Objectives

- Discuss burden of osteoporosis (OP) and clinical consequences of OP fractures.
- Define OP and techniques used to assess bone density and quality.
- Improve awareness, diagnosis, and treatment of OP.
- Discuss how to identify patients with high fracture risk.
- Identify conditions that compromise bone health.

Osteoporosis Burden

- 54 million Americans have osteoporosis or low bone mass
- In 2005, 2 million fractures attributed to OP
- Worldwide 8.9 million fractures annually = 1 fracture every 3 seconds
- 500,000 hospital admissions annually
- Almost 2.6 million office visits annually
- About 180,000 nursing home admissions annually

Osteoporosis Burden

- Fractures in 2005 cost $17 billion.
- Cost estimated to rise to $25 billion in 2025.
- Medical Costs on an individual basis
  - Hip fracture: $32,000 to $35,000
  - Vertebral fracture: $8,000 to $23,000
  - Non-hip, non-vertebral fracture: $12,000 to $13,000
- Aging Population = more osteoporosis

Clinical Consequences

- Fractures
  - 50% of women and up to 25% of men age 50 and older will break a bone due to osteoporosis.
  - Sites and percentages of Osteoporotic Fractures
    - Vertebra (22%)
    - Wrist (19%)
    - Hip (14%)
    - Pelvis (7%)
    - Other (33%)
  - Fractures beget fractures
    - 2.5 x more likely to fracture s/p hip fx
  - 23% of women >67 are dx and fx

Clinical Consequences

- Premature death: 25% of patients die within one year of a hip fracture
- Morbidity, levels of disability, and functional status: Two-thirds of hip fracture patients do not return to their previous level of function.
- Impact on emotional state: FEAR
  - 89% of women surveyed by NOF fear breaking another bone
  - 80% fear inability to perform ADLs
  - 80% fear losing independence
Osteoporosis Definition

- A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.
  - Primary or idiopathic OP – menopausal women with no other contributing underlying medical condition. Caused by estrogen deficiency.
  - Secondary OP – low bone mass associated with co-existing medical condition i.e., rheumatoid arthritis, glucocorticoid use
- Bone strength depends on bone density and bone quality.
- Bone density determined by peak bone mass and amount of bone loss over time.

Axial and Appendicular Skeleton

- Axial Skeleton
  - supports the central axis of the body.
  - Skull
  - Spine
  - Sacrum
  - Sternum
  - Ribs
- Appendicular Skeleton
  - Clavicles
  - Scapula
  - Pelvis
  - Arms
  - Legs

Bone Composition and Mass

- Peak Bone mass is achieved by 18-30 years of age and is affected by:
  - genetic factors
  - nutrition
  - endocrine status
  - physical activity
  - health status during growth
- Constant bone turnover to maintain a health skeleton
  - Osteoblasts (bone matrix synthesis)
  - Osteocytes (mature osteoblasts, bone regulation/remodeling)
  - Osteoclasts (bone resorption)
- Imbalance in osteoblast and osteoclast function = bone loss

Bone Physiology
Case Study

- 80 y/o white female presents s/p hip fracture
- Medical history: cataracts, high cholesterol, hx of bleeding ulcer and basal cell carcinoma
- Meds: simvastatin and omeprazole, calcium and vitamin d when she remembers
- Lives alone in own home
- Reports turning feeling hip “pop” then falling to floor
- Last DKA was approximately 7 years ago. Was told it was ok but she should take calcium and vitamin d. No discussion of future DKA.
- Does she have osteoporosis?
- Is it primary or secondary osteoporosis?
- What is the cause of primary osteoporosis?

Secondary Osteoporosis

- Lifestyle factors: substance abuse, sedentary
- Genetic Disorders: Osteogenesis Imperfecta, hx of parent hip fx
- Hypogonadal States: premature menopause, anorexia, low T
- Endocrine Disorders: Hyperparathyroidism, Diabetes, hyperthyroidism, cushings
- Gastrointestinal diseases: malabsorption, IBS, celiac disease
- Hematologic Disorders: Multiple myeloma, sickle cell anemia
- Rheumatologic and autoimmune disease: RA, Lupus
- Medications: PPI, SSRI, anticonvulsants, Depo, steroids, chemo
- Other: HIV/AIDS, COPD, sarcoidosis

Contributors to OP

- PPI
  - Interferes with calcium absorption
- SSRI
  - Reduces osteoblast activity
- Glucocorticoids
  - Increase bone resorption by increasing osteoclast activity
  - osteoblast cell death = less bone formation
  - Decreased intestinal absorption of calcium and increased renal excretion of calcium
- TZDs
  - Reduce the amount of stem cells differentiating to osteoblasts

Pathophysiology of Primary OP

- Estrogen Deficiency causes increased osteoblast cell death and increase osteoclast activity

Contributors to Osteoporosis

- Diabetes
  - Recent onset Type 1 diabetes = impaired bone formation due to anabolic effects of insulin and amylin
  - Vascular compromise in long-standing disease = BMD and fractures
  - TZDs are associated with higher fracture risk
- CKD
  - Mechanisms of bone loss are complex
  - Patients often have secondary or tertiary hyperparathyroidism, hyperphosphatemia, vitamin d deficiency, and chronic metabolic acidosis

Lab Identification of Secondary Causes

<table>
<thead>
<tr>
<th>Test</th>
<th>Rule out disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum protein electrophoresis/CBC</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Serum Calcium and phosphorus</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Serum intact parathyroid hormone</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>Liver failure</td>
</tr>
<tr>
<td>24-hour urine free cortisol or dexamethasone suppression test</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Renal failure, malabsorption</td>
</tr>
<tr>
<td>TSH</td>
<td>Hyperparathyroid</td>
</tr>
<tr>
<td>FSH</td>
<td>Menopause/premenopause</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>Male hypogonadism</td>
</tr>
<tr>
<td>Urine calcium/magnesium ratio and/or 24 hour urine for calcium excretion</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>25-monohydroxy vitamin d3 and alkaline phosphatase</td>
<td>Vitamin d deficiency or osteomalacia</td>
</tr>
<tr>
<td>Antiendomysial antibodies</td>
<td>Celiac Disease</td>
</tr>
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</table>
**Osteoporosis Diagnosis**

- **DXA**
  - Dual-energy x-ray absorptiometry
  - Introduced in the late 80s
  - Gold Standard test
  - Can also be used to monitor treatment response
  - Lower radiation than x-ray
  - Sites scanned
    - Lumbar spine, hip, and forearm
- Limitation
  - Degenerative disease, fracture, osteophytes, scoliosis, and artifact

**Before Dxa**

- Tell your patient
  - Not for pregnant women
  - Eat normal diet before
  - Take medication normally
  - Do not take calcium 24 hours before test
  - Do not perform test within 7 days of oral, rectal, or IV contrast
  - The test only takes a few minutes
  - You will need to change into a gown and will need to remove all jewelry

**Artifact falsely increases T-score**

**WHO Osteoporosis Diagnosis**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>BMD within 1 SD of young normal adult, T-score = 1.0 or higher</td>
</tr>
<tr>
<td>Low bone mass, or osteopenia</td>
<td>BMD between 1 and 2.5 SD lower than that of young normal adult, T-score between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>BMD more than 2.5 SD lower than that of young normal adult, T-score &lt; -2.5 or lower</td>
</tr>
</tbody>
</table>

WHO: World Health Organization; DXA, dual-energy x-ray absorptiometry; BMD, bone mineral density; SD, standard deviation.

**T score and Z score**

- **T-score**
  - Statistical description.
  - T-score -2.5 reflects the lowest 2.5% of population at risk for fragility fractures.
  - 2.5 standard deviations below normal bone density.
  - Look at T scores on men and postmenopausal females over 50.
  - Do not use T-scores to monitor treatment response.
- **Z-score**
  - Age matched
  - Premenopausal women
  - Men under 50
  - Children
  - Z-score less than -2 is low
**NOF Osteoporosis Diagnosis**

- NOF
  - Osteopenia + fracture
  - Osteopenia + elevated FRAX
  - Clinically significant fracture
    - Hip fracture and/or vertebral fracture
    - Fractures may be called non-traumatic, low-trauma, or fragility fracture

**Assessing fracture risk**

- FRAX [https://www.shef.ac.uk/FRAX/tool.jsp](https://www.shef.ac.uk/FRAX/tool.jsp)

**Trabecular Bone Score**

- Software that can be added to DXA
- Evaluates bone microarchitecture
- Quantifies trabecular bone texture
- Can be used with FRAX

**Case study**

81 year old Caucasian Female

History of tripping, falling, stumbling

FRAX Score
- Major: 13
- Hip: 3.3

Should she be treated?

**Identifying high risk patients**

- Women over 65 and men over 70
- Fracture history (with exception of fingers, toes, face, and skull – which are typically results of trauma rather than OP)
- Postmenopausal females and males 50-69 with risk factors.
- Ask your patient about height loss.
Vertebral Fracture
- If height loss present check lateral spine x-ray or VFA on DXA machine
- Most vertebral fractures will be asymptomatic

Special Populations
- Men
  - Less common, need to rule out:
    - Hypogonadism
    - Cushing’s syndrome
    - Celiac disease
    - Primary hyperparathyroidism
    - Alcoholism
- Children
  - Consider factors impacting peak bone mass
    - Genetics, lifestyle, activity, and nutrition
- Medications
  - Inhaled glucocorticoids
  - Anticonvulsants
  - Cancer treatments
  - Systemic glucocorticoids

Case Study
- 59 y/o white male
- Vertebral compression fracture T12
- PMH:
  - Chronic low back pain = long term opioid use, OA, anxiety, vitamin D deficiency, high cholesterol, COPD, sleep apnea, diabetes type 2, depression, spinal stenosis, GERD, low trauma fractures, RLS
- PSH:
  - ½ -1 ppd smoker, hx of meth and marijuana use
  - Low dietary calcium, sedentary lifestyle
- Meds:
  - Gabapentin, ibuprofen, clonazepam, hydroxyzine, metformin, Spiriva, Ropinirole, aspirin
- DXA in 2015 T scores:
  - LS -2.6, FN -2.2, TH -1.2
- Does he have osteoporosis?
- Are there red flags in his PMH, PSH, nutrition/lifestyle, and medications?
- What is the best treatment?

Osteoporosis Treatment
- Clinician’s Guide to Prevention and Treatment of Osteoporosis
- Lots of different options
  - Nonpharmacological interventions
    - Calcium – dietary or supplement 1200mg daily
    - Vitamin D3 – replace if low then supplement with 400 to 800 iu daily
    - Weight bearing exercise daily – avoid extreme flexion and rotation of spine.
    - Free NOF video and handout free or low cost.

Safe Movement and Exercise
Treatment Considerations

- How do you know what is the best treatment for your patient?
  - Compliance
  - Cost
  - Accessibility

Treatment: Bisphosphonates

- Alendronate and Risedronate — second generation
  - MOA: reduces osteoclast differentiation and recruitment, inhibits the ability of osteoclast to attach to bone surface, inhibits osteocyte cell death.
  - Reduces fracture risk at hip, spine, and non-vertebral sites.
  - Given orally or IV.
    - Cold next time 30-60 minutes before taking, sit up for 30 minutes.
  - Contraindicated if GFR less than 30.
  - Lower cost.
  - Oral med take in morning, empty stomach, full glass of water.
  - Side effects: GI, ONJ, AFF

- Zoledronic Acid and Ibandronate — third generation
  - MOA: reduces osteoclast differentiation and recruitment, inhibits the ability of osteoclast to attach to bone surface, inhibits osteocyte cell death.
  - Reduces fracture risk at hip, spine, and non-vertebral sites.
  - Given orally or IV.
    - Cold next time 30-60 minutes before taking, sit up for 30 minutes.
  - Contraindicated if GFR less than 30.
  - Weekly, monthly, or yearly administration.
  - Lower cost.
  - Side effects: GI, ONJ, AFF

Selective Estrogen Receptor Modulators

- Reduces vertebral fractures by 30-50%
- No reduction in non-vertebral fracture risk
- Side effects: hot flashes, blood clots (similar risk to hormone therapy), increase risk of fatal stroke.
-Raloxifene 60mg po daily
- Tibolone — not available in US
- Consider this for newly menopausal female with increased risk for invasive breast cancer.

RANK Ligand Inhibitors

- Denosumab
  - First FDA approved biologic
  - MOA: reduces osteoclast differentiation and activation of osteoclasts.
  - Reduces fracture risk at vertebral and non-vertebral sites and increases BMD
  - Side effects: can reduce serum calcium especially in renal failure, skin rashes, and infections.
  - 60mg SC q 6 months

Calcitonin

- Polypeptide hormone
- Antiosteoclastic properties
  - Decreases osteoclast function, motility, and formation
  - Derived from salmon, pig, or eel
  - Given IM, SC, or intranasal
  - May help reduce acute pain after vertebral fracture
  - Side effects: GI, metallic taste, flushing, rash, itching and nose bleeds with nasal spray
  - Reduces vertebral fracture risk by 30%
  - No effect on cortical bone
  - 200 IU daily alternating nostrils or 100 IU SC/IM every other day
**Parathyroid Hormone 1-34**

- Teriparatide
- Increases trabecular and cortical bone
- Stimulates new bone growth
- Increases osteoblast replication and reduces cell death
- Reduces vertebral and non-vertebral fracture risk and increases BMD
- Black box warning for osteosarcoma
- Contraindication for kids/young adults, Paget's disease, hypercalcemia, pregnancy, bone cancer, cancers with bone mets, and past bone radiation.
- 20mcg daily SC injection
- 2 year max
- Side effects: nausea, dizziness, leg cramps

**Other Treatment**

- Not approved for use in the US
  - Estrogens and/or hormone therapy — no longer approved in US for treatment of OP
  - Strontium — mechanism of action is not clearly understood, increases vertebral and non-vertebral BMD and lowers fracture risk.

**Treatment for Men**

- Approved treatments include:
  - Alendronate
  - Risedronate
  - Zoledronic acid
  - Teriparatide
  - Denosumab

**Treatment for Children**

- Vitamin D
- Dietary calcium and calcium supplements if needed
- Oral contraceptives — may provide bone boost for girls on chronic glucocorticoid therapy
- Bisphosphonates — used to treat osteogenesis imperfecta with fractures but rarely used in glucocorticoid-associated bone disorders.
- Bisphosphonates have long-lasting effects on bone
- Safety in pregnancy is unknown
- Teriparatide is contraindicated in kids due to risk of osteosarcoma in people with open epiphyses

**Drug Holiday**

- Depends on the type of treatment
  - Bisphosphonates stick around in bone for a long time
    - Consider drug holiday after 5 years of oral therapy or 1 IV infusion of zoledronic acid if no fracture, FRAX score is low, and BMD improving
    - With prolonged use increase risk of atypical femur fracture and ONJ
  - Denosumab does not stick around. Will return to baseline BMD within 12-24 months.
  - Teriparatide should be followed up with an antiresorptive

**References**

- NOF Clinician’s Guide to Prevention and Treatment of Osteoporosis
- Fracture Prevention Central
- Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism 8th Edition
- Diagnosis and Management of Osteoporosis 1st Edition
- A DXA Primer for the Practicing Clinician
- Bone Densitometry in Clinical Practice 3rd Edition