

Disuse and Transient Osteoporosis

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1

Disclosure and Conflicts of Interest Steven T Harris MD 2019-2020

- Speakers Bureaus and Consulting
Amgen
Radius Health

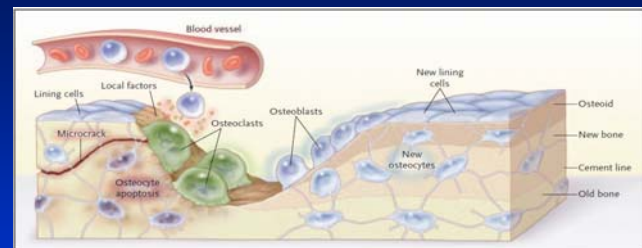
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Educational Objectives

- To review the basics of bone remodeling
- To consider the impact of exercise on bone mineral density (BMD)
- To review the effect of disuse on bone
- To list the various forms of transient osteoporosis
- To itemize the impacts of pregnancy and lactation on bone

3

Bone Structure and Physiology



Osteoclasts remove old bone. **Osteoblasts** make new bone. **Osteocytes** detect mechanical stress and microcracks and direct the activity of osteoclasts and osteoblasts.

Seeman E, et al. *N Engl J Med* 2006;354:2250

4

Unbalanced Remodeling

↑ resorption or ↓ formation



Net bone loss (osteoporosis)



5

Biochemical Markers of Bone Turnover Released During Remodeling Process



- Bone resorption
 - N-telopeptide (NTX)
 - C-telopeptide (CTX)



- Bone formation
 - Bone-specific alkaline phosphatase
 - Osteocalcin
 - C- and N-type I collagen propeptides

Lane NE. *Am J Obstet Gynecol*. 2006 Feb;194(2 Suppl):S3-11

6

Effect of Excess Bone Resorption on Microarchitecture

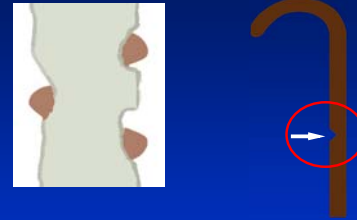


- Excess resorption leads to trabecular thinning
- May also lead to trabecular perforation and loss of connectivity
- Loss of horizontal struts disproportionately reduces strength of cancellous bone (a 10% bone loss that interrupts connectivity reduces strength by 70%)¹

¹ Silva MJ, et al. *Bone* 1997;21:191-9

7

Remodeling Lacunae Are “Stress Risers”



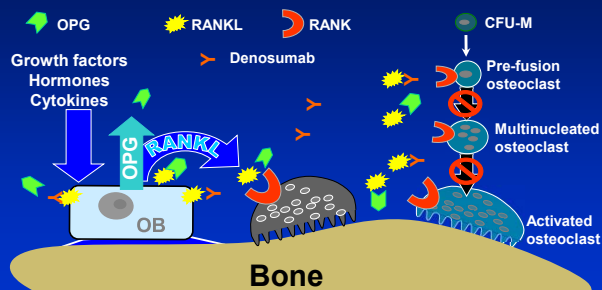
High turnover weakens bone

- More remodeling “pits”
- Decreased mineralization of bone matrix due to reduced time for mineralization

Adapted from Parfitt AM. *Am J Med.* 1987;82:68

8

RANKL Antibody/RANKL: Activation Of Osteoclasts

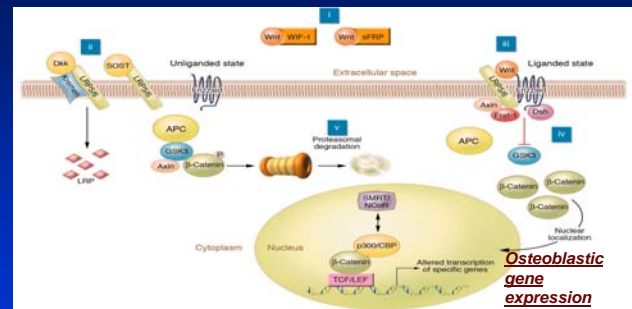


RANK = Receptor Activator of Nuclear factor Kappa B
 RANKL = RANK Ligand
 CFU-M = Colony-Forming-Unit Macrophage
 OPG = Osteoprotegerin

Adapted from Boyle, et al. *Nature* 2003;423:337

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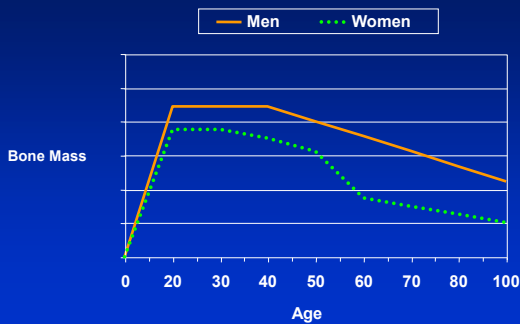
Wnt, LRP5, Sclerostin Pathway



Krishnan V, et al. *J Clin Invest* 2006;116(5):1202-1209

10

Change In Bone Mass With Age

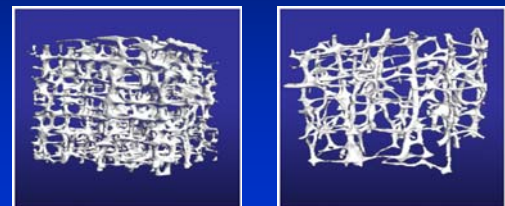


Adapted from Wasnich RD, et al. *Osteoporosis: Critique and Practicum.* Honolulu, Banyan Press 1989;179

11

Postmenopausal Osteoporosis

Increased fracture risk due to low bone density and microarchitectural deterioration: “poor bone quality”



12

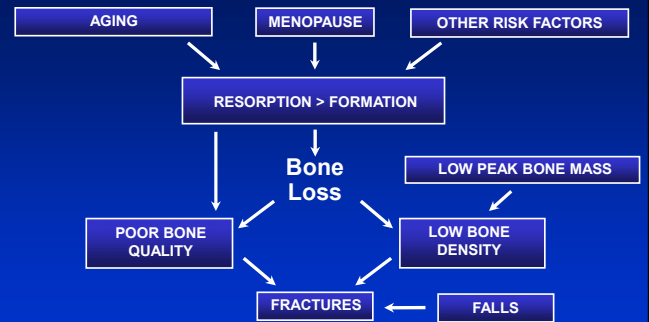
Normal Coupling of Bone Remodeling

Resorption = Formation

- Most treatment agents (bisphosphonates, SERMs, calcitonin, estrogen, denosumab) act primarily on the left side of the equation—to decrease bone resorption
- A decrease in resorption is followed by a decrease in formation—and BMD improvement tends to “plateau” after several years (with the exception of denosumab...)
- Of contemporary treatment agents, only teriparatide, abaloparatide and romosozumab act on the right side of the equation—to stimulate formation

13

Pathogenesis of Osteoporosis



Modified from Riggs BL and Melton LJ III. *Osteoporosis: Etiology, Diagnosis, and Management*. New York: Raven Press; 1988

14

Exercise and Bone

- Bone responds to changes in mechanical loading, affecting both modeling and remodeling
- Loading increases bone mass
- Unloading (disuse) decreases bone mass—with a notable decrease in bone formation
- Immobilization causes dramatic loss (roughly 5% per month from a weight-bearing area such as the calcaneus)¹

Hulley SB, et al. *J Clin Invest*. 1971;50:2506-2518

15

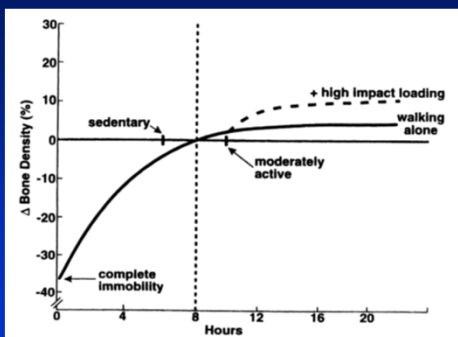
Exercise and Bone

- The relationship between loading and BMD is not linear—it is curvilinear
- Mechanical loading seems to be sensed by a “mechanostat,” per Dr. Harold Frost
 - A function of osteocytes?
- There is bidirectional “crosstalk” between muscle and bone; irisin and myostatin are two myokines that influence bone remodeling
 - “Osteosarcopenia”

Bettis T, et al. *Osteoporos Int* 2018;29:1713-1720

16

BMD and Skeletal Loading



Marcus R. *Rheum Dis Clin North Am*. 2001;27(1):131-41

17

EXERCISE: Meta-analysis

- Randomized and non-randomized controlled trials of exercise (N= 24)--measured BMD
- Postmenopausal women; resistance training alone vs combined training; typically 12 months in duration
- “It was estimated that the beneficial effects induced by combined resistance training could contribute to almost 1.8% and 2.4% BMD gains for the hip and spine in postmenopausal women”

Zhao R, et al. *Osteoporos Int* 2015;26:1605-1618

18

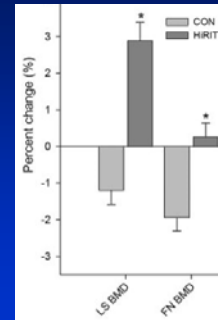
Exercise: LIFTMOR Study

- Postmenopausal women (n = 101) with T-score < -1.0 at spine and/or hip
- 8-month trial; randomized to “HiRIT” (high-intensity, progressive resistance and impact weight-bearing training) or “CON” (unsupervised, low-intensity, home-based exercise)
 - HiRIT = 30-minute, twice-weekly, supervised sessions
 - Deadlift, squat, overhead press
 - Greater than 80-85% of one repetition maximum
 - 5 sets of 5 repetitions
 - Jumping chin-ups with drop landing

Watson SL, et al. *J Bone Miner Res.* 2018 Feb;33(2):211-220

19

Exercise: LIFTMOR Study, con't



Watson SL, et al. *J Bone Miner Res.* 2018 Feb;33(2):211-220

20

Disuse

- Immobilization due to neuromuscular problems such as spinal cord injury, changes in the mechanical environment (long-term bed rest, space flight)
- Unloading effect on musculoskeletal system, impact of central/peripheral nervous system on bone cells, changes in the remodeling environment

Alexandre C and Vico L. *Joint Bone Spine* 2011;78:572-576

21

Spinal Cord Injury (“SCI”)

- All adults with spinal cord injury resulting in permanent motor or sensory dysfunction should have a DXA scan of the total hip, proximal tibia, and distal femur as soon as medically stable
- In adults with SCI, total hip, distal femur and proximal tibia bone density should be used to diagnose osteoporosis, predict lower extremity fracture risk and monitor response to therapy where normative data are available

Morse LR et al. *J Clin Densitom.* 2019;22(4):554-566

22

Spinal Cord Injury, con't

- Serial DXA assessment of treatment effectiveness among individuals with SCI should include evaluation at the total hip, distal femur, and proximal tibia, following a minimum of 12 mo of therapy at 1- to 2-yr intervals. Segmental analysis of total hip, distal femur and proximal tibia subregions from a whole-body scan should not be used for monitoring treatment.
- There is no established threshold BMD value below which weight-bearing activities are absolutely contraindicated. BMD and clinical risk factors should be used to assess fracture risk prior to engaging in weight-bearing activities.

Morse LR et al. *J Clin Densitom.* 2019;22(4):554-566

23

Whole Body Vibration (WBV)

- Based on the notion that mechanical stimulation will enhance bone formation
- Animal data for prevention of bone loss/stimulation of bone formation
- Human data for a beneficial effect on BMD are more mixed
 - Studies of various devices with differing WBV duration, frequency, amplitude
- Some evidence for a reduction in falls
- Role in patients unable to exercise?

Beck BR. *Curr Osteoporos Rep.* 2015;13:381-389

24

Transient Osteoporosis

- Regional migratory osteoporosis (RMO), transient osteoporosis of the hip (TOH), bone marrow edema syndrome (BMES)
- Migrating arthralgia of weight-bearing joints in the lower limb, focal joint pain that progressed to complete resolution, documented imaging showing focal osteoporosis, bone marrow edema
- TOH is most common in the third trimester of pregnancy—and in middle-aged men
 - May be complicated by fracture or avascular necrosis

Cahir JG and Toms AP. *Eur J Radiol.* 2008;67:2-10

25

Pregnancy

- Marked by calcium hyper-absorption—maternal calcium absorption doubles to meet the needs of the fetus
- If maternal calcium intake is inadequate, the maternal skeleton will undergo resorption in the third trimester
- During lactation (decrease in estradiol, increase in PTHrP), there is loss of maternal trabecular bone— independent of calcium intake; this is typically reversible after weaning

Hardcastle SA, et al. *Osteoporos Int.* 2019;30:939-948
Laroche M, et al. *Osteoporos Int.* 2017;28:3135-3142
Kovacs CS and Ralston SH. *Osteoporosis Int.* 2015;26-2223-2241

26

Pregnancy, con't.

- TOH usually presents with the acute onset of pain
- Diagnostic hallmark is bone marrow edema, with a characteristic pattern on MRI
- Tends to be self-limiting over 6-12 months, but anecdotal literature supports treatment with calcitonin, teriparatide—or perhaps a bisphosphonate (but the latter may be problematic in pregnancy...). There are reports of recurrent TOH in subsequent pregnancies
- May be complicated by fracture or avascular necrosis

Asadipooya K, et al. *Osteoporosis Int.* 2017;28:1805-1816

27

Pregnancy, con't

- Multiple vertebral fractures can occur, typically during the third trimester—with or without a precipitant such as heparin administration. Tends not to be a problem in subsequent pregnancies.
- In a small series of patients with vertebral fractures during pregnancy/lactation, BMD improved on average 10% after delivery/weaning

Hardcastle SA, et al. *Osteoporos Int.* 2019;30:939-948
Laroche M, et al. *Osteoporos Int.* 2017;28:3135-3142
Kovacs CS and Ralston SH. *Osteoporosis Int.* 2015;26-2223-2241

28