Osteoporosis

American Association of Clinical Endocrinologists and American College of Endocrinology Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis 2016

Objectives
- Discuss new guidelines from AACE and ACE
- Review workup for secondary osteoporosis
- Review Current Treatments
  - MOA
  - Dosages
  - Duration
  - Adverse Reaction
  - Safety Monitoring

Postmenopausal Osteoporosis
- 30% of postmenopausal women in the U.S. have osteoporosis.
- Women who have sustained a hip fracture have a 10-20% higher mortality than would be expected for their age
- Heredity accounts for 50-70% of peak bone mass
- 10% increase of peak bone mass in childhood reduces risk of an osteoporotic fracture during adult life by 50%
- 1% bone loss per year after age 30-35 years
- Bone loss is accelerated after menopause secondary to estrogen deficiency resulting in bone resorption and decreased bone formation
Osteoporosis Risk Factors

- Age
- Female Gender
- Family History
- Previous Fracture
- Ethnicity
- Menopause/Hysterectomy
- Glucocorticoids > 3 mo
- Rheumatoid Arthritis
- Alcohol
- Smoking
- Low BMI
- Poor Nutrition
- Vitamin D deficiency
- Eating Disorder
- Insufficient exercise
- Low dietary calcium intake
- Frequent Falls

Osteoporosis Prevention

- Ensure a nutritious diet and adequate calcium intake
- Avoid under-nutrition
  - Severe Diets
  - Eating Disorders
- Maintain Adequate Vitamin D
- Regular Weight Bearing Activity
- Avoid smoking and second hand smoke
- Avoid heavy drinking

How is Fracture Risk Assessed and Osteoporosis Diagnosed?

- Evaluate all postmenopausal women aged ≥ 50 years for osteoporosis risk
- Detailed History, physical exam, and FRAX in initial evaluation
- Consider Bone Density Study based on clinical fracture risk
- When BMD is measured – axial dual-energy X-ray absorptiometry measurement (spine and hip) should be used
Major Risk Factors for Osteoporosis and Fracture

- Fragility Fracture
- Fragility Fracture in 1st Degree Relative
- Weight < 127 lbs
- Current Smoker
- Oral steroids for > 3 months

History

- Fractures
  - Femoral neck
  - Pathologic vertebral
  - Lumbar and thoracic vertebral
  - Distal radius
- Medications
  - Anticoagulation
  - Glucocorticoids
  - Lithium
  - PPIs

History

- Past Medical History
  - Endocrine disorders
    - Hyperparathyroidism
    - Hypogonadal states
    - Anorexia nervosa
    - Diabetes
    - Cushing syndrome
    - Excess thyroid hormone
    - Endocrine therapy for cancer
History

Past Medical History
- GI Disorders
  - Celiac Disease
  - Gastric bypass
  - Crohn disease
  - Malabsorption
  - Cirrhosis
- Rheumatologic
  - Rheumatoid arthritis
  - Ankylosing spondylitis
  - SLE
- Central Nervous System Disorders
  - Epilepsy
  - Multiple sclerosis
  - Parkinson disease
- Other conditions
  - HIV, amyloidosis, COPD, CHF, Chronic Kidney Disease
  - Hypercalciuria, weight loss, alcoholism, renal tubular acidosis

Family History
- Genetic factors
- Previous History of hip fracture
- Parental History of hip fracture

Social History
- Alcohol use
- Diet
- Low physical activity
- Smoking
FRAX

- Age
- Sex
- Ethnicity
- Weight
- Previous Fracture
- Parent Fractured Hip
- Current Smoking
- Glucocorticoids
- Rheumatoid Arthritis
- Secondary Osteoporosis
- Alcohol 3 or more units per day
- Bone Mineral Density

How is Fracture Risk Assessed and Osteoporosis Diagnosed?

- Osteoporosis Diagnosis
  - Fragility Fractures in the absence of other metabolic bone disorders
  - T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, and/or 33% radius even in the absence of a fracture
  - Osteopenia and increased fracture risk using FRAX country specific thresholds

Physical Exam for Vertebral Fractures

- 2/3 vertebral fractures are painless
- Rib-pelvis distance < 2-3 finger breadths
- Tooth count < 20
- Wall-occipt distance: inability to touch occiput to wall when standing with back and heels against the wall
- Height Loss
When Osteoporosis is Diagnosed, What is an Appropriate Evaluation?

- Evaluate for causes of secondary osteoporosis
- Evaluate for prevalent vertebral fractures
- Consider using bone turnover markers (BTMs) in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk.

Bone Turnover Markers

- Measure collagen breakdown products and other molecules released from osteoclasts and osteoblasts during bone resorption and formation.
- Bone Formation
  - BALP – bone-specific alkaline phosphatase
  - Osteocalcin
  - P1NP - N-terminal propeptide of Type 1 procollagen
- Bone Resorption
  - NTX – N-telopeptide of type 1 collagen
  - CTX – C-terminal telopeptide of type 1 collagen
  - Pyridinoline cross-links

Bone Turnover Markers

- Generalized Use Confounded by:
  - Large within patient variability
  - Biologic variability
    - Age, gender, BMI, circadian, and menstrual variation
    - Poor standardization
- Potential Use
  - Patients who have conditions that may interfere with bisphosphonate absorption
  - Monitor compliance with bisphosphonates
Bone Turnover Markers
- Monitoring Compliance and Drug Efficacy
  - Fasting urinary NTX, serum CTX, or serum P1NP before and after 3-6 months of therapy
  - 50% reduction in urinary NTX
  - 30% reduction in serum CTX
  - Evidence of compliance and drug efficacy

Secondary Osteoporosis
- Estrogen Deficiency - Premenopausal
  - Hypogonadotropic hypogonadism
    - Low Weight
    - Eating Disorders
    - Excessive Exercise
    - Hyperprolactinemia
    - Hypopituitarism
  - Hypergonadotropic hypogonadism (Turner Syndrome)
  - Premenopausal women with breast cancer
    - chemotherapy

Secondary Osteoporosis
- Drugs
  - Glucocorticoids
  - Anticonvulsants
  - Antidepressants
  - Medroxyprogesterone
  - Cigarette smoking
  - Inflammatory Bowel Disease
  - Celiac Disease
  - Cystic Fibrosis
Secondary Osteoporosis
- Hyperthyroidism
- Hypercalciuria
- Hyperparathyroidism
- Osteogenesis imperfecta
- Depression
- Pregnancy and Lactation

Secondary Osteoporosis
- About 50% of Women Have a Specific Etiology for Osteoporosis
  - Steroids 24%
  - Premature menopause 21%
  - Hyperthyroidism 6%
  - Inadequate Vitamin D 9%
  - Hypercalciuria 9%

Secondary Osteoporosis
- Cost Effective Screening
  - Urine and Serum Calcium
  - PTH
  - TSH
- Diagnose 85% of secondary causes
- Other Labs
  - CBC, Creatinine, AST, Alkaline phosphatase, Phos, 25(OH) D, TTG, Cortisol Levels, SPEP, UPEP, Bone Turnover Markers
What are the Fundamental Measures for Bone Health?

- Measure serum 25-hydroxyvitamin D (25(OH)D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis
- Maintain serum 25-hydroxyvitamin D (25(OH)D) ≥30 ng/mL in patients with osteoporosis (preferable range, 30–50 ng/mL)
- Supplement with vitamin D3 if needed; 1,000 to 2,000 international units (IU) of daily maintenance therapy is typically needed to maintain an optimal serum 25(OH)D level
- Higher doses may be necessary in the presence of certain factors (e.g., obesity, malabsorption, transplant patients, certain ethnicities, older individuals)
- Counsel patients to maintain adequate dietary intake of calcium, to a total intake (including diet plus supplement, if needed) of 1,200 mg/day for women ≥50 years
- Counsel patients to limit alcohol intake to no more than 2 units per day.

Calcium Content of Foods

- Milk 8 oz: 300 mg
- Yogurt 6 oz: 250 mg
- Orange Juice with calcium 8 oz: 300 mg
- Cheese 1 oz: 200-300 mg
- Ice cream ½ cup: 100 mg
- Dark, leafy green veg. ½ cup: 100 mg
- Beans ½ cup cooked: 80 mg
- Almonds 24: 70 mg
**Vitamin D Food Sources**

- Cod liver oil 1 tablespoon: 1360 IU
- Salmon 3 oz: 794 IU
- Mackarel 3 oz: 388 IU
- Milk 8 oz fortified: 120 IU
- Orange Juice 8 oz fortified: 100 IU
- Yogurt 6 oz fortified: 80 IU

**What are the Fundamental Measures for Bone Health?**

- Counsel patients to avoid or stop smoking
- Counsel patients to maintain an active lifestyle, including weight-bearing, balance, and resistance exercises
- Provide counseling on reducing risk of falls, particularly among the elderly
- Consider recommending use of hip protectors in individuals with a high risk of falling
- Consider referral for physical therapy, which may reduce discomfort, prevent falls, and improve quality of life

**Who Needs Pharmacologic Therapy?**

- Strongly recommend pharmacologic therapy for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine
- Strongly recommend pharmacologic therapy for patients with a T-score of −2.5 or lower in the spine, femoral neck, total hip or 33% radius
- Strongly recommend pharmacologic therapy for patients with a T-score between −1.0 and −2.5 if the FRAX® 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% in the U.S. or above the country-specific threshold in other countries or regions
What Medication Should Be Used to Treat Osteoporosis?

- Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, risedronate, zoledronic acid, and denosumab are appropriate as initial therapy for most patients at high risk of fracture.
- Teriparatide, denosumab, or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially high fracture risk.
- Raloxifene or ibandronate may be appropriate initial therapy in some cases where patients requiring drugs with spine-specific efficacy.

Bisphosphonates

- Oral Bisphosphonates
  - Alendronate (Fosamax) 70 mg po q week
  - Risedronate (Actonel) 35 mg po q week
  - Ibandronate (Boniva) 150 mg po q month
    - Reduction in hip fracture risk not demonstrated with ibandronate

Bisphosphonates

- Adverse Reactions
  - Local irritation of the upper GI mucosa
  - Reflux, esophagitis, or esophageal ulcers
  - Low incidence if properly administered
  - Contraindicated
    - Achalasia, esophageal stricture, esophageal varices, or Barrett's esophagus
    - Inability to stay upright for 30-60 minutes
  - Acute-phase reaction within 24-72 hours of infusions
    - Low grade fever, myalgias, arthralgias
    - Treat with antipyretics
    - Decreases over subsequent infusions
Bisphosphonates

- Adverse Reactions
  - Hypocalcemia, more common with IV administration
  - Risk Factors: hypoparathyroidism, Vitamin D deficiency, inadequate calcium intake.
  - Prevention: Vitamin D and Calcium supplementation
  - Calcium interferes with bisphosphonate absorption and should not be given for at least an hour after bisphosphonate oral administration
  - Severe musculoskeletal pain within days to years after starting a bisphosphonate
  - Symptoms don't always resolve with discontinuation
  - Contraindicated in patients with creatinine clearance less than 30-35 ml/min

Osteonecrosis of the Jaw

- Symptoms – pain, swelling, exposed bone, local infection, and pathologic fracture of the jaw.
- Prevalence
  - Most cases in cancer patients or patients with compromised immune systems
  - Breast Cancer, Multiple myeloma

Osteonecrosis of the jaw

- Risk Factors
  - IV administration
  - Cancer and anticancer therapy
  - Dose and duration of therapy
  - Dental extractions, dental implants, poor fitting dentures
  - Glucocorticoids
  - Smoking
  - Diabetes
  - Preexisting dental disease
Osteonecrosis of the Jaw

- Prevention
  - Good oral hygiene and regular dental visits
  - Delay start of bisphosphonate until after invasive dental procedure
  - American Association of Oral and Maxillofacial Surgeons
    - Perform extractions and implants as usual on patients taking bisphosphonates for less than 4 years
    - Discontinue bisphosphonates for 2 months prior to procedure in patients taking bisphosphonates for more than 4 years or concomitant glucocorticoids
    - Restart bisphosphonates after bone has healed

Atypical Femur Fractures

- Rare – median treatment of 7 years
- Thought to be secondary to over suppression of bone turnover and increased skeletal fragility
- There is evidence that suggests bisphosphonates accumulate in areas that are developing stress fractures and suppress intracortical remodeling, impairing normal healing of the stress fracture.
- Patients often have a prodrome that includes dull or aching pain in the groin or thigh.

Evaluation

- Plain x-ray – periosteal thickening and cortical lucency
- MRI

Treatment – Prodromal Phase

- Discontinue bisphosphonate
- Adequate Vitamin D and Calcium
- Limited Weight Bearing for those with incomplete fracture and minimal pain.
- Reduced activity is continued until there is no edema on MRI or no increased activity on bone scan
- Orthopedic intervention if no improvement in 2-3 months
Teriparatide (Forteo)

- 20 mcg SQ q day
- Indication
  - T-score -3.5 or below
  - T-score -2.5 or below + fragility fracture
  - Osteoporosis and intolerance to bisphophonates
- MOA – PTH stimulates bone formation and remodeling. Reduces risk of vertebral and nonvertebral fractures

Teriparatide (Forteo)

- Contraindications
  - Primary or Secondary Hyperparathyroidism
  - Hypercalcemia
  - Increased risk of Osteosarcoma
    - Paget Disease, Radiation Therapy, Elevated Alk Phos,
    - Pre-existing malignancies
  - Renal stones
  - Renal insufficiency

Teriparatide (Forteo)

- Adverse Reactions
  - Osteosarcoma – animal studies
  - Hypotension
  - Depression
  - Pneumonia
  - Transient Hypercalcemia
  - Arthralgia
  - Asthenia
  - Nausea
  - Dizziness
  - Constipation
Teriparatide (Forteo)

- Pre-Treatment
  - DEXA
  - Ca
  - Phos
  - Creatinine
  - Alk Phos
  - Alb
  - 25-hydroxy D
  - 24 hour urine calcium and creatinine

- Supplemental Calcium and Vitamin D
- Replace Vitamin D if deficient prior to starting Teriparatide

- Monitoring
  - Serum Calcium and Renal Function
  - Stop after 24 months
  - No proven efficacy past 2 years
  - Potential risk of osteosarcoma – rats
- For high risk patients, start bisphosphonate or denosumab or raloxifene after Teriparatide course complete.

Denosumab (Prolia)

- 60 mg SQ q 6 months
- MOA – binds RANKL reducing formation, function, and survival of osteoclasts.
- Indication: patients who have difficulty with the dosing requirements of oral bisphosphonates or have markedly impaired renal function
- Hypocalcemia and Vitamin D deficiency should be replaced prior to treatment
- Calcium should be monitored in renal disease and other conditions that predispose to hypocalcemia
Demosumab (Prolia)

- Use in Chronic Kidney Disease
  - No restrictions with creatinine clearances below 35mL/min like bisphosphonates
- Duration
  - No drug holiday required
- Side Effects
  - Back, extremity, and musculoskeletal pain
  - Hypercholesterolemia
  - Cystitis

Denosumab (Prolia)

- Serious Adverse Reactions
  - Hypocalcemia
  - Osteonecrosis of the Jaw
  - Atypical femur fractures
  - Serious infections

Raloxifene (Evista)

- 60 mg po q day
- Raloxifene has estrogen agonist activity in bone.
- Not a first line treatment.
- Reduces risk of vertebral fractures
- Less potent than alendronate
- Safety demonstrated up to 8 years
Raloxifene (Evista)

- Adverse Reactions
  - Hot flushes, leg cramps, and peripheral edema
  - Gallbladder disease
  - Venous thromboembolism
  - Fatal Stroke
- Benefit
  - Decreases risk of breast cancer

How is Treatment Monitored?

- Obtain a baseline axial (spine and hip) DXA, and repeat DXA every 1 to 2 years until findings are stable. Continue with follow-up DXA every 1 to 2 years or at a less-frequent interval, depending on clinical circumstances
- Monitor serial changes in lumbar spine, total hip, or femoral neck BMD; if spine, hip, or both are not evaluable, consider monitoring using the 33% radius site
- Follow-up of patients should ideally be conducted in the same facility with the same machine
- Consider using BTMs for assessing patient compliance and therapy efficacy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction; significant increases indicate good response to anabolic therapy

What is Successful Treatment of Osteoporosis?

- Successful treatment of osteoporosis is defined as stable or increasing BMD with no evidence of new fractures or fracture progression
- For patients taking antiresorptive agents, target for treatment success is BTMs at or below the median value for premenopausal women
- Consider alternative therapy or reassessment for causes of secondary osteoporosis in patients who have recurrent fractures or significant bone loss while on therapy. A single fracture while on therapy is not necessarily evidence of treatment failure, but it does suggest that fracture risk is high.
How Long Should Patients Be Treated?

- Treatment with teriparatide should be limited to 2 years.
- For oral bisphosphonates, consider a “bisphosphonate holiday” after 5 years of stability in moderate-risk patients.
- For oral bisphosphonates, consider a “bisphosphonate holiday” after 6 to 10 years of stability in higher-risk patients.
- For intravenous (IV) zoledronic acid, consider a drug holiday after 3 annual doses in moderate-risk patients and after 6 annual doses in higher-risk patients.

- Teriparatide or raloxifene may be used during the “bisphosphonate holiday” period for higher-risk patients.
- A drug “holiday” is not recommended with denosumab.
- The ending of the “holiday” for bisphosphonate treatment should be based on individual patient circumstances (fracture risk or change in BMD or BTMs).
- Other therapeutic agents should be continued for as long as clinically appropriate.

Is Combination Therapy Better Than Treatment With a Single Agent?

- Until the effect of combination therapy on fracture risk is demonstrated, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis.
- If estrogen is being given for treatment of menopausal symptoms or raloxifene is administered to reduce the risk of breast cancer, an additional agent such as a bisphosphonate, denosumab, or teriparatide may be considered in higher-risk patients.
- Combined denosumab and teriparatide achieves a better BMD response versus either agent alone, but no fracture data are available.
Should Sequential Use of Therapeutic Agents Be Considered?

- Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy.

Should Vertebral Augmentation Be Considered for Compression Fractures?

- Vertebroplasty and kyphoplasty are not recommended as first-line treatment of vertebral fractures given the unclear benefit on overall pain and the potential increased risk of vertebral fractures in adjacent vertebrae.

When Should a Referral to a Clinical Endocrinologist or Osteoporosis Specialist Be Considered?

- When a patient with normal BMD sustains a fracture without major trauma.
- When recurrent fractures or continued bone loss occurs in a patient receiving therapy without obvious treatable causes of bone loss.
- When osteoporosis is unexpectedly severe, has unusual features, or less common secondary conditions (e.g., hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin) are identified.
- When a patient has a condition that complicates management (e.g., chronic kidney disease [CKD]: glomerular filtration rate [GFR] <35, hyperparathyroidism, or malabsorption).
- Patients who experience fragility fractures should be evaluated and treated. Referral to an osteoporosis specialist or a fracture liaison team, if available, should be considered.