Question 1

All of the following are risk factors for osteoporosis EXCEPT:

A. Low calcium intake
B. Smoking
C. Alcohol use
D. Turner’s Syndrome
E. Obesity*

Question 2

Which of the following medical conditions or medications can lead to secondary osteoporosis?

A. Hypothyroidism
B. Zinc deficiency
C. Anticonvulsants (i.e. phenytoin)*
D. ACE inhibitors
Question 3
A 65-year-old Caucasian lady presents to clinic to discuss the results of BMD testing. Her personal medical history is unremarkable. Her mother, however, died at age 75 due to complications with hip fracture. Her T-score is -2.0.

Which of the following choices is the correct interpretation of her BMD and treatment?

A. Normal BMD; calcium supplementation
B. Osteopenia; zinc supplementation for prevention
C. Osteopenia; alendronate for treatment*
D. Osteoporosis; risedronate for treatment

Question 4
Mrs. $ is a 68-year-old Caucasian woman who has been treated with alendronate 70 mg/week for osteoporosis for 2 years. She is otherwise healthy with no previous history of fractures. She has a healthy BMI with a healthy diet and exercises 4x/week, is a non-smoker, and has only the occasional glass of wine with dinner.

A recent DEXA revealed that T-score of her lumbar spine is -2.8 and of her hip is -2.9. This is 5% lower at the spine and 3% lower at the hip compared to her previous testing.

Why did her bone density decrease?

Which of the below could have caused her BMD to decrease?

A. Mrs. $ lost BMD despite a prescription of effective treatment.
B. Measurement imprecision.
C. Mrs. $ is compliant with her bisphosphonate, but does not regularly take calcium and vitamin D.
D. Secondary causes of osteoporosis.
E. All of the above. *
Ms. B is a 72-year-old lady who has been on an oral bisphosphonate for 7 years. Her femoral neck T-score is currently -2.2 and she has had a minimal decline of BMD of 1.5% during duration of therapy. She is compliant with this medication as well as calcium and vitamin D. She has no history of previous fractures, no family history of osteoporosis, and workup for secondary causes is negative. Her FRAX score for major osteoporotic fracture is 12% and for hip fracture is 2.7%.

What should she do now?

Question 5

What should Ms. B do now?
A. Continue bisphosphonate.
B. Take a “bisphosphonate holiday”.*
C. Switch medications.

Objectives

1. Define and understand the basic pathophysiology of osteoporosis
2. Gain an understanding of risk factors and risk assessment for osteoporosis
3. Determine who should be screened for osteoporosis and associated diagnostic criteria
4. Evaluate current treatment recommendations for osteoporosis, both pharmacologic and non-pharmacologic
5. Assess monitoring parameters and duration of therapy for various pharmacologic agents
6. Review means of preventing osteoporosis in multiple populations.
Definition

- National Osteoporosis Foundation: “A chronic, progressive disease characterized by low bone mass, microarchitecture deterioration of bone tissues, bone fragility, and a consequent increase in fracture risk.”

Pathogenesis

- Osteoclasts degrade bone matrix faster than osteoblasts rebuild it
  - Inadequate peak bone mass
  - Excessive bone resorption
  - Inadequate formation of new bone during remodeling
- Maximum bone mineral density (BMD) is achieved by 40 years old as measured by DEXA
  - Peak period of bone mass accrual between 11 and 14 years old
  - Varies by gender, ethnicity, body size, region of bone
- “Silent disease”
Pathogenesis

Epidemiology

- 10.2 Americans with osteoporosis and 43.4 million with low bone mass
- 9 million osteoporotic fractures worldwide (2000)
- 2 million in US, >70% women
- >20% of white women and >20% of white men have osteoporosis-related fracture in their lifetime
- Hip fracture: mortality rate 5 years 20% greater than expected
- <1 in 4 women >67 years old undergo testing or begin treatment
- Annual healthcare costs (2000)
  - 500,000 hospitalizations
  - 800,000 emergency department visits
  - 2.5 million office visits
  - 180,000 nursing home admissions
  - Projected total costs of $25 billion in 2025

Organizations

- National Osteoporosis Foundation
- American Association of Clinical Endocrinologists
- American College of Rheumatology
- US Preventive Services Task Force
- American Academy of Family Physicians
- American College of Obstetrics and Gynecology
- International Society for Clinical Densitometry
- North American Menopause Society
Risk Factors

- Excessive alcohol intake
  - Men: >4 drinks per day; Women: >2 drinks per day
- Excessive caffeine intake
  - >2.5 cups coffee per day, >5 cups tea per day
- Tobacco use
- Family history of osteoporotic fracture
- Immobilization and inadequate activity
- Low body weight
  - <58 kg/128 lb
- Increasing age
- Low calcium or vitamin D intake
- Personal history of fracture
- White or Asian race

Risk Assessment

- Fracture Risk Assessment Tool (FRAX)
  - Launched in 2008 by the University of Sheffield
  - Predicts 10-year probability of fracture based on risk factors with or without BMD
  - Major osteoporotic fracture and Hip fracture

Risk Assessment – FRAX

Calculation Tool

Please select the questionnaire variables for the 10-year probability of fracture with BMD.

Quandnaire:
- Age
- Ethnicity
- Menopausal status
- Height
- Pregnancy history
- Family history
- Previous osteoporotic fracture
- Low body weight
- Current tobacco use
- Current hormone replacement therapy
- Previous hormone replacement therapy
- Current oral glucocorticoid use
- Current vitamin D use
- Current calcium use

Weight Experience
- Pounds

http://www.sheffield.ac.uk/FRAX
Risk Assessment – FRAX

Please answer the questions below to calculate the ten year probability of fracture with FRAX:

1. Age
2. Sex
3. Previous fracture
4. Height
5. Weight
6. Hormone replacement therapy
7. Current glucocorticoids
8. Diabetes mellitus
9. Inflammatory disease
10. Connective tissue disease

For more information, visit http://www.sheffield.ac.uk/FRAX
Clinical Presentation

- No symptoms until fracture occurs
- Most common: vertebral fracture
  - 2/3 are asymptomatic and diagnosed as incidental radiograph findings
- Hip fracture
  - Risk increases with age
  - By age 80, 15% women and 5% men
- Colles/distal radius fracture
  - More common in women shortly after menopause
- Height loss
  - >1.5 in (4 cm)
### Who to Screen

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| American Association of Clinical Endocrinologists (AACE) | All women > age 65. All postmenopausal women with:  
- History of fragility fracture after age 40-45  
- Osteopenia on radiographs  
- Starting or current glucocorticoid therapy ≥ 3 months  
- Increased risk of secondary osteoporosis  
- Perimenopausal or postmenopausal women with risk factors if willing to consider pharmacologic intervention:  
  - Current smoker  
  - Early menopause  
  - Family history of osteoporotic fracture  
  - Excessive alcohol consumption  
  - Low body weight  
  - History of glucocorticoid therapy ≥ 3 months |

| National Osteoporosis Foundation | All women > age 65. All men > age 70. Postmenopausal women and men age 50-69 with risk factors. Perform BMD with vertebral imaging in those with fracture  
- Vertebral Imaging  
  - Women > age 65 and men > age 70 with T-score ≤ -1.5  
  - Women > age 70 and men > age 80 regardless of T-score  
  - Postmenopausal women and men > age 50 with fragility fracture  
  - Postmenopausal women and men age 50-69 with height loss ≥ 4cm or recent or ongoing long-term glucocorticoids  
  - To check for secondary osteoporosis |

| American College of Obstetricians and Gynecologists (ACOG) | All women > age 65. No more than once every two years unless new health risks develop. Selective screening in women < age 65. If postmenopausal and have osteoporosis risk factors or fracture, in absence of new risk factors, do not repeat DEXA if BMD stable or improved |

| U.S. Preventive Services Task Force (USPSTF) | Women > age 65. Younger women whose fracture risk is ≥ 65 year old white woman who has no additional risk factors. Insufficient evidence for screening in men |
Diagnosis

- Dual Energy X-ray Absorptiometry (DEXA)
  - T-score: SD difference between patient’s BMD and young adult reference population
  - Z-score: SD difference between patient’s BMD and age-matched population
  - Used in premenopausal women

- Peripheral testing
  - pDEXA
  - Quantitative ultrasound (QUS)
  - Peripheral quantitative computed tomography (pQCT)

WHO Diagnostic Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Bone Mass (from DEXA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>T-score ≥ -1.0</td>
</tr>
<tr>
<td>Osteopenia (low bone mass)</td>
<td>T-score &lt; -1.0 and &gt; -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T-score ≤ -2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>T-score ≤ -2.5 plus one or more fragility fractures</td>
</tr>
</tbody>
</table>

- T-scores only apply to postmenopausal women and men ≥50 years old
- In premenopausal women and men <50 years old, use Z-scores instead
  - Z-score < -2.0 considered abnormal
Additional Evaluation

- **Most Common**
  - 25-OH vitamin D
  - CMP
  - Creatinine
  - Calcium
  - Alkaline phosphatase
  - TSH

- **Consider in selected patients**
  - Testosterone in men
  - FSH
  - 24-hour urine cortisol
  - 24-hour urine calcium

### Secondary Causes

- **COPD**
- Endocrine disorders
  - Primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, primary or secondary hypogonadism, pituitary adenoma, type 1 diabetes

- **GI disorders**
  - Celiac disease, gastric bypass, IBD

- **Hematologic disorders**
  - Parkinson, multiple myeloma, leukemia

- **Severe liver disease**

- **Renal failure**

- **Nutrition disorders**
  - Anorexia nervosa, malnutrition, alcoholism, vitamin D deficiency

- **Rheumatoid arthritis**

- **Medications**
  - Anticonvulsants, chemotherapeutics, cyclosporine, Depo-Provera, glucocorticoids, SSRIs, heparin, lithium, PPIs, SSRIs, medications for hypertension, diabetes, and osteoporosis.

### Treatment – Non-pharmacologic

- **Alcohol moderation**
  - Men: 4 drinks per day; Women: 2 drinks per day

- **Decreased caffeine intake**
  - 125 mg caffeine per day

- **Exercise**
  - Minimum: 20 minutes per week
  - Resistance training, yoga, walking, balance training

- **Falls risk assessment and education**
  - Hip protectors
  - Physical therapy

- **Smoking cessation**

- **Sunlight**

- **Calcium and vitamin D supplementation**
  - 1200 mg calcium and 800 IU vitamin D per day
Goal of treatment: fracture prevention

- Bisphosphonates: first line
  - Alendronate (po)
  -ibandronate (po and iv)
  - Risedronate (po)
  - Zoledronic acid (iv)
- Human monoclonal antibody
  - Denosumab (subQ)
  - Receptor activator parathyroid hormone
  - Teriparatide (subQ)
- SERM
  - Raloxifene (po)
Treatment – Bisphosphonates

- Mechanism: inhibit osteoclast activity, antiresorptive
- Alendronate and risedronate
  - Dose:
    - Alendronate: 70 mg po once weekly
    - Risedronate: 150 mg po once monthly
  - Reduction in risk of hip and vertebral fractures
  - Decrease vertebral fractures in men and glucocorticoid-induced osteoporosis
- Ibandronate
  - Dose: 150 mg po once monthly or 3 mg IV every 3 months
  - Reduction in risk of vertebral fractures only
- Zoledronic acid
  - Dose: 5mg IV once per year
  - Reduces hip and vertebral fractures

Treatment – Bisphosphonates

- Contraindications
  - Inability to follow dosing requirements (po)
  - Esophageal disorders (po)
  - CKD with GFR <30 mL/min
  - Bariatric surgeries with surgical anastomoses (Roux-en-Y)
- Adverse Reactions
  - GI: reflux, esophagitis, esophageal ulcers (po)
  - Flu-like symptoms (IV)
  - Hypocalcemia
  - Renal impairment
  - Less common: musculoskeletal pain, atrial fibrillation, ocular side effects, osteonecrosis of the jaw, atypical femur fractures

Treatment – Denosumab

- Mechanism of Action of Available Osteoporosis Therapies
  - Reduces osteoclast activity, increases bone density
  - Reduces risk of fractures
  - Safe and effective in men and women
Treatment – Denosumab

- Mechanism: inhibits osteoclast formation and activity by blocking receptor activator of nuclear factor kappa B ligand (RANKL)
- Dose: 60 mg subQ every 6 months
- Decreases risk of hip, vertebral, and non-vertebral fractures compared to calcium and vitamin D supplementation
- Significantly increases BMD compared to alendronate
- Adverse reactions: hypocalcemia, back, extremity, and musculoskeletal pain, hypercholesterolemia, cystitis, eczema

Treatment – Teriparatide

- Mechanism: increases bone anabolic activity
- Candidates: women with severe bone loss (T-score <-3.5 or T-score ≤ -2.5 with fragility fracture) or men with osteoporosis and high fracture risk; failed bisphosphonate therapy
- Dose: 20 mcg subQ once daily
- Decreases risk of vertebral and non-vertebral fractures; follow with bisphosphonate therapy
**Treatment – Teriparatide**

- Contraindications
  - Primary or secondary hyperparathyroidism
  - Hypercalcemic disorders
  - Increased risk for osteosarcoma
  - History of radiation
  - Unexplained elevated alkaline phosphatase

- Adverse reactions
  - Hypercalcemia
  - Hypercalcures
  - Hypertension, tachycardia
  - Osteosarcoma

**Treatment – SERMs**

**Mechanism of Action of Available Osteoporosis Therapies**

**Treatment – SERMs (raloxifene)**

- Mechanism: binds to estrogen receptor and is estrogen agonist to bone, inhibiting bone resorption
- Candidates: postmenopausal women with osteoporosis who cannot tolerate bisphosphonates, have no history of VTE, and are high-risk for breast cancer
- Decreases risk of vertebral fractures only
- Decreased risk of invasive breast cancer
- Contraindications: history of VTE, PE
- Adverse reactions
  - Increased vasomotor symptoms
  - Increased risk of VTE
  - Stroke
Treatment – Other

- Hormone therapy: estrogen with or without progesterone
  - However, risks outweigh benefits
  - Risks of use: VTE, stroke, CAD, breast cancer
- Calcitonin: nasal spray with antiresorptive properties
  - Decreases vertebral fractures only
  - Modest analgesic effect in acute and chronic vertebral fracture
  - Less effective, therefore not first line
  - Increased cancer rate?
- Combination therapy: studies ongoing, but no effectiveness demonstrated

Treatment

Monitoring

- Ideally, complete DEXA at same facility using same machine and technologist with same regions of interest
- Repeat DEXA every 1-2 years or a less-frequent interval depending on clinical circumstance
- Consider monitoring bone tumor markers (BTMs)
  - Antiresorptive therapy: expect reduction in BTMs
  - Anabolic therapy: expect increase in BTMs
Monitoring

- Successful treatment
  - No new fractures
  - Stable or increasing BMD
  - Antiresorptive agents: BTMs at or below median value for premenopausal women
- Consider alternative therapy or reassessment for secondary causes with recurrent fractures or significant bone loss.

Duration of Therapy

- Bisphosphonates: consider “holiday”
- Teriparatide: 2 years
- Denosumab and raloxifene: as long as clinically appropriate

- Bisphosphonate “holiday”
  - Medication accumulates and may have prolonged residence time in bone, therefore residual therapeutic effect after stopping
  - High-risk patients:
    - Oral treatment duration of 10 years
    - Zoledronic acid: treatment duration of 4 years
    - Consider teriparatide or raloxifene during holiday
  - Low-risk patients:
    - Oral: consider drug holiday after 5 years of stability
    - Zoledronic acid: consider drug holiday after 3 years of stability
    - Continue to monitor to determine when “holiday” should end
Up and Coming

- PTH analog: abaloparatide
- Human monoclonal antibody: romosozumab, blosozumab
- Cathepsin K inhibitor: odanacatib

Prevention

**Calcium**
- Women ≤ age 50, men ≤ age 70: 1,000 mg daily
- Women > age 50, men > age 70: 1,200 mg daily
- Dairy products, greens, fortified foods

**Vitamin D**
- < age 50: 400-800 IU
- ≥ age 50: 800-1,000 IU
- Sunlight, wild-caught tuna and salmon, fortified foods

USPSTF: vitamin D supplementation is effective in preventing falls in community-dwelling adults > age 65 who are at increased risk of falls

Prevention

- **Weight-bearing exercises**
  - High-impact: dancing, hiking, jogging, stair climbing, tennis
  - Low-impact: elliptical training, stair-step machines, walking

- **Strengthening exercises**
  - Weightlifting (machine or free weight)
  - Elastic bands
  - Body weight exercises
Prevention

Children and Adolescents

- In addition to school physical education
- Additional increase of BMD: 4% at spine, 2% at proximal femur
- Frequency: 3x/week
- Intensity: high-impact
- Time: 30 minutes after school

Type:
- Aerobic workouts: aerobics, soccer, skipping, ball games, weight training
- Circuit training: 20-minute weight-bearing, strength-building circuit
  - 1 minute per station
  - 1 set of 10 repetitions progressing to 3 sets of 10 over time

Prevention

Young Adults and Pre-Menopausal Women

- Exercise may decrease vertebral fracture risk in addition to increase BMD
- BMD increase: 2% at spine and femoral neck
- Frequency: 3x/week

<table>
<thead>
<tr>
<th>Activity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm-up</td>
<td>15 minutes</td>
</tr>
<tr>
<td>High-impact jumps</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Stretching and non-impact activi</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Cool-down</td>
<td>15 minutes</td>
</tr>
</tbody>
</table>

Prevention

Young Adults and Pre-Menopausal Women

- BMD increase: 5% at spine and 3% at femoral neck
- Frequency: 3x/week

- Class 1: Every 12 minutes, alternate between exercise stations and high-impact aerobic activities
  - Exercise stations: push-ups, sit-ups, arm curls, barbell presses
- Class 2: Moderate weights to exercise gluteus maximus, erector spinae, shoulder girdle muscles
- Class 3: Vigorous, high-impact aerobic workout with HR between 70-85% max
Prevention

Postmenopausal women

- Frequency: 4x/week with two group 60-70 minute sessions and two at-home 25 minute sessions

- Warm up/endurance sequence: walking to running 20 minutes
- Jumping sequence: rope-skipping, closed-leg jumps
- Strength-training sequence: resistance machines and isometric exercises
- Flexibility-training

U.S. Bone and Joint Initiative

- PB&J: Protect Your Bones & Joints
- Fit to a T
Conclusions
- Osteoporosis-related fractures cause decreased quality of life, increased mortality, and significant healthcare costs.
- Screening for osteoporosis is based on age, increased fracture risk, and secondary causes.
- DEXA is the gold standard for screening and diagnosis, using T-scores in postmenopausal women and men over age 50 and Z-scores in premenopausal women and men younger than 50.
- Bisphosphonates are first-line treatment, but denosumab, teriparatide, and raloxifene are additional effective options.
- Lifestyle modification should be discussed with patients of all ages to prevent and treat osteoporosis.

Question 1
All of the following are risk factors for osteoporosis EXCEPT:
A. Low calcium intake
B. Smoking
C. Alcohol use
D. Turner’s Syndrome
E. Obesity*

Question 2
Which of the following medical conditions or medications can lead to secondary osteoporosis?
A. Hypothyroidism
B. Zinc deficiency
C. Anticonvulsants (i.e. phenytoin)*
D. ACE inhibitors
Question 3

A 65-year-old Caucasian lady presents to clinic to discuss the results of BMD testing. Her personal medical history is unremarkable. Her mother, however, died at age 75 due to complications with hip fracture. Her T-score is -2.0.

Which of the following choices is the correct interpretation of her BMD and treatment?

A. Normal BMD; calcium supplementation
B. Osteopenia; zinc supplementation for prevention
C. Osteopenia; alendronate for treatment*
D. Osteoporosis; risedronate for treatment

Question 4

Mrs. S is a 68-year-old Caucasian woman who has been treated with alendronate 70 mg/week for osteoporosis for 2 years. She is otherwise healthy with no previous history of fractures. She has a healthy BMI with a healthy diet and exercises 4x/week, is a non-smoker, and has only the occasional glass of wine with dinner.

A recent DEXA revealed that T-score of her lumbar spine is -2.8 and that of her hip is -2.9. This is 2% lower at the spine and 3% lower at the hip compared to her previous testing.

Why did her bone density decrease?

Which of the below could have caused her BMD to decrease?

A. Mrs. S lost BMD despite prescription of effective treatment.
B. Measurement imprecision.
C. Mrs. S is compliant with her bisphosphonate, but does not regularly take calcium and vitamin D.
D. Secondary causes of osteoporosis.
E. All of the above.*
Question 5

Ms. B is a 72-year-old lady who has been on an oral bisphosphonate for 7 years. Her femoral neck T-score is currently -2.2 and she has had a minimal decline of BMD of 1.5% during duration of therapy. She is compliant with this medication as well as calcium and vitamin D. She has no history of previous fractures, no family history of osteoporosis, and workup for secondary causes is negative. Her FRAX score for major osteoporotic fracture is 12% and for hip fracture is 2.7%.

What should she do now?

A. Continue bisphosphonate.
B. Take a “bisphosphonate holiday”.*
C. Switch medications.

Question 5

What should Ms. B do now?

Key References

“Calcium/Vitamin D.” National Osteoporosis Foundation.
“Exercise Recommendations.” International Osteoporosis Foundation.
“FRAX® Calculation Tool.” The University of Sheffield.
NOF BoneSource – MyNOF.
Questions?

Thank you!

Caitlin Schmitt, DO
Cox Family Medicine Residency – PGY2
caitlin.schmitt@coxhealth.com