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  - Please refer to learning goals and objectives
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  - Presenter: Marti Reiser, RN, MSN, ANP, CCRN, CDE
  - Consultant in Diabetes Interactive Network: Eli Lilly

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Diabetes and Osteoporosis: What’s the Connection?

Osteoporotic Bone Loss

- Osteoporosis
- Normal

Reprinted from the American Society for Bone Mineral Research

Low-power scanning electron microscope image of normal bone architecture in the 3rd lumbar vertebra of a 30 year old woman marrow and other cells removed to reveal thick, interconnected plates of bone

http://www.brsoc.org.uk/gallery/
Definition of Osteoporosis
Osteoporosis results from an imbalance between resorption and bone formation during bone remodeling.

Resorption defined
A process involving breakdown of the bone by the osteoclasts causing release of calcium and other minerals into the blood. It is stimulated or inhibited by biochemical signals in the body depending on calcium need.

Bone Remodeling
Remodeling: continuous, lifelong process; damaged bone is repaired, ion homeostasis is maintained, and bone is reinforced for increased stress. Resorption and deposition of bone are normally balanced, and bone density is maintained. A lytic lesion results when resorptive activity exceeds deposition activity in a pathologic state.

Bone Remodeling (continued)
An entire normal remodeling cycle requires approximately 6 months. Pathological remodeling occurs more rapidly at menopause or in diseases that increased rate of remodeling.
Bone Types (2) and Struts

1. **Compact bone** (dense or cortical bone) composed of deposits of calcium phosphate and Type I collagen, remodels 3% per year
- no cavities in compact bone.
- surrounds the trabecular bone.
- mineral deposits are arranged in a system of struts with bone marrow filling in the spaces between the struts.

2. **Spongy bone** (trabecular or cancellous bone), remodels 25% per year
- sponge-like with numerous cavities.
- more metabolically active than compact bone because of its much larger surface area for remodeling.

Comparison of Microarchitecture

**Normal**

**Osteoporotic**

World Health Organization (WHO) Criteria for Osteoporosis (DEXA) Scan

- Trabecular or cancellous bone forms the struts inside bone like a honeycomb of interconnecting spaces containing the bone marrow.
- Cortical or compact bone forms the outer shell of most bones. It is harder, stronger and stiffer than cancellous bone and provides the strength for the bones.
**DEXA Scan**

Current best way to predict and evaluate osteoporosis when used in conjunction with a comprehensive risk assessment in people with diabetes.

Measures Bone density

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**T-score** compares current bone density to average bone density of young adult at age of peak bone mass (~30 yrs)

**Z-score** compares to persons of same age/sex

**Normal bone density** = T-score on bone densitometry of > -1.0 SD below the mean or higher

**Osteopenia**

T-score < -1.0 to -2.5 SD

**Osteoporosis**

T-score < -2.5 SD; severe is < -2.5 with fracture

If decreased bone density noted on x-ray, then bone loss is ~30%

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**Which Sites to Evaluate?**

DEXA of hip and spine unless hip/spine can’t be measured.

In Hyperparathyroidism or severe obesity over the weight limit of DEXA table, the recommendation is to measure 33% forearm site

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**Recommendations for Screening**
**National Osteoporosis Foundation (NOF)**

**Recommendations for Screening (continued)**

- Adults with a diagnosis or taking a medication associated with low bone mass or loss.
- Women in the menopausal transition with specific risk factors associated with fracture.
- Postmenopausal women stopping Hormone replacement therapy (HRT).

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**What Else to Consider?**

The T-score should not be the only major factor determining the interval for bone mineral density testing.

The presence of multiple clinical risk factors incrementally increases the fracture risk (which can be assessed via FRAX) and may require starting drug therapy earlier.

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**Causes of Inadequate Peak Bone Mass**

- Genetic factors: determining peak bone mass
- Inadequate nutrition during growth and development and limited physical activity
- Diseases: thyrotoxicosis, parathyroid disease, Cushing’s, Type 1 and 2 Diabetes, Vitamin D deficiency
- Drugs: Anticonvulsants, corticosteroids, (e.g., for asthma or rheumatoid arthritis) during growth that impair bone mass acquisition or increase bone turnover.

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**Risk Factors**

- Hyperthyroidism or hypothyroidism over-treated with thyroid med (Increased bone turnover)
- Possibly uncontrolled blood sugars.
- CKD (secondary hyperparathyroidism).
- Elderly
- Family History
Risk Factors for Osteoporosis (continued)
Post-menopause or post oophorectomy with no HRT or ERT.
Low testosterone level in men, not replaced.
Poor absorption of minerals in celiac disease, IBD, Crohn’s, or post-bariatric surgery.
Corticosteroids or Cushing’s disease (reduce calcium absorption and impair vitamin D metabolism).

Lifestyle Risk Factors
Low calcium intake or Vitamin D insufficiency
Excessive vitamin A (thought to trigger an increase in osteoclasts or interfere with vitamin D)
High caffeine intake (in elderly women with low calcium levels, high caffeine intake may cause cortical bone loss from the proximal femur.)
High salt intake (increased Calcium urinary loss)

Lifestyle Risk Factors
Aluminum (in antacids) cause calcium loss
Alcohol (3 or more drinks/day interferes with calcium balance, reduces estrogen or testosterone levels needed for osteoblasts formation, increases cortisol levels (in alcoholism) that decreases bone formation and increases bone breakdown.

Inadequate physical activity
Immobilization (calcium from bone is lost)
Smoking, active or passive, decreases bone density
Falling, poor balance, poor vision
Thinness (small frame)

Drugs Contributing to Osteoporosis
Corticosteroids
Chemotherapy
Anticonvulsants
Heparin
Barbiturates

Drugs Contributing to Osteoporosis
GnRH agonists (leuprolide used for prostate CA)
Aromatase inhibitors (anastrozole-slow rate breast tumor growth)
SSRIs (anti-depressant)
PPIs (Proton Pump inhibitors for GI use)
Medical Conditions Associated with Osteoporosis

Type 1 Diabetes and Osteoporosis
Associated with low Vitamin D levels
Growth can be impaired with hyperglycemia and lower peak bone mass may be caused by insulin deficiency needed for bone growth and strength and is associated with osteoporosis later in life.

Type 2 Diabetes and Osteoporosis
May be associated with low Vitamin D levels
Growth (young Type 2 diabetics) can be impaired with hyperglycemia and lower peak bone mass may be caused by insulin deficiency needed for bone growth and strength.

Type 2 Diabetes and Osteoporosis
Type 2 diabetes: Fracture rate is increased, that maybe due to neuropathy, increased fall rates and hyperglycemia.
TZDs (pioglitazone and rosiglizone) used to treat diabetes, may cause bone loss and increased fracture risk.

Type 2 Diabetes
High body fat in women (greater than 32% body fat) had bones that were 8 to 9% weaker than those with normal body fat.
Hyperglycemia leads to glycosuria, which causes hypercalciuria, leading to decreased levels of calcium in the body and poor bone quality.

Hyperthyroidism
Increased, rapid bone remodeling due to increased metabolism can lead to decreased bone strength.
Increased number of bone-remodeling cycles deceases bone mass rather than building it; the more cycles you go through, the more bone mass you lose.
Osteoporosis Changes with Age

Who Do We Treat?

T-score between -1 and -2.5 at the femoral neck, total hip, or spine
10-year probability of hip fracture >3%
10-year probability of any major osteoporosis-related fracture >20 percent based upon the US adapted WHO algorithm (FRAX)

FRAX
The World Health Fracture Risk Assessment Tool can be accessed at:

www.NOF.org
or
www.shef.ac.uk/FRAX
Medications Used to Treat

**Bisphosphonates**
Inhibit osteoclast resorption

**Oral preparations:**
1. Alendronate daily or weekly dose
2. Ibandronate monthly
3. Risedronate daily or monthly

Take on empty stomach and stay upright for at least 30 minutes

**IV Bisphosphonates Used for Osteoporosis**
1. Zolendronic acid annually or every 2 years
2. Ibandronate every 3 months
   - Flu-like febrile illness lasting approx. 1-2 days
   - Decreases with adequate hydration and acetaminophen pre-treatment
   - Check creatinine prior to ordering

**Side effects** (Any route):
- Hypocalcemia if vitamin D deficient
- Ocular side effects are rare: formation of cataracts
- Osteonecrosis of the jaw
  - Uncommon in oral, but is reported in IV use for multiple myeloma
- Renal function: do not use if GFR is below 30 to 35 ml/min
- Atypical fracture in subtrochanter or femoral after long term use.
- Esophagitis, gastric ulcer, dysphagia

**Vitamin D**
(D\textsubscript{2}) or (D\textsubscript{3})

Adults age 50 and above: Vitamin D 800 to 1000 IU daily (NOF)
Adults age 50 to 70: 600 IU daily (IOM)
Adults age 71: 800 IU daily (IOM)
   - Maintaining serum 25-OH D levels at 30-40 ng/ml may be most effective
   - Vitamin D from diet is preferred
   - Safe upper daily limit is 4000 IU

**Calcium**
Dosage: 800 to 1000 mg. daily of elemental calcium
   - Dosages >500 mg. should be divided
   - No decrease in fracture incidence although bone density increases
Calcium carbonate should be taken with meals to enhance absorption
In patients taking Proton pump inhibitors (PPIs), calcium citrate absorbs better
Side effects
- Kidney stones
- Dyspepsia and constipation

Interactions
- Interfere with absorption of iron and thyroid hormone and should be taken at different times

Estrogen Agonist/Antagonist (aka SERMs)
- Raloxifene
  - Tissue selective estrogen properties
  - Prevention and treatment of osteoporosis in postmenopausal women
  - Due to their lower efficacy, use in patients who can’t take bisphosphonates

Adverse effects: Hot flashes
- No increase in stroke

Teriparatide
- SubQ, parathyroid hormone
  - Pharmacology
    - Extensively absorbed after SubQ injection
    - Half life in serum 1 hr. SubQ
  - Method of action: Anabolic action and initiates greater bone formation in trabecular and cortical bone surfaces by stimulating osteoblastic over osteoclastic activity.

Side effects
- Transiently increases serum calcium
- Allergic response
- Muscle spasms, usually after 1st dose
- May precipitate gout
- Osteosarcoma (1 case in 300,000 users)

Dose: 20 mcg/day Subcu

Receptor Activator of Nuclear Factor kappa-B (RANK) Ligand (RANKL)/ RANKL Inhibitor:
- Indicated to increase bone mass in men and women
- Dose is 60 mg SubQ in clinic q6 months
- Can cause hypocalcemia so check Calcium level prior.
- Could cause osteonecrosis of jaw especially when used to treat patients with cancer and has been associated with atypical fractures.
- Used in patients with bone loss from breast/prostate cancer who are high risk for fracture.

Choosing a Medication
- First-line therapy for postmenopausal osteoporosis
- Oral bisphosphonates or
  - IV Zolendronic acid or Ibrandronate for those who can’t tolerate oral
- Estrogen Agonist/Antagonist: Raloxifene
  - Antiresorptive effects less than bisphosphonates
  - Use in patients who can’t tolerate bisphosphonates
  - Use in women with osteoporosis and increased risk of breast cancer
Choosing a Medication

Teriparatide: For use in patients with severe osteoporosis and fracture risk
- T-scores <-3.5
- T-scores <-2.5 with fragility fracture
- Not used as first-line drug for treatment or prevention due to cost, side effects, and daily SubQ injections

RANKL Inhibitor: patients with bone loss due to breast or prostate cancer

Length of Treatment

Bisphosphonates
- For patients with stable BMD and no fractures: Discontinue and monitor after 5 years
- In patients with previous fractures, older, frail, high risk for falls:
  Continue medication and Surveillance DEXA in 2 years

Teriparatide: Use only for 24 months due to possible osteosarcoma risk. In patient who are still at high risk, start raloxifene or bisphosphonate if not contraindicated. DEXA in 1-2 years

Estrogen/HRT

In post-menopausal patients without uterus
Recommended for short term
Yearly mammograms and monthly self breast exam
When stopped, bone loss can be rapid and alternative agents should be considered

When to Retest DEXA?

Clinicians can choose to shorten the testing interval if there is evidence of decreased activity or mobility, weight loss, or other risk factors not considered in their analysis.

Not all insurances will pay for yearly DEXA
Other Treatments
1. Safe exercise as able
2. Reduce fall risks for patients with neuropathy or retinopathy and the elderly by ensuring a safe living environment (remove throw rugs, etc.), use of assistive devices such as canes/walkers
3. Glycemic control

Take Home /Summary
Patients who are at high risk for osteoporosis include:
People with Type 1 and Type 2 Diabetes
Patients with history of hyperthyroidism
Earlier screening and treatment is recommended for these patients.

Take Home /Summary
Adequate glycemic control (for growth in young) and the prevention of diabetic complications (neuropathy, retinopathy, nephropathy) in all Type 1 and Type 2 patients to help to reduce other risks such as falls.

CDEs are well placed to help with screening and referrals for patients with diabetes and osteoporosis risk factors.

Thank you for your attention!