Bone Health in Midlife

Questions:

1. How does the hormonal shift of menopause, particularly declining estrogen, accelerate bone loss, and what should clinicians be watching for in this transition?

2. What are the most effective screening strategies for identifying women at high risk for osteoporosis during midlife?

3. How do you approach the conversation about bone-density testing timing and frequency with your patients?

4. When should the screening DXA scan take place?

5. What is work up for low bone mass that an OBGYN or PCP should do? When to send on to your bone health experts?

6. Which lifestyle and nutritional interventions have the strongest evidence for preserving bone health in postmenopausal women?

7. Can you walk through when to initiate pharmacologic treatment, and how you weigh options such as bisphosphonates, SERMs or hormone therapy? (costs to patients?)

8. How do comorbidities like early menopause, history of fractures, cancer therapies or chronic steroid use change your management approach?

9. What emerging therapies or diagnostics in bone health are you most excited about, and how might they change practice in the coming years?

Bone Health in Women during Midlife

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Skeletal Changes in Women during the Hormonal Shift of Menopausal

- Decreases in supportive hormones (Estrogen) lead to bone loss
    - Estrogen inhibits osteoclast activity (bone break-down)
        - Suppresses osteoclast differentiation
        - Induces osteoclast apoptosis
        - Impairs the bone reabsorption activity of osteoclasts
    - Estrogen promotes osteoblast activity (bone building)
        - Enhances osteoblast survival
        - Stimulates osteoblast recruitment
        - Enhances mineralization
    - Bone loss can occur as early as 3 years before the final menstrual period
    - Trabecular bone takes the biggest hit early on followed by cortical bone
        - Sites with more trabecular bone suffer first (wrists, humerus, vertebrae)
        - Sites with more cortical bone suffer later (hips)

Osteoporosis Screening Recommendations

- Women <u>who are undergoing or have completed</u> the hormonal shift of menopause
    - Women 50 should begin osteoporosis screening at the age of 50
        - Guidelines recommend in office risk assessment
            - FRAX is most commonly used and can guide decision to get DXA in women with elevated risk
            - DXA can also be used
    - DXA recommended for **all women starting at age 65**
    - Clinical Tip for DXA ordering
        - Private Insurance will often cover DXA for screening in women <65
        - Medicare will not cover DXA for "screening" so it is best to use the most appropriate applicable diagnosis that applies to your patient
            - For example: Osteoporosis, Low bone Density (osteopenia), postmenopausal status, etc.
- Women <u>who have not yet reached the hormonal shift of menopause</u>
    - Women 50 should begin osteoporosis screening at the age of 50

        - Guidelines recommend in office risk assessment
            - FRAX is most commonly used and can guide decision to get DXA
            - Considerations when ordering DXA in women who are menstruating regularly and so have not yet reached the hormonal shift (perimenopause)
                - DXA in this group is read based on Z-scores and not T-scores so you will (or should) get a different looking result
                    - Bone Density within the Expected Range for Age
                    - Bone Density below the expected range for Age
                - Osteoporosis diagnosis cannot be made based on DXA alone in women who are in this group
                - Medications for osteoporosis treatment are not recommended for patients who could become pregnant because they change bone turnover and interfere with bone growth

Osteoporosis Prevention

- **Use a Lifetime STRATEGY!**
    - Bone loss is a lifetime issue so manage it as such
    - All interventions should be part of a lifetime strategy for bone loss and fracture prevention
- Estrogen replacement
    - Doses of 0.3-0.45mg/dL CEEs oral or 50mcg Transdermal prevent bone loss. Higher doses show BMD gains.
        - Bone resorption decreases rapidly in 3-6 months after starting MHT
        - Reduces fracture risk by 20-40%
            - Works to reduce risk even in patients already at low risk
            - Risk reduction rapidly disappears and bone loss resumes rapidly after estrogen is stopped
    - Benefit/risk profile most favorable for women < 60 or within 10 years of menopause
- Bone medications approved for prevention
    - Bisphosphonates (alendronate or Zoledronic acid)
        - Emerging strategy for single dose zoledronic acid
    - Denosumab (only in cancer patients)

- Effects of Exercise on the skeleton
    - Different at different phases of the life cycle
        - Large impact in teens and pre-teens of variable impact exercise (ball sports) of up to 1 standard deviation higher bone density
        - Helps to support bone during middle life
        - Helps to reduce fracture risk through improvements in balance and modest effects on BMD in the post-menopausal skeleton
            - 10-11% reduction in fracture risk with consistent weight bearing exercise.
                - Effect is largely due to improved balance and strength rather than the modest possible effects on BMD
                - Effects are more pronounced with more intense and frequent exercise
                - Effects disappear rapidly when regular exercise is discontinued.
    - Exercise is a part of a complete bone health strategy
        - AACE recommends 30-40 minutes of walking combined with pack and posture exercises be completed 3-4 days per week throughout life for postmenopausal women
- Dietary Factors for Skeletal Support
    - Optimize Calcium and Vitamin D
    - Avoid vitamin K2 (for now)
        - The claim that K2 helps to support bone mineralization is not yet fully understood or substantiated by the evidence and there are not any documented benefits for fracture risk reduction at this time
        - There is concern that K2 may interfere with the clotting cascade and reasonable evidence that it interferes with anticoagulant efficacy
    - Avoid strontium citrate
        - Potential cardiac risks
        - Erroneously elevates BMD without known or significant effects on fracture risk
- Diagnosis and Initial Workup of Osteoporosis
    - Diagnosing Osteoporosis AACE 2020
        - Take a fracture history to look for low trauma fractures in adult life

- What bone? Specific as possible because some lower trauma (forces equivalent to fall from a standing height or less) fractures might change the diagnosis.
- How did you break it? Specific as possible… Did the patient slip on the ice or fall off the roof, etc.
- When did it break? (How old was the patient at the time of the fracture… fractures in adult life and especially after age 50 are most impactful on fracture risk calculation)

- Take a medical history to look for conditions that increase the risk of additional bone loss. Look for things like diabetes, chronic steroid use, rheumatoid arthritis, malabsorption, etc. See compiled list from the BHOF at the end of this document
- If you have not already gotten a DXA then get one
- If your DXA did not come with a FRAX then calculate it
  - https://www.fraxplus.org/calculation-tool/
- Apply the AACE 2020 guidelines for diagnosis
  - T-score -2.5 or below in the lumbar spine, femoral neck, and/or 33% (one-third) radius.
  - **Low-trauma spine or hip fracture (regardless of BMD)**
  - Osteopenia or low bone mass (T-score between -1 and -2.4) with a fragility fracture of the proximal humerus, pelvis, or distal forearm.
  - Low bone mass or osteopenia and high FRAX fracture probability based on country-specific thresholds. (US 3% hip; 20% any major osteoporosis related fracture)

- Initial Workup once the diagnosis is made
  - Initial workup: Complete blood count, CMP (Calcium, Renal function, LFTs including Alk Phos) Phosphorus, Magnesium, 25(OH) D, Thyroid stimulating Hormone, Parathyroid Hormone.
  - Can also consider in selected patients: gonadotropin levels, 24-hour urinary calcium, Serum protein electrophoresis, Urine protein electrophoresis, Tissue transglutaminase, etc.
- Refer to Bone Health and Osteoporosis specialist
  - When patient is in the very high fracture risk category by AACE
  - When the answer is not clear after your initial workup
  - When you need assistance with the workup

        - When you are not familiar or comfortable with long term strategic management of a relatively young patient with poor bone mass
- Osteoporosis Treatments and how to pick one
    - Consider the patient's risk level, functional status, contraindications, and preferences
        - Patients at highest risk of fracture should be considered for more robust therapies
        - As part of a lifetime management strategy, more robust therapies should be considered initially in younger patients with higher functional status and longer expected management course.
        - Patient's at very high risk should be considered for the most robust therapies
        - Consider the patient's ability to comply with the course of therapy
    - Risk assessment
        - AACE 2020 guidelines
            - Once the diagnosis of Osteoporosis is made all patients are at either high or Very high risk of fracture
            - Very High Fracture Risk by AACE 2020
                - a T-score less than -3.0
                - experienced a fracture within the past 12 months
                - fractured while on approved osteoporosis therapy
                - had multiple fractures, have fractured while on drugs that cause skeletal harm (such as glucocorticoids)
                - high risk for falls or history of injurious falls
                - very high FRAX fracture probability (> 30% 10 year risk of major osteoporotic fracture and/or >4.5% 10 year risk of hip fracture)
                    - https://www.fraxplus.org/calculation-tool/
    - Sequence matters for osteoporosis medications
        - Anabolics (bone Builders) are most effective when used before a patient has had antiresorptive meds
        - PTH analogs can be considered WITH but not AFTER Denosumab
        - Denosumab MUST be followed by another med to avoid rebound fracture risk
        - Anabolics (bone builders) must be followed by an antireabsorptive (bone keeper) to avoid losing the bone that was built
    - Osteoporosis treatments grouped by effect on fracture risk

        - Anabolics/bone builders(teriparatide, abaloparatide, and Romosozumab) ~80% fracture risk reduction (WOW)
        - Injectable Antiresorptives/bone keepers(zoledronic acid and Denosumab) ~60% fracture risk reduction
        - Oral Antiresorptives/bone keepers(alendronate and Risendronate) ~40% fracture risk reduction
        - SERMs(raloxifene and tamoxifen) and Estrogen Replacement ~20% fracture risk reduction
        - Exercise/lifestyle mods alone ~10% fracture risk reduction
- Exciting New and Emerging things
    - New studies suggesting extended efficacy of zoledronic acid
    - TBS (Trabecular Bone Score) entering clinical use for FRAX adjustment
    - Denosumab biosimilars (generics) entering the market

Conditions that Increase the Risk of Bone Loss and Osteoporosis

Compiled list from the Bone Health and Osteoporosis Foundation

- Lifestyle Factors
  - Alcohol Abuse
  - Smoking
  - Low body weight
  - Immobilization
  - Excessive Falling
  - Excess Vitamin A
  - Vitamin D insufficiency
  - Low calcium intake
- Medications
  - Glucocorticoids
  - Tamoxifen
  - Anticonvulsants
  - Aromatase inhibitors
  - Chemotherapy drugs
  - GnRH agonists and antagonists
  - Tacrolimus and Cyclosporin A
  - Methotrexate
  - TPN
  - Thiazolidinedione
  - SSRIs
  - PPIs (maybe)
  - Aluminum (in antacids)
  - Heparin
  - Lithium
  - Barbiturates
- Genetic Factors
  - CF
  - Ehlers-Danlos
  - Gaucher's Disease
  - Glycogen storage Diseases
  - Hemochromatosis
  - Homocystinuria
  - Hypophosphatemia
  - Idiopathic hypercaliuria
  - Marfan Syndrome
  - Menkes steely hair syndrome
  - osteogenesis imperfecta
  - parental history of hip fracture
  - porphyria
  - Riley-Day Syndrome
- Hypogonadal states
  - Androgen insensitivity
  - Anorexia and Bulimia
  - Hyperprolactinemia
  - Premature menopause (Less than Age 45)
  - Turner's and Kleinfelter's
  - premature ovarian failure
  - athletic amenorrhea
  - panhypopituitarism
- Endocrine disorders
  - Adrenal insufficiency
  - Diabetes mellitus
  - Hyperparathyroidism
  - Cushing's Syndrome
  - Thyrotoxicosis
- Rheumatologic/ Autoimmune
  - Ankylosing Spondylitis
  - Lupus
  - Rheumatoid Arthritis
- GI disorders
  - Celiac disease
  - Gastric Bypass
  - Inflammatory Bowel disease
  - Malabsorption
  - Pancreatic disease
  - GI surgery
  - Primary Biliary Cirrhosis
- Hematologic disorders
  - Multiple myeloma
  - Leukemia and Lymphoma
  - Hemophilia
  - Thalassemia
  - Monoclonal gammopathies

- Sickel Cell Disease
- Systemic mastocytosis

- CNS Disorders
  - Epilepsy,
  - Multiple Sclerosis
  - Parkinson's disease
  - Stroke
  - Spinal cord injury
- Others
  - HIV/AIDS
  - Amyloidosis
  - CHF
  - Muscular dystrophy
  - Sarcoidosis
  - Post Transplant bone disease
    Idiopathic scoliosis
  - End stage renal disease
  - Hypercalciuria
  - COPD
  - Chronic metabolic acidosis