Osteoporosis

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Case

- 55 y.o. caucasian woman
  - Postmenopausal x 3 years
  - No personal history of fragility fracture
  - PMH: COPD
  - Meds: Advair
  - Soc Hx: ½ ppd since teenager
  - Fam Hx: Mother disabled by hip fracture
  - Exam 125 lbs, 5' 5'', normal exam
  - Lumbar spine T-score -2.0, Hip -2.1

Osteoporosis

“A skeletal disorder characterized by compromised bone strength predisposed to an increased risk of fracture.

Bone strength reflects an integration of two main features: bone density and bone quality.”

### Functional Definition

- **Clinical Definition:**
  - “fragility” fracture in the absence of trauma or in the setting of minimal trauma, such as after a fall from a standing height or less.

- **Densitometric:**
  - T-score:
    - Osteoporosis: $\leq -2.5$
    - Osteopenia: $>-2.5$ and $<-1.0$
    - Normal: $\geq -1.0$

  *(Applies to postmenopausal women and men $\geq 50$ years)*

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### Medical Impact of Osteoporosis

- In 2012, $\sim$12 million have osteoporosis 4:1 female:male
- $\sim$ 34 million with osteopenia
- At age 50, $\frac{1}{2}$ women and $\frac{1}{4}$ men will have osteoporotic fracture in their remaining lifetime
- 2 million fractures annually in men and women age $\geq 50$ years
  - $\sim$300,000 hip fractures
  - $\sim$550,000 spine fractures
  - $\sim$400,000 wrist fractures
  - $\sim$800,000 fractures at other sites

*Medical Impact of Hip Fractures*

- 10-20% excess mortality within 1 year
- 2 $\frac{1}{2}$ fold increase in subsequent fracture
- 20% require long-term nursing home care
- Only 40% regain pre-fracture level of independence
- 50% previously ambulatory, unable to walk independently after fracture

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*Burge, R. JBMR 2007;22:465-75*
Medical Impact of Spine Fractures

• Back pain, height loss, kyphosis
• Loss of function
  • bending, reaching
  • restrictive lung disease
• early satiety, decreased appetite, constipation, abdominal pain, distension
• Increased risk of mortality beyond 1 year
  • 86.5% vs. 93.6% (expected) at 1 year
  • 56.5% vs. 69.9% (expected) at 5 year

Postmenopausal Osteoporosis

• High bone turnover state
  – Perforation of trabecular plates → rods
  – Loss of connectivity
  – Increase in stress risers in trabecular bone
  – Increase in cortical bone porosity
• Bisphosphonate therapy improves bone strength by preventing deterioration and allows filling in of the remodeling space
• Fracture reduction occurs mainly through ↓ high bone turnover

Bone Turnover

- High bone turnover state
  - Perforation of trabecular plates → rods
  - Loss of connectivity
  - Increase in stress risers in trabecular bone
  - Increase in cortical bone porosity
- Bisphosphonate therapy improves bone strength by preventing deterioration and allows filling in of the remodeling space
- Fracture reduction occurs mainly through ↓ high bone turnover
**Indications for DXA**
International Society for Bone Densitometry

- Women ≥ 65
- Postmenopausal women < 65 with risk factors for fracture
- Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use
- Men ≥ 70
- Men < 70 with clinical risk factors for fracture.
- Fragility fracture

**DXA Scan Indications**

- US Preventive Task Force
  - Universal screening in woman ≥ 65 years
  - Women ≥ 60 + Risk Factors

**Indications for DXA**
International Society for Bone Densitometry

- Disease/condition associated with low bone mass or bone loss
- Medications associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy
- Anyone being treated, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
### Factors Contributing to Osteoporosis and Fracture

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism</td>
<td>Glucocorticoid</td>
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<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Heparin</td>
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<tr>
<td>Hypercortisolism</td>
<td>Aromatase inhibitor</td>
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<tr>
<td>Vitamin D deficiency/insufficiency</td>
<td>GnRH agonist</td>
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<tr>
<td></td>
<td>Cyclosporin</td>
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</table>

### Common ICD-9 Codes for DXA in Primary Care Setting

- **733.00** OSTEOPOROSIS UNSPECIFIED
- **733.01** POSTMENOPAUSAL/SENiLE OSTEOPOROSIS
- **733.90** DISORDER OF BONE AND CARTILAGE UNSPECIFIED (osteopenia)
- **V49.81** ASYMPTOMATIC POSTMENOPAUSAL STATUS (AGE-RELATED) (NATURAL)
- **627.2** SYMPTOMATIC MENOPAUSAL OR FEMALE CLIMACTERIC STATES
- **627.4** SYMPTOMATIC STATES ASSOCIATED WITH ARTIFICIAL MENOPAUSE
- **V58.65** LONG-TERM (CURRENT) USE OF STEROIDS
- **V58.69** LONG-TERM (CURRENT) USE OF OTHER MEDICATIONS

### Factors Contributing to Osteoporosis and Fracture

<table>
<thead>
<tr>
<th>Other Disorders</th>
<th>Lifestyle</th>
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<tbody>
<tr>
<td>Gastrointestinal: sprue, IBD, PBC</td>
<td>Ethanol</td>
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<tr>
<td>Hematologic: myeloma, leukemia, lymphoma</td>
<td>Cigarettes</td>
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<tr>
<td>Rheumatologic: RA, SLE, AS</td>
<td>Immobilization</td>
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<td>Renal: CKD, Hypercalciuria</td>
<td>Dietary calcium (lactose intolerance)</td>
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<tr>
<td>Genetic: OI</td>
<td>Hypervitaminosis A</td>
</tr>
<tr>
<td>Miscellaneous: Transplantation</td>
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</tr>
</tbody>
</table>

### Common ICD-9 Codes for DXA in Primary Care Setting

- **627.2** SYMPTOMATIC MENOPAUSAL OR FEMALE CLIMACTERIC STATES
- **627.4** SYMPTOMATIC STATES ASSOCIATED WITH ARTIFICIAL MENOPAUSE
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2008 NOF Treatment Intervention

- Hip fracture, clinical or radiographic spine fracture; OR
- Osteoporosis by DXA at femoral neck, total hip, or lumbar spine; OR
- Osteopenia by DXA and any of the following:
  - 10 year estimated risk of hip fracture risk ≥ 3%
  - 10 year major osteoporotic fracture risk ≥ 20%
  - Secondary causes associated with a high risk of fracture (e.g. glucocorticoid therapy)
  - Other prior fragility fractures

FRAX Limitations

- Does not take into account dose-response
  - Higher GC dose
  - 1 vs. >1 prior fracture
  - cigarettes, alcohol
- Does not apply to patients on osteoporotic drug treatment
- US database does not include age <50
- Future FRAX: add spine BMD

Calcium and Vitamin D 2011 IOM Report

<table>
<thead>
<tr>
<th>Year</th>
<th>Calcium (mg/d)</th>
<th>1997 RDA</th>
<th>1997 UL</th>
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<tr>
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<tr>
<td>4-8 yr</td>
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<tr>
<td>51-70 F</td>
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<tr>
<td>&gt;71 M+F</td>
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Calcium and Vitamin D 2011 IOM Report

<table>
<thead>
<tr>
<th>1997 Vitamin D (IU/d)</th>
<th>2011 Vitamin D (IU/d)</th>
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<tbody>
<tr>
<td>0-50 yr</td>
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<tr>
<td>200</td>
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<tr>
<td>51-70</td>
<td>UL 2500</td>
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<tr>
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<td>600</td>
<td>400</td>
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<tr>
<td>&gt;70</td>
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</table>

Treatment of Osteoporosis

- Calcium and vitamin D
- Estrogen and SERMs
- Bisphosphonates
- Anabolic therapy (Forteo)
- RANKL inhibitor – “biologic” therapy

Treatment of Postmenopausal Osteoporosis

Laura Ryan, MD, Clinical Assistant Professor
Department of Internal Medicine
Division of Endocrinology, Diabetes, & Metabolism
Ohio State University Medical Center

Estrogen/Progesterone

- Effective in both primary prevention of hip and vertebral fractures as well as secondary prevention in those with established osteoporosis
- Dose: Premarin 0.625mg qd (+/- provera)
- Results in increase in both vertebral and spine BMD
- Reduction in hip Fx by 29%; compression fractures by 33%
- Divergence from placebo seen as early as after first year of primary prevention treatment
- Big problem: breast cancer, stroke, dementia, CAD
  - No longer considered first-line therapy
Kaplan-Meier Estimates of Cumulative Hazards for Hip Fracture

- HR 0.66
- CI (0.45, 0.98)

E+P
Placebo

Time (years)

Number of women at risk

Raloxifene

- Found in the MORE trial (Ettinger, JAMA, 1999) to increase BMD in spine and hip by 2.4% (slightly less than estrogen)
- Also prevents vertebral fractures by 38-52%
- Has not been proven to prevent hip fractures
- May make hot flashes worse
- Studies underway looking at Raloxifene for prevention of breast CA and CAD
  - 76% reduction of breast CA and 90% reduction of ER+ breast cancer in MORE trial (5160 pts)

Attributable Risk Summary

- Excess risk per 10,000 women per year on E+P
  - 8* more women with breast cancer
  - 6* more women with CHD
  - 7* more women with strokes
  - 8* more women with PE
- Risk reduction per 10,000 women per year
  - 6 fewer colorectal cancer
  - 5* fewer hip fractures

Writing Group for WHI Investigators: JAMA 2002; 288: 321-333

*2003 UPDATES: CHD (Manson); Stroke (Wassertheil-Smoller); Breast Cancer (Chlebowski); Hip Fractures (Cauley)

Effects of Bisphosphonates on Osteoclast Function

- Normal Osteoclast
- Osteoclast Following Uptake of Bisphosphonate
  - Cytokinitial disorganization
  - Cell death by apoptosis
  - Altered: vesicuolar matricin
Functional Domains of Bisphosphonate Chemical Structure

- $R^1$ is an -OH group that binds to bone via $\text{Ca}^{2+}$
- $R^2$ determines anti-resorptive potency and affects binding to HAP
- Both phosphonate groups act as a "Bone Hook" and are essential both for binding to hydroxyapatite (HAP) and within the FPPS enzyme

Bisphosphonate Action at the Cellular Level

Inhibition of osteoclast resorption activity

- Concentrate at sites of bone resorption
- Release and intracellular uptake during resorption

Oral Bisphosphonate Dosing

- Once daily, weekly or monthly
- On completely empty stomach
  - No coffee, juice, food – reduces absorption to almost 0%
  - **Cannot be taken with other pills, either!**
  - 30min except for monthly Ibandronate: 45min
- Upright x 30 minutes following dosing
  - Do take the pill with 8oz water
- If dose missed, can make it up within 5 days then resume normal day of dosing
**Alendronate (Fosamax)**

- **Fracture Intervention Trial (FIT)**
  - In all pts with T-score <-1.6, sig reduction in vertebral fractures
  - In pts with T-score <-2.5, or 1 or more previous fragility fractures, sig reduction hip and all clinical fractures

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**Continuous Increases in Lumbar Spine BMD with Alendronate 10 mg over 10 Years**

The mean percent change from baseline to year 10 appears in parentheses following each treatment group.


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**Risedronate Reduces Risk of Clinical Vertebral Fractures Within 6 months**

**VERT:** Pts with 2 or more Fx or T-score <-2.0 and one fracture

* p <0.05

VERT-NA / VERT-MN (ITT)

Watts et al. *JBR 2001; 16 (S1): SU409*

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**Annualized Incidence of Subjects Experiencing Any New Vertebral Fracture Over Years 0-3, 4-5 or 6-7**

* Annualized fracture incidence represents the percentage of subjects experiencing any new vertebral fracture divided by the number of years in the observed interval. Sorensen, et al. ISCD abstract, 2/03 annual meeting.
Upper GI Tolerability Comparable to Placebo in Over 5700 “Real World” Patients

<table>
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<tr>
<th>Disease</th>
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<th>Actonel</th>
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</thead>
<tbody>
<tr>
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<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>NSAID Users</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Aspirin Users</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>H₂ Antagonist/</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>PPI Users</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

PPI = proton pump inhibitor.
Please see Actonel package insert for full prescribing information.

Ibandronate (Boniva)

- MOBILE study – 1609 postmenopausal women with osteoporosis
  - Significant increase in BMD at LS and TH
  - Significant reduction in vertebral fracture incidence
  - No sig reduction in hip fracture
- Once monthly dose, 150mg
- IV infusion every three months, 3mg

Oral Ibandronate reduces vertebral fractures


Zoledronic Acid for treatment of PMO, Reclast

Initial trial evaluating Zoledronic acid in the setting of PMO – One year BMD results

HORIZON Pivotal Fracture Trial: Overview and Study Design

- **Objective:** To evaluate the potential of once yearly Reclast to decrease fracture risk in postmenopausal women with osteoporosis
- **3-year, randomized, double-blind, placebo-controlled clinical trial**
  - 7736 women from 239 clinical centers in 27 countries
- **Treatment**
  - Annual infusion of either Reclast or placebo
  - Calcium 1000–1500 mg/d; vitamin D 400–1200 IU/d
- Follow-up visits at 6, 12, 24 and 36 months
  - Telephone interviews every 3 months

Reclast Reduced Cumulative 3-Year Risk of Hip Fractures (Strata I + II)

![Graph showing reduced cumulative 3-year risk of hip fractures with Reclast compared to placebo.](image)

Reclast Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)

![Graph showing reduced 3-year risk of vertebral fractures with Reclast compared to placebo.](image)

Most Common Adverse Events Within 3 Days After Infusion

![Table showing the most common adverse events within 3 days after infusion.](image)
Adverse Reactions

- Atrial Fibrillation
  - Adjudicated SAEs of atrial fibrillation occurred in 1.3% of patients (59 out of 3862) compared to 0.4% (17 out of 3852) in the placebo group.
  - Overall incidence of atrial fibrillation AEIs was 2.5% of Reclast patients (96 out of 3862) vs 1.9% (75 out of 3852) in placebo.
  - Over 90% of these events in both groups occurred more than a month after the infusion.
  - In an ECG sub-study:
    - ECG measurements were performed on a subset of 559 patients before and 1 to 11 days after treatment.
    - There was no difference in the incidence of atrial fibrillation between treatment groups suggesting these events were not related to the acute infusion.

Teriparatide (Forteo)

- 1-34 PTH, synthetic
- Anabolic agents – main action is to stimulate osteoblasts
- Daily subcut injection, 20mcg
- Very expensive - $20/d; $6,000/year
- Osteosarcoma warning
- Use for two years, then follow with bisphosphonate
- Currently FDA approved for:
  - Postmenopausal osteoporosis
  - Senile or hypogonadal osteoporosis in men
  - Glucocorticoid-induced osteoporosis

Important Safety Information about FORTEO

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

FDA warning regarding osteosarcoma
Forteo was approved for use in PMO 2002 – since then, no increase in incidence of osteosarcoma over the population in general.

64 Year-Old Woman (M H)

Before PTH(1-34)
- ClTh: 0.32 mm
- CD: 2.9/mm³

After PTH(1-34)
- ClTh: 0.42 mm
- CD: 4.6/mm³
Teriparatide Reduces the Risk of Vertebral Fractures - GHAC

- RR 0.31 (0.19, 0.50)*
- RR 0.35 (0.22, 0.55)*

Current therapeutic deficiencies
- Oral bisphosphonates may be difficult to tolerate
- 1/6 of bisphos users “fail” therapy
- <50% of oral bisphosphonate users are compliant
- Bisphosphonates cannot be used in renal insufficiency
- Rare incidence of significant bone pain
- What to do with prior jaw non-healing?
- Teriparatide is expensive; works best for 18 – 24 months only
- SERMs never proven to prevent non-vert Fx
- Strontium results not yet reproduced

Teriparatide Reduced Nonvertebral Fragility Fractures - GHAC

- RR 0.46 (0.25, 0.86)
- RR 0.47 (0.25, 0.88)

Denosumab – “Prolia”

- Fully human monoclonal antibody to the receptor activator of nuclear factor-kb ligand (RANKL) that blocks its binding to RANK
- Inhibits development and activity of osteoclasts
- Decreases bone resorption, increases bone density
- RANKL expressed on precursors of osteoblasts, marrow stromal cells and activated T cells
FREEDOM Trial

- Multicenter randomized, placebo-controlled trial
- 7868 postmenopausal women aged 60-90
- T-score <-2.5 at LS or total hip eligible
- Excluded if on bisphos within past 5 yrs
- Everyone received daily calcium and vitamin D
- Study group: denosumab 60mg subcut q6mo for 36 months
- Lat spine Xray performed annually
- BMD measured annually
- BTM only measured on 160 subjects

Cummings S et al, NEJM, August 2009, 756 - 765
**FREEDOM Trial: Baseline characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexamet (n = 1987)</th>
<th>Raloxifen (n = 1989)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>73.4 (5.1)</td>
<td>73.5 (5.2)</td>
</tr>
<tr>
<td>Group (n)</td>
<td>1987</td>
<td>1989</td>
</tr>
<tr>
<td>African</td>
<td>53 (2.7)</td>
<td>54 (2.7)</td>
</tr>
<tr>
<td>White</td>
<td>1484 (74.8)</td>
<td>1482 (74.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 (4.4)</td>
<td>25.4 (4.4)</td>
</tr>
<tr>
<td>T-score</td>
<td>0.0 (3.8)</td>
<td>0.0 (3.9)</td>
</tr>
<tr>
<td>History of new Vertebral Fracture</td>
<td>246 Fx</td>
<td></td>
</tr>
</tbody>
</table>

Cummings S et al, NEJM, August 2009, 756 - 765

**FREEDOM Trial: Incidence of new Vertebral Fracture**

Cummings S et al, NEJM, August 2009, 756 - 765
Predefined adverse events:

- Osteonecrosis of the jaw
- Non-healing non-vertebral fractures
- Femoral shaft fractures
- Hypocalcemia
- Opportunistic infections
- Atrial fibrillation
FREEDOM Trial

Adverse Events

- Delayed Fracture healing
  - 2 cases in denosumab group
  - 4 cases in placebo group

- Femoral shaft fracture
  - 0 cases in denosumab group
  - 3 cases in placebo group**

- Cellulitis
  - Serious AE: 12 in denosumab, 1 in placebo
  - All AE: 47 denosumab, 36 in placebo (no diff)

Serial Monitoring

- Spine – significant gains from treatment can usually be seen in one year
  - Hip often takes 24 months

- See changes (↑ or ↓) in six months with patients on glucocorticoids

- ISCD recommends yearly BMD until bone mass stable or improving, then every two years