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Science, Knowledge & Education

IOF ADVANCED COURSE ON OSTEOPOROSIS

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1. Pathophysiology, epidemiology and genetics

Lecture 1.1 - Determinants of bone structure and strength

V1 2024

Content

- Anatomy, microarchitecture, and material composition
- Biomechanics
- Pathophysiology of the aging skeleton

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1. Pathophysiology, epidemiology and genetics

1.1 - Determinants of bone structure and strength

Anatomy, microarchitecture, and material composition

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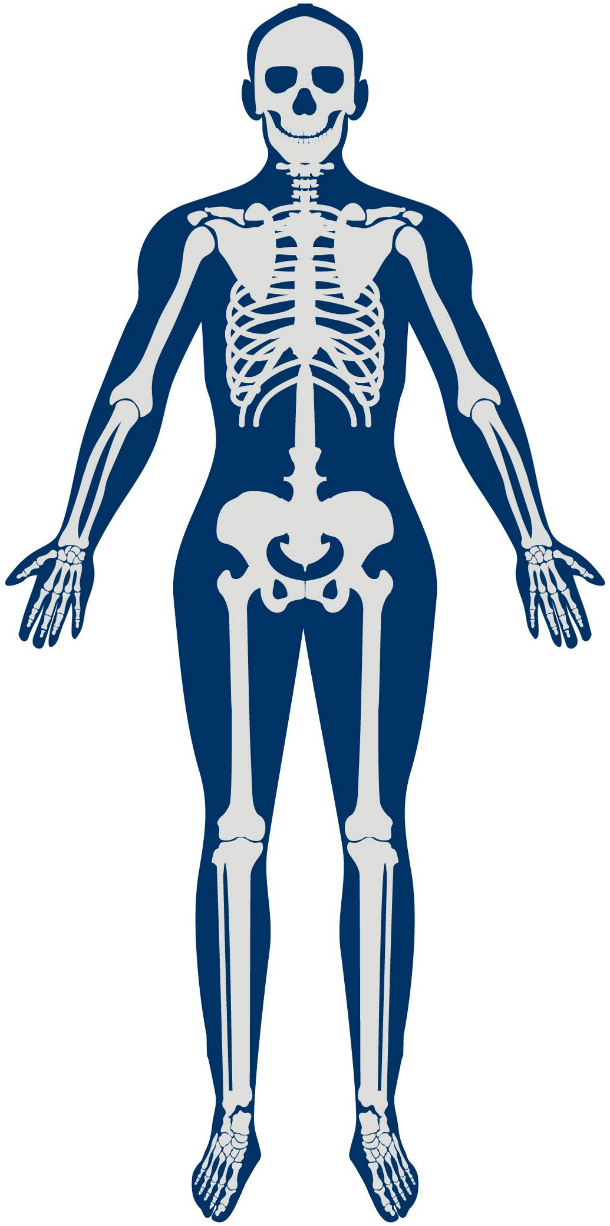
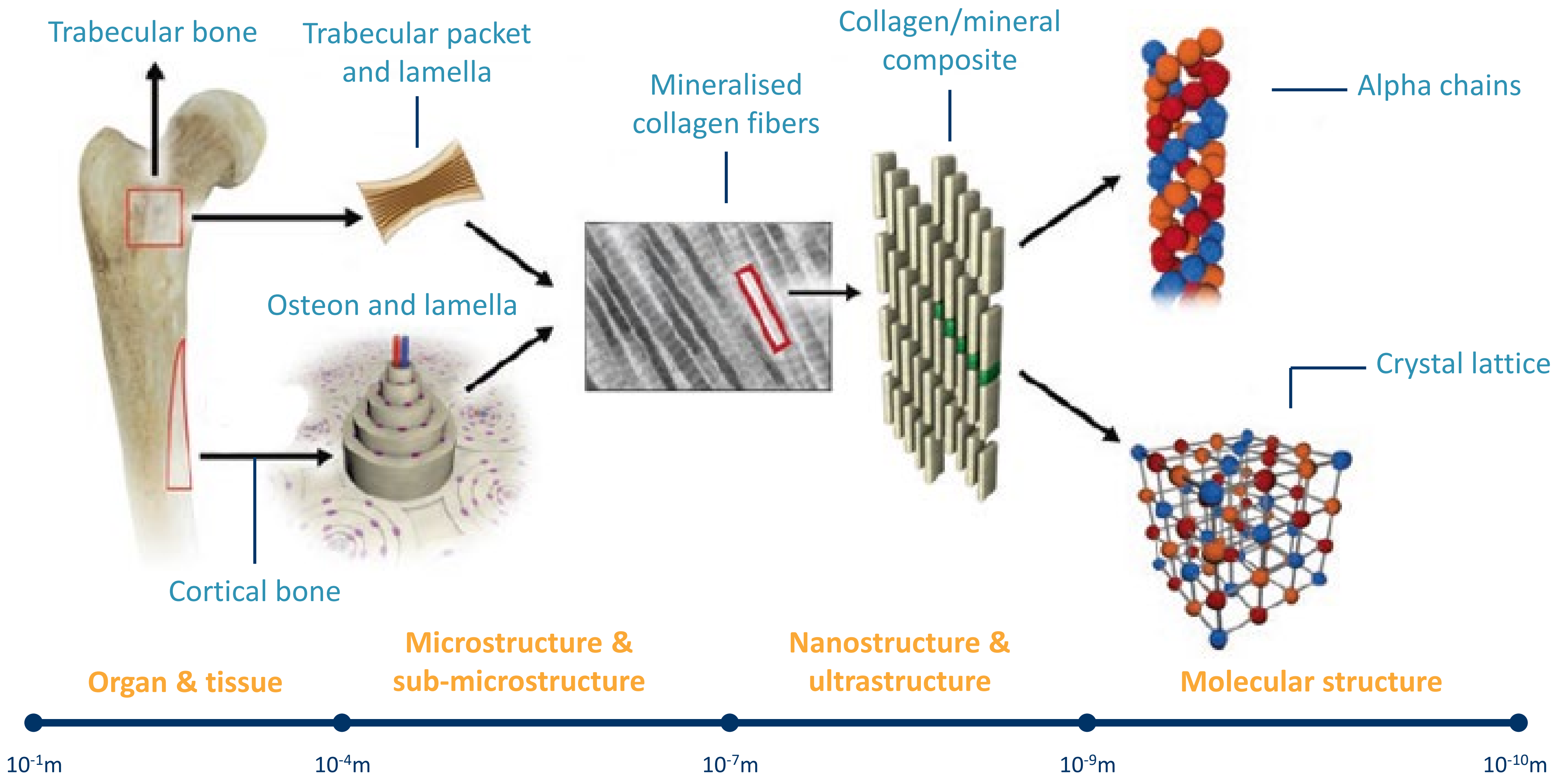
Functions of the skeleton

- Supports the body
- Protects vital internal organs (e.g., skull, ribs, sternum, scapula, pelvis)
- Muscles attached for movement – locomotion
- Cavities for blood formation (hematopoiesis)
- Reservoir of minerals (calcium and phosphate ions) and homeostasis
- Metabolism and endocrine functions



Hierarchical organisation of the bone



Gasser J, Bone Physiology and Biology, Chapter 2 in Bone Toxicology. 2017. Eds: SY Smith, A Varela, R Samadfam, Springer: Molecular and Integrative Toxicology series.

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Macroscopic structure of mature bone

- Two types of bones can be distinguished based on their rough appearance

- Cortical bone (or compact bone)
  - Appears as a compact, dense, solid mass
  - 80% of the skeleton
  - Composed of multiple osteons (Haversian system) with interstitial lamellae
  - Thick cortical bone in the diaphysis of long bone
  - Function: locomotion and protection

- Trabecular bone (or cancellous or spongy bone)
  - Appears as a network of trabeculae surrounded by the bone marrow
  - 20% of the skeleton
  - Commonly found in the epiphysis and metaphysis of long bones
  - Function: metabolism and transmission of loads from the articular surface to the cortex

Trabecular and cortical bone differences in mass, surface area and turnover

	Mass	Surface area	Turnover each year*
Trabecular	20%	80%	25%
Cortical	80%	20%	3%

*Up to 10% of the adult skeleton is being remodelled at any one time (remodelling rates can be affected by age and diseases)

Parfitt AM, Osteoporosis Springer 2nd edition, 2001, 433-447.

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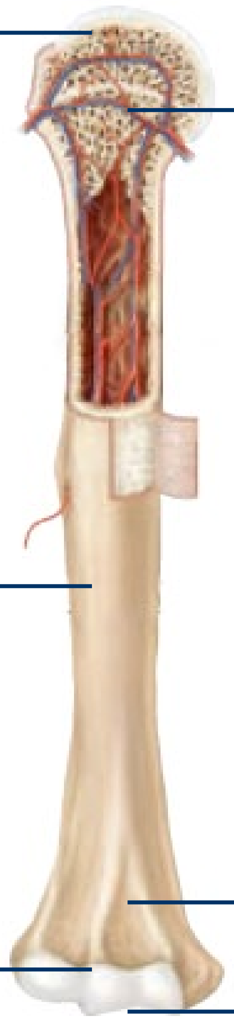
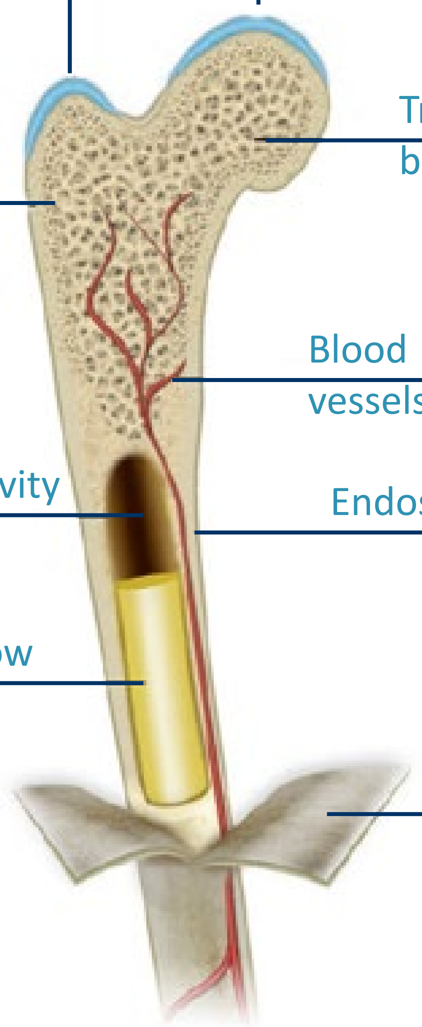
Anatomy of a long bone





Gasser J, Bone Physiology and Biology, Chapter 2 in Bone Toxicology. 2017. Eds: SY Smith, A Varela, R Samadfam, Springer: Molecular and Integrative Toxicology series.

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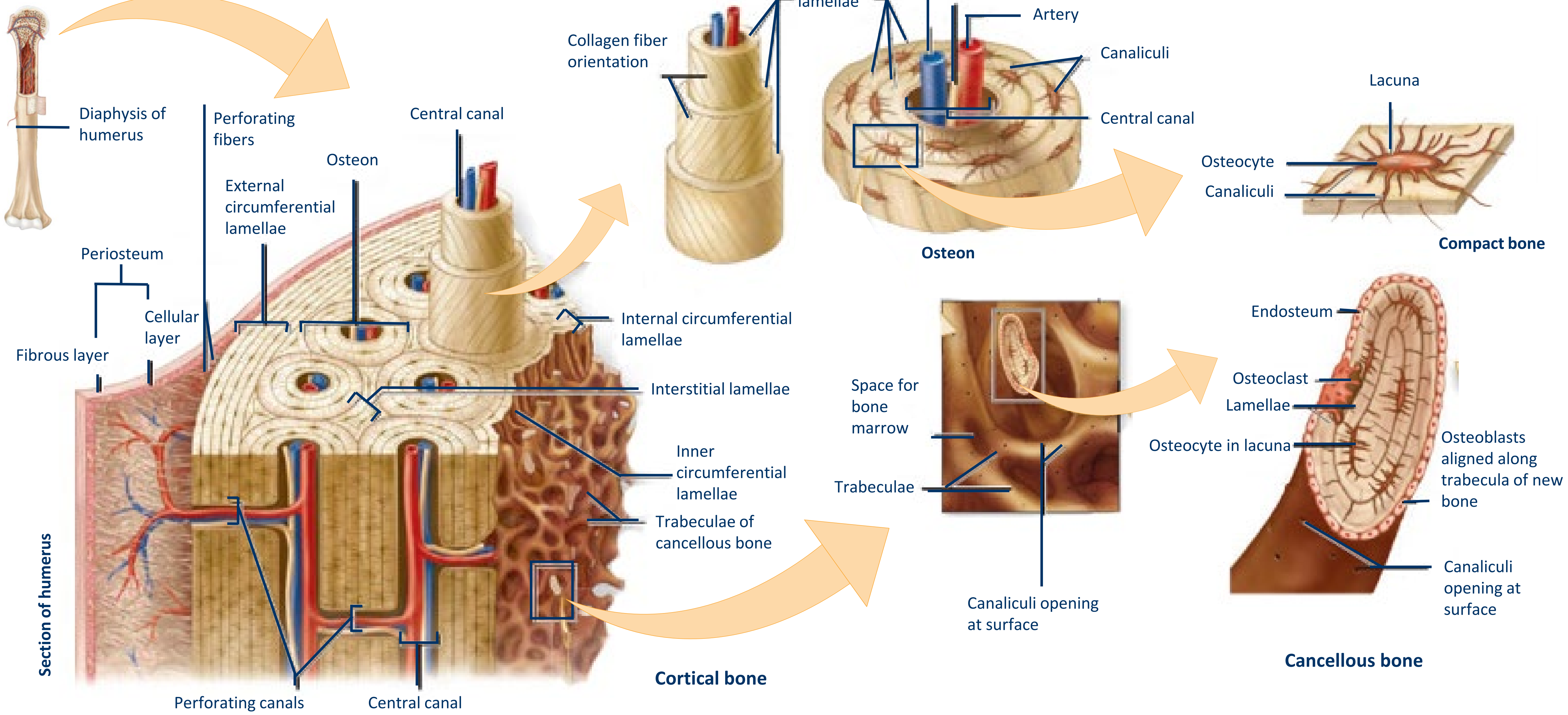
Microscopic structure of long bone

- Two types of bones can be distinguished based on their microscopic three-dimensional arrangements of the collagen fibres

- Woven bone
  - Typical of developing bone or pathological bone
  - Nonlamellar, poor alignment of the collagen fibres, with no stress orientation
  - Mechanistically weak
  - Rapid formation and then remodelled in lamellar bone
  - Formed during embryonic development and fracture repair (fracture callus)

- Lamellar bone
  - Typical of the mature bone
  - High alignment of the collagen fibres, with stress orientation
  - Mechanically strong
  - Slow formation
  - Cortical and cancellous bones are both made up of lamellar bone

Haversian system of the cortical bone



Meschler AL, chap. 8 in Junqueira's Basic Histology: Text and Atlas, 17th ed. New York McGraw Hill, 2023.

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Structure of cortical (compact) bone

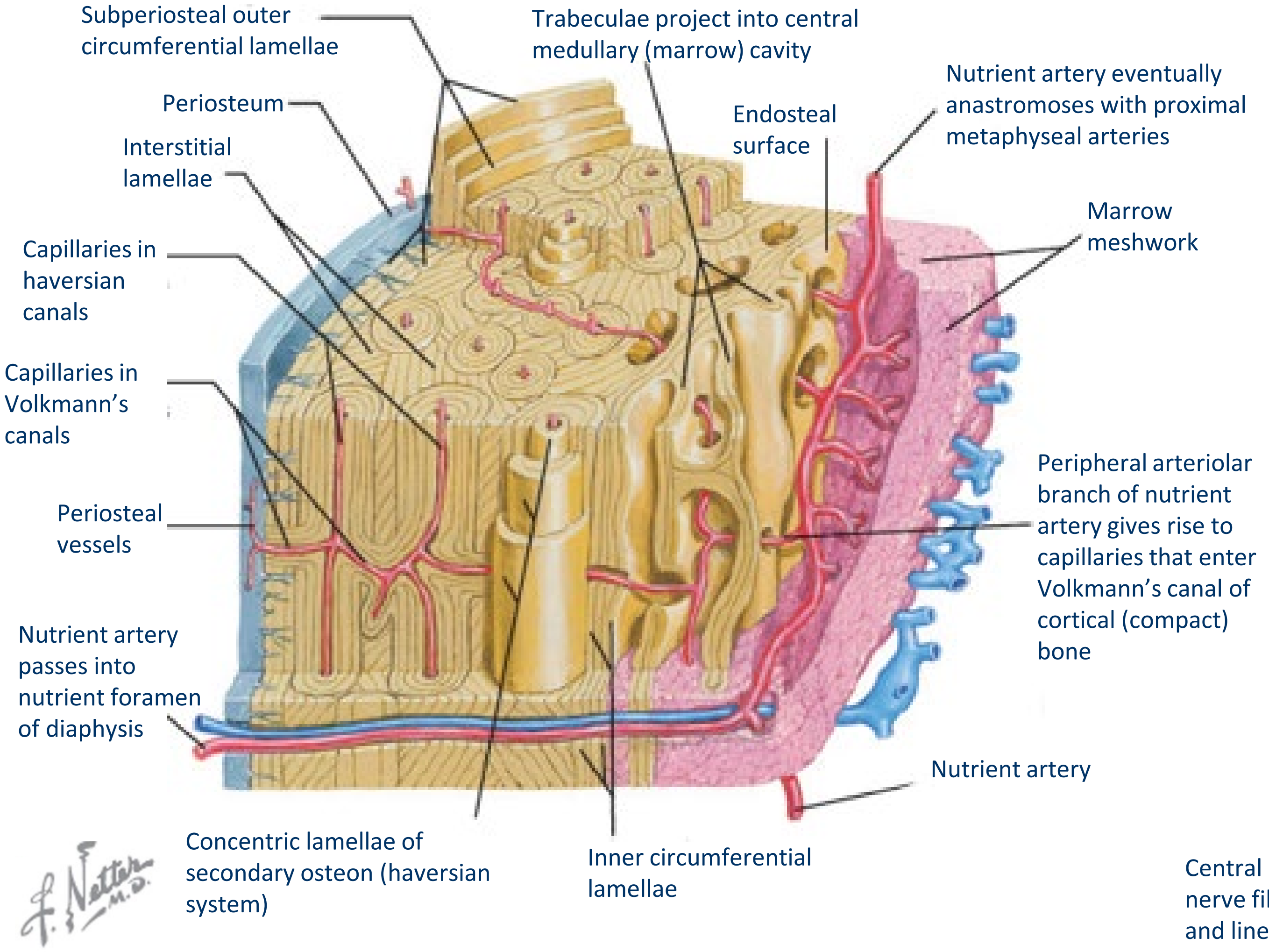
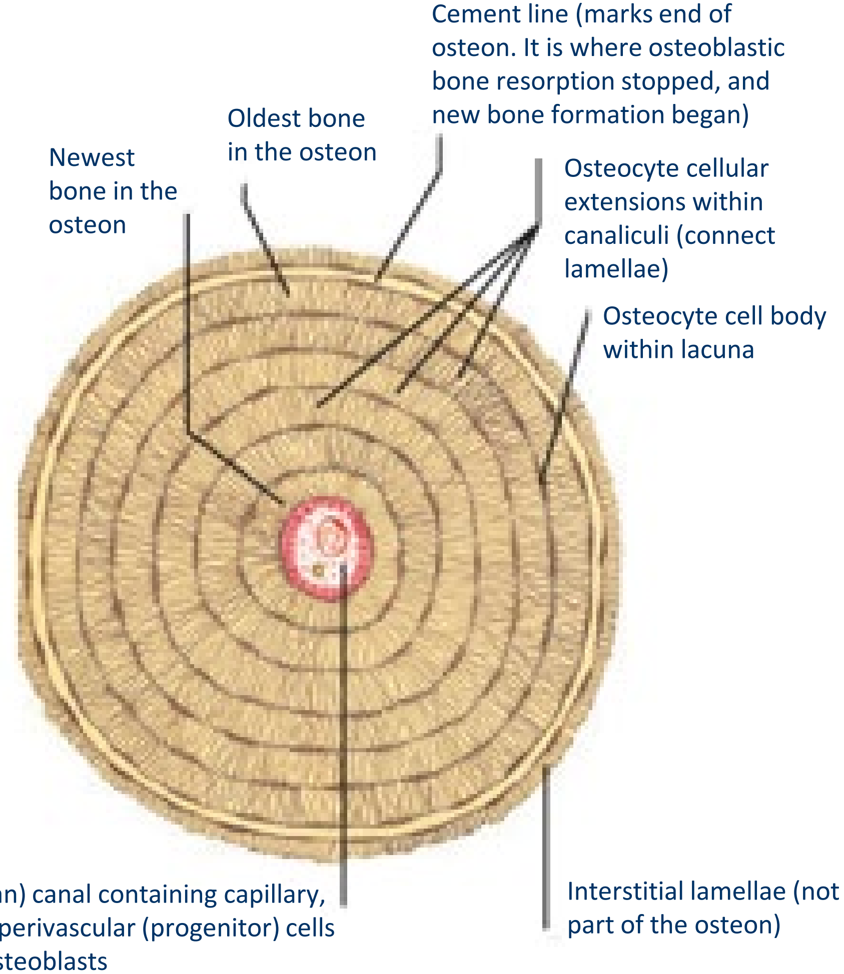


Diagram of osteon (haversian system) with 6 concentric lamellae (greatly enlarged)



Netter's Concise Orthopaedic Anatomy, 2nd Edition, 2016 by Thompson J, eds Elsevier

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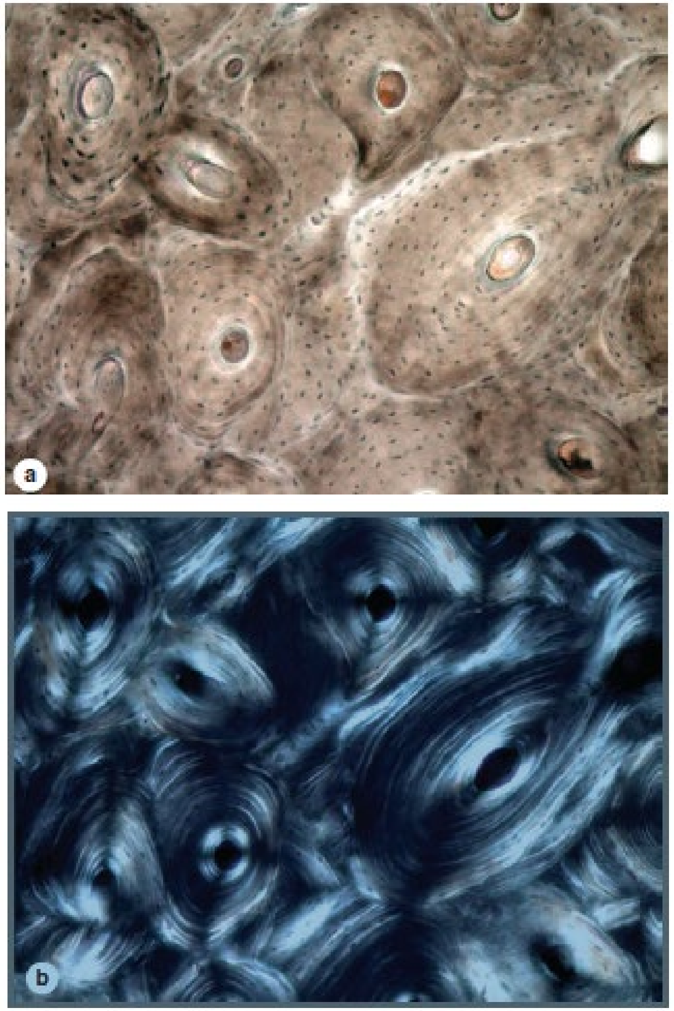
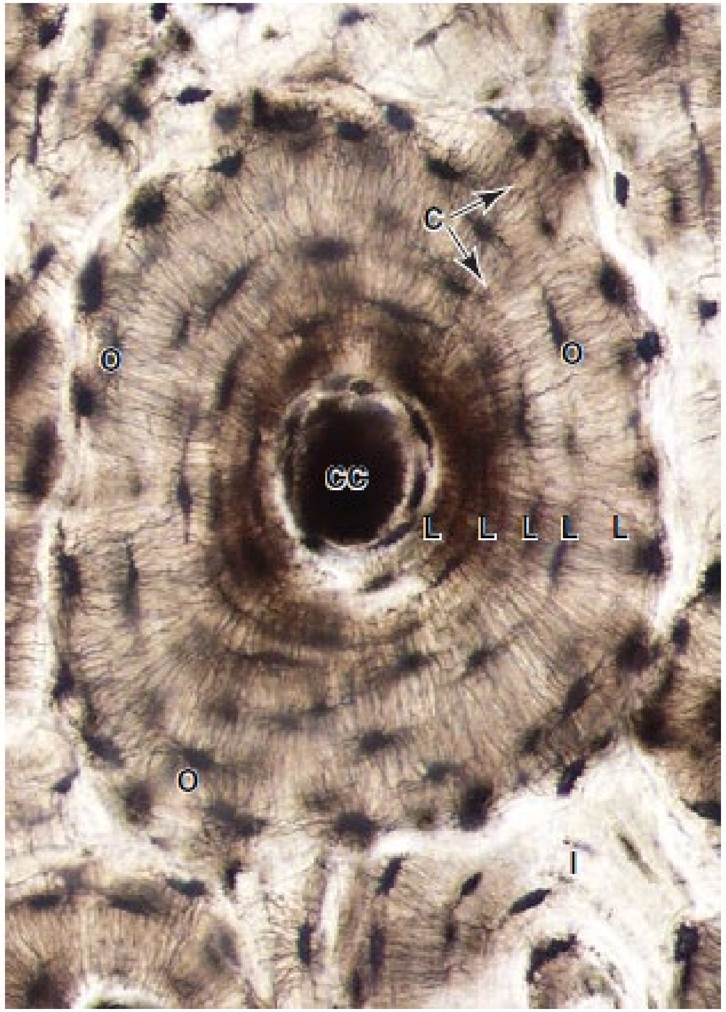
Cortical bone – haversian system – osteon





L: lamella
C: canaliculi
O: osteocyte
CC: central canal

Meschler AL, chap. 8 in Junqueira's Basic Histology: Text and Atlas, 17th ed. New York McGraw Hill, 2023.

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Material composition

- **Organic (30-40% of bone weight)**
  - Matrix (98%)
    - Type 1 collagen gives tensile strength
    - Proteoglycans give bone compressive strength
    - Non collagen proteins (osteocalcin, osteonectin, osteopontin)
    - Cells: osteoblast, osteocyte, osteoclast, lining cells

- **Inorganic (60% of bone weight)**
  - Calcium hydroxyapatite: $Ca_{10}(PO_4)_6 (OH)_2$ main mineral in the bone – mineralisation of the matrix between and at ends of collagen fibres
  - Osteocalcin phosphate: minor mineral

- **Water (approx. 5% of bone weight)**

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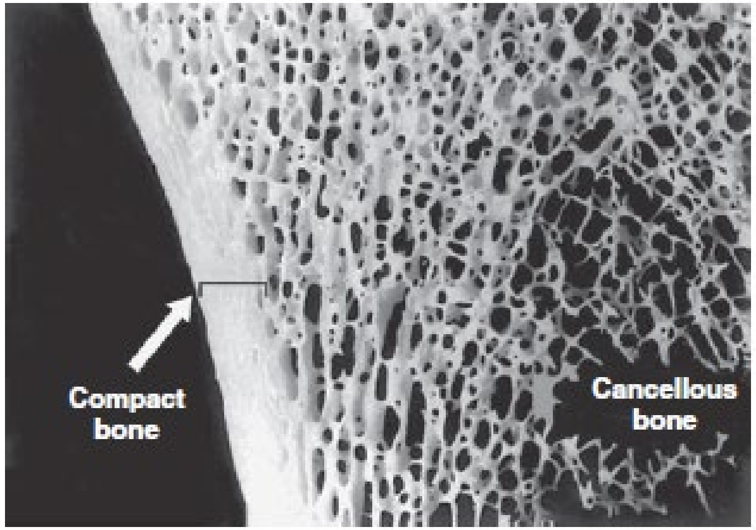
Microarchitecture

- How to measure
  - Histomorphometry (quantitative histology)
  - Computed tomography (CT)
  - High-resolution peripheral quantitative computed tomography (HR-pQCT)* (more detailed under lecture 2.1.2 part 2)
  - Magnetic resonance



Netter's Concise Orthopaedic Anatomy, 2nd Edition, 2016 by Thompson J, eds Elsevier

- Some parameters measured by HR-pQCT
  - Cortical site
    - Porosity
    - Cortical thickness
  - Trabecular site
    - Tb number (Tb N)
    - Tb thickness (Tb Th)
    - Tb separation (Tb Sp)
    - BV/TV (bone volume/tissue volume)
    - Connectivity

*Cheung AM, Curr Osteoporos Rep. 2013; 11:136-146.

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1. Pathophysiology, epidemiology and genetics

1.1 - Determinants of bone structure and strength

Biomechanics

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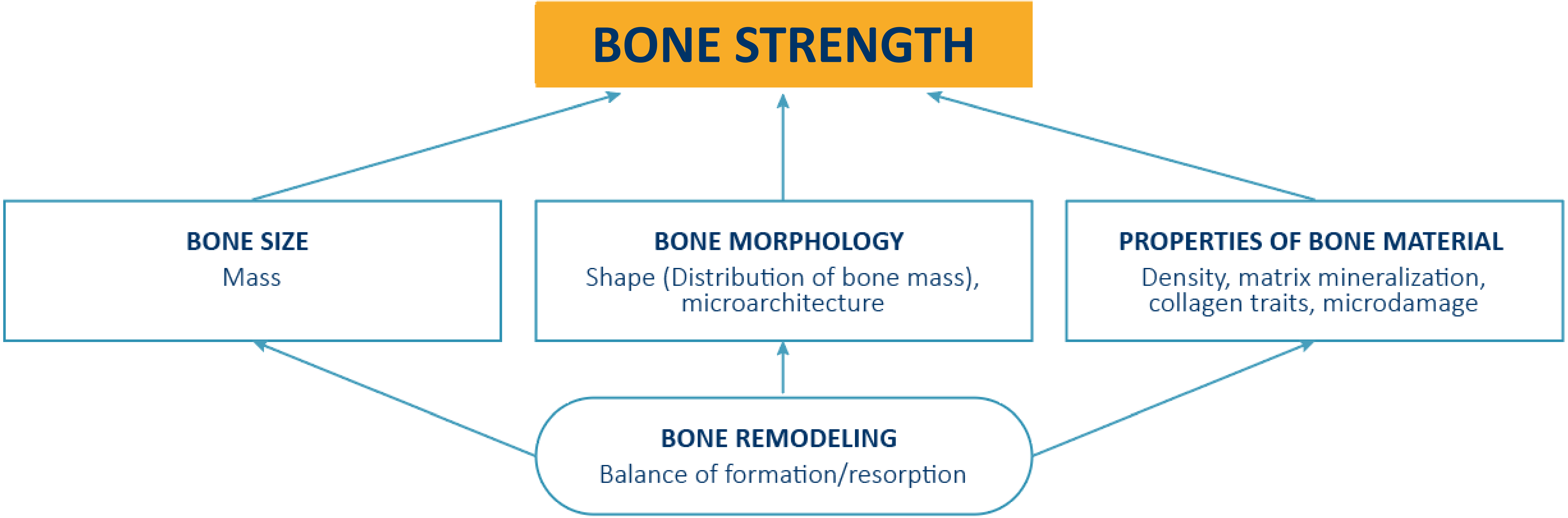
Determinants of bone strength



Bouxsein M, Best Pract Res Clin Rheumatol. 2005; 19:897-911.

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Bone strength: material and structural properties

- Bones must be stiff so that they do not bend when loaded
- Bones must be flexible so that they can absorb the energy imposed by loading
- The material composition and the structural design of the bone determine its strength
  - Material properties:
    - Reflect the intrinsic biomechanical properties of cortical and trabecular bone
    - Independent of bone geometry
    - Cortical bone: porosity and mineralisation density of the bone matrix
    - Trabecular bone: apparent density, microarchitectural arrangement of the trabecular network

- Structural properties:
  - Relationship between the forces applied to the bone and the resulting deformation
  - Influence of bone size, shape and properties

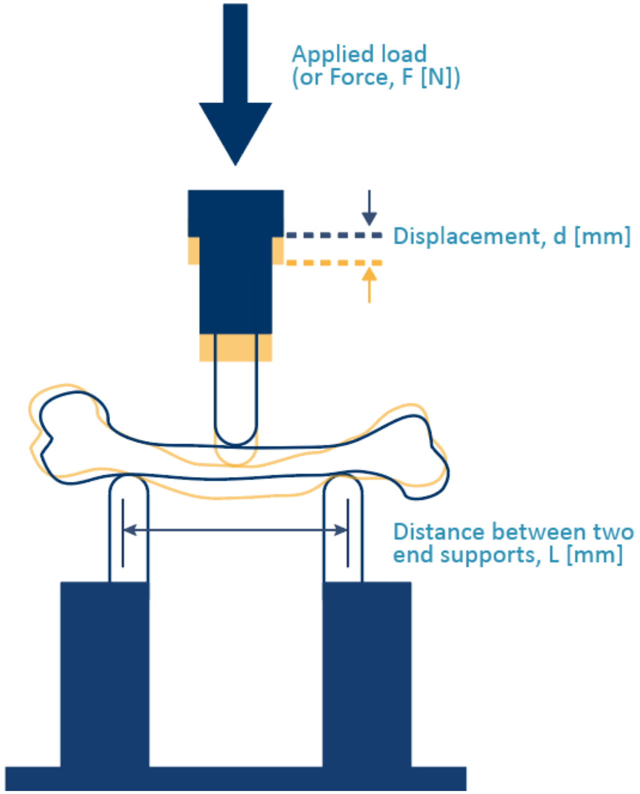
Bouxsein M, Best Pract Res Clin Rheumatol. 2005; 19:897-911.
Seeman E, J Bone Miner Metab. 2008; 26:1-8.

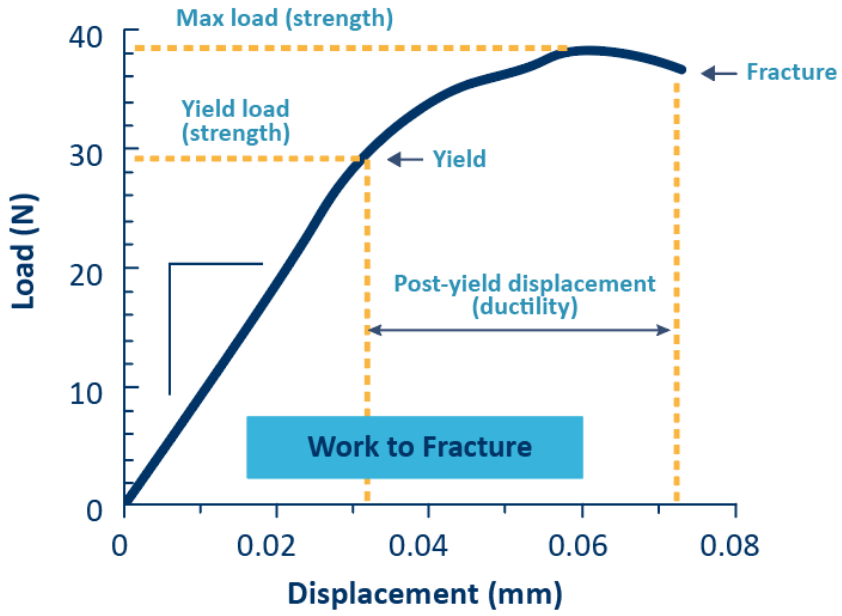
Whole-bone mechanical testing

Three-point bending

- To test the mechanical properties of the mid-diaphysis, which is typically all cortical bone

- Basic description of whole-bone mechanical properties:
  - Stiffness (N/mm)
  - Yield load (N)
  - Ultimate load (N)
  - Pots-yield displacement (mm)
  - Work-to-fracture (Nmm)





Dubois-Ferrière V, Biomed Res Int. 2014; 2014:185075.

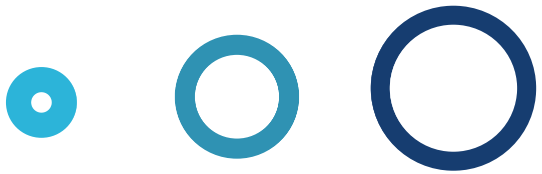
Role of bone geometry

- Overall size of the bone (mass) and its shape (distribution of shape)
- Larger bones are stronger than smaller bones
  - Smaller vertebral bodies – increased risk of vertebral fractures
- Most efficient design to resist bending and torsional loads: bone material far from the centre of the bone

Gilsanz V, Radiology 1994; 190:673-677.
Gilsanz V, J Clin Invest. 1995; 95:2332-2337.
Duan Y, J Bone Min Res. 2001;16:2267-2275.
Seeman E, J Bone Miner Metab. 2008; 26:1-8.
Bouxsein M, Best Pract Res Clin Rheumatol. 2005; 19:897-911.

Role of bone geometry

Influence of bone geometry on BMD and compressive and bending strength



aBMD (by DXA)	1	1	1
Compressive strength	1	1.7	2.3
Bending strength	1	4	8

Influence of periosteal apposition on BMD and compressive and bending strength

Outer diameter	+10%
Inner diameter	No Change
BMD	+16%
Compressive strength	+28%
Bending strength	+42%

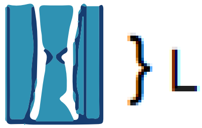
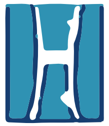
Gilsanz V, Radiology 1994; 190:673-677.
Gilsanz V, J Clin Invest. 1995; 95:2332-2337.
Duan Y, J Bone Min Res. 2001;16:2267-2275.
Seeman E, J Bone Miner Metab. 2008; 26:1-8.
Bouxsein M, Best Pract Res Clin Rheumatol. 2005; 19:897-911.

Role of bone microarchitecture

Trabecular microarchitecture

- Influence on trabecular strength
  - Importance of trabecular connectivity - for the same decline in bone loss, loss of trabecular elements is 2 to 5x more deleterious to bone strength than thinning of the trabecular struts[1]
  - Loss of horizontal trabeculae decreases its buckling strength[2]

Effect of trabecular architecture on buckling strength

# Horizontal trabeculae	Effective length	Buckling strength	
0	L	S →	
1	½ L	4xS →	
3	¼ L	16xS →	

1. Silva M, Bone 1997; 21:191-199.
2. Bell G, Calcif Tissue Research 1967; 1:75-86.
Bouxsein M, Best Pract Res Clin Rheumatol. 2005; 19:897-911.

Role of bone matrix properties

- Relative ratio of inorganic (i.e., mineral) to organic (i.e., water, collagen and non-collagen proteins)
- Degree of matrix mineralisation
- Mineral crystal size and maturation
- Extent and nature of collagen cross-links
- Amount and nature of matrix microdamage

Abel RL, Current Osteoporosis Report 2021; 19:318-326.

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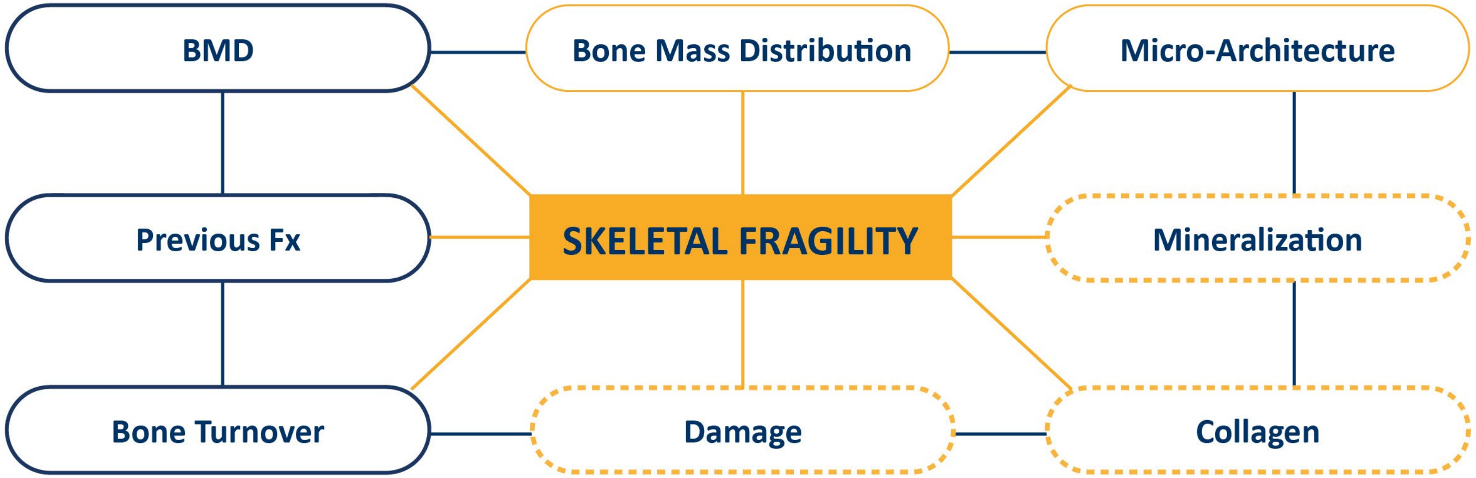
Determinants of skeletal fragility

Determinants that can be assessed or not

- The boxes on the left indicate tools that the clinician has in hand today to assess skeletal fragility
- In comparison, the importance of assessing bone mass distribution and microarchitecture is currently being evaluated in clinical studies (solid orange boxes)
- Assessment of bone mineralization, collagen characteristics and microdamage is currently not possible by non-invasive assessments (dotted orange boxes), though these factors likely influence bone strength and skeletal fragility



Bouxsein M, Best Pract Res Clin Rheumatol. 2005; 19:897-911.

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1. Pathophysiology, epidemiology and genetics

1.1 - Determinants of bone structure and strength

Pathophysiology of the ageing skeleton

Pathophysiology of the ageing skeleton

- **Genetics:**
  - Failure to achieve peak bone mass in adolescence contributes to skeletal fragility with age
  - Genetic variations explain up to 70% of the variance in BMD in the population
  - Heritability explains up to 80% of the variance in peak bone mass in the population
  - Difference between men and women
  - Tracking: stability of a trait from childhood over time, with peak bone mass being a determinant of future bone mass

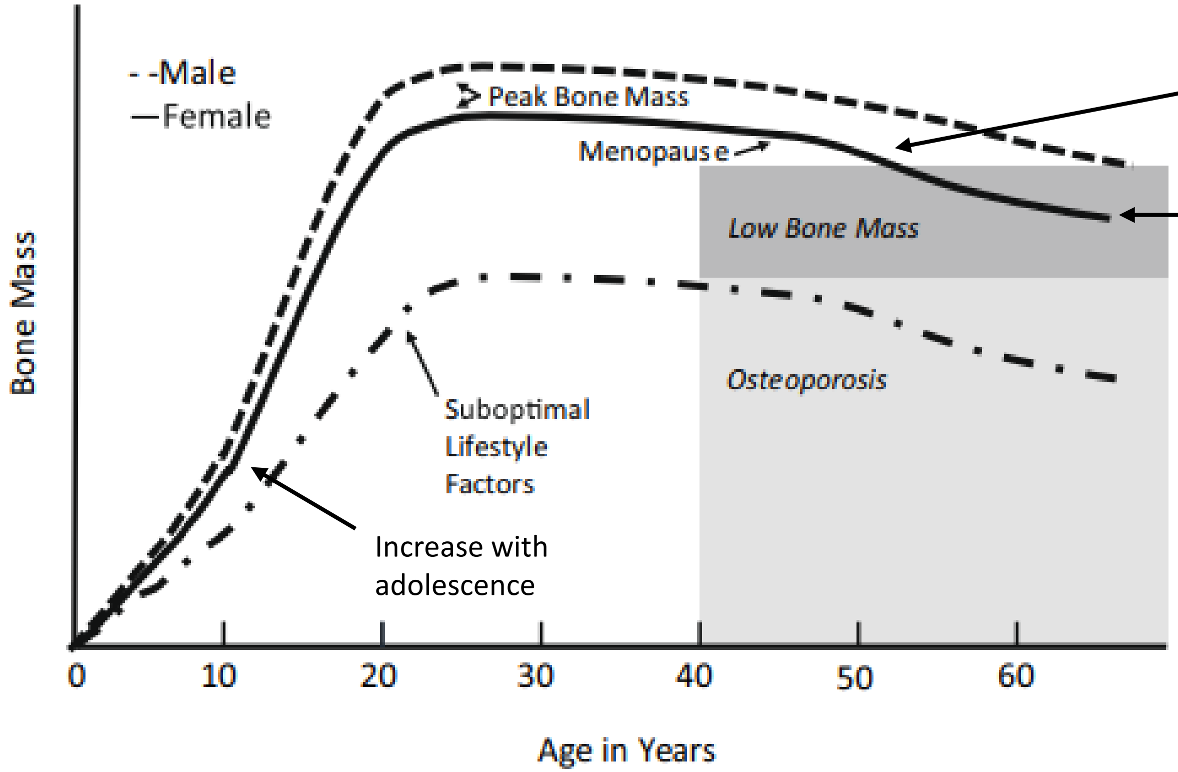
- **Hormonal changes:**
  - Drastic decrease in serum oestrogen levels at the menopause
  - Decline in testosterone levels by 63% and bioavailable oestrogen by 4% in men
  - Higher FSH levels are correlated with greater bone resorption
  - Growth Hormone (GH): decrease in the amplitude and frequency of GH pulses
  - Decrease in hepatic IGF-1 (and IGF-2)

Syed F, Current Osteoporos Rep. 2010; 8:235-240.
Ferrari SL, Mol Aspects Med. 2005; 26:145-167.
Weaver CM, Osteoporos Int. 2016; 27:1281-1386.

Development of Peak Bone Mass

The importance of the early environment

Development of bone mass over the lifecourse

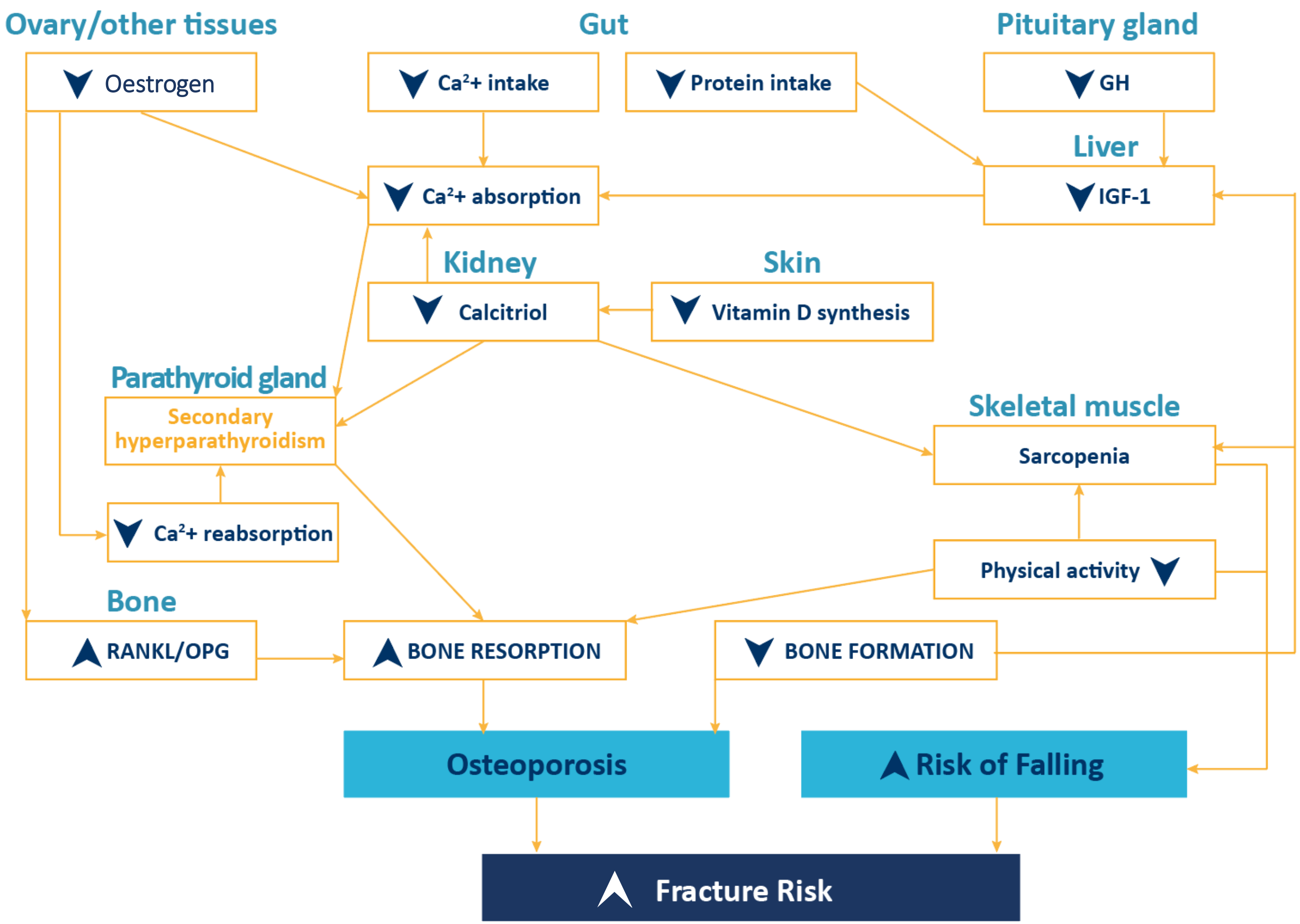


Age-related bone loss
(~0.5%-1.0% per year)

Bone loss accelerates with Menopause
(~1%-2% per year)

Adapted from Cooper C, Trends Endocrinol Metab. 1992; 3:224-229.
Weaver CM, Osteoporos Int. 2016; 27:1281-1386.

Metabolic changes in age-related osteoporosis

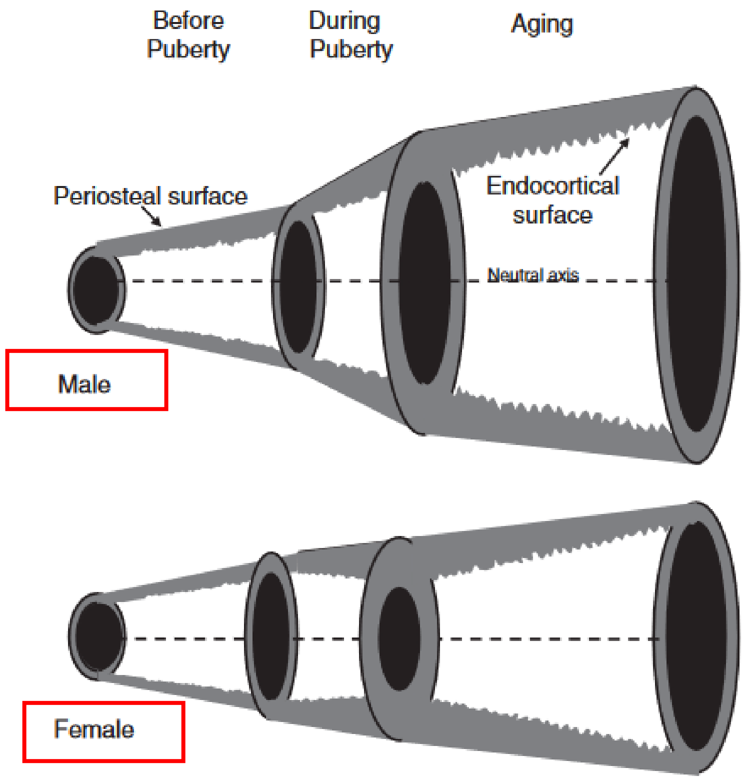


Biver E, Osteoporosis. In: Lammert, E., Zeeb, M. (eds) Metabolism of Human Diseases. Springer, Vienna. 2014.

Pathophysiology of the ageing skeleton

At the skeletal level

- Cortical bone
  - Reduction in the formation of periosteal bone with increased endosteal bone resorption in both sexes
  - Cortical thinning
  - Increased porosity
- Trabecular bone
  - Thinning of the trabeculae
  - Loss of connectivity
- Bone marrow: a shift from osteoblastogenesis to adipogenesis
- Osteoblasts/osteocyte apoptosis
- Accumulation of senescent cells
- Immune factors: IL-1, IL-6, TNF-α



Demontiero O, Ther Adv Musculoskelet Dis. 2012; 4:61-76.
Sfeir J, Mayo Clinic Proc 2022; 97:1194-1208.
Seeman E, J Bone Miner Metab. 2008; 26:1-8.

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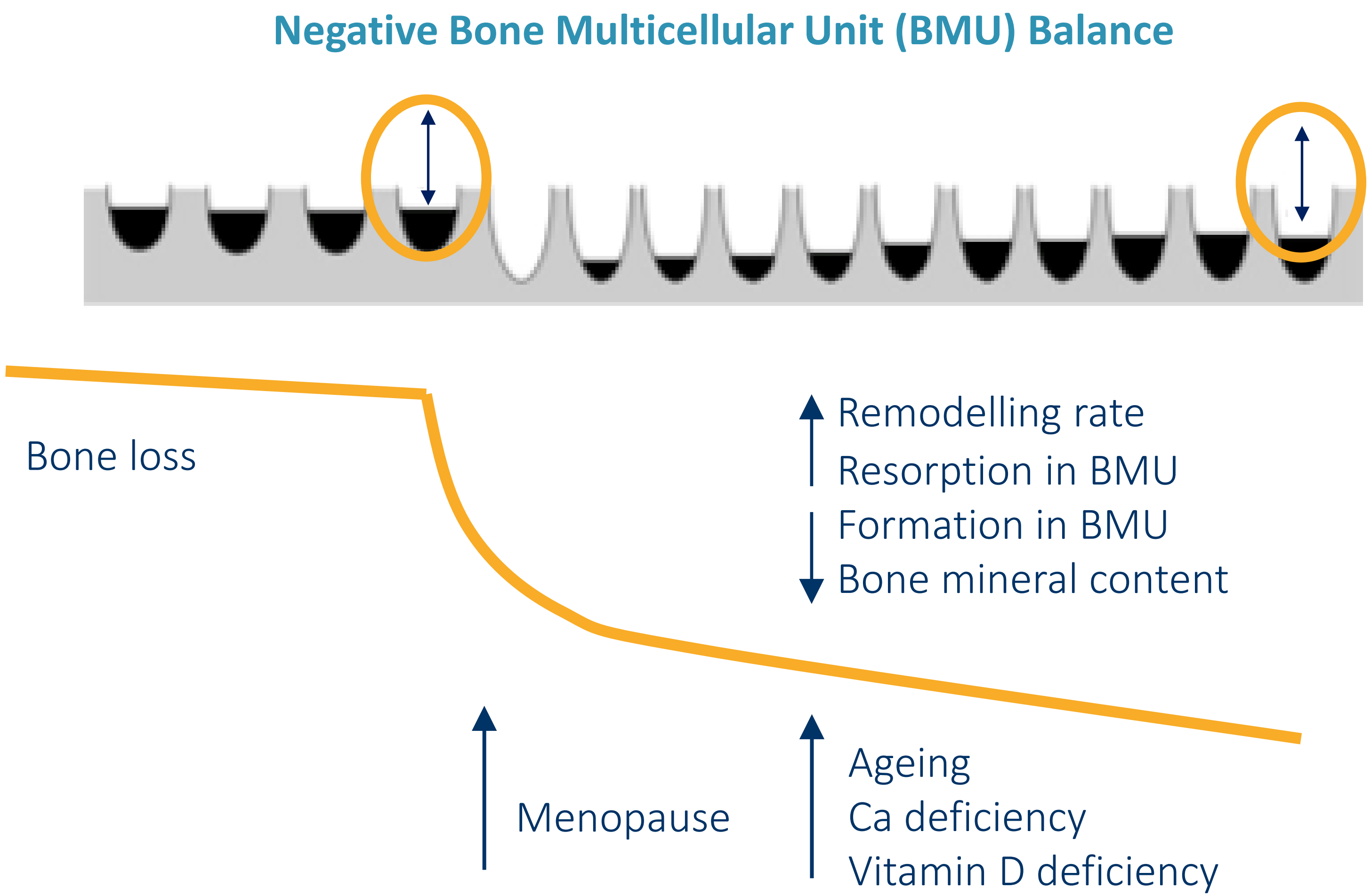
Pathophysiology of bone loss in women



Adapted from Seeman E, J Appl Physiol. 2003; 95:2142-2151.

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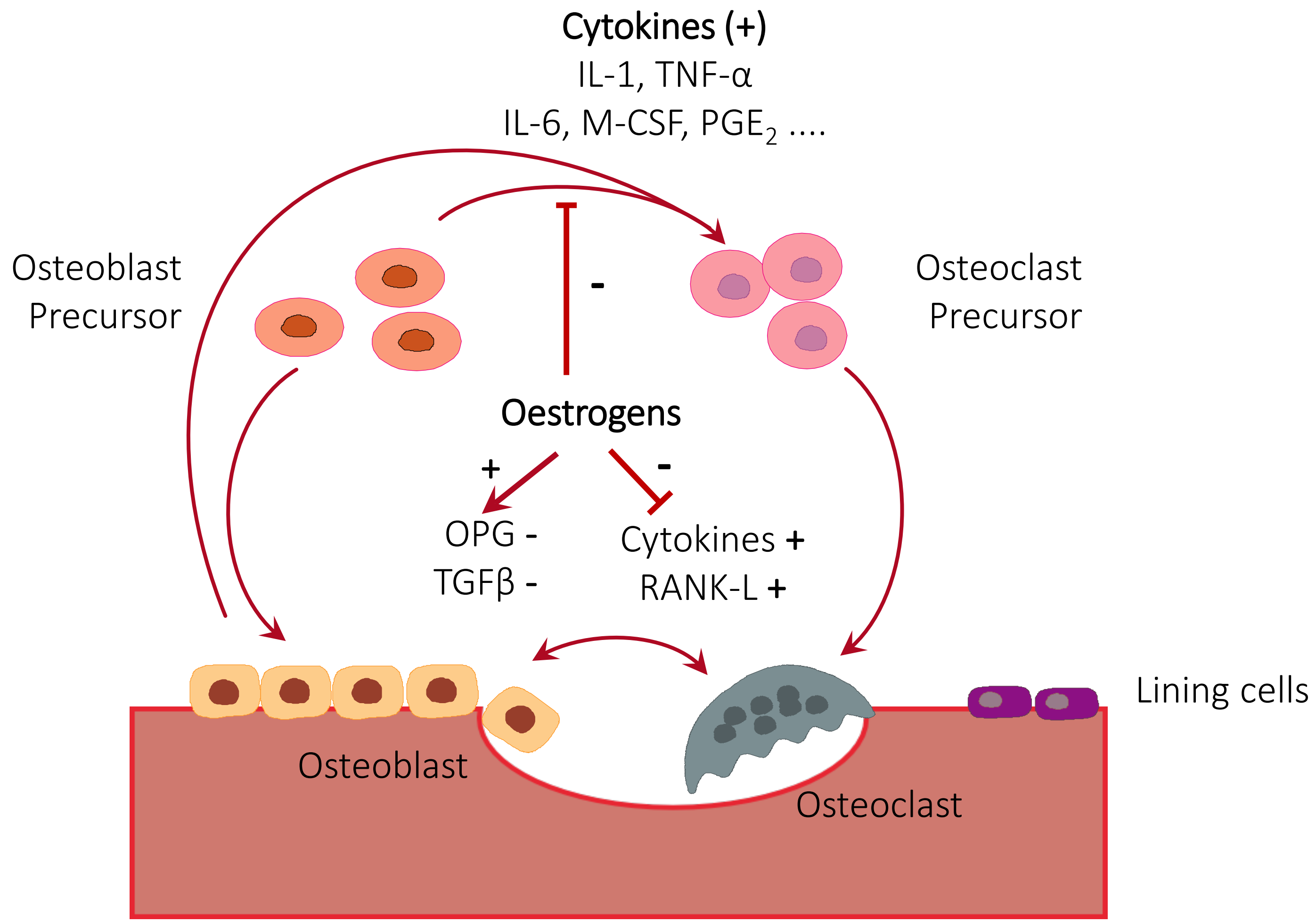
Bone remodelling is coupled to and regulated by many factors including oestrogens and cytokines



Adapted from Riggs B.L., Endocr Rev. 2002; 23:279-302.
Manolagas S, Gondal Steroids. Primer on Metabolic Bone. 8th ed. 2013.

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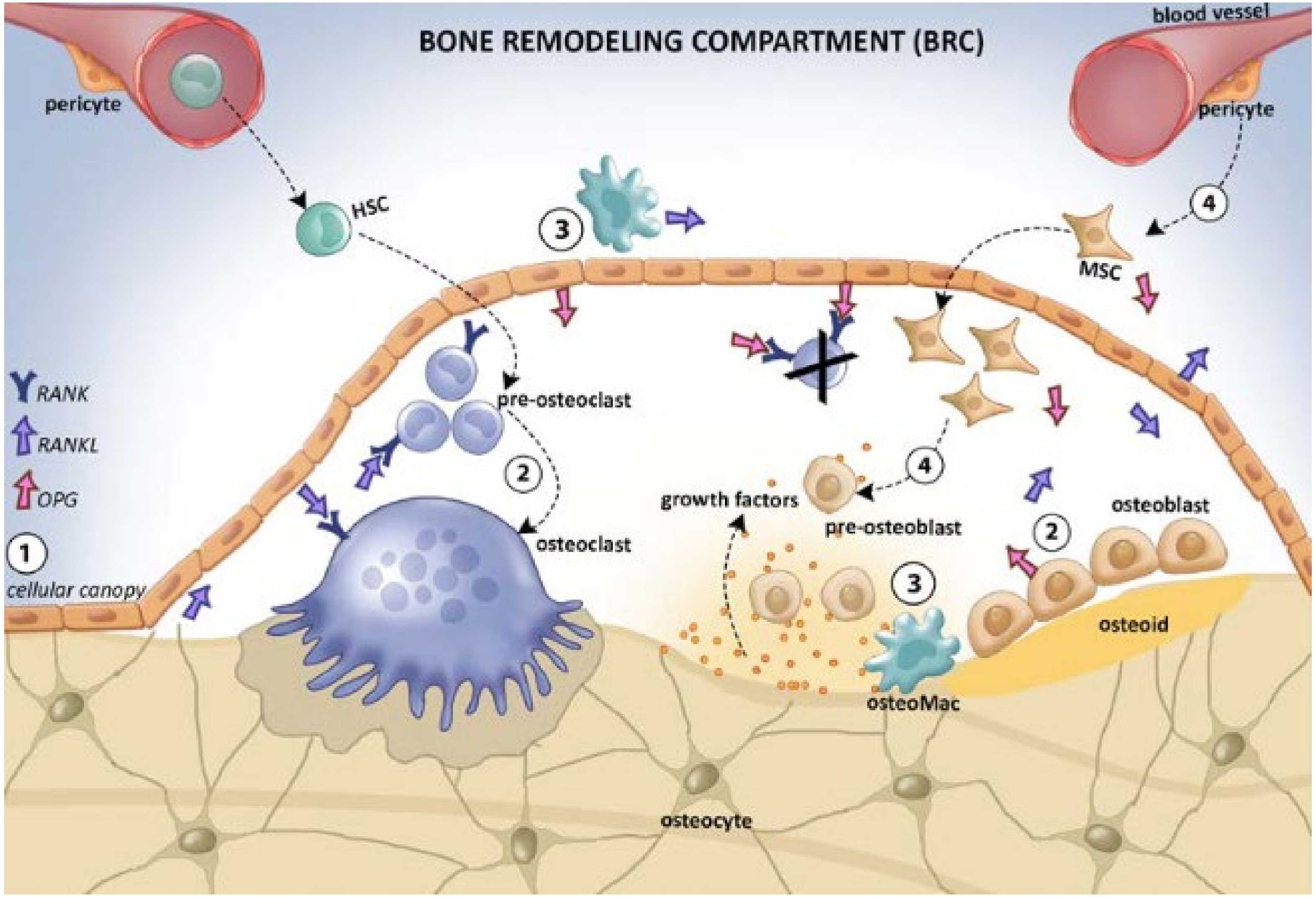
Hallmarks of skeletal ageing in old bone



Matsumoto M, Journal of Molecular Signaling Updates, 2016; 1:33-4.

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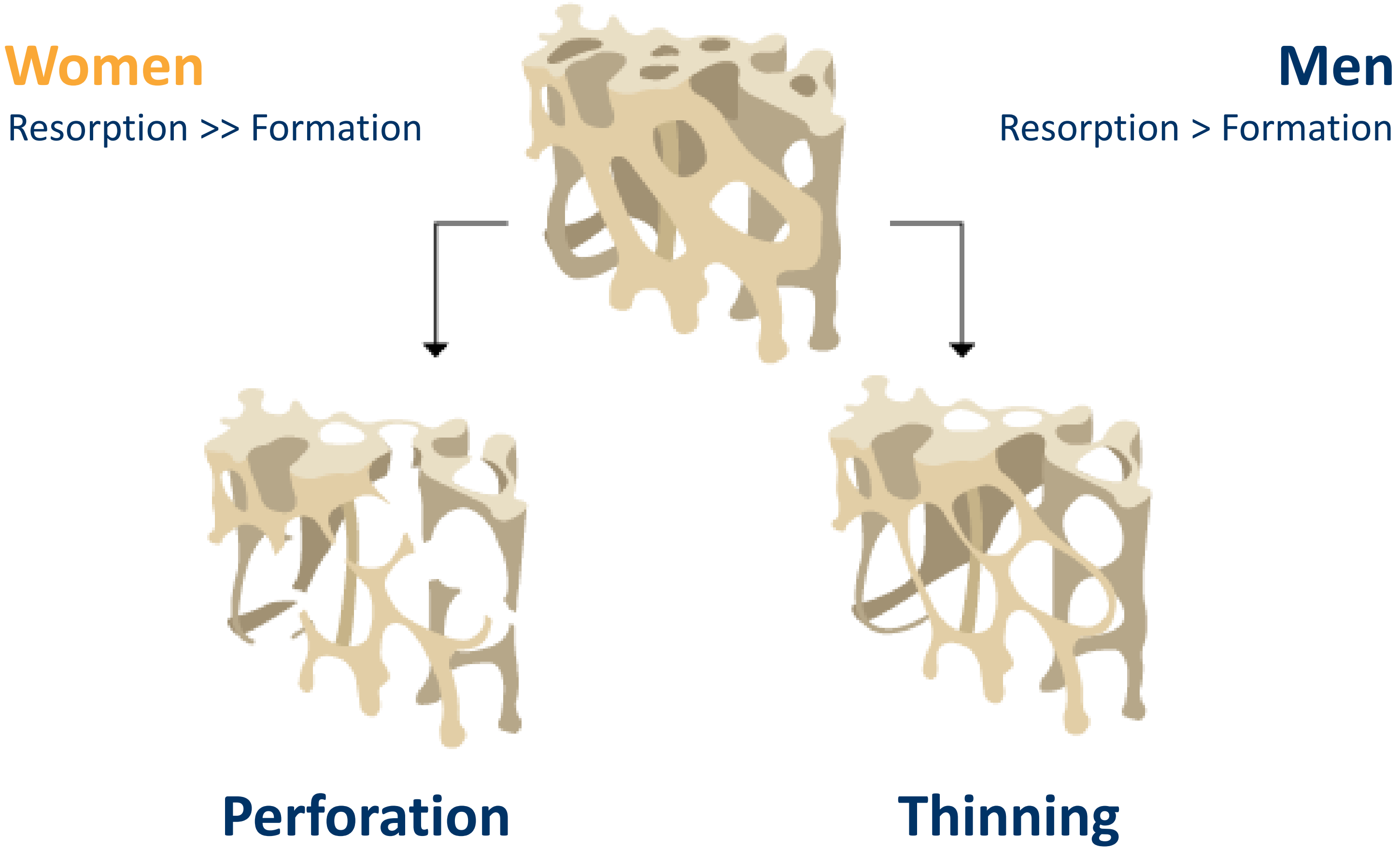
Bone modelling and remodelling

- Growth
  - Modelling and remodelling assemble the 3-dimensional structure of the bone using the void volume, in order to achieve bone strength for loading and lever function and lightness for mobility
- Menopause
  - BMU (Bone Remodelling Unit) balance becomes negative
  - Remodelling accelerates
  - Cortices become thin and porous
  - Trabeculae disappear and become disconnected
  - More rapid remodelling and bone loss on trabecular surfaces
  - Slower cortical loss by endocortical and intracortical remodelling
  - However, trabecular bone represents only for 20% of the total volume of mineralised bone matrix, compared with 80% for cortical bone in the skeleton,
    - Intracortical and endocortical remodelling contribute an equal amount to bone loss as trabecular remodelling during the first decade of menopause
    - Intracortical and endocortical remodelling is responsible for the majority of bone loss after the age of 60

Seeman E, J Gerontol A Biol Sci Med Sci. 2013; 68:1218-1225.

Trabecular bone – age related loss differs between men and women



Adapted from Seeman E, J Appl Physiol. 2003; 95:2142-2151.

Key messages

- Bone is a living organ with a well-organised structure comprising
  - A macroscopic structure: cortical and trabecular component
  - A microscopic structure: woven and lamellar bone
  - Composed of an organic matrix (collagen, cells), crystals of hydroxyapatite and water
  - Bone strength: bone must be both stiff and flexible
  - Bone geometry (size, shape) and bone microarchitecture (trabeculae) are strong determinants
- Pathophysiology of the ageing skeleton
  - Genetics
  - At the menopause, metabolic and hormonal changes with a decrease in oestrogen levels and an increase in cytokines
  - Increased remodelling rate, especially of the trabecular surfaces

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in which healthy mobility is a reality for all

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