Age-Related Bone Changes: Structure, Function, and Loss

Nekoo Panahi
MD-MPH, PhD
Assistant professor of endocrinology
Tehran university of Medical Science

An overview of the skeletal system's functions, composition, and the inevitable deterioration that occurs with aging, leading to conditions like osteoporosis.

The Multifaceted Role of Bone Tissue

Structural Support

Supports locomotion and protects vital internal organs.

Metabolic Regulation

Involved in glucose metabolism and interacts with renal and reproductive systems.

Mineral Reservoir

Acts as a critical reservoir for calcium and phosphorus, maintaining mineral homeostasis.

Hematopoiesis

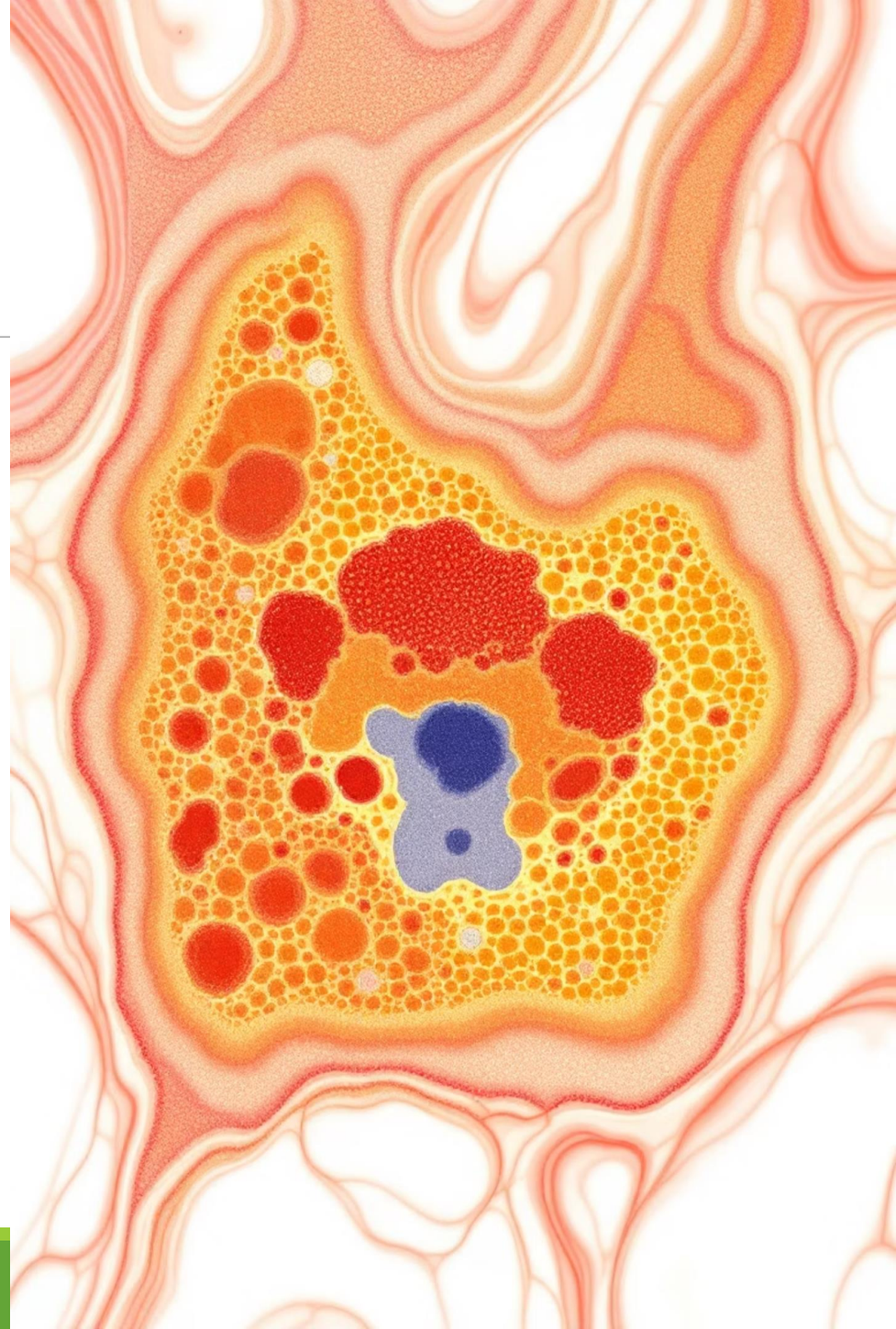
Contains cavities necessary for blood cell formation.

Bone is composed of an extracellular matrix, inorganic mineral (hydroxyapatite), and resident cells (osteoblasts, osteoclasts, osteocytes).

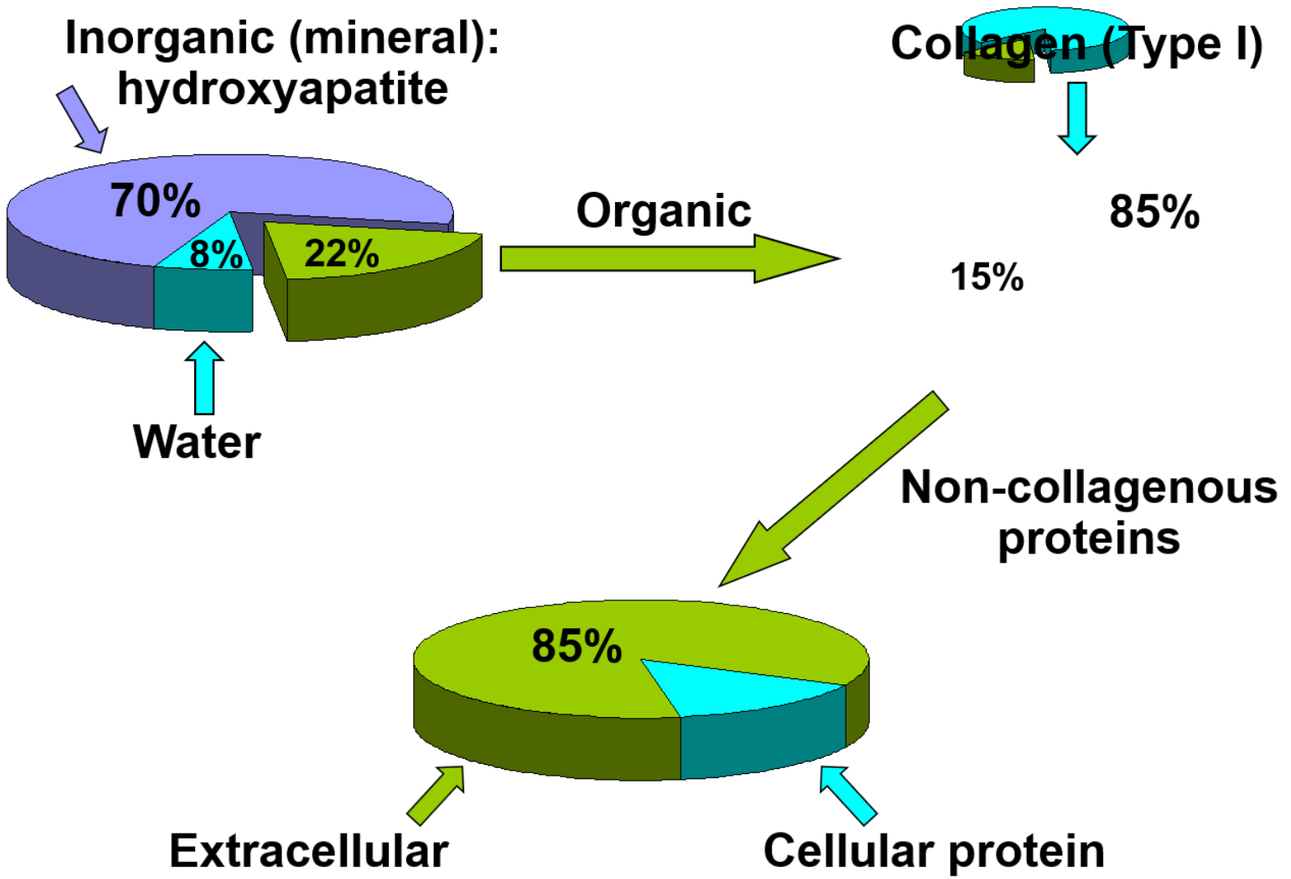
What is Osteoporosis?

Skeletal disorder
Compromised bone strength and increased fracture risk.
Beyond low bone mineral density, it involves disrupted microarchitecture, cortical porosity, material quality impairment, and decreased osteocyte viability.
Diagnosis relies on imaging surrogates like DXA, though bone fragility—not BMD alone—defines the disease.

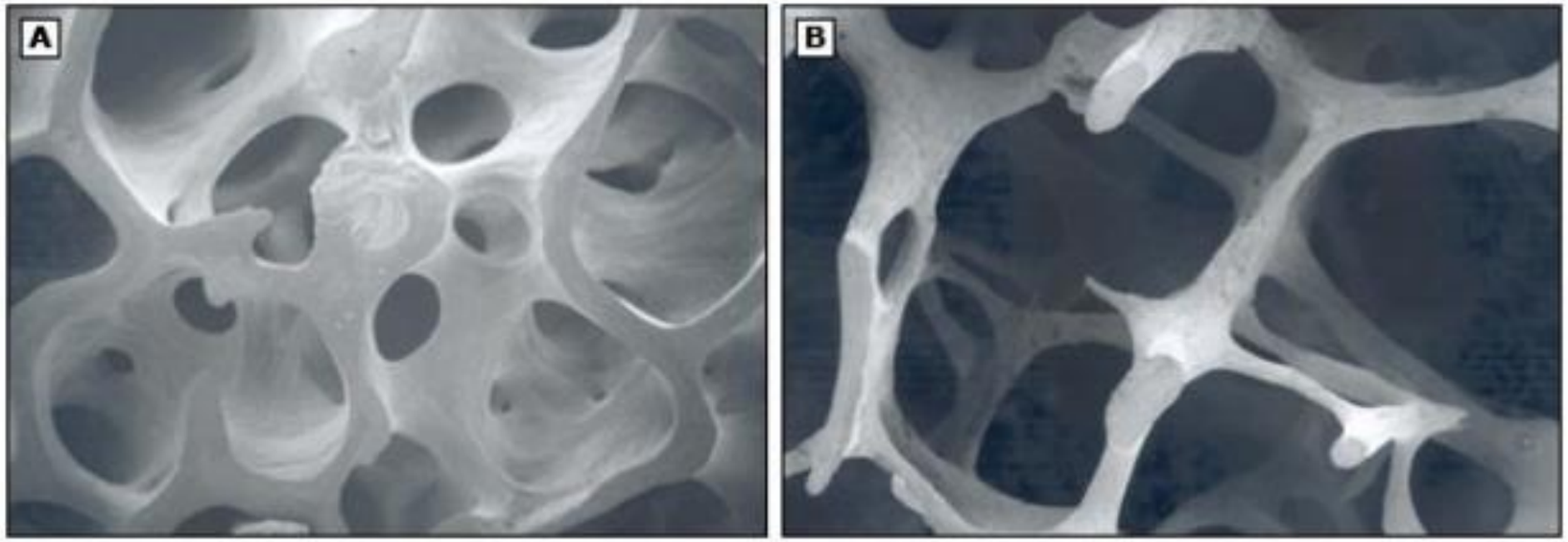
Key concept: Osteoporosis is fundamentally a disorder of bone quality and strength, not just quantity.



Bone composition

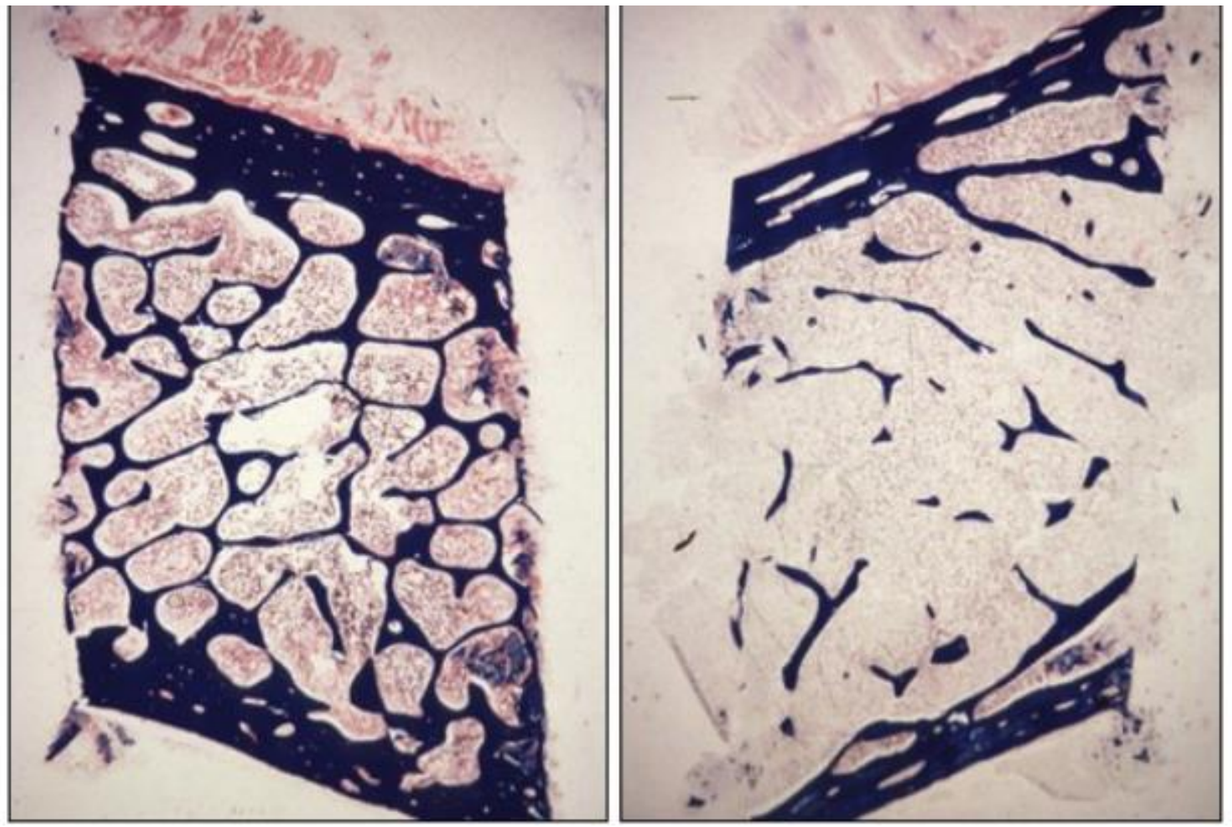


Three-dimensional CT images



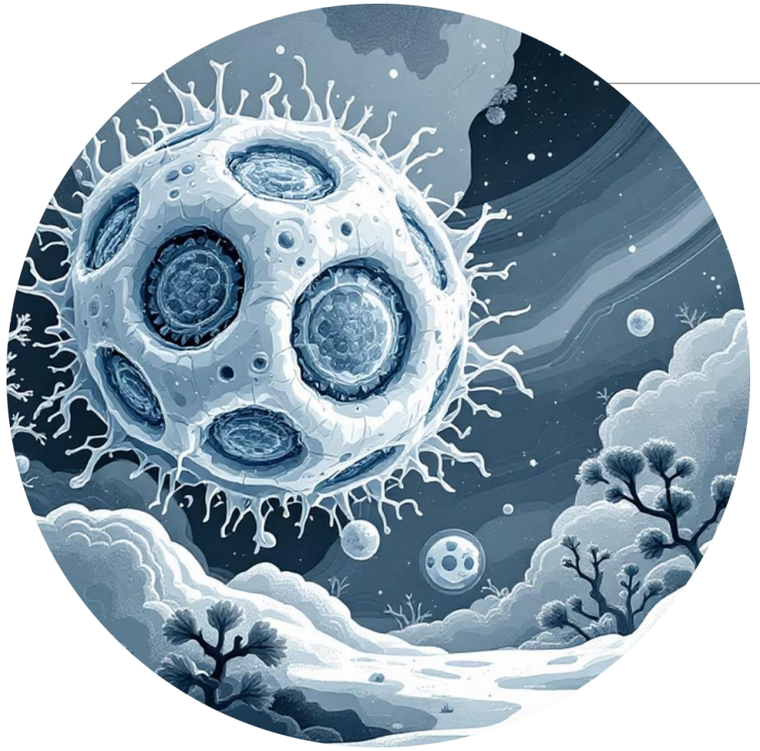
cancellous bone from an individual without (A) and with (B) osteoporosis. trabeculae in (B) are thinner, disconnected, and further apart.

Two-dimensional histologic images



cortical and cancellous bone from iliac bone biopsies
without (left panel) and with (right panel) osteoporosis.
cortices are thinner and more porous
trabeculae are fewer, thinner, disconnected, and further apart

Cellular Players in Bone Homeostasis



Osteoclasts

Large, multinucleate cells responsible for bone resorption by secreting acid and enzymes.

Osteoblasts

Differentiate from BMSCs; promote new bone formation and matrix mineralization.

Osteocytes

Terminally differentiated osteoblasts; sense mechanical load and direct remodeling.

The balance between these cells is crucial. Osteoprotegerin (OPG) inhibits osteoclast activity by binding to RANKL.

The Fundamental Imbalance in Bone Remodeling

Bone remodeling is a continuous process where old bone is resorbed by osteoclasts and replaced by new bone made by osteoblasts, orchestrated by osteocytes.

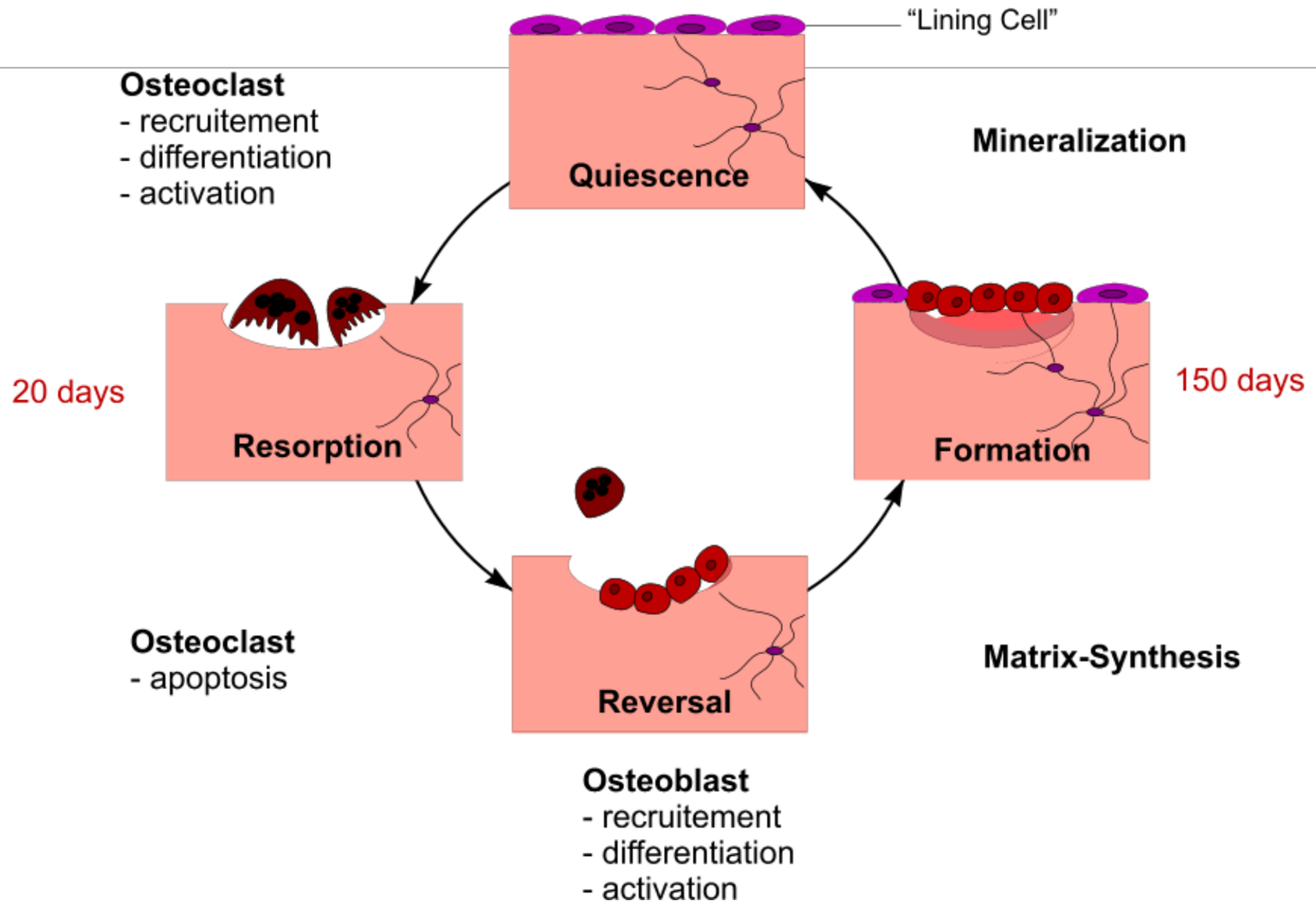
Normal Remodeling

Osteoclasts and osteoblasts maintain a balance to repair and replace bone tissue.

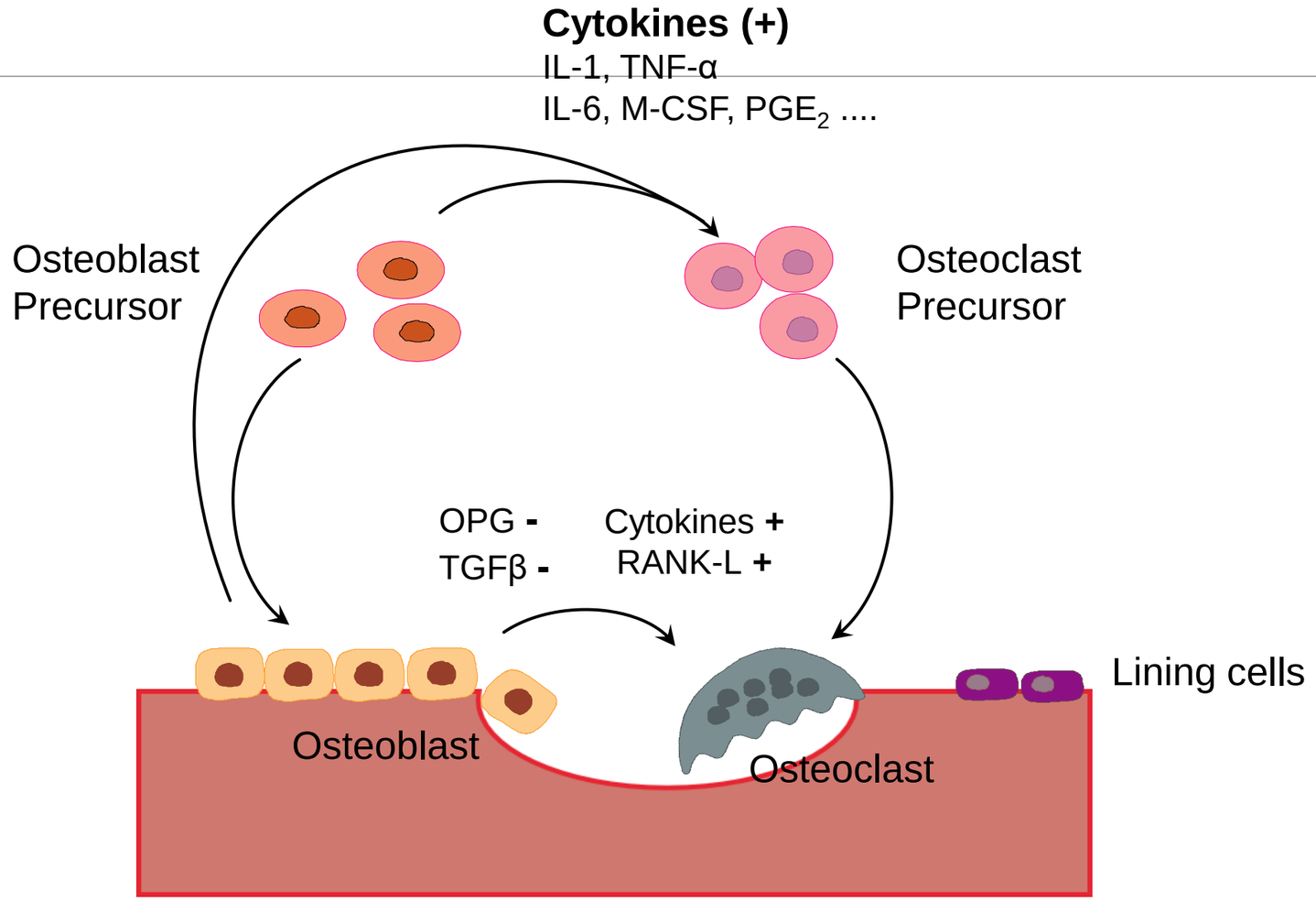
Osteoporosis Pathophysiology

oversupply of osteoclasts or an undersupply of osteoblasts relative to the need for repair.

The Bone Remodeling Cycle



Bone Remodeling



Riggs B.L., et al. Endocr Rev. 2002; 23:279

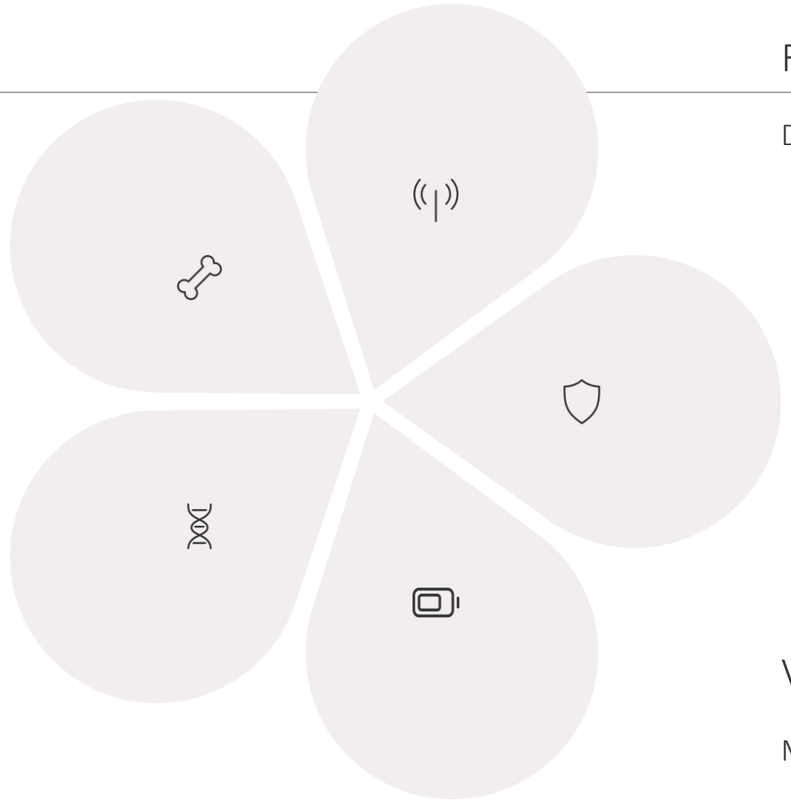
Osteocyte Dysfunction: The Master Regulator of Bone Remodeling

RANKL Production

Direct osteoclast recruitment and bone remodeling

Sensing Function

Detect mechanical strain and matrix damage



Protective Signaling

Sclerostin secretion and mineralization control

Mechanotransduction

Convert mechanical forces to biological signals

Vascular Support

Maintain bone perfusion and hydration

Osteocyte death increases with age independent of subject age, leading to hypermineralization, micropetrosis, and brittleness. Age-related osteocyte decline reduces bone strength through impaired microdamage repair and decreases bone vascularity and hydration.

Defining Bone Fragility Beyond BMD

While decreased Bone Mineral Density (**BMD**) is often synonymous with osteoporosis, the disease is fundamentally about bone **fragility**, which is influenced by multiple factors.

Microarchitecture

Disrupted structure, cortical porosity, and compromised material quality.

Macroarchitecture

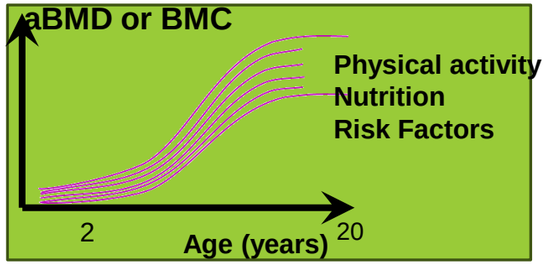
Unfavorable structure, such as increased femoral neck length.

Osteocyte Viability

Decreased viability of osteocytes, which sense and respond to mechanical forces.

Diagnosis relies heavily on imaging (DXA, QCT) as clinical surrogates for bone mass.

Peak Bone Mass Acquisition



Peak bone mass—the maximum bone mass achieved in life—typically occurs in the **third decade** of life and represents a critical determinant of **future fracture risk**. Genetic factors, ethnic variation, environmental influences including physical activity, and childhood health status substantially influence peak bone mass achievement.

Genetic Basis

Approximately 518 genetic loci influence BMD through Wnt/beta-catenin signaling and RANK/RANKL/OPG pathways.

Ethnic Variation

African Americans exhibit higher BMD; Asian Americans show lower BMD compared to White Americans.

Environmental Factors

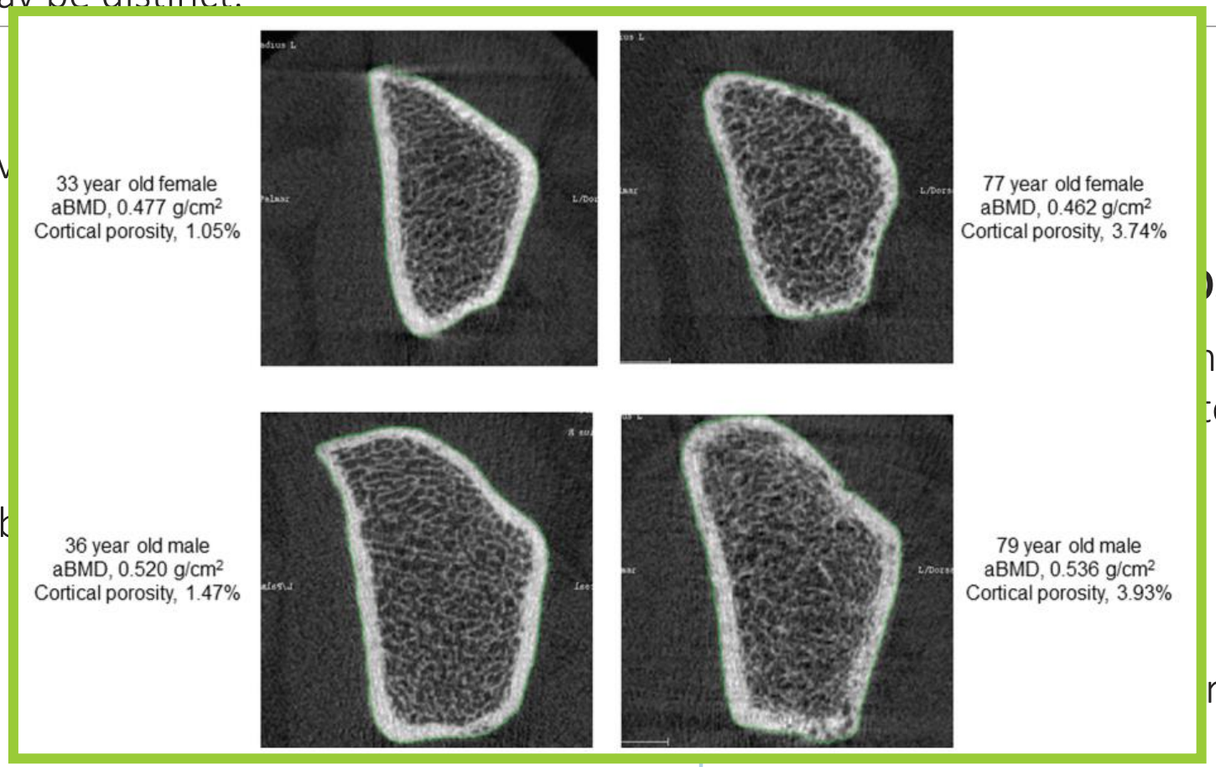
Physical activity during childhood augments bone mass; chronic disease and malnutrition impair bone accrual.

Age-Related Bone Loss: Critical Determinants

Old age and sex steroid deficiency are the two most critical factors for osteoporosis development in both sexes, though the underlying mechanisms may be distinct.

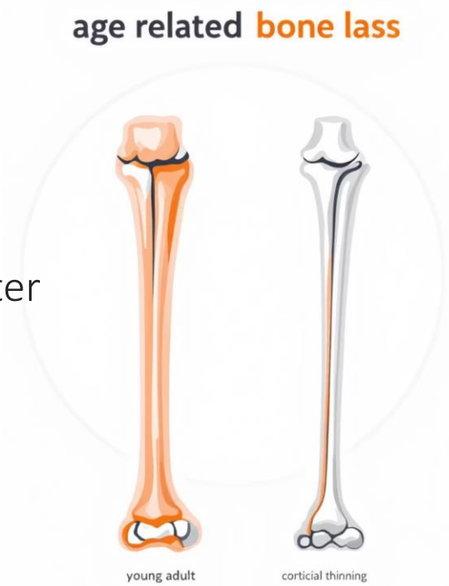
Achiev

Women experience ab



ss

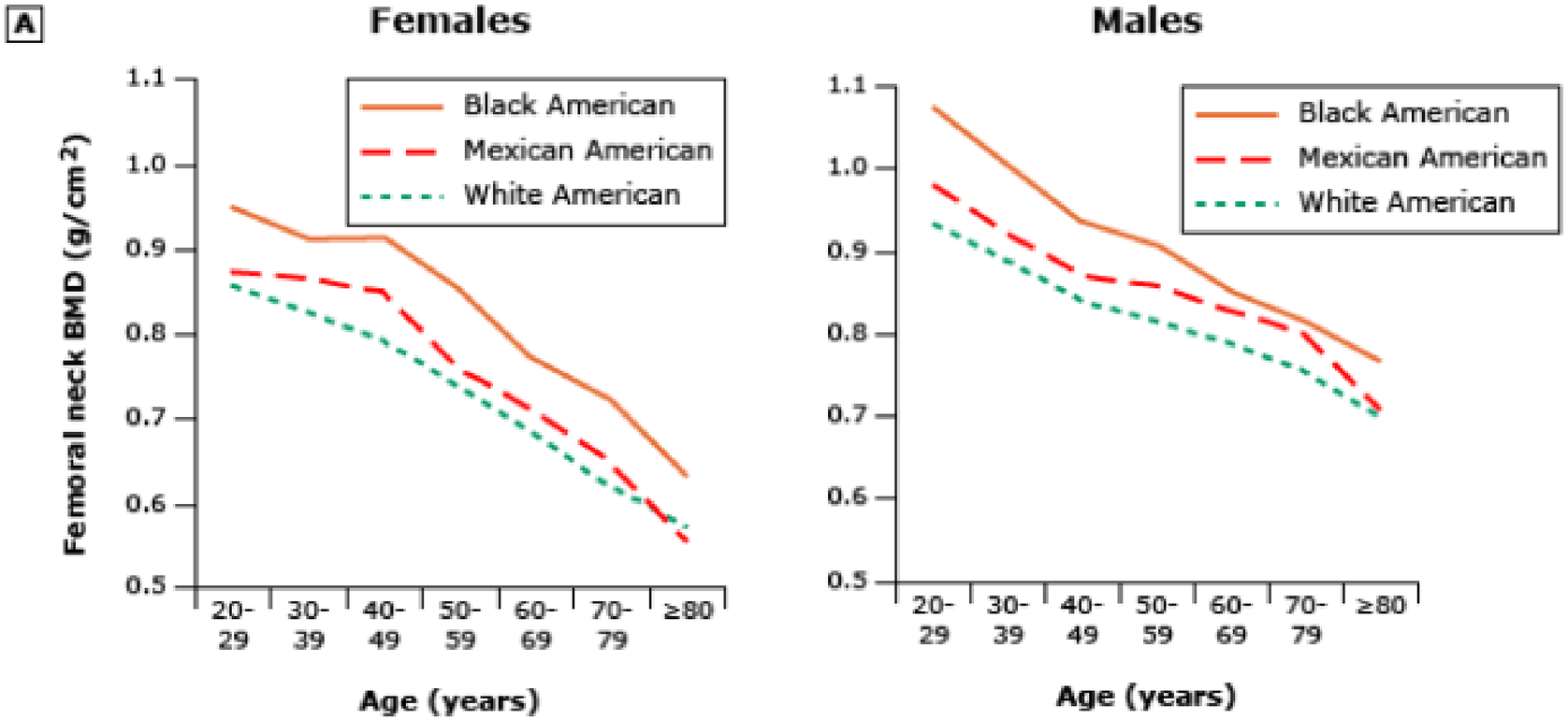
mediately after
ter age 65.



r age 65 occur at predominantly
increased porosity. (a change not captured by standard DXA imaging.)

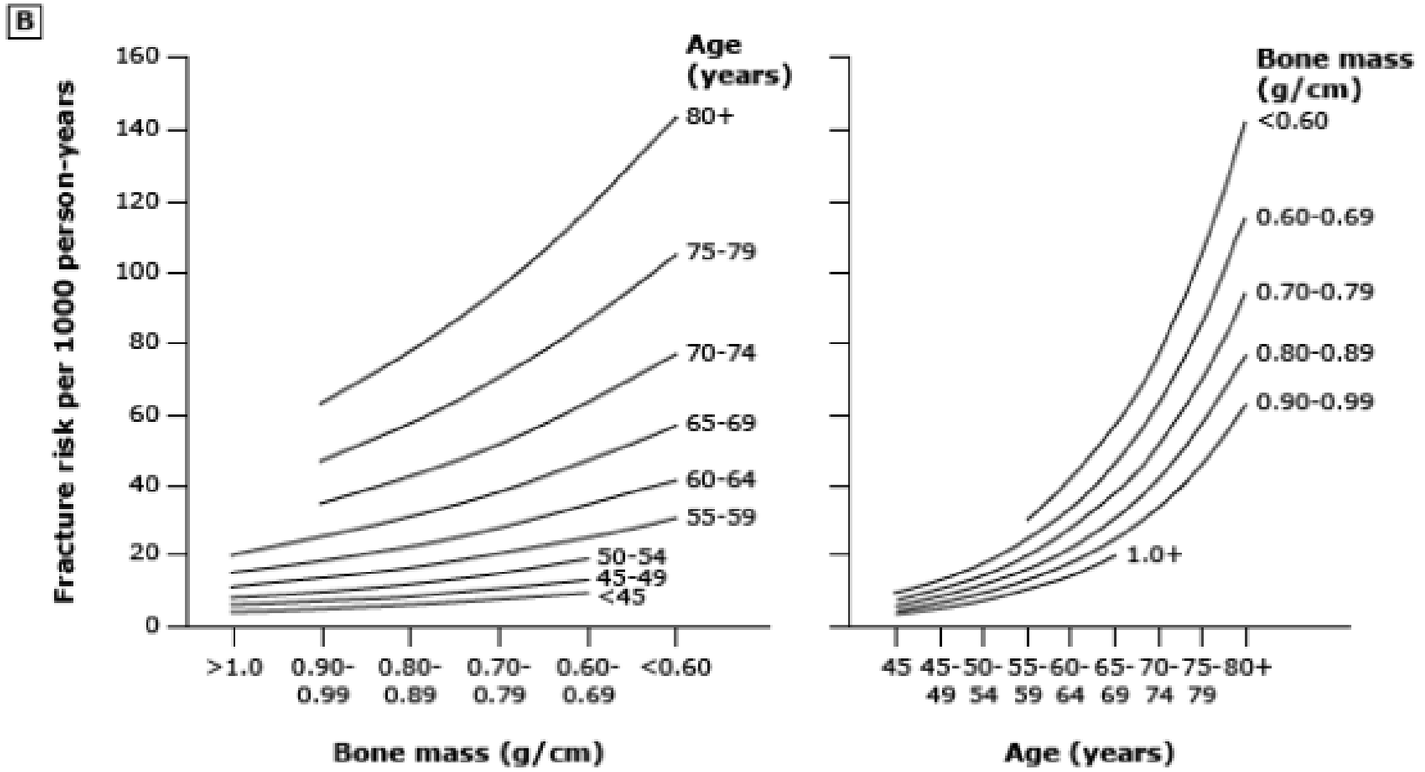
- For the same BMD, a 20-year increase in age is accompanied by a fourfold increase in fracture risk.

Bone loss after peak



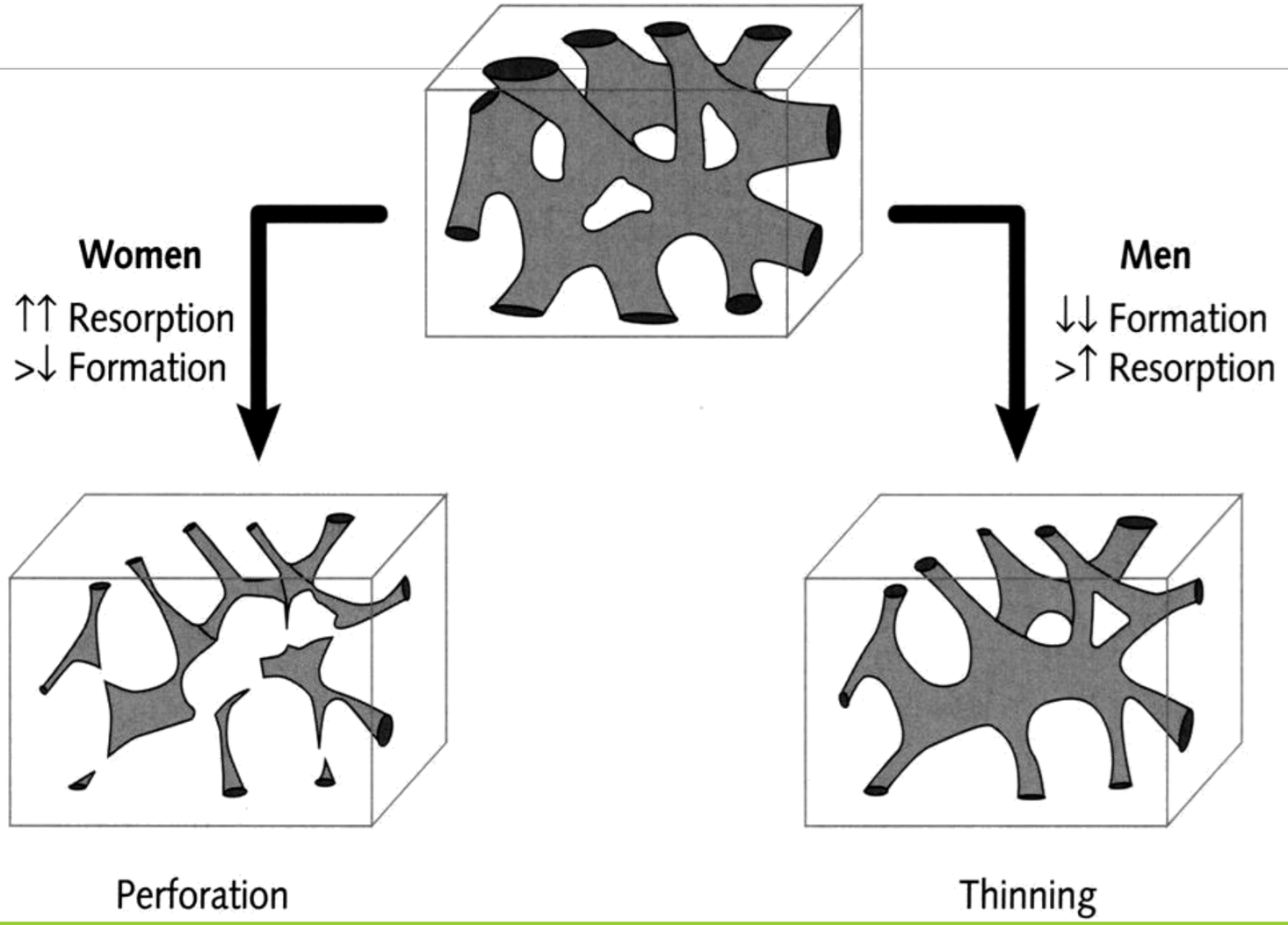
Bone loss begins in the third decade of life in both sexes.
NHANES I.

Age vs bone mass and Fx risk



Age is a more critical determinant of fracture risk **than bone mass** in humans

Trabecular Bone – Age Related Loss



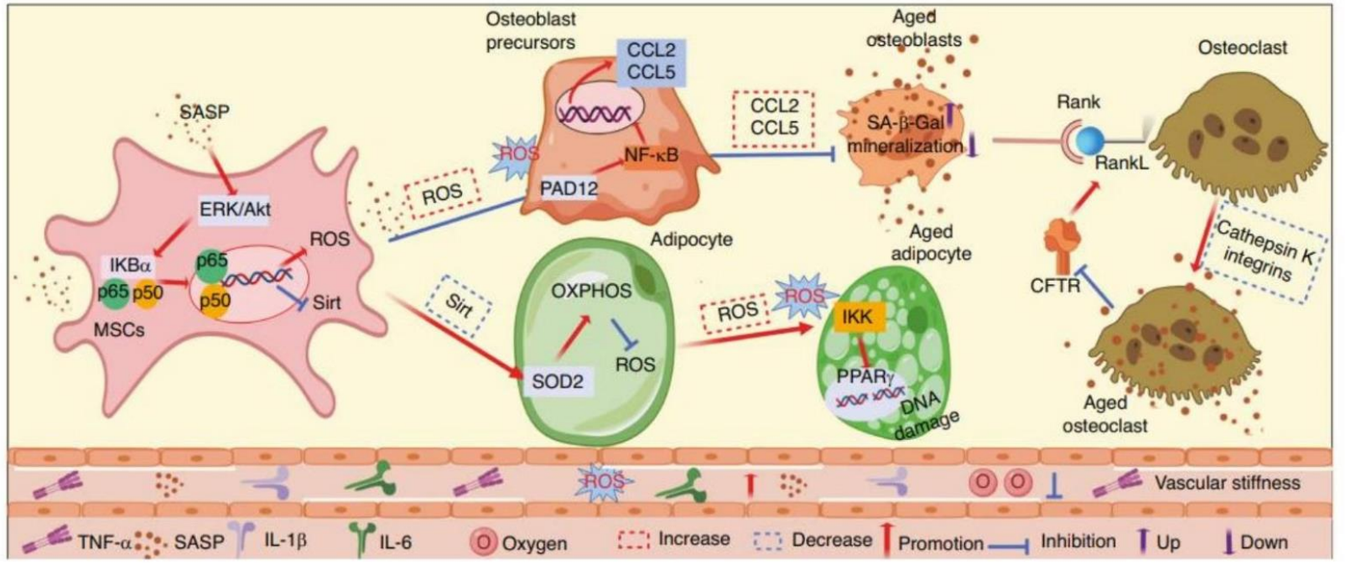
Seeman E., J Appl Physiol 2003; 95:2142

Molecular and Cellular Senescence

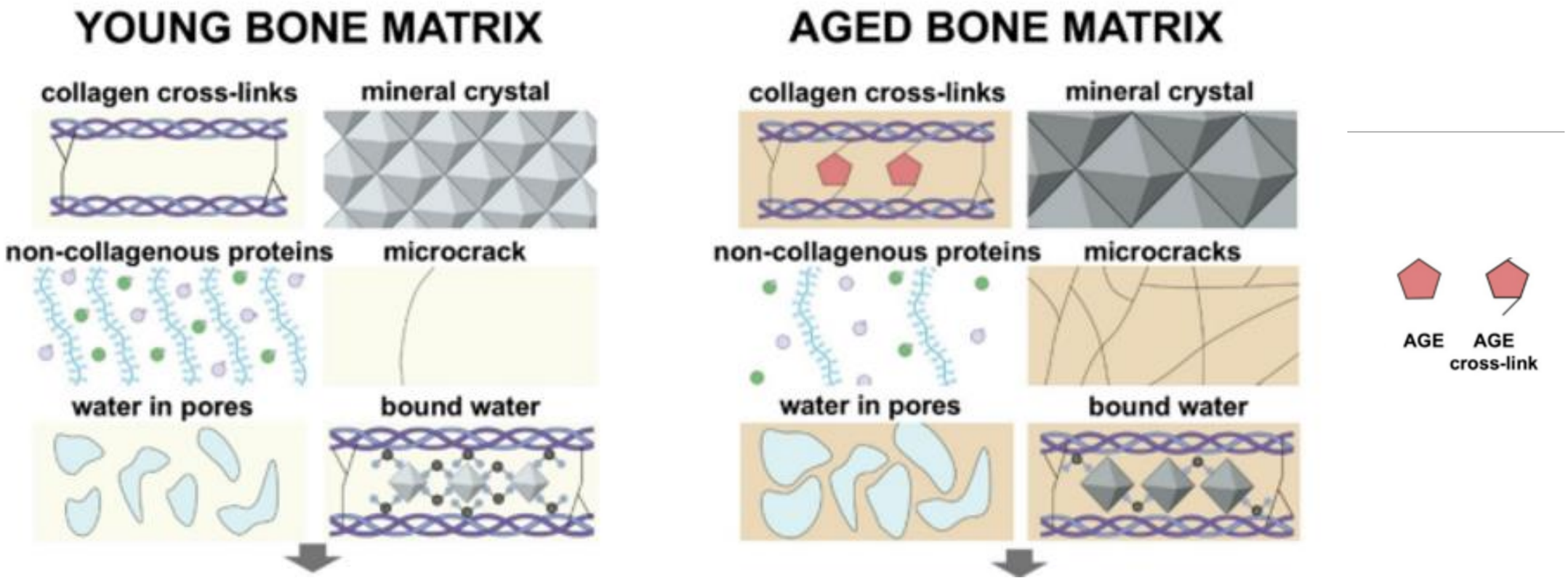
Cellular aging, particularly in Bone Marrow Mesenchymal Stem Cells (BMSCs), is a central factor in bone health deterioration.

BMSC Aging

- ROS production, inhibits osteoblast precursor differentiation.
- adipocyte differentiation: increase in ROS levels, adipocyte ageing.
- secondary ageing in osteoblasts and vascular cells.
- increased inflammatory cytokines
- reduced oxygen availability in the vasculature
- vascular stiffness and a disruption of blood flow
- deficiency in molecular cathepsin K and integrins
- ageing in osteoclasts, preserving their bone resorption capacity



Age-Related Changes in Bone Matrix Ultrastructure



Collagen Stiffening

Increased Advanced Glycation End Products (AGEs) lead to stiffer collagen fibrils and bone brittleness.

Mineral Alterations

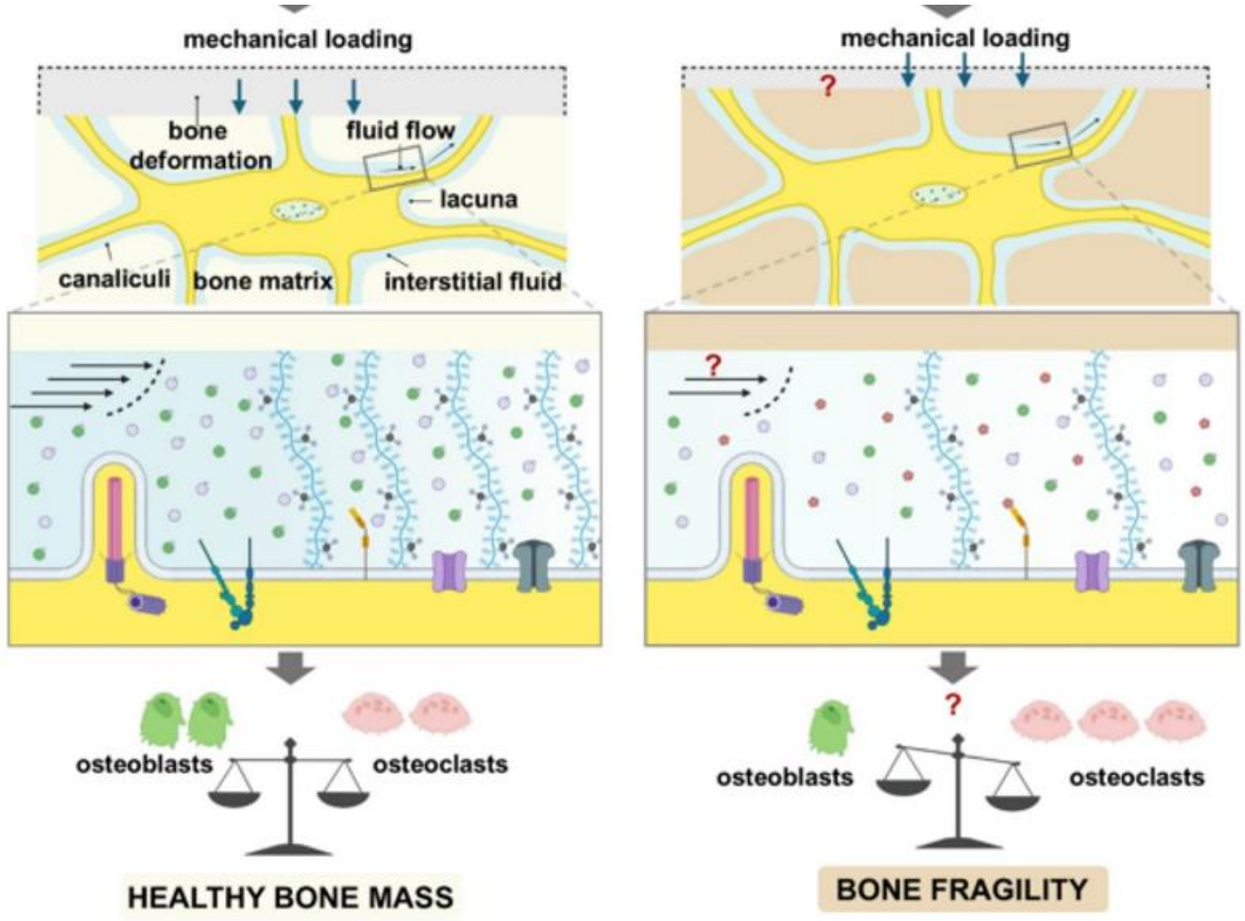
Increased mineral crystal size and carbonate substitution change bone crystallinity.

Water Content

Pore water increases (expanding voids), while bound water decreases (destabilizing collagen).

3-2008

Age-Related Changes in Bone Matrix Ultrastructure



Changes in the non-cellular components of bone significantly reduce mechanical resilience and increase fracture risk.

Impact of Aging on Bone Structure

Skeletal aging is characterized by a decline in integrity, compromised mechanical properties, and reduced

most bone loss in old age: result of increased intracortical porosity

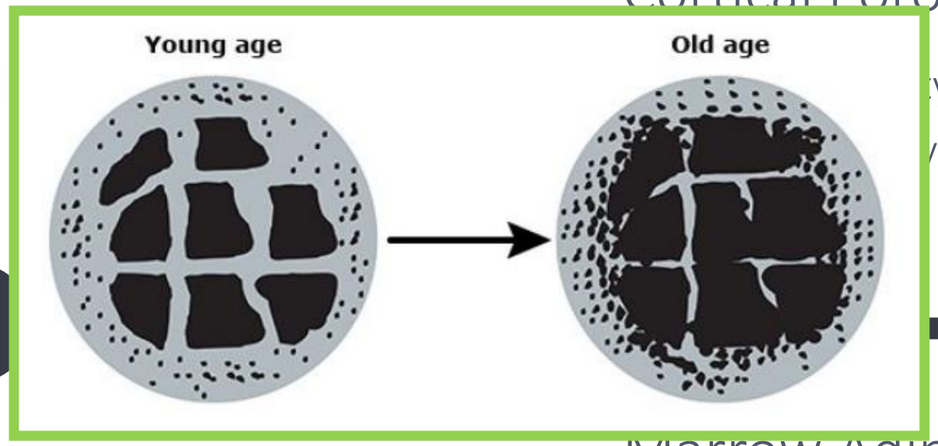
not captured by DXA BMD

Trabecular Thinning

Loss of trabecular number and
women.

Cortical Porosity

y and thinning of cortical bone after sex
.

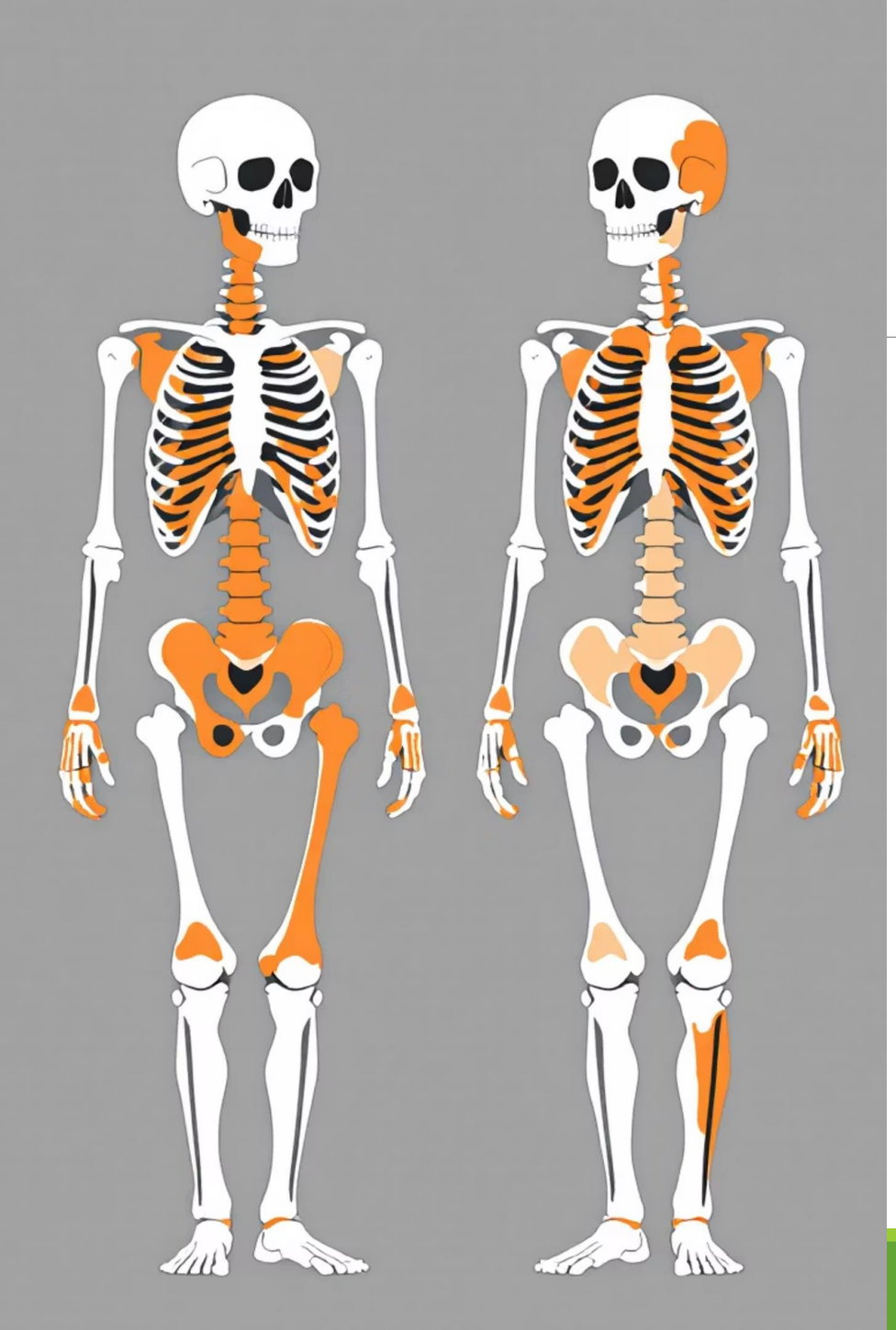


Microcracks

Accumulation of microcracks due to reduced repair, contributing to fragility.

Marrow Adiposity

Red marrow converts to yellow fatty marrow, correlating with decreased BMD.



Sex Steroid Deficiency: Distinct Pathways in Bone Loss

Estrogen or androgen deficiency increases the bone remodeling rate, leading to unbalanced resorption and formation.

Estrogen Effects

- Accelerated trabecular perforation at menopause
- Later cortical porosity in both sexes
- Estrogens protect cancellous bone via **ER-alpha** in osteoclasts.
- Accounts for 70% of sex steroid skeletal protection

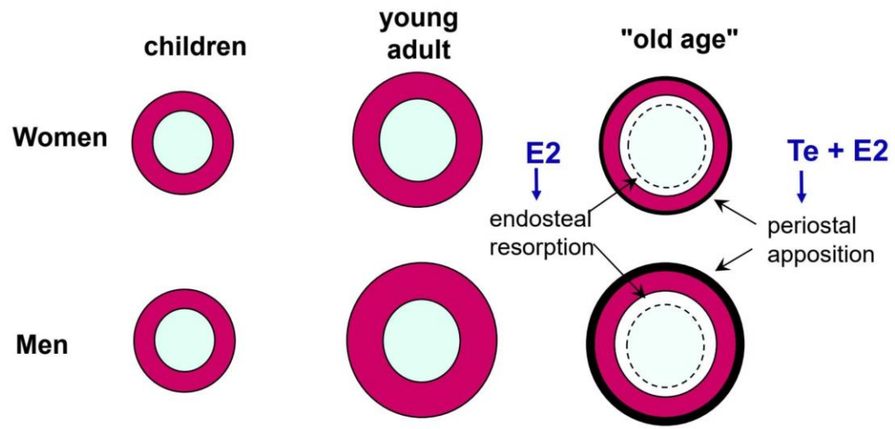
Androgen Effects

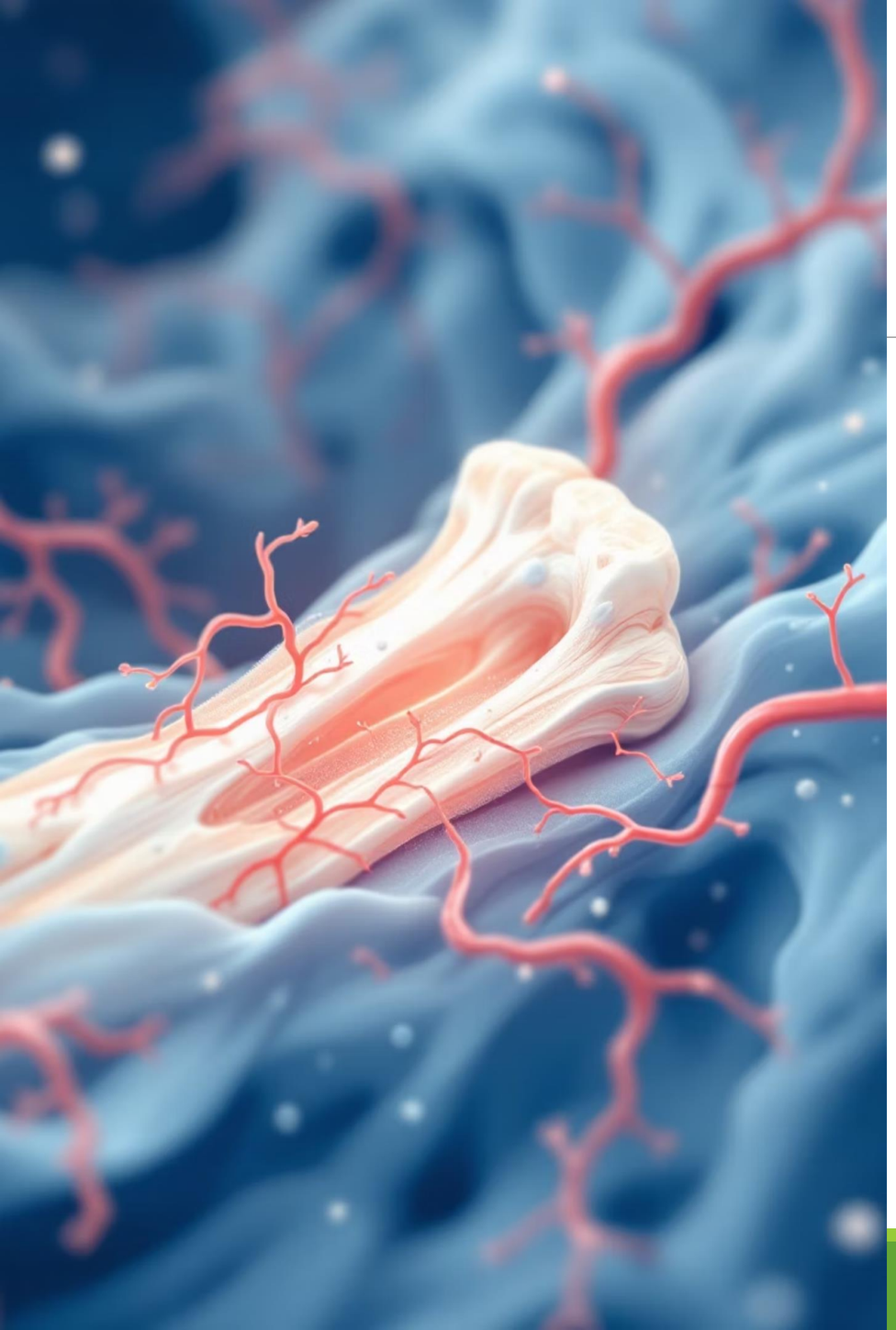
- **Indirect** cancellous bone protection via osteoblasts
- Critical in male skeletal homeostasis
- Estrogens (from aromatization) protect cortical bone in men via ER-alpha.
- Accounts for ~30% of protective effects

Gender Differences in Bone Loss

While both sexes experience age-related bone loss, women face accelerated loss post-menopause due to estrogen deficiency.

	Women	Men
Peak Bone Mass	Lower	Higher
Bone Loss Pattern	Rapid loss post-menopause	Slower, more gradual loss
Trabecular Loss	Greater decrease in number	Greater decrease in thickness
Secondary Causes	Less frequent	More frequent (50% of cases)





Glucocorticoid Excess and Oxidized Lipids

Two additional factors significantly compromise bone strength, often independent of BMD loss.

Glucocorticoid Excess

Common cause of osteoporosis; predominant abnormality is decreased bone formation and increased osteocyte apoptosis.

Leads to fractures (spine, ribs, hip) early in therapy, before detectable BMD decline.

Oxidized Lipids

Link between osteoporosis, atherosclerosis, and cardiovascular disease.

Oxidized LDL cholesterol causes skeletal inflammation, attenuating Wnt signaling and bone formation.

Key Takeaways: Managing Skeletal Health

1

Remodeling is Continuous

Bone is constantly renewed, adapting to physical changes and maintaining mineral stores, regulated by systemic and local factors.

2

Peak Bone Mass is Critical

Risk of osteoporosis depends on peak bone mass (influenced by genetics, nutrition, puberty, and activity) and subsequent bone loss.

3

Aging Disrupts Balance

Negative balance at remodeling sites due to aging and estrogen deficiency leads to progressive erosion of skeletal architecture.

In men, secondary causes (e.g., glucocorticoid excess, hypogonadism) account for about 50% of osteoporosis cases, highlighting the need for thorough diagnosis.

References:

- Mi B, Xiong Y, Knoedler S, Alfertshofer M, Panayi AC, Wang H, Lin S, Li G, Liu G. Ageing-related bone and immunity changes: insights into the complex interplay between the skeleton and the immune system. Bone Research. 2024 Aug 5;12(1):42.
- Chen Y, Klein-Nulend J, Bravenboer N. Ageing-Related Changes in Ultrastructural Bone Matrix Composition and Osteocyte Mechanosensitivity. Current osteoporosis reports. 2025 Dec;23(1):35.
- Manolagas SC. Pathogenesis of osteoporosis. UpToDate [online serial]. Waltham, MA: UpToDate. 2025
- Khosla S. Pathogenesis of age-related bone loss in humans. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2013 Oct 1;68(10):1226-35.
- Pignolo RJ, Law SF, Chandra A. Bone aging, cellular senescence, and osteoporosis. Journal of Bone and Mineral Research Plus. 2021 Apr 1;5(4):e10488.
- Föger-Samwald U, Kerschan-Schindl K, Butylina M, Pietschmann P. Age related osteoporosis: targeting cellular senescence. International journal of molecular sciences. 2022 Feb 28;23(5):2701.
- Boskey AL, Coleman R. Aging and bone. Journal of dental research. 2010 Dec;89(12):1333-48.
- Rizzoli R., Atlas of postmenopausal osteoporosis
- Ralston S., Clin. Manual on Prev. and Management of Osteoporosis. London Science Press 2001