Bone Health in Women: Getting Strong and Staying Strong
Family Medicine Refresher Course

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Disclosure

- I am not on any industry speaking bureaus but have used certain slides provided by Proctor and Gamble and Amgen corporations.
Learning Objectives

- Recognize the risk factors for osteoporosis and the impact of co-morbidities
- Discuss an approach to screening, diagnosing and treating osteoporosis
- Understand the behavioral and pharmacologic treatments that can benefit the patient with decreased bone density
Osteoporotic Fractures in Women, Compared With Other Diseases

Processes Resulting in Osteoporosis

- Poor bone mass acquisition during adolescence
- Accelerated bone loss during the peri-menopausal period (mid 50’s – the sixth decade)
Fractures

- Eight million women have a documented fracture
- Female-to-male fracture ratios are 7:1 for vertebral fractures, 1.5:1 for distal forearm fractures; and 2:1 for hip fractures
- More common in Caucasians and Asians than in African Americans and Hispanics
- More common in women than in men
Primary Osteoporosis

- Bone loss unassociated with other chronic illness
- Related to increasing age and decreased gonadal function (e.g. early menopause or premenopausal estrogen deficiency)
Etiology - Genetic

- **Women > men; but 30% of hip fractures > 65 years of age are in men.**
- **More common in elderly, and in white and Asian women**
- **Family history of osteoporosis confers a greater risk for osteoporosis.**
- **Genetic disease such as Turner’s syndrome (45XO gonadal dysgenesis)**
Etiology - Nutritional

- Adolescent milk intake improves bone mineralization
- Balanced nutrients including calcium are essential for bone health
- Eating disorders problematic because below normal body mass promotes bone loss.
• Sedentary lifestyle and/or immobility
• Low body weight
• Cigarette smoking
• Excessive alcohol consumption
Risk Factors For Osteoporosis

- Petite body frame
- Smoking
- Caucasian or Asian race
- Excessive alcohol use
- Female gender
- Sedentary lifestyle
- Immobilization
- Renal disease
- Nulliparity

- Lifelong low calcium intake
- Long-term use of certain drugs
- Postmenopausal status
- Increasing age
- Low body weight
- High caffeine intake
- Impaired calcium absorption
Less Modifiable Risk Factors For Osteoporosis

- History of fracture as an adult
- Fracture in first degree relative
- Advanced age
- Female gender
- Dementia
- Excessive alcohol consumption
- Poor health/ frailty
Potentially Modifiable Risks

- Sedentary lifestyle and/or immobility
- Low body weight
- Current Cigarette smoking
- Excessive alcohol consumption
- Estrogen deficiency
- Lifelong poor Calcium intake
- Recurrent falls
WHEN TO SCREEN - National Osteoporosis Foundation

• Counsel all women on the risk factors for osteoporosis.
• Perform BMD testing on postmenopausal women presenting with fractures to determine the disease severity.
• Recommend BMD testing to postmenopausal women under age 65 with one or more additional risk factors for osteoporosis besides menopause.
• Recommend BMD testing to all women aged 65 and older regardless of additional risk factors.
• Advise patients to avoid tobacco smoking and to keep alcohol intake moderate.
• Consider all postmenopausal women who present with vertebral or hip fractures candidates for osteoporosis treatment.
• Recommend adequate dietary calcium (at least 1200 mg/d) to all patients.
• Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
B RECOMMENDATION – Women aged 65 and older should be screened routinely for osteoporosis. Begin screening at age 60 for women at increased risk for osteoporotic fractures.

• **C RECOMMENDATION** – USPSTF makes no recommendation for or against routine osteoporosis screening in postmenopausal women who are younger than 60 or in women aged 60-64 who are not at increased risk for osteoporotic fractures

SECONDARY OSTEOPOROSIS

- Results from chronic conditions
- Underlying condition must be treated to halt progression of osteoporosis
Bone Mineral Density

- Dual energy x-ray absorptiometry (DXA) - most precise
- Quantitative CT - most sensitive, greater radiation exposure
- Peripheral measuring systems available but value for assessing fracture risk is unclear.
- T score (SD above or below the mean BMD for sex and race matched to young controls) or Z score (adjusted for age, sex, race) - little value to the practicing clinician.
- Normals; Osteopenic; Osteoporotic (T score 2.5 SD below the sex-adjusted mean for normal young adults at peak bone mass)
• Risk factors are stronger predictors of hip fracture than low bone density:
  • age > 80
  • poor health
  • limited physical activity
  • poor vision
  • prior postmenopausal fracture
  • psychotropic drug use

• Plain radiographs only evidence osteoporosis when total bone density is decreased by 50%.
INDICATIONS FOR MEASURING BONE DENSITY

- Concerned perimenopausal women willing to start therapy
- Radiographic evidence of bone loss
- Long-term glucocorticoid therapy (more than 1 mo at >=7.5mg of prednisone/d)
- Asymptomatic hyperparathyroidism where osteoporosis would suggest parathyroidectomy
- Monitoring therapeutic response in women undergoing treatment for osteoporosis if the result of the test would affect the clinical decision
Fracture Risk Assessment (FRAX) Tool

- Sophisticated fracture risk calculator created from large worldwide population-based cohorts – endorsed by WHO
- Integrated femoral neck BMD and individual clinical risk factors
- Estimates the 10 yr, patient-specific absolute risk for hip fractures and major osteoporotic fractures (spine, forearm, hip or shoulder)
- FRAX results can be used to guide treatment decisions

- FRAX=registered trademark of ProfJA Kanis, Univ of Sheffield
Risk factors for osteoporotic fracture used in FRAX®

- Age (50 to 90 years)
- Sex
- Weight \( a \)
- Height \( a \)
- Low femoral neck BMD
- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Long-term use of glucocorticoids
- Rheumatoid arthritis
- Other causes of secondary osteoporosis
- Alcohol intake of more than two units daily

Adapted from World Health Organization Collaborating Centre for Metabolic Bone Diseases.
NOF Guidelines for Pharmacologic Therapy – initiate in postmenopausal women with …

- Fracture – Vertebral or hip fracture
- T-Score - \(<or = -2.5\) at femoral neck or spine
- FRAX Assessment (T-score between -1 and -2.5)
  - WHO 10-yr probability of any major osteoporotic fx \(> or = 20\%\)
  - WHO 10-yr probability of hip fx \(> or = 3\%\)

[Recommendations also apply to men>50 after exclusion of secondary causes.; NOF. Clinicians Guide to Prevention and Treatment of Osteoporosis. 2008]
NOF Recommendations on Non-Pharmacologic Interventions to Reduce Fracture Risk

- Discourage tobacco, excess alcohol and caffeine;
- Adequate intake of total elemental calcium (at least 1200 mg/d) for women 50 yo or >;
- Vitamin D (800-1200 IU/d) for women 50 yo or >;
- Regular weight-bearing and muscle strengthening exercises;
- Fall prevention

• Initiate therapy to reduce fracture risk in women with BMD T-scores below \(-2\) in the absence of risk factors and in women with T-scores below \(-1.5\) if other risk factors are present.

• Consider hormone replacement therapy, bisphosphonate, raloxifene (prevention), and calcitonin (treatment) for prevention and/or treatment of osteoporosis.
• Adequate estrogen levels remain the single, most important therapy for adequate bone density in women
• Women’s Health Initiative (2002) – excessive risk for CAD, breast CA, and strokes; less risk for colorectal and endometrial CA and hip fracture
• Assess risk of fracture vs CAD and breast CA

• Current users who started ERT at menopause had the highest BMD levels
• Current users who started estrogen within 5 years of menopause had a decreased risk of hip, wrist, and all non-spinal fractures
• Early initiation of estrogen with respect to menopause may be more important than the total duration of use.
• Calcium supplementation may reduce fracture rates by more than the change in BMD would predict – possibly as much as 50%.
• Vitamin D increases calcium absorption in the gastrointestinal tract
• 1200 mg of elemental calcium per day for optimal bone health in adults
• 1500 mg/d for teenagers, pregnant/lactating women, women greater than 50 years of age taking ERT, and everyone greater than 65 years of age
Calcium With or Without Vitamin D

• Systematic review and meta-analysis (63,897 people analyzed) of all randomized trials that used calcium with or without vitamin D – primary outcome was fracture at any site
• Secondary outcome was BMD
• Calcium with/without vitamin D - associated with 12% reduction in risk for fractures

CALCIUM RICH FOODS (APPROX 300 MG)

- Milk (skim, lowfat, or whole), 8 oz
- Plain yogurt, 8 oz
- Frozen yogurt, fruit, 8 oz
- Gouda, Colby, (Mozzarella), 1 oz
- Calcium-fortified orange juice, 8 oz
- Sardines, canned, 3 oz
- Cooked greens, collards or mustard, 8 oz
- Firm cheeses (Edam, Brick, Cheddar, Swiss cheese, 1 oz
- Ricotta cheese, part skim, 4 oz
CALCITONIN

- Hormone directly inhibiting osteoclastic bone resorption
- An alternative for patients with established osteoporosis who cannot/will not use ERT
- Analgesic effect on bone pain (useful for acute osteoporotic fractures)
- Effective in decreasing the fracture rate of vertebrae and peripheral bones
BISPHOSPHONATES

- Structural analogs of pyrophosphates
- Pharmacologic specificity for bone = affinity to hydroxyapatite
- Target bone mineral and bind to osteoclasts for a long-term effect
- Inhibit production of essential lipid compounds inside osteoclasts producing decreased osteoclast activity
BISPHOSPHONATES

- Food/liquids reduce absorption, so give with water 30 mins before first meal/beverage of day
- Avoid recumbency for at least 30 mins to minimize esophageal irritation.
- Comparable efficacy to ERT in preventing bone loss and positive effect on vertebral fracture rate
Bisphosphonates reduce mortality risk

- Bisphosphonate use was associated with a reduced mortality risk in both women and in men
  Dana Bliuc, PhD, Garvan Institute of Medical Research, Sydney, Australia, American Society of Bone and Mineral Research 2016 Annual Meeting.
- Effect largely attributable to alendronate - significant benefit, risedronate - possible benefit, and etidronate - no benefit
- The apparent survival advantage associated with bisphosphonate use - not related to a decline in subsequent fractures in this large Canadian Multicentre Osteoporosis study (CaMos).

Bisphosphonates reduce mortality risk

• Canadian Multicentre Osteoporosis Study (CaMos) enrolled women and men 50 y and older (1995 – 2012)).
• Participants took alendronate for about 5 years; risedronate introduced later.
• 2173 BP users included in the whole cohort; 1265 HRT users served as a healthy-user group. Approx 1889 received no Rx
• Baseline characteristics somewhat different – 35% of BP women had experienced a prior fracture compared with 17% in the HRT group
• Mortality risk among women reduced by 42% among current BP users and by 47% in past users

Ibandronate

- FDA-approved for the treatment and prevention of osteoporosis in postmenopausal women
- Reduces incidence of new, vertebral fractures by 52% and to increase BMD at the spine by 5%
- Can be used once per month
Guidance on BP Use


- Two trials provided evidence for long-term BP use - Fracture Intervention Trial Long-term Extension (FLEX) and the HORIZON extension trial

DOI: 10.1002/jbmr.2708
Guidance on BP Use

- American Society for Bone and Mineral Research task force suggested that after 5 years of oral BP or 3 years of IV BP Rx, clinicians should reassess risk.
- Hi risk – eg. Older, with low hip T-score or high fx risk score, previous major osteoporotic fx or a fx on Rx > continuation of Rx for up to 10 y (oral) or 6 y (IV), with periodic evaluation

DOI: 10.1002/jbmr.2708
SELECTIVE ESTROGEN RECEPTOR MODULATORS

- Multiple Outcomes of Raloxifene (MORE) trial (n=7000 postmenopausal, osteoporotic x 3y) - Decreased breast cancer risk in those already at low risk for the disease.
- New fractures in 10% placebo gp, 6.6% 60mg gp, 5.4% in 120mg Raloxifene gp
- Group with pre-existing fractures had 4.5 times greater chance of recurrence than did those with osteoporosis, but no fracture
- Side effects – vaginitis, hot flashes, leg cramps, peripheral edema

Ettinger B, Black DM et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. JAMA 1999;282:637-645
SELECTIVE ESTROGEN RECEPTOR MODULATORS

• Raloxifene (Evista) blocks estrogen similarly to tamoxifen
• Estrogen agonist effects on bone and estrogen antagonist effects on breast and endometrium
• Results in decreased serum total and LDL cholesterol without any beneficial effects on serum total HDL cholesterol or triglycerides
• Side effects - vaginitis and hot flashes
• Multiple Outcomes of Raloxifene (MORE) trial (n=7000 postmenopausal, osteoporotic x 3y) - Decreased breast cancer risk in those already at low risk for the disease.
COPD and Osteoporosis

- 35-72% of patients with COPD are osteopenic and 36-60% are osteoporotic
- The increased risk is multifactorial
Contributing Factors to Osteoporosis in COPD

- Smoking
- Vitamin D deficiency
- Low BMI
- Hypogonadism
- Immobility
- Glucocorticoids

Biskobing DM. COPD and osteoporosis. Chest 2002;121:609-620
Glucocorticoid-Induced Osteoporosis

- Long-term use of oral glucocorticoids in chronic diseases
  - Asthma
  - COPD
  - Rheumatoid arthritis
  - Inflammatory bowel disease
  - Lupus
- Significant bone loss can occur in as little as 3 months
- Up to 50% of patients taking $\geq 7.5$ mg/d of prednisone or equivalent will fracture
- Regardless of age or gender
Effects of Glucocorticoids on Bone Metabolism

- Decreased bone formation
- Decreased intestinal calcium absorption
- Increased urinary calcium excretion
- Increased osteoclast differentiation

Biskobing DM. COPD and osteoporosis. Chest 2002;121:609-620
ACR Recommendations for Bisphosphonate Use in GIO

- Prevention of bone loss in patients initiating long-term (≥3 months) glucocorticoid therapy
- Patients with low BMD (T-score < −1) receiving long-term glucocorticoid therapy
- Patients receiving long-term glucocorticoid therapy who have had fractures on, or cannot tolerate, hormone replacement therapy

ACR = American College of Rheumatology.
ACR Ad Hoc Committee on GIO. Arthritis Rheum. 2001;44:1496-1503
TREATMENT STRATEGIES FOR PATIENTS ON GLUCOCORTICOIDS

• Lowest dose of short-acting glucocorticoid or topical preparations whenever possible
• Maintain well-balanced, 2-3 g sodium diet
• Weight-bearing and isometric exercise to prevent proximal muscle weakness
• Calcium intake of 1500 mg/day and vitamin D intake of at least 800 IU/day after hypercalciuria is controlled
TREATMENT STRATEGIES FOR PATIENTS ON GLUCOCORTICOIDS

- Gonadal hormones in all postmenopausal women, premenopausal women with low estradiol, and men with low testosterone
- Thiazide diuretic to control hypercalciuria
- BMD at baseline and q6-12mos during first 2y of therapy to assess treatment efficacy
- If bone loss occurs while being treated, or HRT contraindicated, treat with calcitonin or bisphosphonate.

From Lane NE, 1998
OVERALL TREATMENT STRATEGIES

• Calcium-rich diet +/- Vitamin D supplements
• Weight-bearing exercise
• Avoidance of alcohol, tobacco products, excess caffeine and drugs
• Antiresorptive therapies
  • Estrogen replacement within 5 years of menopause, and used for 10+yrs
  • Bisphosphonates (Risedronate, Alendronate, Ibandronate)
  • SERMs (Raloxifene)
  • Calcitonin
• Anabolic therapy (Teriparatide-PTH 1-34)
Anabolic Therapy

• Anabolic therapy with Teriparatide (Forteo, Parathyroid hormone) expands the treatment approaches for osteoporosis in patients who continue to experience fractures or bone loss on an adequate program of general prevention and antiresorptive therapy.
• Approved in women and in men who have very low BMD or hi risk for fracture
• Can only be taken for 2 years

www.nof.org — accessed 3/20/08
Newer Therapies

- Questions re bisphosphonates and atypical fractures – no conclusive evidence, studies by Dennis Black
- Monoclonal antibody (first in class biologic) targeting RANK-Ligand (necessary to activate osteoclasts) – available in prefilled syringe used twice yearly
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<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
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<tbody>
<tr>
<td>Estradiol patch</td>
<td>0.05mg q week</td>
<td>Topical</td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td>0.625 – 1.25 mg/d</td>
<td>Oral</td>
</tr>
<tr>
<td>Elemental Calcium</td>
<td>At least 1200 mg/d</td>
<td>Oral</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>200 IU/d 50-100 IU/d</td>
<td>IN SC/IM</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>For repletion – 50,000U PO 8 wks – then maintenance</td>
<td>800 IU/d – 1000IU/d</td>
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<tr>
<td>Alendronate</td>
<td>5mg/d(prev)10 mg/d(Rx)</td>
<td>Oral</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35mg qwk or 150mg qmo</td>
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<tr>
<td>Ibandronate</td>
<td>2.5mg qd or 150mg qmo</td>
<td>Oral</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>60 mg/d</td>
<td>Oral</td>
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SUMMARY

- Osteoporosis is a silently progressive condition that is best managed through prevention - nutrition, activity, and lifestyle
- Incorporate screening into the periodic examination of women of all ages and men in their senior years
- BMD is a useful adjunct to comprehensive evaluation
- Use behavior modification early and pharmacotherapy later in the disease process.
Osteoporosis Indications for Risedronate

• Postmenopausal osteoporosis (PMO)
  – Risedronate 35 mg Once-a-Week and Risedronate 5 mg daily are indicated for the treatment and prevention of osteoporosis in postmenopausal women

• Glucocorticoid-induced osteoporosis (GIO)
  – Risedronate 5 mg daily is also indicated for the prevention and treatment of GIO in men and women who are either initiating or continuing systemic glucocorticoid treatment (≥7.5 mg/d prednisone or equivalent) for chronic diseases
Risedronate

- Reduces vertebral fractures by 41-49%, nonvertebral fractures by 39%, and hip fractures by 40-60%.

- In postmenopausal, osteoporotic women with no previous fracture (incidence of vertebral fx 9.4% (placebo) vs 2.6% (treated)


- In postmenopausal, osteoporotic women with two prior fractures by 62% vs control

Alendronate

• Increases BMD by 6-8% at the spine and by 3-6% at the hip over a three year period in women with PMO
• Both vertebral and nonvertebral fractures were reduced by approx 50% over this period of treatment
• Has FDA-approved labeling for the treatment of male osteoporosis
CASE STUDY

• EF is a 68 yo WM who is S/P successful treatment for prostate CA 5 years previously. He has a long history of tobacco and alcohol abuse and intermittent courses of glucocorticoids for COPD.

• He is hypogonadal and has suffered two vertebral compression fractures. His BMD (male reference range) is T= -2.2 Spine and -1.8 Hip. What should his family physician do?

AMA Online CME Program – accessed 11/12/05
CASE STUDY

- Men experience fractures at higher bone density values (measured by DXA) than do women.
- One year mortality rate after hip fracture is about twice as high in men compared to women.
- BMD machine manufacturers use gender-specific T scores. Use of female reference range instead would classify only about 3% of older men as having osteoporosis as compared to 19% based on the male reference range for the spine, femoral neck and radius.
- Estrogen (esp Estradiol) levels are better predictors of BMD in men than testosterone levels.

AMA Online CME Program – accessed 11/12/05
CASE STUDY

• Medicare rules limit BMD studies in men to those with x-ray evidence of vertebral fractures, men with hyperparathyroidism, men with glucocorticoid excess, or those men with known osteoporosis treated with and FDA-approved treatment being followed for response.

• Men with fragility fractures, a bone density T score at or < -1.0 with risk factors, and men with T score = -2.0 or less regardless of risk factors, should be considered for therapy.

• Risedronate and alendronate are approved in men and increase BMD and reduce fracture risk of vertebrae…

AMA Online CME Program – accessed 11/12/05
SECONDARY FORMS OF OSTEOPOROSIS

ENDOC/METAB CAUSES

- Acromegaly
- Anorexia nervos
- Athletic amenorrhea
- Type 1 Diabetes mellitus
- Hemochromatosis
- Hyperadrenocorticism
- Hyperparathyroidism
- Hyperprolactinemia
- Thyrotoxicosis

DRUGS

- Cyclosporine
- Glucocorticoids
- Prolonged heparin Rx
- Excess thyroid med
- Phenytoin
- Methotrexate
- Phenobarbital
- GnRH agonists
- Phenothiazines
SECONDARY FORMS OF OSTEOPOROSIS

COLLAGEN/GENETIC DISORDERS
• Ehlers/Danlos syndrome
• Homocystinuria
• Marfan syndrome
• Glycogen storage diseases
• Osteogenesis imperfecta
• Hypophosphatasia

NUTRITIONAL
• Calcium deficiency
• Gastric operations
• Chronic liver disease
• Vitamin D deficiency
• Malabsorptive syndromes
LABORATORY FINDINGS AND SUGGESTED PATHOLOGY

Abnormal Study
- ↑Creatinine
- ↑Hepatic transaminases
- ↑Calcium
- ↓Calcium
- ↓Phosphorus
- ↑Alkaline phosphatase
- ↓Albumin
- ↓TSH
- ↑ESR
- Anemia
- ↓24 hour calcium excretion

Suggested Pathology
- Renal disease
- Hepatic disease
- Primary HPT or malignancy
- Malabsorption, vitamin D deficiency
- Osteomalacia
- Liver disease, Paget’s disease, fracture, other bone pathology
- Malnutrition
- Hyperthyroidism
- Myeloma
- Malabsorption, vitamin D deficiency
Antiresorptive Agents

- **Bisphosphonates**
  - Alendronate, Ibandronate, Risedronate, Zoledronic acid
- **Others**
  - Calcitonin, Estrogen, SERMs)

These agents act to lessen the risk of bone fracture by decreasing bone turnover, reducing bone loss, and stabilizing bone microarchitecture. All these agents, including Vitamin D, reduce the risk of vertebral fractures.

AMA Online CME Program – accessed 11/12/05