Osteoporosis

An Under-Diagnosed and Under-Treated Disease

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Medicine Grand Rounds

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Disclosures for Catherine Womack

• None
Objectives

• Understand how osteoporosis is an under-diagnosed and under-treated disease.
• Be able to make the diagnosis and provide the correct treatment for your patients.
• Know the appropriate work-up and how to assess risk.
• Understand the side effects of the medications and why your patients may not take the medications that you prescribe.
• Be able to treat patients, but if they are too complicated then refer them to an osteoporosis expert or endocrinologist in your community.
Case 1

- A patient who was previously treated with oral bisphosphonates presents to clinic after a 2 year drug holiday. Her DXA results are listed below. She has recently fractured her wrist while walking her dog. She fell from a standing height. Her eGFR is $\leq 35$ mL/min. What is the best approach for the management of this patient?

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD</th>
<th>T-Score</th>
<th>Z-Score</th>
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<tbody>
<tr>
<td>AP Lumbar (L1-L4)</td>
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<td>Left Hip (Total)</td>
<td>0.970</td>
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<td>Right Hip (Total)</td>
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<td>Right Femoral Neck</td>
<td>0.618</td>
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Case 2

A patient who was previously treated with oral bisphosphonates presents to clinic after a 2 year drug holiday. Her DXA results are listed below. She has clinically significant GERD. What is the best approach for the management of this patient?

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD</th>
<th>T-Score</th>
<th>Z-Score</th>
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<tbody>
<tr>
<td>AP Lumbar (L1-L4)</td>
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<td>Left Hip (Total)</td>
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<td>-1.1</td>
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<tr>
<td>Left Femoral Neck</td>
<td>0.545</td>
<td>-2.7</td>
<td>-1.3</td>
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<tr>
<td>Right Hip (Total)</td>
<td>0.621</td>
<td>-2.6</td>
<td>-1.4</td>
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<tr>
<td>Right Femoral Neck</td>
<td>0.514</td>
<td>-3.0</td>
<td>-1.5</td>
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</table>
Osteoporosis
Definition and Cost
Definition of Osteoporosis

- Low bone mass
- Micro architectural deterioration
- Consequences of both lead to
  - Bone fragility
  - Susceptibility to fracture

What is osteoporosis?

- Osteoporosis, or porous bone is a disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures especially of the hip, spine and wrist although any bone can be affected.
Fractures

• More than 2 million osteoporosis-related fractures occur annually in the U.S., more than 70% of these occur in women\(^1\)

• In the U.S., Medicare currently pays for most of these costs, and as the population ages, the costs of these fractures are estimated to exceed $25 billion by 2025.\(^2\)

• Despite these significant costs, fewer than 1 in 4 women aged 67 years or older with an osteoporosis-related fracture undergoes bone density measurement or begins osteoporosis treatment.\(^3\)

\(^1\)The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. JBone Miner Res. 2014;29:2520-2526.

\(^2\)www.nof.org

NOF President comments regarding the 2 million fractures that occur each year

“Over 300,000 of those broken bones will be hip fractures – the most life changing of all fractures. In fact, 25% of women over the age of 50 who sustain a hip fracture die in the year following the fracture, 50% never walk independently again and 20% require permanent nursing home placement. We can and we must do more to prevent these fractures.”
Universal Prevention / Treatment Strategies

• Advise all patients about their risk for bone loss
• Advise daily intake of calcium and vitamin D
• Provide guidelines for regular participation in weight-bearing exercise like Tai Chi to reduce risk of falls and to prevent fractures
• Educate about fall prevention
• Stop smoking and moderate alcohol intake
Lifestyle Factors that increase risk

• Low calcium intake
• High salt intake
• Vitamin D insufficiency
• Inadequate physical activity
• Immobilization
• Excessive Thinness
• Falling
• Alcohol abuse
• Smoking (active or passive)

Disorders that Increase Risk

- Multiple myeloma
- Sickle Cell disease
- Lupus
- Ankylosing spondylitis
- Rheumatoid arthritis
- Systemic mastocytosis
- HIV/AIDS
- Epilepsy
- Parkinson’s disease
- Spinal cord injury
- Stroke
- Multiple Sclerosis
- Amyloidosis

## Disorders that Contribute

### Endocrine Disorders
- Adrenal Insufficiency
- Cushing’s syndrome
- Diabetes mellitus (Type 1 and Type 2)
- Hyperparathyroidism
- Thyrotoxicosis

### Gastrointestinal Disorders
- Celiac Disease
- Gastric Bypass
- Inflammatory Bowel Disease
- Malabsorption
- Pancreatic Disease

Hypogonadal States

• Hyperprolactinemia
• Anorexia nervosa and bulimia
• Premature menopause
• Premature ovarian failure
• Athletic amenorrhea
• Androgen Insensitivity

Genetic Factors

• Parental History of hip fractures
• Hypophosphatemia
• Idiopathic Hypercalcemia
• Hemochromatosis
• Porphyria
• Cystic Fibrosis

Medications that Contribute

- Aluminum (in antacids)
- Anticoagulants (heparin)
- Anticonvulsants
- Proton pump inhibitors
- SSRI
- Thyroid Hormones
- Aromatase inhibitors
- Methotrexate

- Lithium
- Depo-medroxyprogesterone
- Glucocorticoids
- GnRH
- Barbiturates
- Cancer chemotherapeutic drugs

Neurological and Musculoskeletal Risk Factors

- Kyphosis
- Poor Balance
- Reduced proprioception
- Weak Muscles

Glucocorticoids Increase Risk

- Activate osteoclasts and decrease osteoblast activity
- Increase calcium excretion and decrease calcium absorption
- Turn-off sex hormone production

2010 National Osteoporosis Foundation. www.nof.org
Vertebral Fractures
Fracture Begets Fracture in a Cascade

While the progression of bone loss leading to osteoporosis is gradual over time, once a patient experiences a vertebral fracture, the risk of subsequent fractures can be surprisingly rapid.
Risk of Another Vertebral Fracture Higher in Year Following Fracture

20% will have new vertebral FX within one year

- Overall
- 0 Baseline Vertebral Fractures
- 1 Baseline Vertebral Fractures
- 2+ Baseline Vertebral Fractures

$p<0.05$ vs. patients with no vertebral fractures (12-Fold Increased Risk)

Vertebral Fractures

• Mortality is increased following vertebral fractures
• It is the most common fracture type
• Often silent but insidious and progressive in nature
• Associated with
  – Deformity, height loss, back pain and impaired breathing
  – Predicts future hip and spine fractures

Black, Melton, Sirus and many other studies
Vertebral Fractures

- Only about 1/3 of vertebral fractures found on radiographs come to medical attention because only 10% require admission to the hospital.

- Radiographs are usually not performed when evaluating asymptomatic patients with osteoporosis.

Cooper et al, J of Bone Min Res. 1992:6:221
Hip Fractures

- Hip fractures are associated with an 8.4% to 36% excess mortality within one year\(^1\)
- Higher mortality in men than in women
- Hip fractures are followed by a 2.5–fold increased risk of future fracture\(^2\)
- Approximately 20% of hip fracture patients require long-term nursing home care\(^3\)
- Only 40% fully regain their pre-fracture level of independence\(^3\)

\(^1\)Abrahamsen et al. 2009;20:(10):1633-1650
\(^2\)Colon-Emeric C et al. *Osteoporosis Int.* 2003;(14) 879-883
Osteoporosis Diagnostic Techniques
Note this is not a bone scan. A bone scan is done at a hospital. A bone scan is a nuclear medicine study looking for metastatic disease or a fracture.
DXA Instrumentation and Output

- Hologic QDR4500, QDR2000, 2000+
- Rigorous QA/QC protocol
- Total & Regional
  - Bone,
  - Lean
  - Fat

<table>
<thead>
<tr>
<th>Region</th>
<th>BMC (grams)</th>
<th>Fat (grams)</th>
<th>Lean (grams)</th>
<th>Lean+BMC (grams)</th>
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<td>38871.5</td>
<td>40387.2</td>
<td>52032.8</td>
<td>23.6</td>
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</table>

~assumes 17.8% brain fat
LBM 73.2% water
Bone Mineral Density Testing

• Central DEXA of the hip and spine is the preferred method for diagnosing osteoporosis

• Peripheral machines can measure at other sites like forearm, heel or finger using x-ray or ultrasound (Not advised because can be falsely elevated)
If a patient brings in 3 DXA’s, why are the results not comparable?
World Health Organization (WHO) Definition of Osteoporosis

- Normal BMD = T-score between -1 and +1 SD
- Low BMD (Osteopenia) = T-score between -1.1 and -2.4 SD
- Osteoporosis = T-score of -2.5 SD or lower
- Severe Osteoporosis = T-score of -2.5 SD and fracture(s)

Kanis et al J Bone Miner Res 1994; 9: 1137
WHO Osteoporosis Guidelines

The U.S. Preventive Services Task Force Recommendations for DEXA

- BMD testing for all women aged $\geq 65$
- Younger women with fracture risk
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY (AACE)

• New Guidelines 2016 recommend BMD testing for women aged 65 and older
• Younger postmenopausal women > 50 at increased risk for bone loss and fracture based on fracture risk analysis. (FRAX tool without BMD)
• BMD measurement is not recommended in children, adolescents, or healthy young men or premenopausal women, unless there is a significant fracture history or there are specific risk factors for bone loss (e.g., long-term steroid use)
ACP Osteoporosis Guidelines 5/2017

• Treat known osteoporosis with alendronate, risedronate, zolendronic acid or Denosumab. (Strong)
• Treat Osteoporosis for 5 years (Weak)
• Treat Men with “clinically recognized” Osteoporosis with bisphosphonates. (Weak)
• Do not monitor during the 5 year course of therapy. (Weak)
• Do not use SERMs or Estrogen to treat Osteoporosis (Strong)
• In women 65+, decision to treat should be based on a discussion of patient preferences, risk profile, benefits/harm/cost of medications. (Weak)
Covered Services (CMS)

- A bone density is covered every 2 years by Medicare for estrogen deficient (menopausal) at clinical risk for osteoporosis or for patients on treatment.
- ACP Osteoporosis guidelines issued June 6, 2017 advise against repeating the DEXA for patients on therapy.

Covered Services (CMS)
Who else is eligible?

- A patient with a vertebral abnormality on X-ray
- Individuals on long-term glucocorticoid therapy
- Primary Hyperparathyroidism
- Individuals being monitored on osteoporosis medication
- Notice men are not on this list unless they have Hyperparathyroidism or vertebral abnormality
- Check with local CMS carrier for appropriate ICD-10 codes

So will Medicare pay for the following DXA scans?

• 75 yo frail WM on Lupron for 2 years
• 80 yo BM with height loss but no history of fracture
• 65 yo BM with hypogonadism for many years who did not use testosterone replacement

The answer is no unless the scan makes the diagnosis of osteopenia or osteoporosis. If they have lost height, you can get an x-ray and if compression fracture, Medicare will pay.
Osteoporosis Prevention
Regular Weight-Bearing and Muscle Strengthening Exercise

• Reduce the risk of falls and fractures
• Increase agility, strength, posture and balance which may reduce the risk for falls
• May modestly increase bone density
• Examples
  – Walking, jogging, Tai-Chi, stair-climbing
  – Dancing, hiking and tennis
  – Swimming is non weight-bearing
Calcium and Vitamin D
Calcium

- Need to obtain adequate intake of calcium as this is necessary to obtain peak bone mass\(^1\)
- If you do not take in enough calcium then your body takes it from your bones to maintain serum calcium at a constant level\(^1\)
- However too much calcium may increase the risk for cardiovascular disease and stroke. This is controversial.\(^2\)
- There are no large randomized controlled trials that have looked at CV risk with Ca supplementation.

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\(^1\) NOF 2013 CLINICIAN'S GUIDE TO PREVENTION AND TREATMENT OF OSTEOPOROSIS\(^1\)
\(^2\) Reid IR et al, *Heart*. 2012;98(12):895-896
\(^3\) Bolland MJ et al, BMJ.2011;19;342:d2040
Calcium cont.

- The NOF and Institute of Medicine (IOM) recommend\(^1\) the same dose as the AACE
  - Men aged 50-70 should take 1000mg per day
  - Women over 51 and men over 71 should take 1200 mg per day

WHI Fracture Risk was Dependent on Adherence to Calcium and Vitamin D

- 36,282 women 50-70 years old followed for 7 years
- Intention to treat analysis no significant reduction but if you looked at subset of those that had > 80% adherence there was a significant reduction in hip fracture
- There was also a significant increase in the incidence of kidney stones

Jackson RD, et al. NEJM. 2006 354(7) 669
Vitamin D

• Plays a major role in calcium absorption which has effects:
  – on bone health
  – muscle performance
  – balance and risk of falling
Vitamin D (cont)

- AACE Guidelines advise 1000 IU of vitamin D daily for adults 50 or older.
- Patients with osteoporosis will often require higher doses to get their level to 30 ng/ml. The safe upper limit for vitamin D intake according to IOM is 4000 IU daily.
Vitamin D Deficiency
Who is at risk?

• Elderly patients
• Patients who malabsorb secondary to intestinal disease
• Chronic renal insufficiency
• Patients on medications that increase breakdown of vitamin D
• Individuals with very dark skin
• Obese individuals
What about Fall Risk?

Hip fracture due to osteoporosis

Femoral head
Diseased bone

Femur
(cross section)
Fall Prevention in the Home

- Avoid throw rugs and slippery mats
- Have a safe bathroom with grab bars
- Correct visual and hearing impairment
- Reduce clutter - no electrical cords
- Do exercises to strengthen balance
- Use handrails on stairs and walking aids if needed
- Avoid sedating medication
- Have good lighting throughout home
Cessation of Tobacco Use and Avoidance of Excessive Alcohol Intake

• Ask your patients to stop smoking because it is detrimental to bone but also to overall health.

• Ask your patients to drink in moderation. Excess alcohol (greater than 3 alcoholic units per day) may be detrimental to bone health as it increases the risk of fall. As a clinician, it should alert you to assess the patient for alcoholism.
Osteoporosis Treatment
AACE Recommendations for Initiation of Therapy

- Those with osteopenia or low bone mass and a history of fragility fracture of the hip or spine.
- T-score ≤ -2.5 at the femoral neck, total hip or lumbar spine by DXA after appropriate evaluation
- Those patients with a T-score between -1.0 and -2.5 osteopenia at the femoral neck, total hip or lumbar spine who have a 10-year risk of ≥ 3% at the hip or ≥ 20% for a major osteoporotic fracture based on FRAX
Osteoporosis FDA Approved Medications
Mechanism of Action of Bisphosphonates: Osteoclasts Are Targets

Bisphosphonate attaches to exposed bone mineral surfaces

Osteoclast takes up bisphosphonate → loss of ruffled border, inactivation, detachment

New bone formation by osteoblasts renders bisphosphonate inert, inaccessible

Bisphosphonates

- Alendronate, ibandronate, risedronate, and zolendronic acid are FDA approved.
- Inhibit resorption of bone and may lead to increase in bone density.
- Reduce Fracture risk.
Oral Bisphosphonates
Alendronate and Risedronate

• Directions for the patient are cumbersome
  – Take first thing in the morning with 8 oz of water
  – Don’t eat or drink anything but tap water for 30 minutes
  – Patients cannot lie back down for 30 minutes

• Alendronate is typically dosed once weekly

• Risedronate typically given weekly after eating or once monthly
Oral Ibandronate

- Similarly patient must take first thing in the morning with 8oz of water
- With this drug you cannot eat/drink or lie back down for 60 minutes
- Ibandronate is taken monthly
- Only has vertebral fracture risk reduction not non-vertebral or hip (not preferred in patients who have low bone mass at wrist or hip).
Side Effects of All Bisphosphonates:

- Hypocalcemia
- Abdominal Pain
- Bone, joint or muscle pain
- Uveitis, or other inflammatory eye disorders
- Rash/allergy
- Renal dysfunction
- Not Atrial Fibrillation\(^1\)
- Not Esophageal Cancer\(^2\)
- Osteonecrosis of the Jaw (ONJ)
- Atypical femur fractures (AFF)

\(^1https://www.fda.gov/cder/drug/early_comm/bisphosphonate_update_200811.htm\)
Side Effects of Oral Bisphosphonates:

- Difficulty swallowing
- Nausea
- Heartburn
- Inflammation of the esophagus
- Gastric ulcer
IV Bisphosphonates
Zolendronic Acid (IV Ibandronate not recommended)

• You must check lab, calcium, creatinine and 25OH vitamin D prior to dosing
• Acute phase reaction 12-48 hours. This usually lessens with subsequent dosing
  – arthralgias
  – headache
  – myalgia
  – fever
  – flu like symptoms
Oral and IV Bisphosphonates

- You should not give these drug to patients with hypocalcemia so check blood levels prior to dosing.

- A creatinine clearance above 30-35 is needed with the bisphosphonates.
Do Bisphosphonates decrease mortality after hip fracture?

• An annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival.¹

• For oral bisphosphonates given after hip fracture that were followed for three years there was also reduced mortality

Major Side Effect of Antiresorptive Agents

- Antiresorptive agent that can cause Osteonecrosis of the jaw (ONJ) and Atypical femur fracture (AFF).
Osteonecrosis of the Jaw

- Exposed bone in the maxillofacial area for 6-8 weeks or more in absence of radiation therapy to that area
- May be associated with pain, swelling and infection
- Most cases in patients with cancer and high dose IV bisphosphonate (BP) often in combination with glucocorticoids or chemotherapy
- Risk in oral BP users of 1: 10,000 to 1:100,000
- Causal relationship not clearly established
- Unclear if stopping therapy prior to invasive dental procedures is helpful but not unreasonable if elective procedure and appropriate to wait.

Khesie S et al, J Bone Miner Res 22:1479
American Dental Association (ADA) General Treatment Recommendations 2011

- Providers generally should not modify routine dental treatment solely because of the use of anti-resorptive agents.
- All patients should receive routine dental examinations.
- Patients to whom anti-resorptive agents have been prescribed and who are not receiving regular dental care would likely benefit from a comprehensive oral examination before or early in their treatment.

Hellstein et al, JADA 2011;142 1243-1251
ADA Dental Care Points for Dental Care Providers to Discuss with Patients

- Anti-resorptive therapy places them at low risk for developing Osteonecrosis of the jaw (ONJ). The highest prevalence in a large sample is about 0.10%.
- The low risk can be minimized but not eliminated
- No validated diagnostic technique currently is available to determine who is at increased risk.
- At present there is insufficient evidence to recommend the use of serum markers such as CTx as a predictor of risk
- Discontinuing therapy may not eliminate the risk
- There is insufficient evidence to recommend a drug holiday from therapy before performing dental treatment as a prevention of ONJ.

Hellstein et al, JADA 2011;142 1243-1251
Typical Femur Fracture
Atypical Femur Fracture

Khelsa et al J of Bone Miner Res 2007,22:1479
Atypical fractures increase after 5 years of bisphosphonate use.

- If you treat 1000 women with bisphosphonates for 5 years, 35-50 non-vertebral and 50-115 vertebral fractures are prevented. Five atypical fractures might be seen.

Park-Willie LY et al. JAMA 2011 305:783-789
Balancing the Risks vs. Benefits

• If you look at the risk per 100,000 people per year
  – Any fragility fracture- 2668
  – Hip fracture-387
  – Anaphylaxis from a Penicillin shot-32
  – Death by MVA-11
  – Death by Murder-6
  – ONJ-osteoporosis pt- 0.7
  – Lightning strike- 0.6
Other therapies for treatment of Osteoporosis
ACP Guidelines for treatment

• ACP advises against Estrogen and Raloxifene because of the Cardiovascular risk- stroke/MI/other thromboembolic event.
What does the FDA advise for Estrogen therapy

- Non-estrogen products should be considered first for prevention of osteoporosis.\(^1\)
- Prescribe the smallest dose for the shortest period of time.\(^1\)
- Prescribe when the benefits are outweighed by the risks.\(^1\)
- Estrogen was never approved by FDA to treat osteoporosis, but it does prevent fractures—spine, hip and nonvertebral.\(^2\)

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\(^1\) US Food and Drug Administration News *FDA News* Jan 8 2003

Raloxifene
Selective Estrogen Receptor Modulator

- This drug is an antiresorptive agent
- It increases BMD at the spine
- It reduces the risk of vertebral fractures
- No proven benefit for nonvertebral fractures or hip fractures
- There is some reduction in risk of breast cancer
- Does not reduce hot flashes
- It has Venous Thromboembolic Risk
- Does not stimulate endometrium

(Lose bone immediately after stopping this medication)

Bazedoxifene/Estrogen

- SERM plus estrogen recently approved for the prevention of Osteoporosis.
- No Randomized Controlled Trials with this combination with primary fracture outcomes
- ACP Clinical Practice Guidelines- advised against this drug.
Teriparatide (Forteo)

- It is the only anabolic agent that has been proven to work on osteoblast to build bone.
- Administered by daily subcutaneous injection (must be refrigerated).
- Decreases risk vertebral fractures and nonvertebral fractures.
- Treat for up to 24 months.
Teriparatide Indications

• Woman and men with glucocorticoid-induced osteoporosis at high risk of fracture

• Postmenopausal woman with osteoporosis at high risk of fracture

• Men with primary or hypogonadal osteoporosis at high risk of fracture
Teriparatide Side Effects

• It has side effects completely different than the anti-resorptive agents- leg cramps, nausea and dizziness.
• This drug has a black box warning for osteosarcoma (none reported in humans).
• No ONJ
• No AFF
• Patient must be given bisphosphononate either PO or IV after treatment to keep gains made in BMD.
Prolia® (denosumab) targets and binds to RANK Ligand, inhibiting osteoclast formation, function, and survival,

**Prolia**

**MECHANISM OF ACTION**

- **Binds to and inhibits RANK Ligand**
- **Prevents RANK Ligand from activating the receptor RANK on osteoclast precursors**
- **Inhibits formation of differentiated osteoclasts**
- **Inhibits osteoclast function and survival**

Mechanism of action representations are for illustrative purposes only and are not meant to imply clinical efficacy.
Denosumab (Prolia)

- Human monoclonal antibody that targets and binds to RANK ligand
- It inhibits development, activity and longevity of osteoclasts
- Decreases
  - incidence of vertebral fractures
  - nonvertebral fractures
  - hip fractures in postmenopausal woman with osteoporosis

NO DRUG HOLIDAY AS RAPIDLY LOSE BONE WHEN STOPPING IT.
Denosumab Warnings

- Hypocalcemia
- Serious Infections including skin infections
- Dermatologic reactions: dermatitis, eczema
- When you stop it you lose gains in bone density similar to estrogen replacement
- ONJ
- AFF
Emerging Therapies: PTHrP

- Abaloparatide (Tymlos) is a synthetic analog of PTHrP developed for the treatment of osteoporosis.
- Data from Phase III Clinical Trials showed significant reductions in vertebral and non-vertebral fractures, and it was approved by the FDA May 2017.
- Abaloparatide-SC does not require refrigeration.
- A transdermal dosing system is also being developed.

Emerging Therapies: Cathepsin K Inhibitors

- Cathepsin K is a major proteolytic enzyme produced by osteoclasts. Inhibition of Cathepsin K results in decreased capacity of osteoclasts to resorb bone while maintaining their ability to regulate osteoblast function.

- Odanacatib is a cathepsin K inhibitor that was being developed. Phase III Clinical Trials showed significantly reduced incidence of vertebral, hip, and non-vertebral fractures, but current trials have been halted. There was a significant increased risk of stroke.


Emerging Therapies: Sclerostin Inhibitors

- Sclerostin is a glycoprotein produced by osteoclasts that inhibits osteoblasts function.
- Romosozumab is a monoclonal antibody to sclerostin. In phase 3 clinical trials Romosozumab significantly reduced the incidence of new vertebral fracture through months 12 to 24 in postmenopausal women.
- There were CV events so no FDA approval
- Recently cardiac ischemia and stroke.


World Health Organization (WHO) 2008 Assessment of Absolute Fracture Risk FRAX

- http://www.shef.ac.uk/FRAX/
What is the FRAX?
The FRAX tool was developed to be used for those patients who have low bone mass to determine their 10 year risk.

Patients with low bone mass or normal bone mass have the majority of fractures but treatment is expensive, so the FRAX tool helps calculate individual 10 year risk. Thus, patients who are at highest risk are appropriately treated.
WHO Risk Factors Estimate 10 year Risk of Fracture

- Age (40-90)
- Glucocorticoid Use
- Gender
- Ethnicity
- Rheumatoid Arthritis
- Previous Fragility FX
- Parental Hx of hip FX

- Current Tobacco Use
- Alcohol intake of greater than 3 units/day
- Low BMI Kg/M$^2$
- Secondary Osteoporosis-
  - IDDM, osteogenesis imperfecta in adults,
  - untreated long-standing hyperthyroidism,
  - premature menopause (<45 years),
  - chronic malnutrition, malabsorption or chronic liver disease

Kanos et al Osteoporosis Intl 2008 19:385-397
App From AHRQ
Welcome to FRAX®

The FRAX® tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.

The FRAX® models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).
Limitations of FRAX

- Risk factors not considered include falling, rate of bone loss, bone turnover
- Medications other than glucocorticoids
- Family history of fractures other than parental hip fracture
- Secondary osteoporosis is a dummy risk factor that does nothing if BMD is provided.
Limitations of FRAX

• BMD input is for hip only
• “Dose Effect” not considered with “yes” or “no” input for risk factors, e.g. prior fracture (number, site, severity), smoking, glucocorticoids, alcohol and RA
• Limited to ages 40-90
• Does not apply to premenopausal women
### Examples of Untreated patients include:

- No ET/HT or SERM for the past one year
- No calcitonin for the past one year
- No PTH in the past one year
- No Denosumab for the past one year
- No bisphosphonates for the past two years unless it is an oral agent taken for less than two months

Note: calcium and vitamin D do not constitute “treatment” in this context.
Osteoporosis Office Evaluation
What lab work is necessary?

- We mentioned secondary causes, so a good history is mandatory to see if the patient needs a work-up for other causes. They need a physical and assess them for kyphosis.

- Blood and urine tests that are usually advised
  - cbc, cmp, 25 OH vitamin D
  - If cbc is abnormal suspect myeloma ?SPEP and UPEP
  - If calcium is high, check intact PTH
  - 24 hour urine to check for hypercalcuria
  - If worried about sprue check celiac antibody panel
  - AACE recommends biochemical markers of bone turnover
Biochemical Markers of Bone Turnover

Bone Formation
- N-telopeptide-NTx
- C-telopeptide-CTX
- Deoxypyridinoline (free,total)

Bone Resorption
- Bone Specific Alkaline Phosphatase (BSAP)
- Osteocalcin
- Procollagen Type I N-terminal propeptide (P1NP)
Biochemical Markers of Bone Turnover

• Have been used in clinical trials to evaluate therapy
• They are noninvasive and easily collected
• They are independent predictors of fracture
• May be useful in monitoring response to therapy and promoting adherence
• They may not be covered by insurance and have diurnal variation so collect in am fasting

Delmas PD et al; JCEM.92(4)1296-2304
ISCD Osteoporosis Clinical Evaluation of Bone Health p223
2016 AACE definition of Osteoporosis

- T-score –2.5 or below in the lumbar spine, femoral neck, total, 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 –2.5) with a fragility fracture of proximal humerus, pelvis, or possibly distal forearm
- Low bone mass or osteopenia and high FRAX® fracture probability based on country-specific thresholds
Which treatment do you chose?

- Oral generic Alendronate and Risedronate are generally used first. Can use weekly or monthly and they are inexpensive. Use in moderate risk patients.
- Zolendronic Acid is once yearly, so if you think noncompliance is an issue or the patient is at high risk, pick this one.
- Teriparatide is expensive but if patient is at high risk especially if already fractured it is a consideration.
- Remember have to follow Teriparatide treatment with a bisphosphonate to keep gains in BMD. Especially important for Glucocorticoid induced osteoporosis.
Which treatment do you chose?

- Denosumab may be more potent and it is a subQ injection twice yearly. It now has data that show gains in BMD out to eight years.
- For the majority of the patients, treat for 5 years and then reassess the patients risk. Remember fracture begets fracture so if they have an osteoporotic hip or spine fracture they are at high risk. A drug holiday is not an option as patients lose bone rapidly after stopping this medication.
Duration of Treatment

When should we give patients a drug holiday from their bisphosphonate?

• “Patients with low BMD at the femoral neck (T-score below -2.5) despite 3-5 years of therapy are at the highest risk for vertebral fractures and therefore benefit the most from continuation of bisphosphonates.

• Patients with an existing vertebral fracture who have a somewhat higher (although not higher than -2.0) T-score may also benefit from continued therapy.

• Patients with a femoral neck T-score above -2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment”

Black et al NEJM 2012 ; 366 2051-2054
ISCD Osteoporosis Essentials Fracture Risk Assessment 270 2013
When Should Therapy Be Restarted After a Drug Holiday?

• “Another untested approach is to reevaluate the patient 2-3 years after discontinuation, making the decisions to restart therapy based on an updated assessment of fracture risk using algorithms initially developed for untreated individuals. For example, if the patient has a T-score ≤ -2.5, or if the patient has a T-score between -1.0 and -2.5 and a World Health Organization’s Fracture Risk Assessment estimate of fracture risk that meets treatment guidelines, consider reinitiating therapy.”

When Should Therapy Be Restarted After a Drug Holiday?

• “It would be reasonable to consider withholding therapy as long as BMD is stable and to restart BP therapy (or an alternate osteoporosis medication) if the T-Score is ≤ -2.5, or if other new/additional risk factors for fractures emerge. However, this approach is based on expert opinion.”

• “The ‘drug holiday’ can be continued until there is a significant loss of BMD, or the patient has a fracture, whichever comes first.”

Case 1

- A patient who was previously treated with oral bisphosphonates presents to clinic after a 2 year drug holiday. She has recently fractured her wrist while walking her dog. She fell from a standing height. Her DXA results are listed below. Her eGFR is <35 mL/min. What is the best approach for the management of this patient?

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD</th>
<th>T-Score</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Lumbar (L1-L4)</td>
<td>0.933</td>
<td>-1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Left Hip (Total)</td>
<td>0.970</td>
<td>-1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Left Femoral Neck</td>
<td>0.630</td>
<td>-2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Right Hip (Total)</td>
<td>0.768</td>
<td>-1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Right Femoral Neck</td>
<td>0.618</td>
<td>-2.1</td>
<td>-0.1</td>
</tr>
</tbody>
</table>
Case 2

- A patient who was previously treated with oral bisphosphonates presents to clinic after a 2 year drug holiday. Her DXA results are listed below. She has clinically significant GERD. What is the best approach for the management of this patient?

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD</th>
<th>T-Score</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Lumbar (L1-L4)</td>
<td>0.808</td>
<td>-2.2</td>
<td>-0.4</td>
</tr>
<tr>
<td>Left Hip (Total)</td>
<td>0.663</td>
<td>-2.3</td>
<td>-1.1</td>
</tr>
<tr>
<td>Left Femoral Neck</td>
<td>0.545</td>
<td>-2.7</td>
<td>-1.3</td>
</tr>
<tr>
<td>Right Hip (Total)</td>
<td>0.621</td>
<td>-2.6</td>
<td>-1.4</td>
</tr>
<tr>
<td>Right Femoral Neck</td>
<td>0.514</td>
<td>-3.0</td>
<td>-1.5</td>
</tr>
</tbody>
</table>
Summary

• Osteoporosis is a major health problem in the US.
• Evaluate patients at risk and when you make the diagnosis of osteopenia or osteoporosis spend some time going over their risk, treatment options and when they should follow-up. Use the shared decision making model with the patient.
• ONJ and AFF are out there, but risk is low and with AFF the major risk is 7-10 years after starting treatment. You need to address this with your patients, or they will stop medication and put themselves at risk for fracture.
• The NOF is a great resource for patients and physicians.
• Any Questions?