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

Shoback D et al. *Greenspan's Basic and Clinical Endocrinology*. The McGraw-Hill Companies, Inc.; 2007. http://www.accessmedicine.com/resourceTOC.aspx?resourceID=13. Gupta R et al. *Current Diagnosis & Treatment in Orthopedics*. The McGraw-Hill Companies, Inc.; 2007. http://www.accessmedicine.com/resourceTOC.aspx?resourceID=20.

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

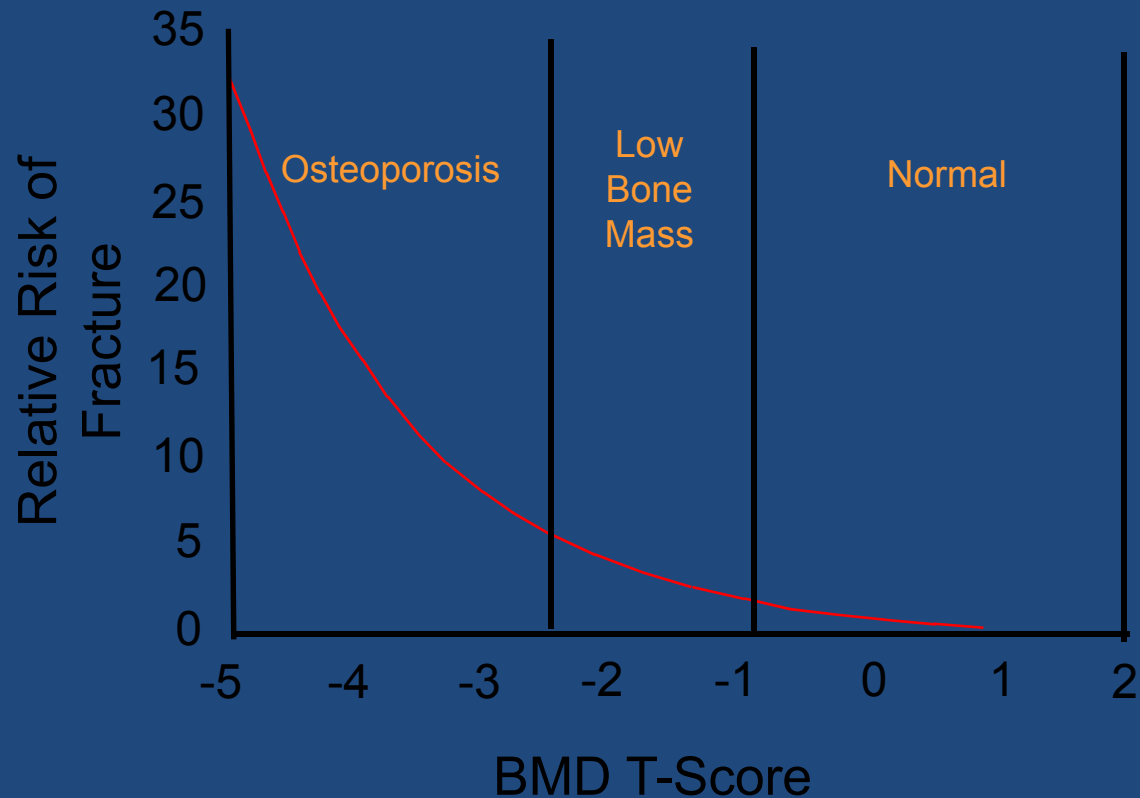rel risk fracture by 1.5-2.5x per SD

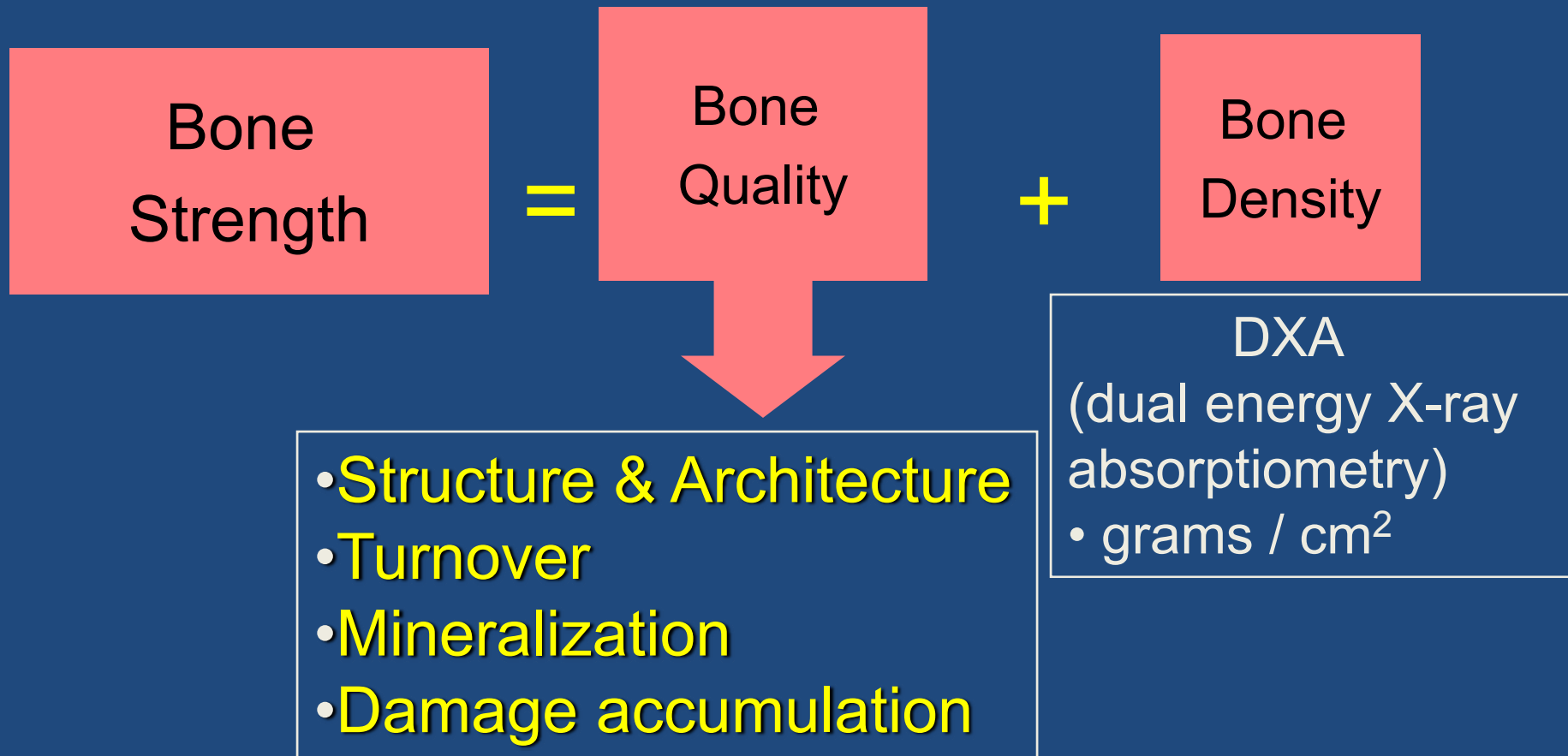|	T-Score (SD)
Normal	-1 and above
Low bone mass (osteopenia)	-1 to -2.5
Osteoporosis	< -2.5

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

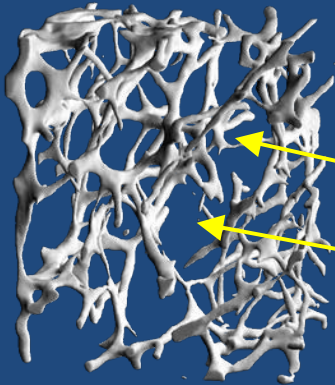# Bone density is a major determinant of fracture risk

Meunier P. et al. Clin Ther 1999: 21:1025

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 / cm^2

Impairments in Bone Mass and Quality in Osteoporosis

Osteoporotic

Young Normal

<u>**Strength**</u> **of osteoporotic bone is impaired by:**
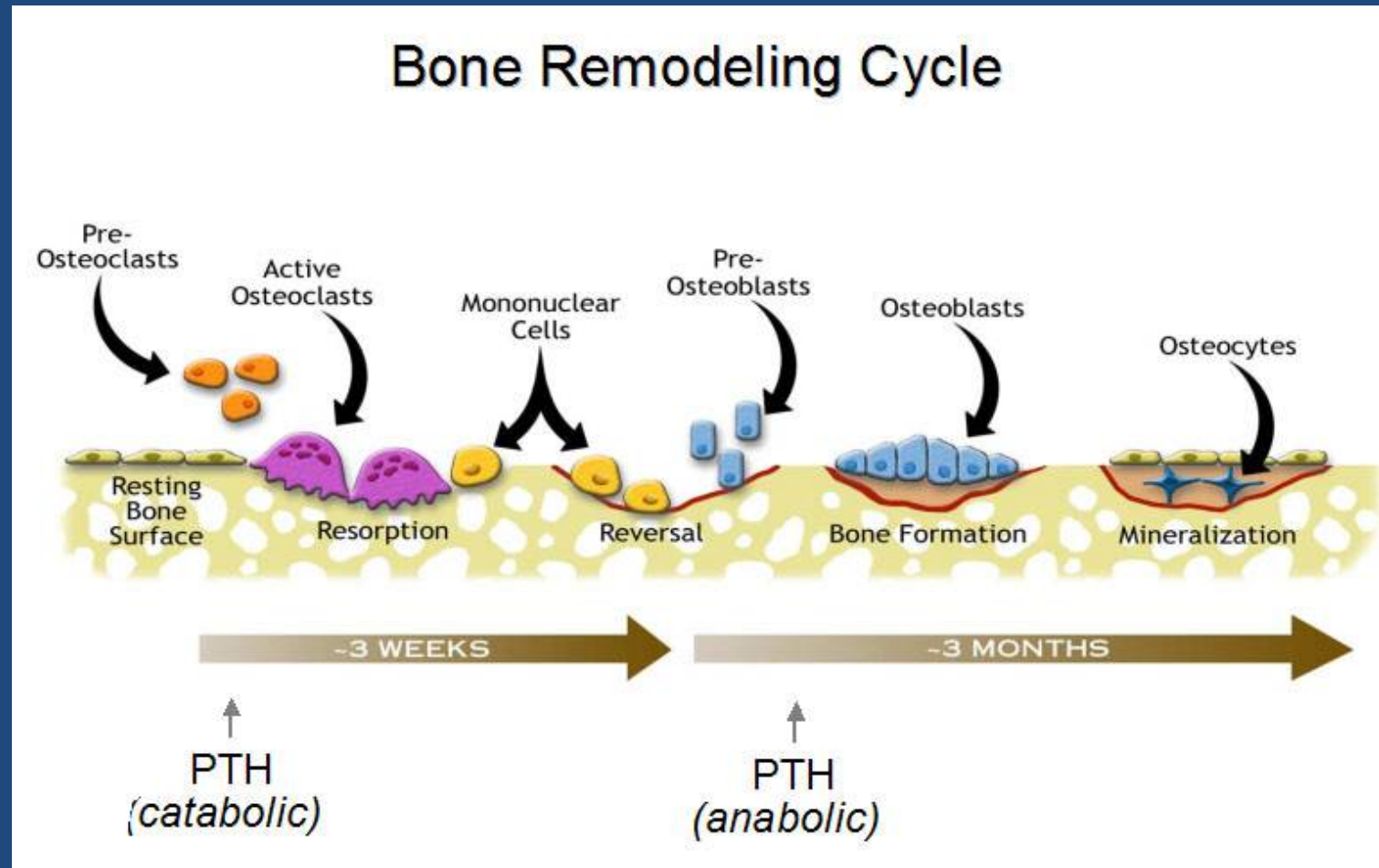
- **Loss of bone mass**
- <u>**Reduction in bone quality**</u>**:**
    - **Loss of horizontal struts**
    - **Loss of connectivity**
    - **Conversion of trabecular plates to rods**
    - **Resorption pits are "stress concentrators"**
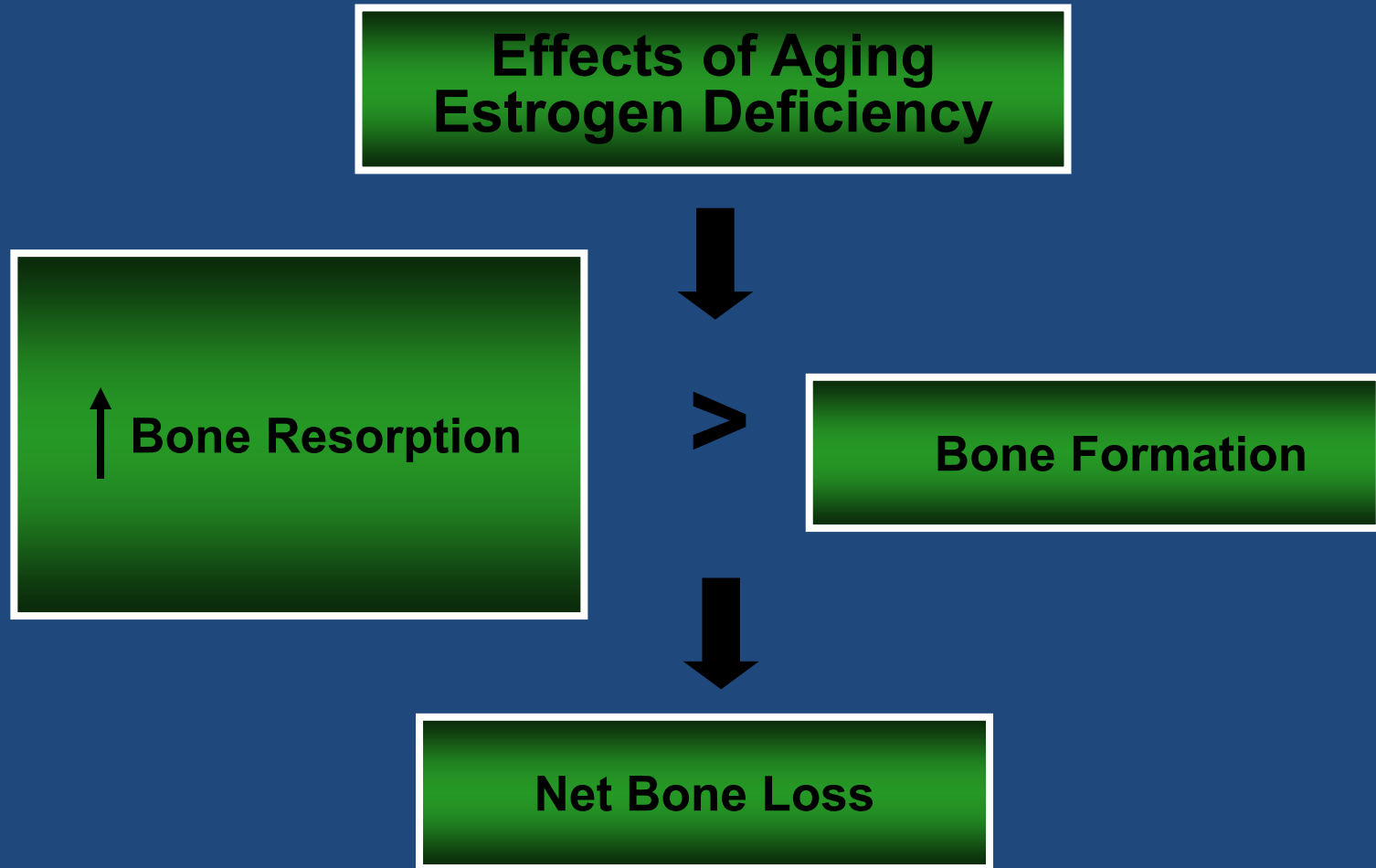   - **Unfavorable geometry**

Young normal

Images courtesy of Ralph Müller
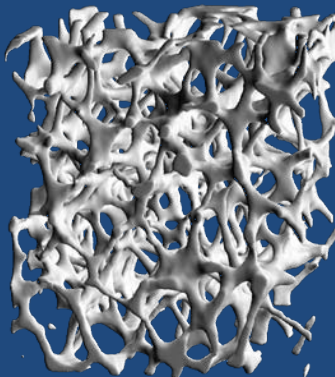
Physiologic Bone Remodeling: In osteoporosis: imbalance causes net bone loss

Unbalanced Remodeling in Menopause Leads to Osteoporosis

Effects of Aging Estrogen Deficiency

↑ **Bone Resorption** > **Bone Formation**

Net Bone Loss

Shoback D et al. *Greenspan's Basic and Clinical Endocrinology*. The McGraw-Hill Companies, Inc.; 2007. http://www.accessmedicine.com/resourceTOC.aspx?resourceID=13. Tortora GJ et al. *Principles of Anatomy and Physiology*. John Wiley & Sons, Inc.; 2003:162-184.
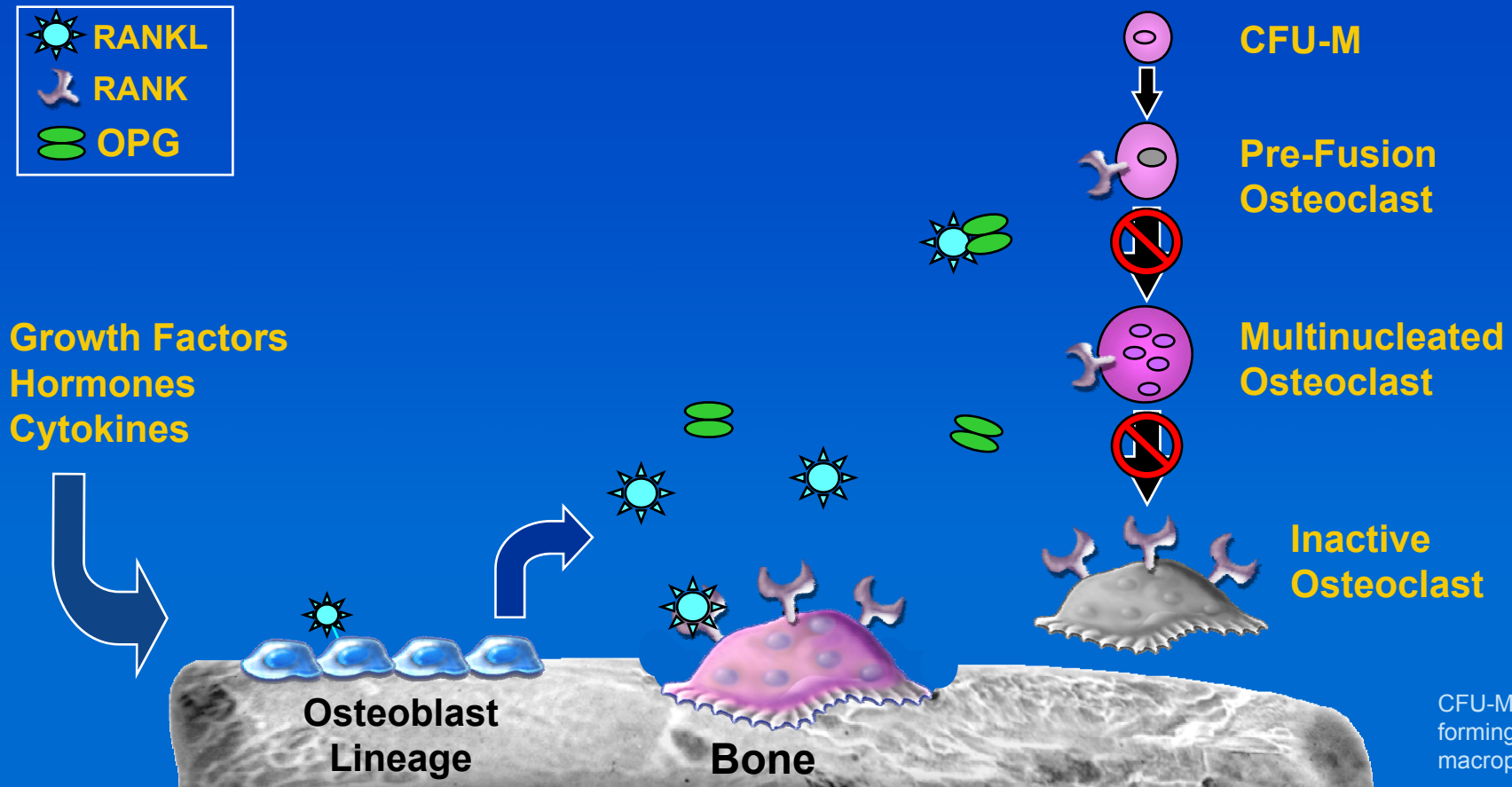
RANK receptor - RANK Ligand pathway essential for Osteoclast Activity

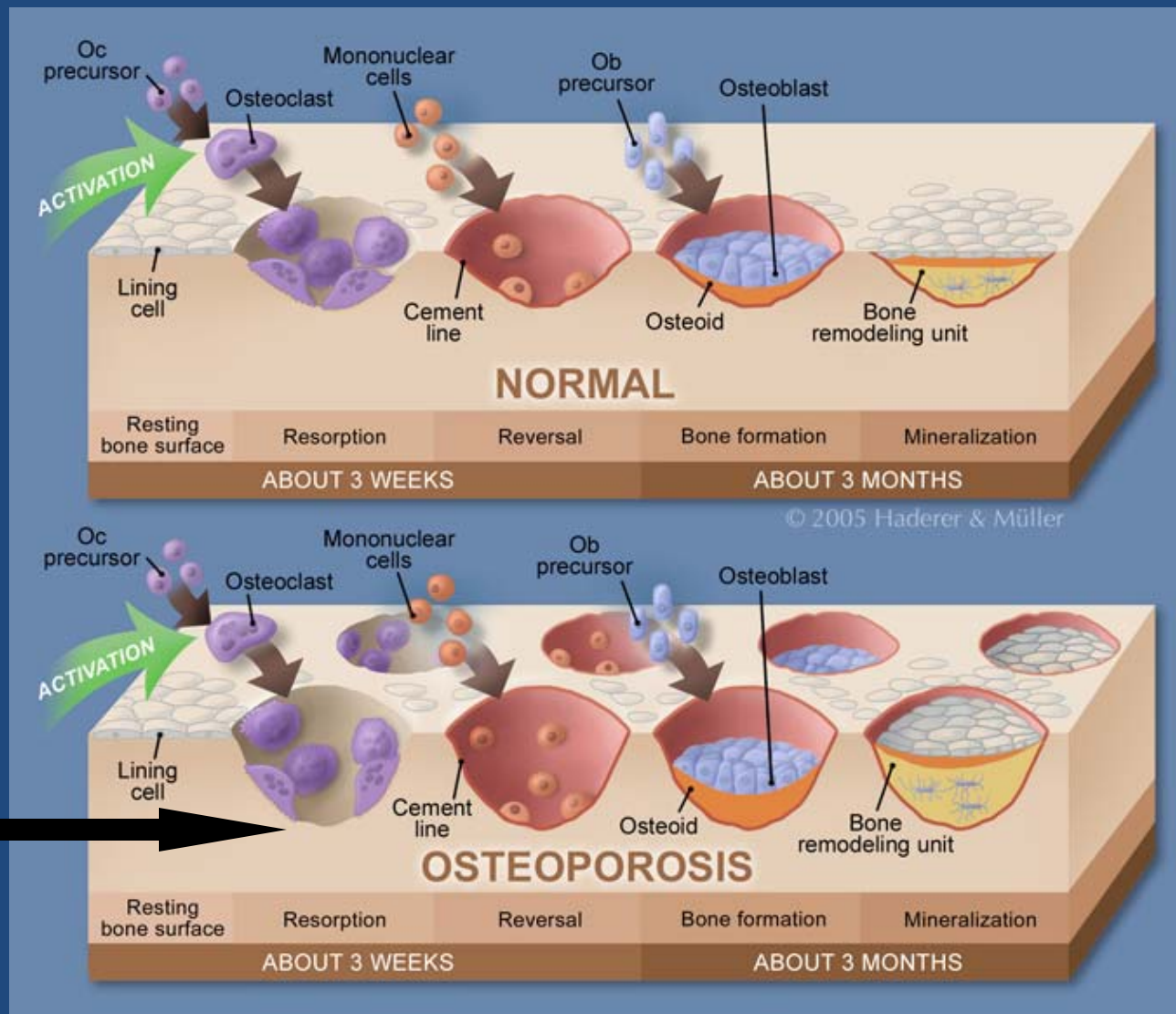**RANK Ligand Is Essential for Osteoclast Formation, Function, and Survival**

- ✴ **RANKL**
- 🦴 **RANK**

CFU-M

Pre-Fusion Osteoclast

Multinucleated Osteoclast

Growth Factors Hormones Cytokines

Activated Osteoclast

Osteoblast Lineage

Bone

CFU-M = colony forming unit macrophage
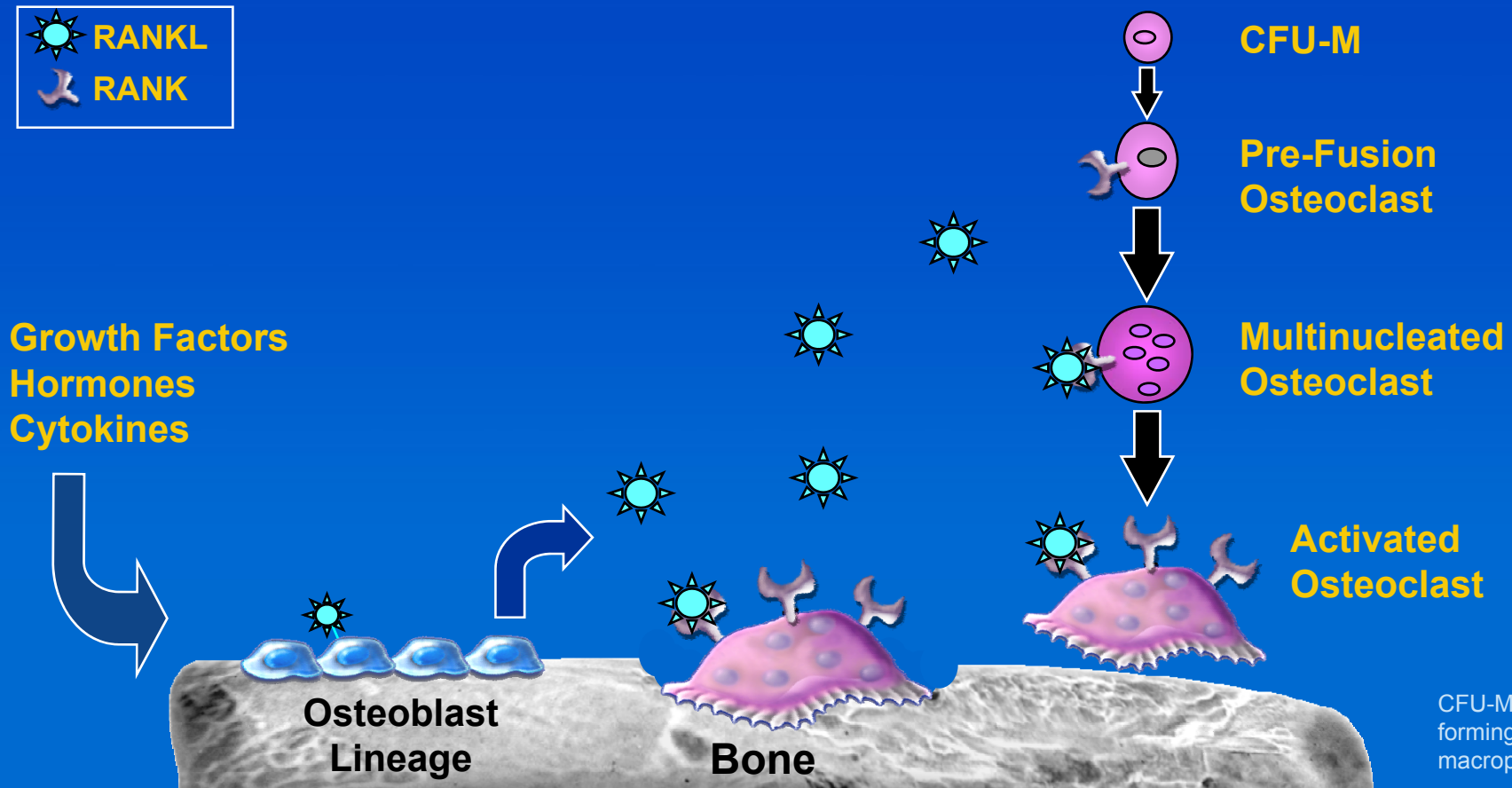
To Neutralize the Effects of RANK Ligand, the Body Produces a Protein Called Osteoprotegerin (OPG)

**Osteoclast Formation, Function and Survival Inhibited by OPG**

- RANKL
- RANK
- OPG

CFU-M

Pre-Fusion Osteoclast

Multinucleated Osteoclast

Inactive Osteoclast

Growth Factors
Hormones
Cytokines

Osteoblast Lineage

Bone

CFU-M = colony forming unit macrophage

Overactive bone remodeling in osteoporosis: <u>deeper</u> 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)

Borah et al, The *Anatomical Record, 265:101-110,* 2001.
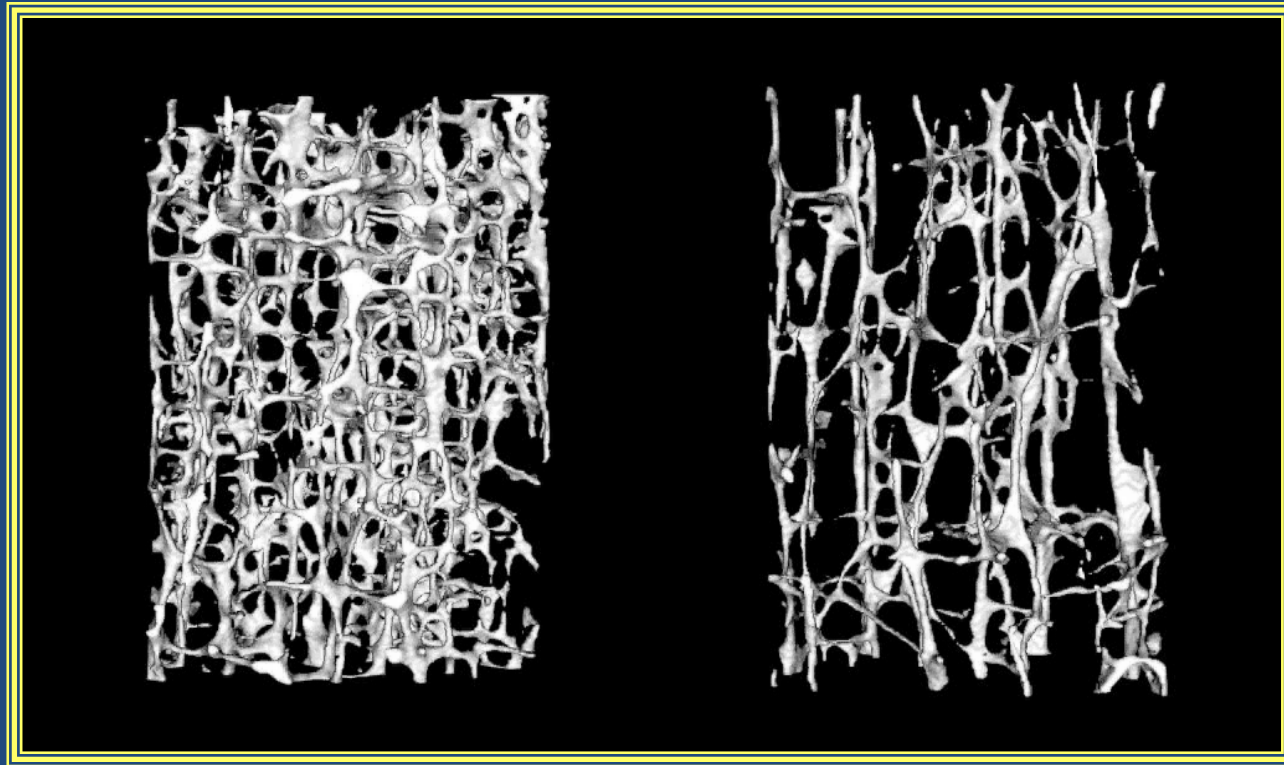
XtremeCT: see trabeculae

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]

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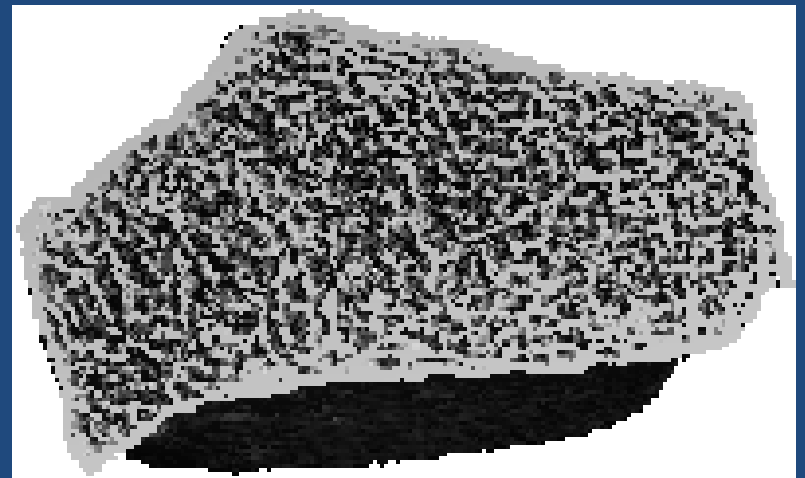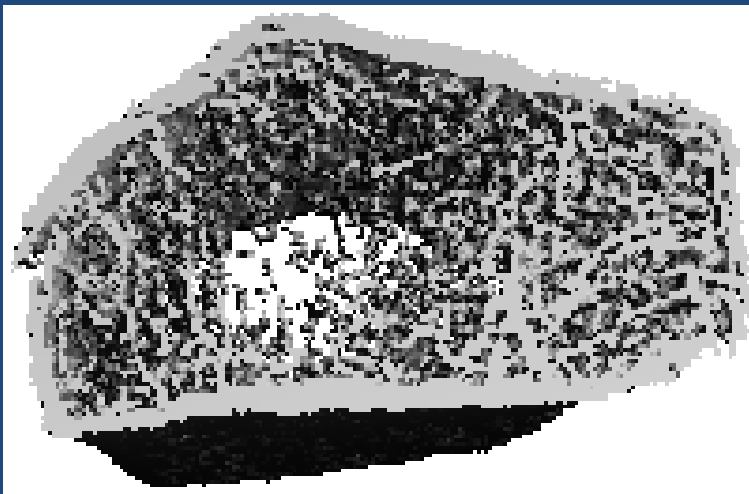
Peak bone mass & strength

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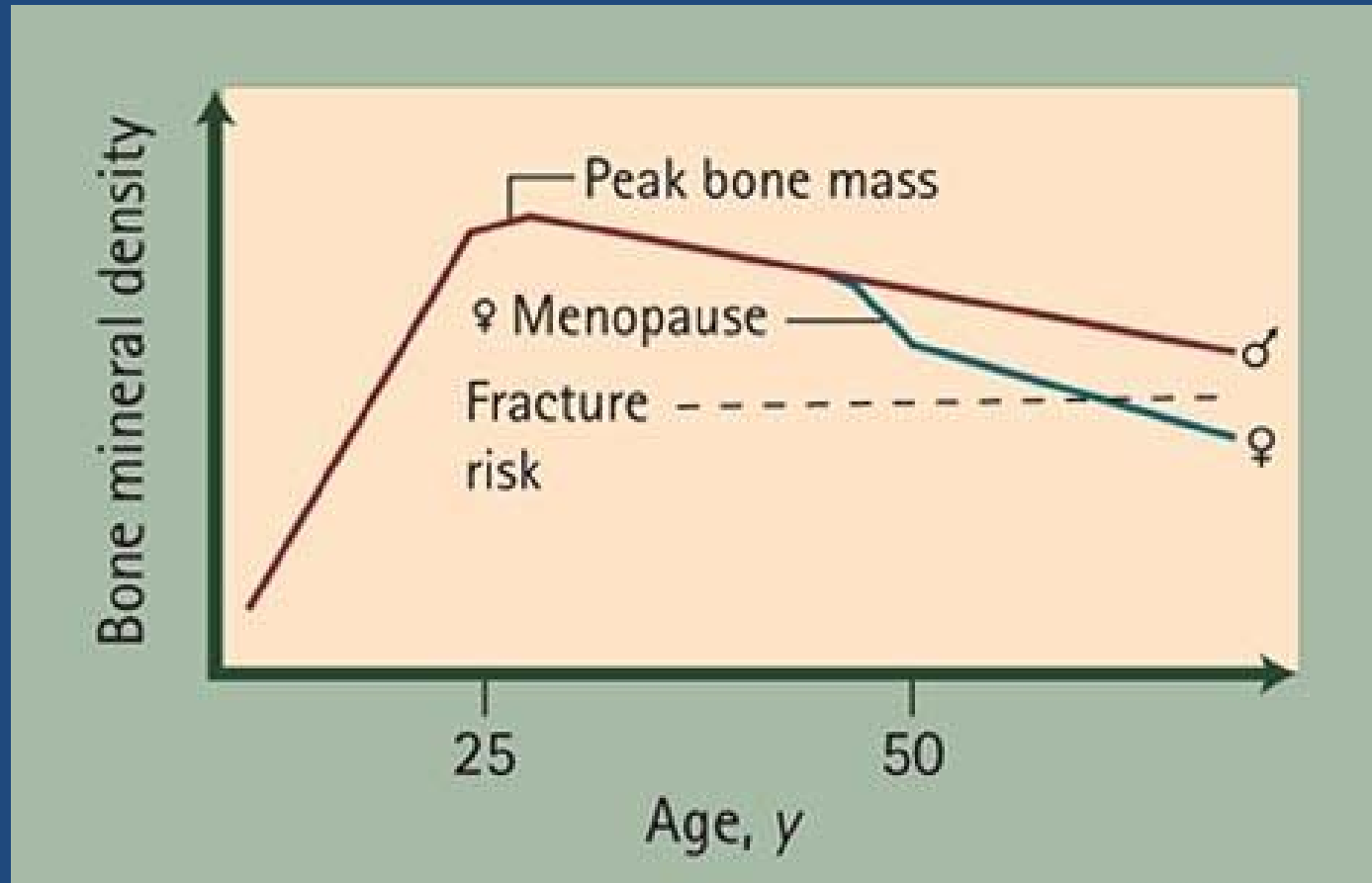
Healthy 40 yo, Zscore = -2.1 (low bone mass) → microarchitecture intact

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 $\uparrow$ 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

Coetzee M. *Southern Medical Journal. 2004*;97(5):506-11

Turner RT, et al. *Endocr Rev*. 1994;15:275-300

Riggs BL, et al. *J Clin Invest*. 2000;106:1203-1204

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]

1. Parfitt AM et al. *Am J Clin Nutr*. 1982;36:1014–1031.
2. Allain TJ, Dhesi J. *Gerontology*. 2003;49:273–278.
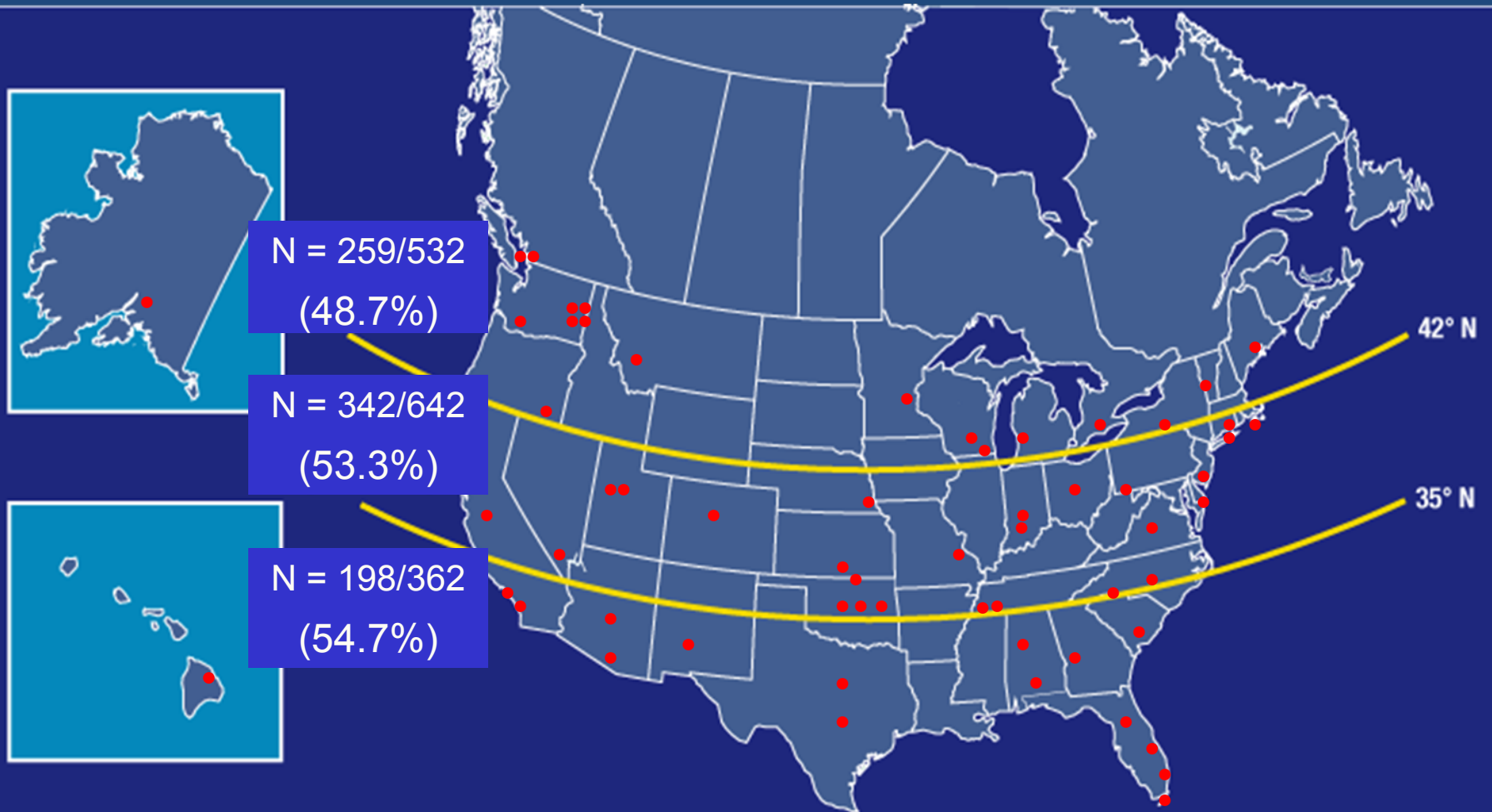**3.** Lips P. *Endocrine Rev*. 2001;22:477–501.
4. LeBoff MS et al. *JAMA*. 1999;281:1505–1511.
5. Gallacher et al. *Curr Med Res Opin*. 2005;21:1355–1361.
6. Bischoff HA et al. *J Bone Miner Res*. 2003;18:343–351.
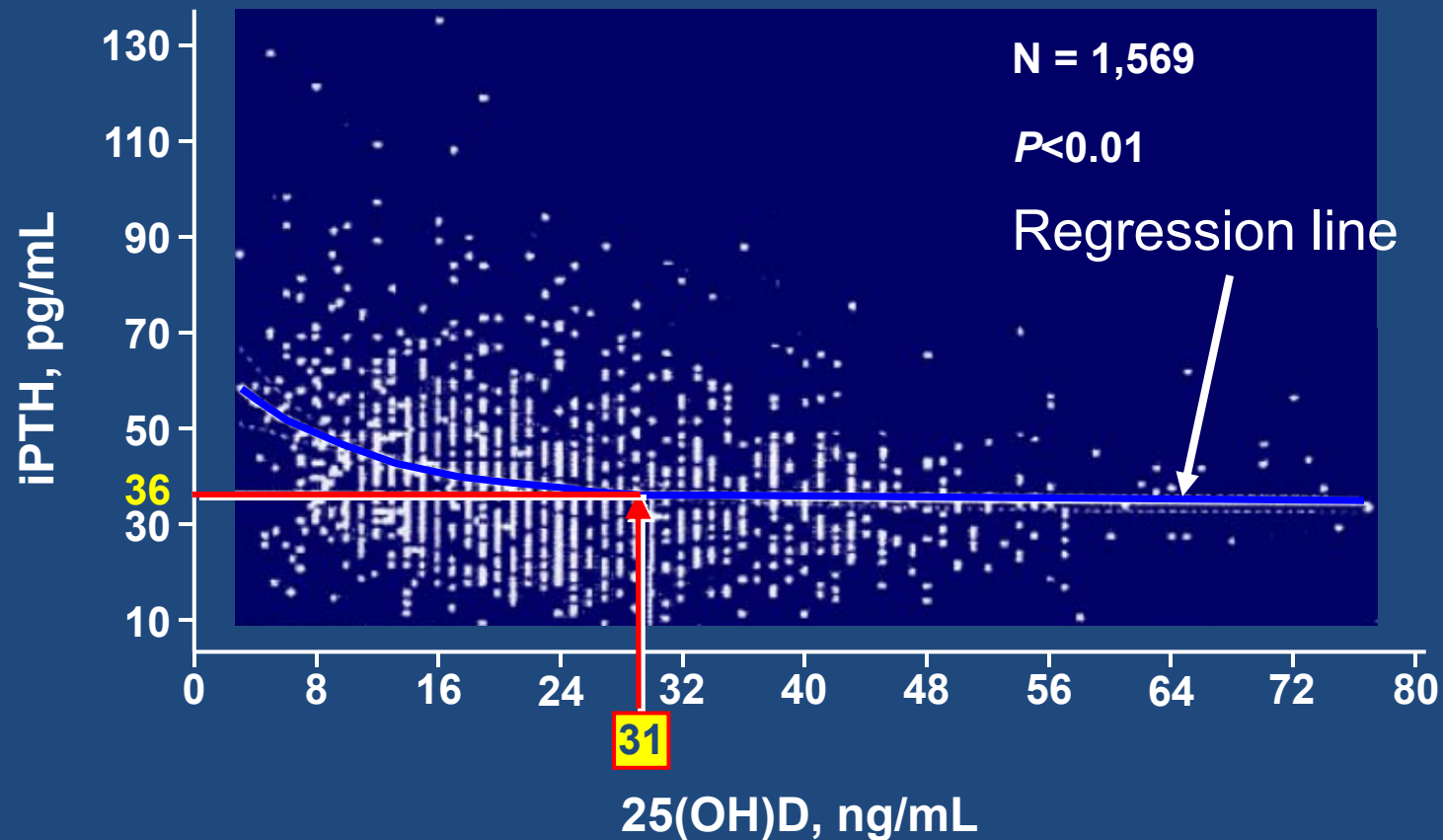**7.** Bischoff-Ferrari HA et al. *Am J Clin Nutr*. 2004;80:752–758.

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

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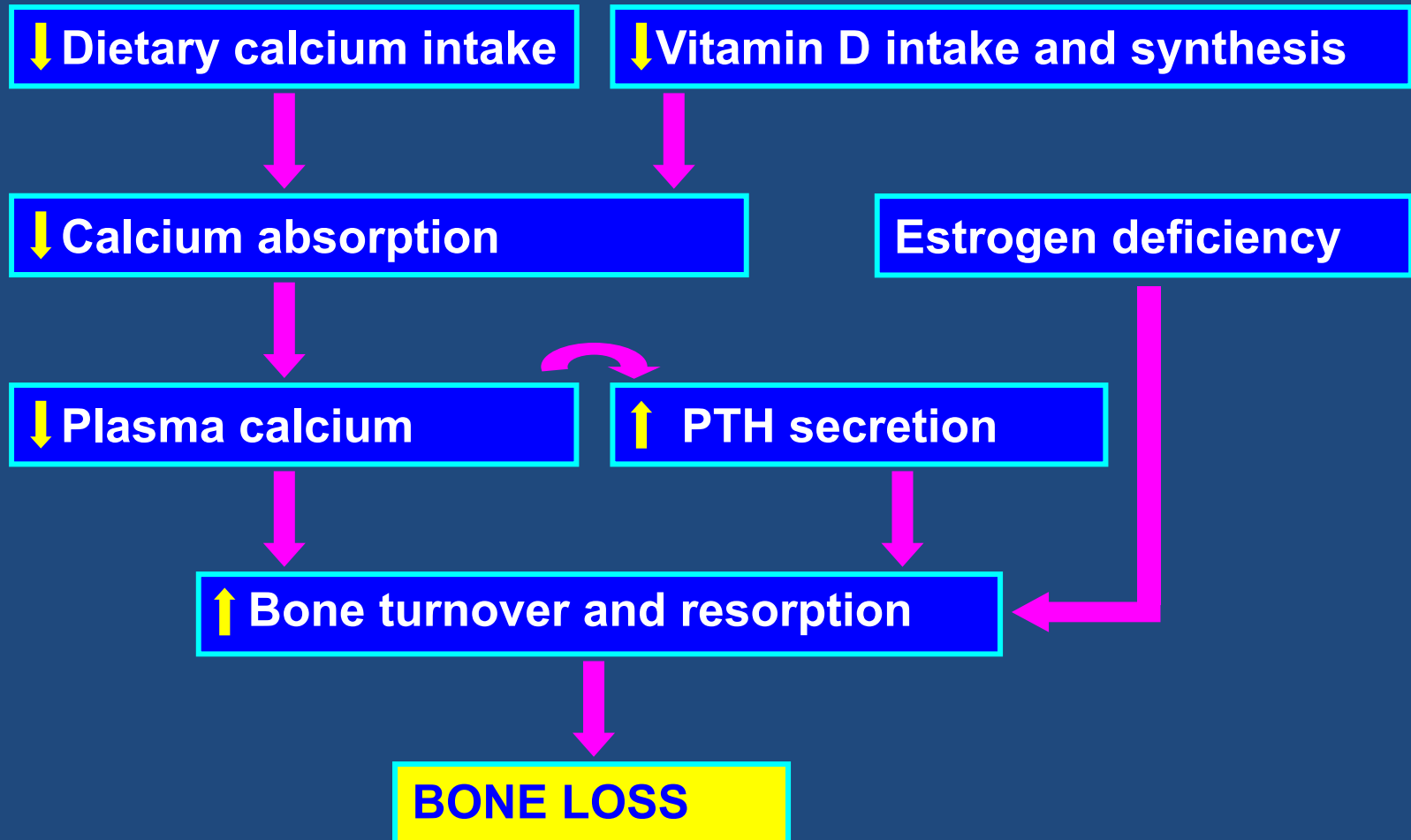
N = 342/642
(53.3%)

N = 198/362
(54.7%)

42° N

35° N

P = NS for test of trend.

Holick MF et al. *J Clin Endocrinol Metab*. 2005;90:3215–3224.

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

N = 1,569

P<0.01

Regression line

iPTH, pg/mL

25(OH)D, ng/mL

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 and the Risk of Falling

Primary Analysis	Odds Ratio (95% CI)
Pfeifer et al, 2000	0.47 (0.20–1.10)
Bischoff et al, 2003	0.68 (0.30–1.54)
Gallagher et al, 2001	0.53 (0.32–0.88)
Dukas et al, 2004	0.69 (0.41–1.16)
Graafmans et al, 1996	0.91 (0.59–1.40)
Pooled (uncorrected)	0.69 (0.53–0.88)
Pooled (corrected)	0.78 (0.64–0.92)

Favors vitamin D — Favors control

Odds Ratio: 0.1 0.5 1.0 5.0 10.0
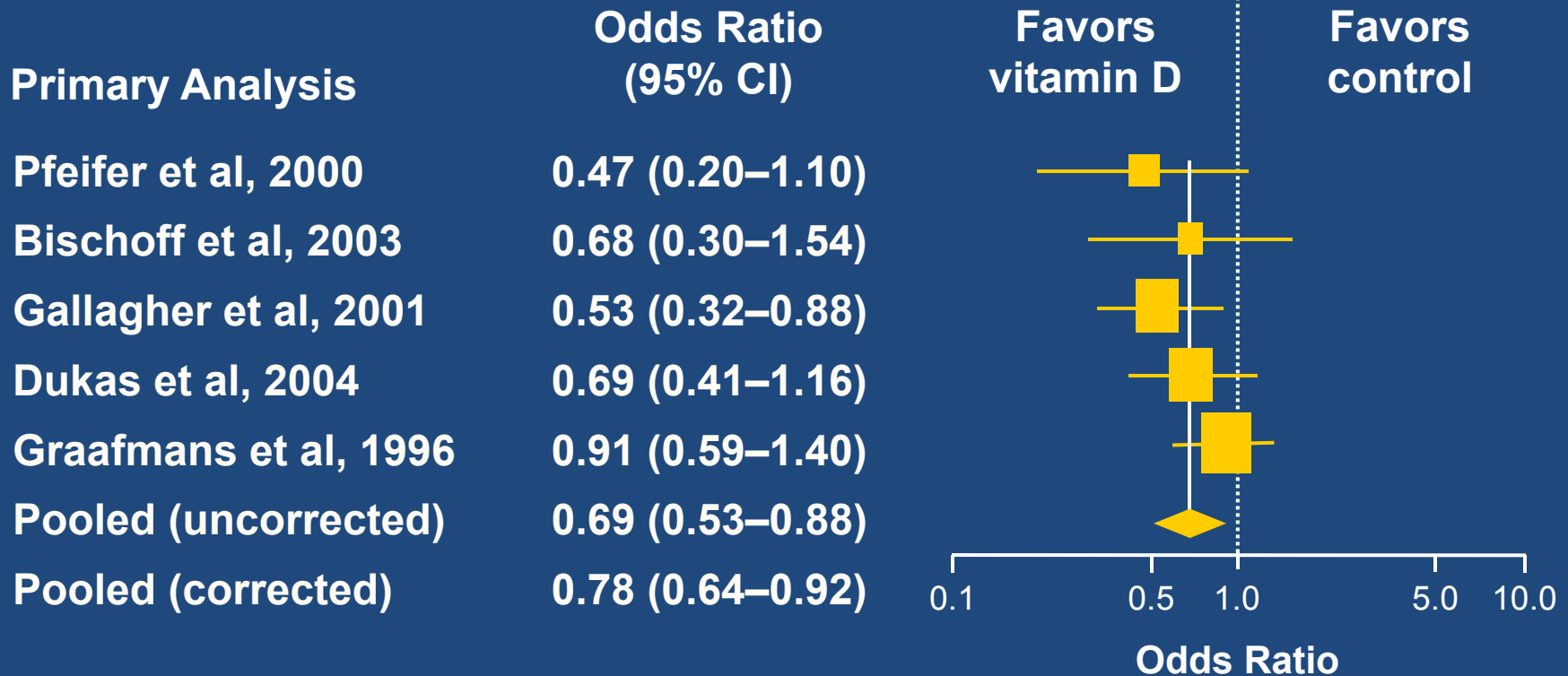
- Vitamin D, compared with calcium or placebo, reduced the risk of falling by 22%[1]

1. Bischoff-Ferrari HA. *JAMA.* 2004;291:1999–2006, with permission.

Independent risk factors for fragility fracture

- AGE ($\uparrow$ 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
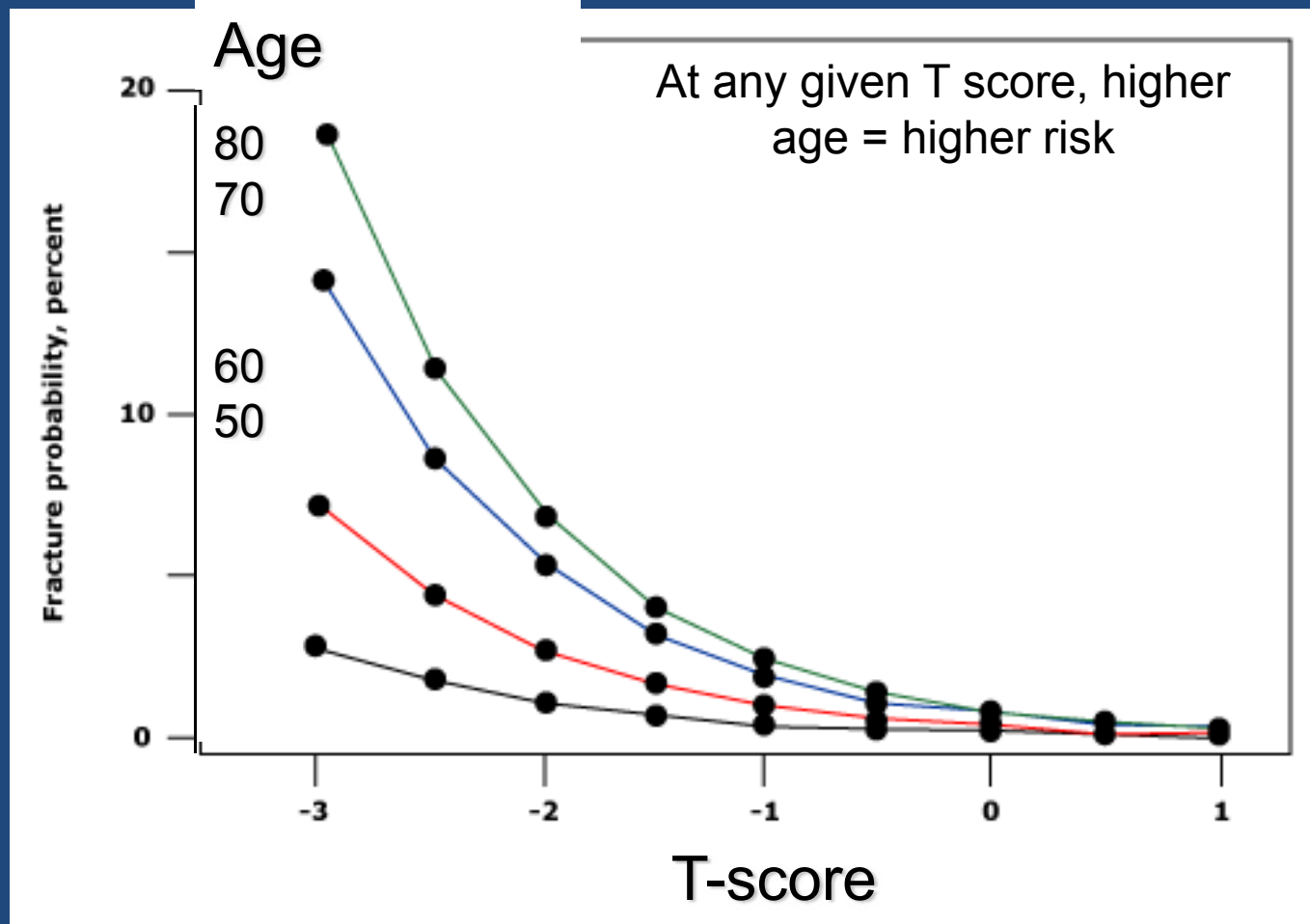
Prior Fracture as a Predictor of Fracture Risk

Prior Fracture	Relative Risk of Future Fractures		
	Wrist	Vertebral	Hip
Wrist	3.3	1.7	1.9
Vertebral	1.4	4.4	2.3
Hip	NA	2.5	2.3

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.
Klotzbuecher CM et al. *J Bone Miner Res.* 2000;15:721-739.

NORA: Relationship of BMD with Risk of Fracture in Postmenopausal Women
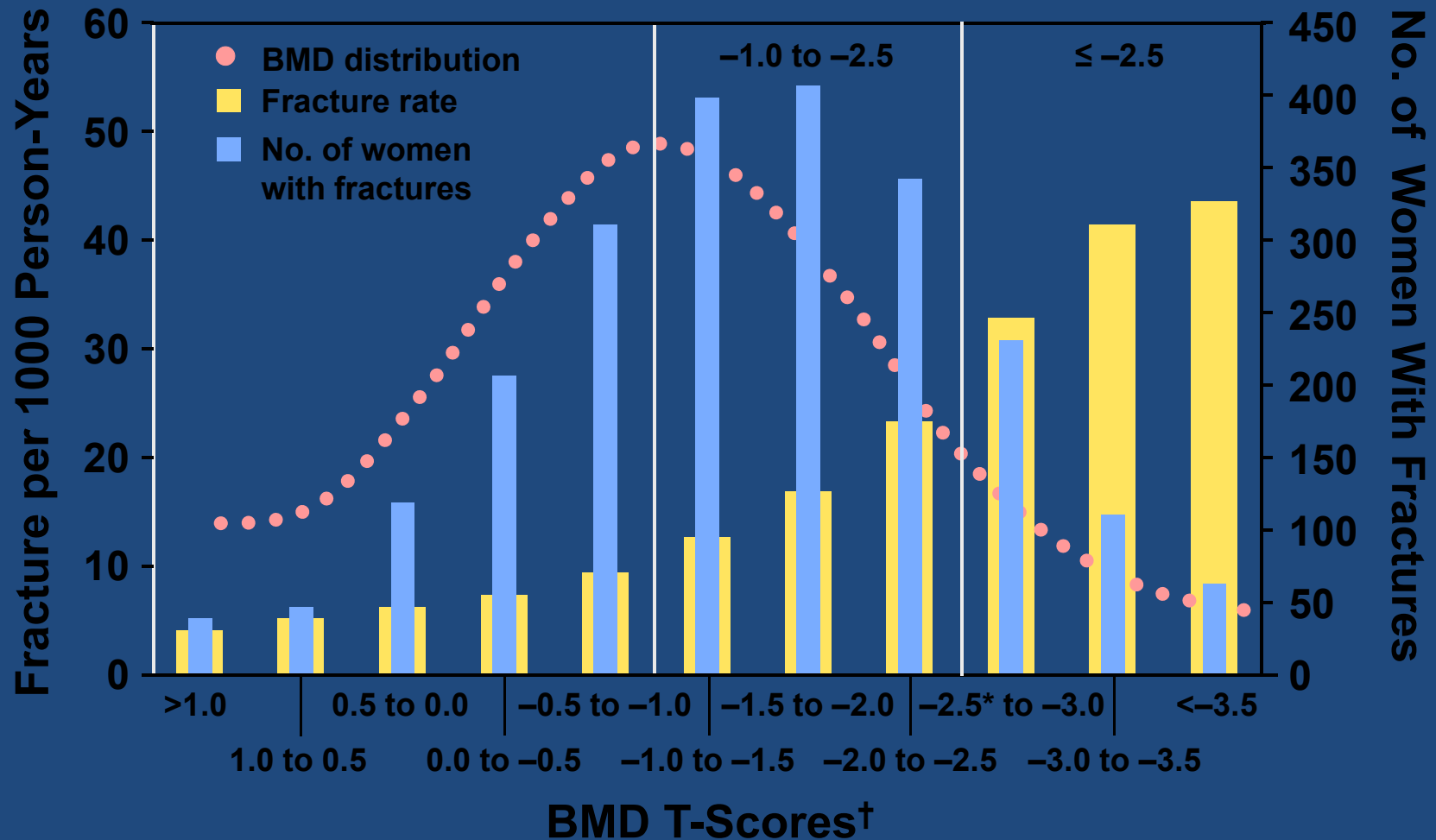
Which women or men with osteopenia should be treated?

→ *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

http://www.shef.ac.uk/FRAX/index.htm

Treatments: FDA approval requires ↓ spine fractures

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[1]

Anabolics

- Teriparatide
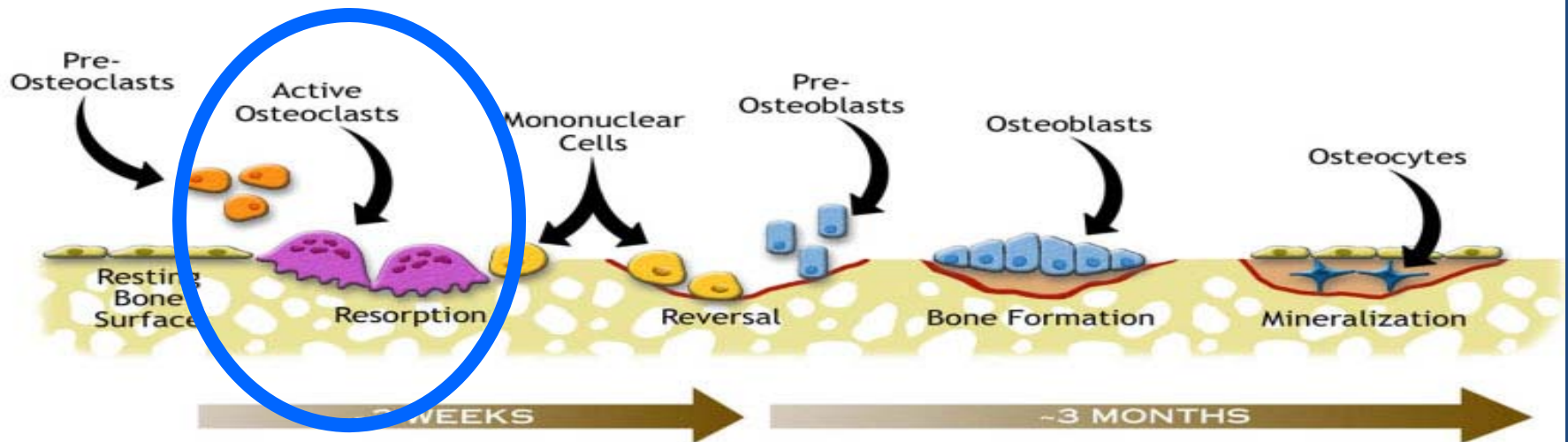- ? Strontium ranelate[2]

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

Bone Remodeling Cycle

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)
  - 35mg/week
  - 150 mg once monthly
- Ibandronate (Boniva) → no hip fracture data
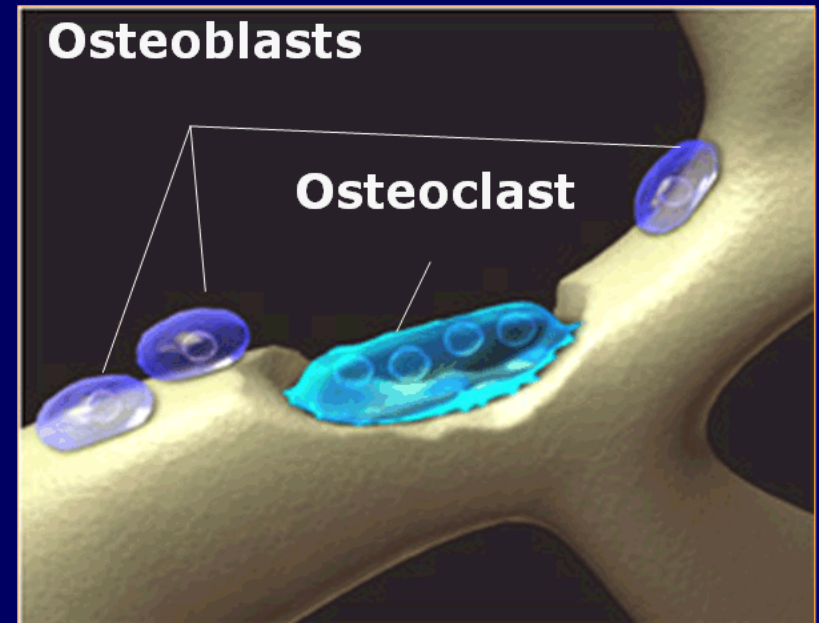 - 150 mg/month
  - 3 mg IVP every 3 months

Commonly Used Biochemical Markers of Bone Turnover

▶ **Formation**

— Bone-specific alkaline phosphatase (BSAP)
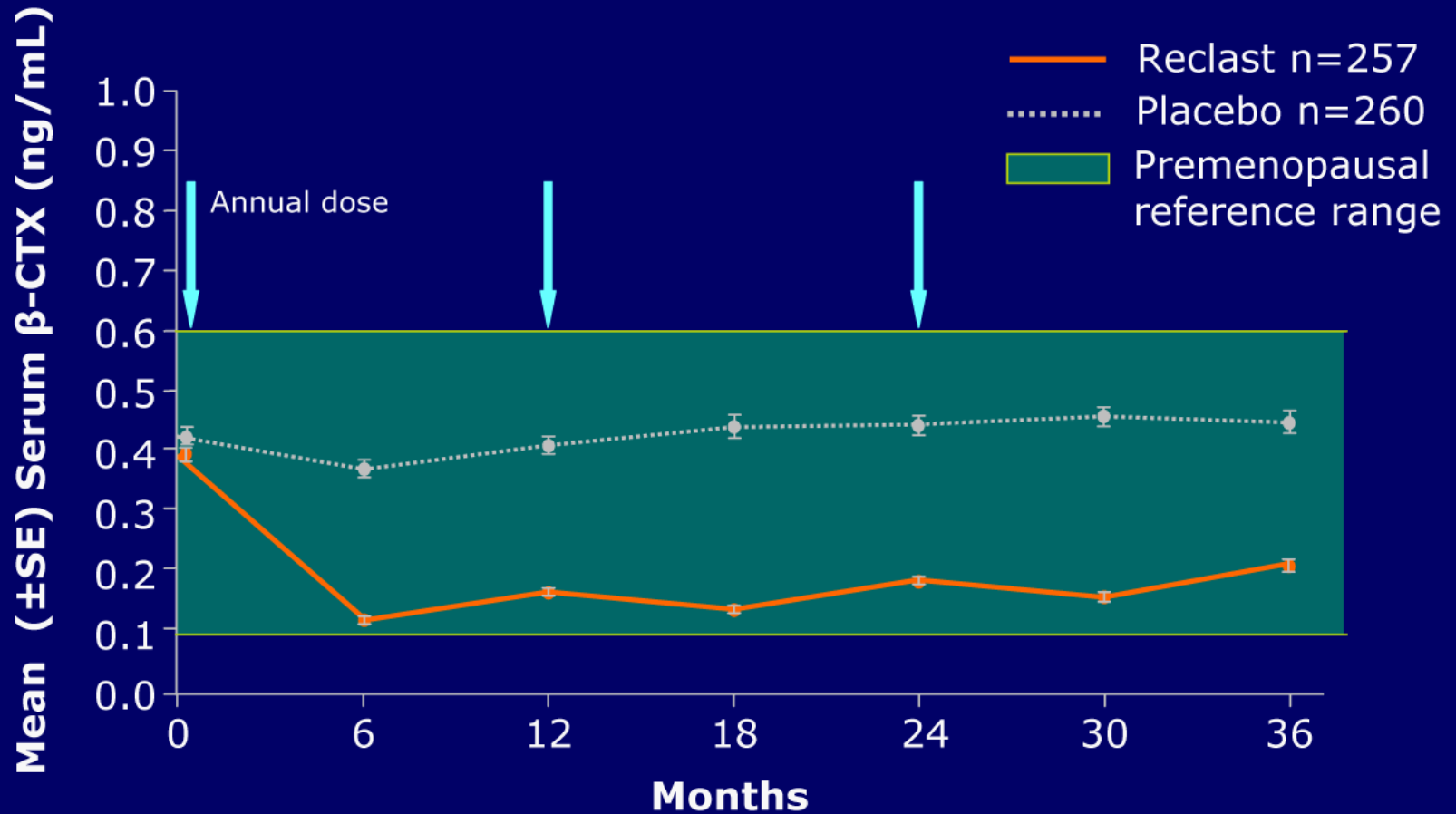
— Osteocalcin (OC)

— Propeptide of type I collagen (P1NP)

▶ **Resorption**

— N-telopeptide of type I collagen (NTX)

— C-telopeptide of type I collagen (CTX)

Osteoblasts

Osteoclast

Active Bone Resorption Site

Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, Md: US Department of Health and Human Services; 2004:187-217.

Reclast Reduced Mean Serum β-CTX

Mean (±SE) Serum β-CTX (ng/mL)

- Reclast n=257
- Placebo n=260
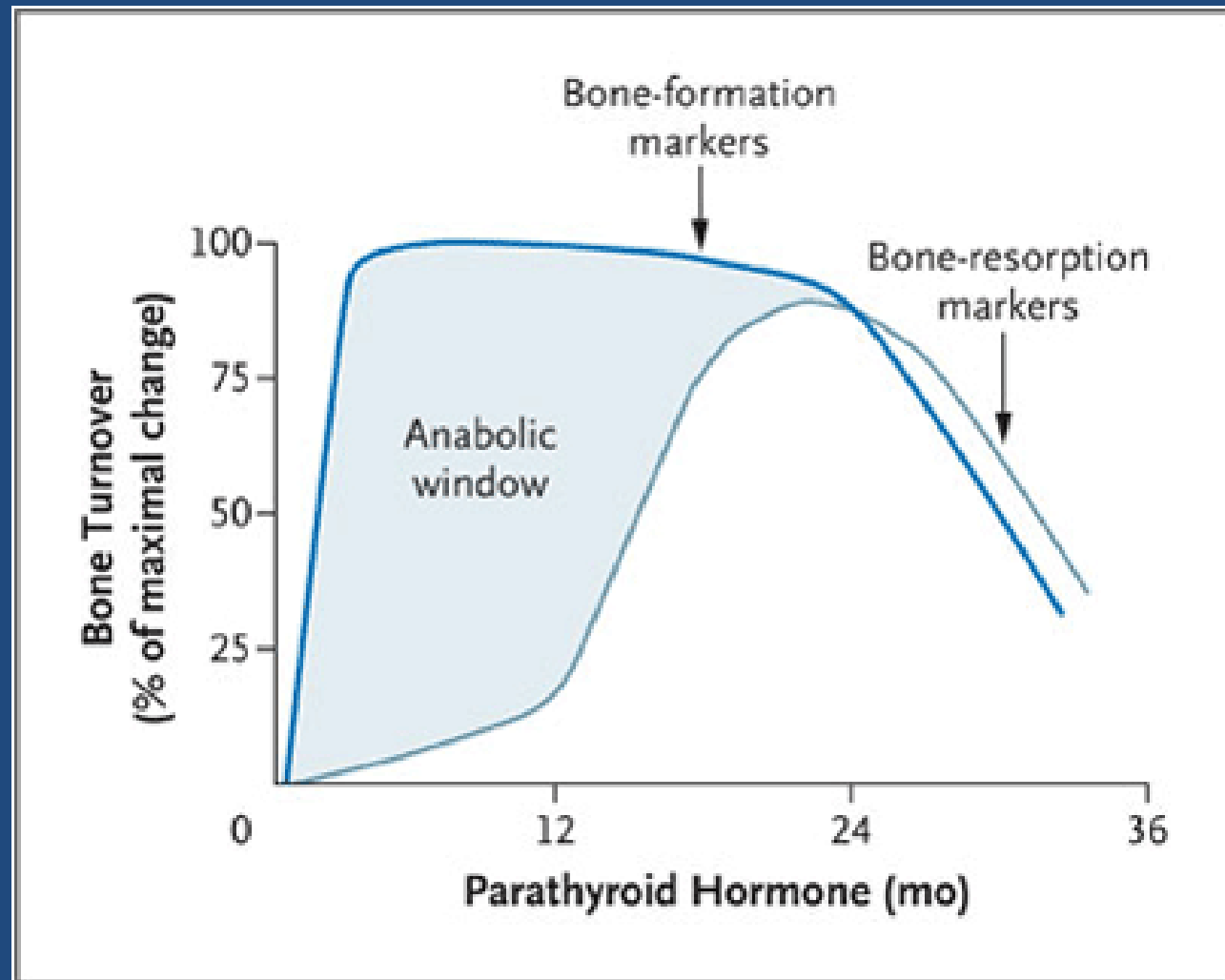- Premenopausal reference range

Annual dose

Months

teriparatide rPTH (Forteo)

- appears to create new trabeculae
- Increase osteoblast lifespan
- ↑ bone formation → resorption follows
- Given as a daily subcutaneous "pulse"

Bone Remodeling Cycle
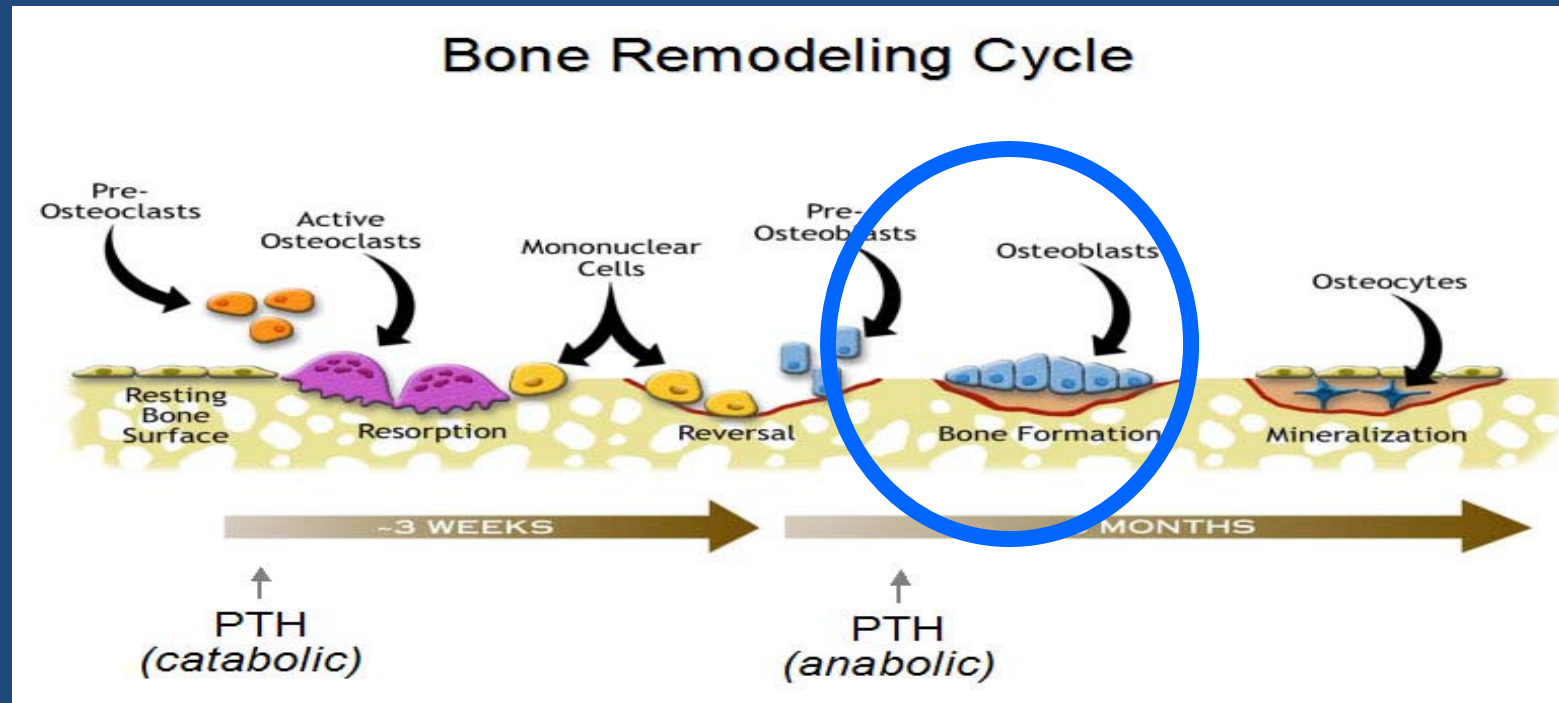
Teriparatide: sequential increase in bone formation→ resorption

Pathogenesis of osteoporotic fracture

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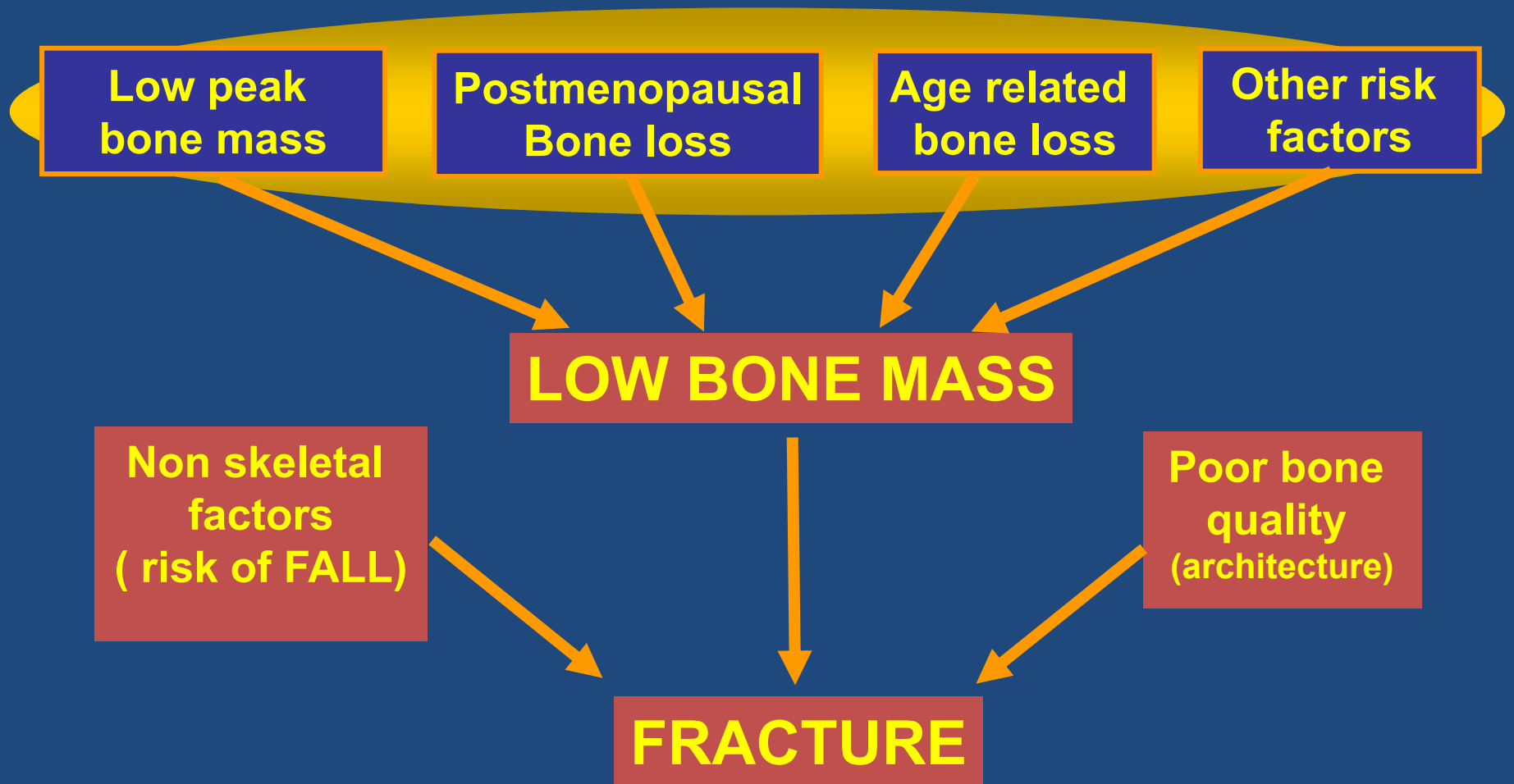
Case of 65 year old lady

- 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 osteopor fx risk: 23%; Hip fx risk: 2.6%

- Take away hx of writst fx: 14% / 1.6%