Osteoporosis: key concepts

Azeez Farooki, MD
Endocrinologist
Outline

I) Composition of bone
II) Definition & pathophysiology of osteoporosis
III) Peak bone mass
IV) “Secondary” osteoporosis
V) Vitamin D insufficiency / deficiency
VI) Fracture risk
VII) Pharmacotherapies
Characteristics of Bone

• Bone functions as\(^1\):
  – Mechanical scaffolding
  – Metabolic reservoir (calcium, phosphorous, magnesium, sodium)

• Bone contains metabolically active tissue capable of\(^2\):
  – Adaptation to load
  – Damage repair (old bone replaced with new)
  – Entire skeleton remodeled ~ every 10 yrs

Definition of osteoporosis

• A disease characterized by:
  – low bone mass and,
  – structural deterioration of bone tissue
• leads to bone fragility & susceptibility to fractures (commonly: spine, hip & wrist)
• Silent until a fracture occurs
T-score: standard deviations away from average
sex matched 30 year old

rel risk fracture by 1.5-2.5x per SD

<table>
<thead>
<tr>
<th>T-Score (SD)</th>
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<tbody>
<tr>
<td>Normal</td>
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<tr>
<td>Low bone mass (osteopenia)</td>
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<tr>
<td>Osteoporosis</td>
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Why -2.5? Yielded 17% prevalence of osteoporosis @ femoral neck among women 50 years or older; similar to the estimated 15% lifetime risk of hip fracture for 50 yo white women in US
Bone density is a major determinant of fracture risk

Bone Strength: NIH consensus Statement 2000

Bone Strength = Bone Quality + Bone Density

- Structure & Architecture
- Turnover
- Mineralization
- Damage accumulation

DXA (dual energy X-ray absorptiometry)
- grams / cm²
Impairments in Bone Mass and Quality in Osteoporosis

Strength of osteoporotic bone is impaired by:

- Loss of bone mass
- Reduction in bone quality:
  - Loss of horizontal struts
  - Loss of connectivity
  - Conversion of trabecular plates to rods
  - Resorption pits are “stress concentrators”
  - Unfavorable geometry

Images courtesy of Ralph Müller
Physiologic Bone Remodeling:

In osteoporosis: imbalance causes net bone loss

Bone Remodeling Cycle

- Pre-Osteoclasts
- Active Osteoclasts
- Mononuclear Cells
- Pre-Osteoblasts
- Osteoblasts
- Osteocytes

Resorption
Reversal
Bone Formation
Mineralization

-3 WEEKS
-3 MONTHS

PTH (catabolic)
PTH (anabolic)
Unbalanced Remodeling in Menopause Leads to Osteoporosis

Effects of Aging Estrogen Deficiency

↑ Bone Resorption > Bone Formation

Net Bone Loss

RANK receptor - RANK Ligand pathway essential for Osteoclast Activity

RANK Ligand Is Essential for Osteoclast Formation, Function, and Survival

Growth Factors
Hormones
Cytokines

CFU-M
Pre-Fusion Osteoclast
Multinucleated Osteoclast
Activated Osteoclast

Osteoblast Lineage
Bone

To neutralize the effects of RANK ligand, the body produces a protein called Osteoprotegerin (OPG).

Growth Factors
Hormones
Cytokines

RANKL
RANK
OPG

Osteoclast Formation, Function and Survival Inhibited by OPG

CFU-M
Pre-Fusion Osteoclast
Multinucleated Osteoclast
Inactive Osteoclast

Osteoblast Lineage
Bone

Overactive bone remodeling in osteoporosis: deeper resorption cavities concentrate stress
3-D Micro CT: loss of horizontal trabeculae in osteoporosis

52 year old Female

84 year old Female (with vertebral fracture)

XtremeCT: see trabeculae

Measurement of BMD was a good beginning, but the dual photons of the bone densitometer are blind to the 3-D world of bone and the behavior of the cells that fashion and refashion its dimensions, architecture, and strength

1. Seeman E, NEJM 2003
Peak bone mass & strength

• Achieved by ~ age 30 (latest)
• Genetic factors: account for 40-80% of differences in peak bone mass (twin studies)
• Calcium, vitamin D and physical activity
  – Bone mineral matrix: Ca2+, D, PO4, Mag
  – Collagen synthesis: protein, copper, zinc, iron
• Early pubertal girls: pint of milk/day vs nothing
  – ↑ BMD and ↑ serum IGF-I (a growth factor)
Life Cycle of Bone Mass: failure to accrue vs loss

Healthy 40 yo, Zscore = -2.1 (low bone mass) → microarchitecture intact
Primary osteoporosis

- Heterogenous, multiple mechanisms
- Postmenopausal, senile & idiopathic

Overlap: premenopausal & younger men w/ osteoporotic fractures
Treatable “secondary” causes of bone loss

- Celiac sprue: suspect with weight loss
  TTGAb
- Hyperthyroidism
  TSH
- Vitamin D deficiency / insufficiency
  25-OHD
  - Extreme form = osteomalacia
- Hyperparathyroidism (1ry vs 2ry)
  Ca / PTH
- Multiple myeloma (suspect with spine fractures above T7)
  SPEP
- Paget’s disease
  ↑ ALK phos
- Cushing’s syndrome
  24 urine cortisol
  - Can be iatrogenic
- Medical Noncompliance
  urine NTX
Additional causes

• Hypogonadism
  ➔ (men) AM serum testosterone level
  ➔ early menopause / amenorrhea
• Rheumatoid Arthritis (inflammation)
• Idiopathic hypercalciuria 24 hr urine Ca$^{2+}$
• Tumor induced osteomalacia PO4

* If Z score (comparison to peer) < -2.0, secondary cause more likely
Secondary Causes of Osteoporosis: Drugs

- Glucocorticoids (PO + high dose inhaled)
- Excessive thyroid replacement
- Anticonvulsants, Lithium
- Long-term heparin use
- GnRH agonists (Leupron): prostate cancer
- Aromatase inhibitors: ↓ estrogen in breast cancer patients
- Methotrexate, cyclosporin A
- Sedative hypnotics (FALL risk)
- TPN
Bone Remodeling: causes of imbalance / bone loss

**Increased Resorption**
- Glucocorticoids
- Low estrogen levels
  - ↓ Osteoprotegerin production
- Hyperthyroidism
- Cytokine release (inflammation)
  - TNF alpha and beta
  - IL1 alpha
  - IL 6
  - PGE2

**Normal/Decreased Resorption**
- Normal sex steroid levels (estrogen/androgens)
  - ↑ Osteoprotegerin production
- Cytokine release
  - TGF beta

Key Facts About Vitamin D

- **essential for adequate intestinal absorption of calcium**\(^1\)
- **favorable direct effects on bone cells**
- **Insufficient vitamin D levels leads to increased release of PTH and increased bone resorption**\(^1–^3\)
- **Evidence suggests that suboptimal levels of vitamin D increases the risk of fractures**\(^4,^5\)
- **Vitamin D insufficiency can compromise muscle strength, impair lower extremity function, and increase the risk of falls**\(^6,^7\)

Serum 25(OH)D Levels <30 ng/mL: 50%
US postmenopausal women across all latitudes

N = 259/532 (48.7%)
N = 342/642 (53.3%)
N = 198/362 (54.7%)

P = NS for test of trend.

PTH, a calcium thief, most ↓ when 25(OH)D value is > 30 ng/mL

iPTH = intact parathyroid hormone.

Age-related bone loss

- Dietary calcium intake
- Vitamin D intake and synthesis
- Calcium absorption
- Estrogen deficiency
- Plasma calcium
- PTH secretion
- Bone turnover and resorption
- BONE LOSS
Vitamin D, compared with calcium or placebo, reduced the risk of falling by 22%\textsuperscript{1}

\textsuperscript{1} Bischoff-Ferrari HA. JAMA. 2004;291:1999–2006, with permission.
Independent risk factors for fragility fracture

- AGE (↑ Rel Risk 1.5-2.0 x with each decade)
- Prior fragility fracture *
- Low BMD
- Family history hip fracture
- High fall risk
- Elevated bone turnover markers: urine, blood (peptides of type I collagen)
- Rheumatoid arthritis
- steroid use x > 3 months
  - (> 5 mg / day prednisone)

* Fracture without trauma or after fall from standing height
10 yr hip fracture risk according to T-score and age

At any given T score, higher age = higher risk

Kanis et al, Osteoporos Int 2001
## Prior Fracture as a Predictor of Fracture Risk

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<tr>
<th>Prior Fracture</th>
<th>Relative Risk of Future Fractures</th>
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<tbody>
<tr>
<td></td>
<td>Wrist</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.3</td>
</tr>
<tr>
<td>Vertebral</td>
<td>1.4</td>
</tr>
<tr>
<td>Hip</td>
<td>NA</td>
</tr>
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</table>

In this study, a systematic literature review was performed to discern the relative risk of fracture by location of prior and subsequent fracture.

Fragility fracture = without trauma or after fall from standing height

NA = not available.

NORA: Relationship of BMD with Risk of Fracture in Postmenopausal Women

*The World Health Organization defines osteoporosis as a T-score ≤ –2.5
†Peripheral devices used to measure T-score
Which women or men with osteopenia should be treated?

→ *Those who have risk for fracture*

**NOF (old thinking – BMD centered)**
- $T < -2.0$ without risk factors for fracture
- $T$ score $< -1.5$ with risk factors

**WHO (new thinking – absolute risk)**
- % risk over the next 10 years - calculation based on major risk factors
- “Treat the patient, not the T-score”
FRAX
WHO Fracture Risk Calculator

• Estimates the 10-year patient-specific absolute fracture risk
  – Hip or
  – Major osteoporotic (spine, forearm, hip or shoulder)
• Evaluates fracture risk from epidemiological data (USA, Europe, Australia and Japan)
• Integrates clinical risk factors as well as BMD (femoral neck)
• Incorporated into NOF treatment guidelines and other country specific recommendations
• Restricted to untreated patients
Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian)  Name / ID:  About the risk factors

Questionnaire:

1. Age (between 40-80 years) or Date of birth
   Age: 75  Date of birth: Y: ______ M: ______ D: ______

2. Sex  Male  Female

3. Weight (kg)  47

4. Height (cm)  152

5. Previous fracture  No  Yes

6. Parent fractured hip  No  Yes

7. Current smoking  No  Yes

8. Glucocorticoids  No  Yes

9. Rheumatoid arthritis  No  Yes

10. Secondary osteoporosis  No  Yes

11. Alcohol 3 more units per day  No  Yes

12. Femoral neck BMD
   T-score: -2.5

BMI 20.3
The ten year probability of fracture (%) with BMD

- Major osteoporotic 40
- Hip fracture 8.5

For the clinical risk factors a yes or no response is asked for. If the field is left blank then a "no" response is assumed.

http://www.shef.ac.uk/FRAX/index.htm
Nonpharmacologic
- Exercise / balance
- Calcium
- Vitamin D
- ↓ alcohol, d/c tobacco
- Stop causative agents
- Fall proof the home
- Hip protectors

Antiresorptives
- Bisphosphonates
- SERMs
- Calcitonin
- Estrogen
- RANKL antibody

Anabolics
- Teriparatide
- ? Strontium ranelate

1. Investigational- likely FDA approval
2. Approved in Europe but not US
Antiresorptives: bisphosphonates

• Inhibit osteoclast activity and thus bone resorption - increase mineralization of existing sites
Bisphosphonates: less frequent dosing to improve compliance

- **Zolendronate (Reclast):** 5 mg yearly IV
- **Alendronate (Fosamax)**
  - Prevention: 35 mg/week
  - Treatment: 70 mg/week PO or oral solution
    - Plus D: 70 mg, 2800 IU / 5600 IU vitamin D
- **Risedronate (Actonel)**
  - 35 mg/week
  - 150 mg once monthly
- **Ibandronate (Boniva)** ➔ no hip fracture data
  - 150 mg/month
  - 3 mg IVP every 3 months
Commonly Used Biochemical Markers of Bone Turnover

**Formation**
- Bone-specific alkaline phosphatase (BSAP)
- Osteocalcin (OC)
- Propeptide of type I collagen (P1NP)

**Resorption**
- N-telopeptide of type I collagen (NTX)
- C-telopeptide of type I collagen (CTX)

Reclast Reduced Mean Serum β-CTX


*Please see full prescribing information.*
teriparatide rPTH (Forteo)

- appears to create new trabeculae
- Increase osteoblast lifespan
- ↑ bone formation → resorption follows
- Given as a daily subcutaneous “pulse”
Teriparatide: sequential increase in bone formation → resorption
Pathogenesis of osteoporotic fracture

**Low peak bone mass**

**Postmenopausal Bone loss**

**Age related bone loss**

**Other risk factors**

**LOW BONE MASS**

**Non skeletal factors (risk of FALL)**

**Poor bone quality (architecture)**

**FRACTURE**

Melton LJ & Riggs BL. *Osteoporosis: Etiology, Diagnosis and Management*. Raven Press, 1988
Case of 65 year old lady

- bone mineral density (DXA) shows T-score of -2.0 at all sites. BMD = 0.759 g/cm\(^2\)
- takes a multivitamin and calcium
- History of wrist fracture 4 years ago
- LABS: 25OH-vitamin D = 18 n/mL, PTH = 88 (ULN = 65), CMP = nl
- What is your advice, doctor?
- Is patient at high risk for fracture over next 10 yrs?
- Any major osteoporosis fx risk: 23%; Hip fx risk: 2.6%
- Take away hx of wrist fx: 14% / 1.6%