental hygiene
f. Atypical femoral shaft fractures - very rare side effect
i. May present with pain in leg prior to fracture
ii. Low impact fracture
iii. On therapy >5 years
iv. <1% of hip or thigh fractures
g. Esophageal Cancer
   i. Equivocal results
   ii. Rare side effect from oral bisphosphonates
   iii. Under FDA investigation
6. Nasal calcitonin spray (Miacalcin®) - approved for treatment of postmenopausal osteoporosis
a. Calcitonin: hormone
b. Efficacy
   i. Prevents spinal bone loss, unknown efficacy at hip
   ii. Reduces vertebral fractures up to 37%
   iii. Analgesic effect
c. Dose: 200 IU/day (1 inhalation daily in alternate nostrils)
d. Side effects: nasal congestion
e. 2013 FDA advisory panel no longer supports calcitonin for osteoporosis
7. Denosumab (Prolia®)- approved for treatment of patients at high risk for fracture including 1) postmenopausal women with osteoporosis, 2) men with osteoporosis, 3) women with breast cancer on aromatase inhibitors, 4) men with prostate cancer on androgen deprivation therapy.
a. Fully monoclonal antibody to RANK Ligand that inhibits the activity of osteoclasts
b. Given as a subcutaneous injection 60 mg, every 6 months, reversible
c. Efficacy in pivotal trial for postmenopausal osteoporosis
   i. Increases in spine and hip bone density
   ii. Decrease in vertebral fractures by 68%, nonvertebral fractures by 20% and hip fractures by 40% over 3 years
d. Adverse events: Serious infections, hypocalcemia

8. Teriparatide- approved for treatment for patients at high risk and glucocorticoid induced osteoporosis
   a. Anabolic therapy
   b. Given as daily subcutaneous injection [PTH(1-34), teriparatide (Forteo®) 20 mcg/d]
   c. Studies demonstrate increase in bone mass and reduction in vertebral and nonvertebral fractures in 18 months
   d. Improves connectivity and biomechanical strength (animal studies)
   e. Black box warning about osteosarcoma in rats
   f. Combination therapy with PTH and an antiresorptive agent: no additional benefit combining PTH plus alendronate, give PTH alone
   g. Additional benefit from PTH followed by alendronate

9. Investigational approaches
   a. New forms of parathyroid hormone and PTHrP
   b. Antibody to sclerostin
   c. New estrogen agonists/antagonists

VIII Practical Considerations and Questions
A. Combination therapy: limited benefit, no data on additional fracture risk reduction
B. Long term therapy:
   1. Antifracture effect throughout at least 5 years
   2. No abnormalities on bone biopsy after 10 years of alendronate
C. Discontinuation of treatment
   1. Bone loss when estrogen, raloxifene, denosumab and probably calcitonin stopped
   2. Patients who discontinued alendronate after 5 years of treatment compared to those that continued for 10 years
      a. Bone loss in hip after 1 year
      b. More clinical vertebral fractures
      c. Higher rate of nonvertebral fractures if hip T-score ≤ -2.5 at end of 5 years
D. How long should therapy be continued?
   1. Raloxifene or calcitonin: no limit
   2. Estrogen: Not recommended long term
   3. Bisphosphonates:
      a. Low risk patients- consider drug holiday at 5 year, restart if BMD declines
      b. High risk patients- after 10 years consider holiday or consider
teriparatide or raloxifene during bisphosphonate holiday

IX Summary Points
- Osteoporosis is common and costly
- Screen all women ≥ 65 and men ≥ 70 years or younger postmenopausal women with risk factors.
- Rule out secondary causes of bone loss- vitamin D deficiency common
- Calcium 1200 mg/d in divided doses
- Vitamin D 1000 IU/day
- Weight bearing exercise
- FRAX- new WHO intervention guidelines
- Many good therapies available with reduction in vertebral fractures (all) or hip fracture (selective agents)

GENERAL REFERENCES