DEFINITION OF BONE TISSUE

- Bone tissue forms most of the skeleton, the framework that supports and protects vital organs, bone marrow, acts as mineral reservoir for calcium, has function in acid-base homeostasis and, of course, allows movement.
- Bones are characterized their rigidity, hardness, and power of regeneration and repair.
- Strong but light weight, bone is a dynamic, ever changing tissue. Throughout life, it is continually being broken down and formed.
FUNCTIONS OF BONE TISSUE

- Supports the muscles, teeth
- Protects the brain, spinal cord, heart, lungs and other inner organs
- Allows movement
- Maintains ion balance
- Helps with maintaining of acid-base balance
- Bone marrow produces blood cells

CLASSIFICATION OF BONES

ACCORDING TO POSITION

- Axial skeleton
  - Skull, vertebral column, ribs, sternum
- Appendicular skeleton
  - Skeleton of limbs
CLASSIFICATION OF BONES
ACCORDING TO SHAPE

Long bones
- Longer than they are wide (e.g. humerus)
- Consist of a long shaft with two bulky ends or extremities
- Primarily compact bone but may have a large amount of spongy bone at the ends or extremities

Short bones
- Cube shaped bones of wrist and ankle
- Consist mainly of spongy bone, which is covered by a thin layer of compact bone
- Bones that form within tendons (e.g. patella)

Flat bones
- Thin, flattened and a bit curved (e.g. sternum and most skull bones)

Irregular bones
- Bones with complicated shapes (e.g. vertebrae, hip bone, maxilla, mandible)
- Primarily spongy bone that is covered with a thin layer of compact bone

CLASSIFICATION OF BONES
ACCORDING TO STRUCTURE

- Compact bone
- Spongy bone
- Woven bone
- Immature bones
  - Fetal bones
  - Fracture healing
  - Areas surrounding tumors or inflammation
- Collagen fibers lay in disorganized manner
- Lamellar bone
  - Mature bone
  - Regular parallel alignment of collagen fibers into sheets (lamellae)
ANATOMY OF BONES

Long bone
- Diaphysis
- Epiphysis – proximal, distal
- Metaphysis
- Articular cartilage
- Periosteum
- Endosteum
- Medullary cavity

Flat bone
**BONE MATRIX**

- **Inorganic components (cca 70%)**
  - Hydroxyapatite \( \text{Ca}_{10} \left( \text{PO}_{4} \right)_{6} (\text{OH})_{2} \) (99 %)
  - Other - \( \text{CaHPO}_{4} \), \( \text{MgHPO}_{4} \), \( \text{CaCO}_{3} \)
- **Organic components (cca 25%)**
  - Collagen 1 (90 – 95 %)
  - Osteocalcin (protein)
  - Osteonectin
  - Proteoglycans
  - Glycoproteins
  - Sialoproteins
  - Lipids
- **Water (cca 5%)**

**BONE CELLS**

**Osteoprogenitor cells**
- Unspecialized cells derived from mesenchyme
- Undergo mitosis and develop into osteoblasts
- They are found in the periosteum, endosteum and in canals that contains blood vessels

**Osteoblasts**
- Bone building cells that secrete bone matrix
- They lost the ability to divide by mitosis
- Secrete collagen and other organic components needed to build bone tissue
- The differentiation of osteoprogenitor cells into osteoblasts is accelerated by skeletal growth factors

**Functions**
- Role in formation of bone matrix
- Role in calcification (through the alkaline phosphatase enzymes)
- Synthesis of proteins
BONE CELLS

Osteocytes
- Maintenance of bone
- Small flattened and rounded cells embedded in bone lacunae
- Derived from mature osteoblasts
- Functions
  - Help to maintain the bone as living tissue because of their metabolic activity
  - Maintain the exchange of calcium between the bone and ECF.

Osteoclasts
- Bone resorption
- Giant phagocytic multinucleated cells found in the lacunae of bone matrix, derived from hemopoietic stem cells via monocytes
- Functions
  - Responsible for bone resorption during bone remodelling
  - Synthesis and release of lysosomal enzymes necessary for bone resorption

OSTEOSTEGENESIS (BONE GROWTH)

Ossification (osteogenesis) - process of formation of new bone by osteoblasts.

Types of osteogenesis
1. Intramembranous ossification
   - Laying down of bone into the primitive connective tissue (mesenchyme) resulting in the formation of bones (skull, clavicle, mandible).
   - Healing process of fractures
2. Endochondral ossification
   - Cartilage acts as a precursor (e.g., femur, tibia, humerus, radius)
   - Growing of the length of long bones
   - Fracture healing.

Steps of osteogenesis
1. Synthesis of extracellular organic matrix (osteoid)
2. Matrix mineralization leading to the formation of bone
3. Remodeling of bone by the process of resorption and reformation
**ENDOCHONDRAL OSSIFICATION**

Steps

1. Development of cartilage model
2. Growth of cartilage model
3. Development of the primary ossification center
   - fetal development of bones
   - a few short bones begin their primary ossification after birth
4. Development of the secondary ossification center
   - after birth
   - forms the epiphyses of long bones and the extremities of irregular and flat bones
5. Formation of articular cartilage and epiphyseal plate
   - after reaching of skeletal maturity (14–18 years of age), all of the cartilage is replaced by bone, fusing the diaphysis and both epiphyses together (epiphyseal closure).

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**BONE REMODELING**

- a lifelong process - old bone is removed from the skeleton (bone resorption), and new bone is added (bone formation)

Function

- maintaining of normal function, structure and mineral homeostasis of bone
- healing of injuries like fractures but also microdamage which occurs during normal activity

The average lifespan of each remodeled unit in humans is 2–8 months.
In the young skeleton, the amount of resorbed bone is proportional to the newly formed - balanced process.
Up to the third decade – positive balance.
In the third decade - bone mass is at its maximum, and this is maintained with small variations until the age of 50.
After the age 50 resorption predominates and the bone mass begins to decrease.
Bone remodeling increases in perimenopausal and postmenopausal women.
REMODELING UNIT

Osteoclasts
- resorbing of bone
- derived from mononuclear precursor cells
Bone resorption depends on osteoclast secretion of hydrogen ions and cathepsin K enzyme. $H^+$ ions acidify the resorption compartment to dissolve the mineral component of bone matrix. Cathepsin K digests the proteinaceous matrix, which is mostly composed of type I collagen.

Osteoblasts
- bone formation
- stimulated by growth hormone, thyroid hormones, estrogens, androgens

REMODELING UNIT

RANK
The cell surface receptor RANK (receptor activator of NFkB) activate osteoclast precursor cells to develop into fully differentiated osteoclasts when RANK is activated by its RANK ligand (RANKL). RANKL is produced mainly by marrow stromal cells and osteoblasts.

Osteoprotegerin
Osteoprotegerin (OPG), also known as osteoclast inhibiting factor (OCIF) or osteoclast binding factor (OBF), is a key factor inhibiting the differentiation and activation of osteoclasts. Osteoprotegerin inhibits the binding of RANK to RANKL and inhibits the activation of osteoclasts.

Abnormalties in the balance of OPGL/RANK/OPG system lead to the increased bone resorption that underlies the bone damage of postmenopausal osteoporosis, Paget’s disease, bone loss in metastatic cancers, and rheumatoid arthritis.
REMODELING PHASES

1. **Quiescent Phase**
   bone is at rest

2. **Activation Phase**
   activation of the bone surface to resorption
   activation of osteoclast precursors - differentiation, migration, and fusion of the large multinucleated osteoclasts. These cells attach to the mineralized bone surface and initiate resorption by the secretion of hydrogen ions and cathepsin K, which degrade bone matrix.

3. **Resorption Phase**
   the osteoclasts dissolve the mineral matrix

4. **Reversal Phase**
   bone resorption transitions to bone formation

5. **Formation Phase**
   osteoclasts have resorbed a cavity of bone, they detach from the bone surface and are replaced by the osteoblast lineage which in turn initiate bone formation

6. **Mineralization Phase**

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**Bone Remodeling Cycle**

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

- Resorption
- Reversal
- Bone Formation
- Mineralization

- PTH (catabolic)
- PTH (anabolic)

- 3 WEEKS
- 3 MONTHS
**Parathyroid Hormone**
- Peptide hormone (84 amino acids), produced by parathyroid glands
- regulates serum calcium and phosphorus concentrations through its receptor-mediated, combined actions on bone, intestine, and kidney
- high levels of PTH increase osteoclastic bone resorption
- low levels increase osteoblastic bone formation
- PTH receptor mainly at the osteoblasts

**Calcitonin**
- Peptide hormone (32 amino acids) produced by parafollicular C-cells of thyroid gland
- inhibit osteoclast-mediated bone resorption
Vitamin D (calcitriol)

**Intestinum**
- increases intestinal calcium absorption by increasing calcium uptake (calbindin)

**Bone**
- promotes the mineralization of osteoid and causes bone resorption by mature osteoclasts
- regulates the expression of several bone proteins (osteocalcin)

**Kidney**
- decreases calcium and phosphorus excretion

**Blood**
- increases calcium and phosphorus levels
**REGULATION OF SKELETAL METABOLISM**

**Other hormones**
- Parathyroid hormone-related protein (PTHrP)
  - Function as parathyroid hormone, produced by cancers but also physiologically.
- Androgens
  - Anabolic effect through the stimulation of the osteoblast receptors
  - In childhood activate growth factors – increase bone density
  - On the end of puberty activate epiphyseal closure
- Estrogens
  - After puberty - epiphyseal closure, but stimulate bone remodeling – after menopause deficit causes osteoporosis
- Glucocorticoids
  - Bone cell differentiation during development
- Insulin
  - Stimulates matrix synthesis together with IGF-1
- Growth hormone
  - Stimulates osteoblasts activity
- Thyroid hormones
  - Stimulate growth resorption but also formation, stimulate the synthesis of osteoid matrix and its mineralization
- Growth factors and cytokins (IGF-1)

**REGULATION OF SKELETAL METABOLISM**

- Decrease bone resorption
  - Calcitonin
  - Estrogens
- Increase bone resorption
  - PTH/PTHrP
  - Glucocorticoids
  - Thyroid hormones
  - High-dose vitamin D
- Increase bone formation
  - Growth hormone
  - Vitamin D metabolites
  - Androgens
  - Insulin
  - Low-dose PTH/PTHrP
  - Progestogens
- Decrease bone formation
  - Glucocorticoids
Osteoporosis

- common metabolic disorder of the skeleton
- bone mineral density is reduced
- the bone microarchitecture is disrupted (perforation of trabecular plates)
- the amount and variety of noncollagenous proteins in bone is altered

Leads to
- increased risk of fracture

Causes
- **Primary** – postmenopausal, senile
- **Secondary** – nutrition, endocrine, drug, malignancy, chronic diseases, idiopathic
OSTEOPOROSIS

Risk factors
- Age
- Female mainly postmenopausal
- Family history
- Sedentary lifestyle
- Defficiency of calcium or vitamin D
- High protein, alcohol, caffeine intake
- Smoking
- Hyperparathyroidism
- Other diseases (diabetes mellitus, celiac disease)
- Drugs (Al-containing antacids)

Mechanisms
- ↓ estrogens → ↑ cytokines → ↑ RANKL → ↑ activity of osteoclasts

OSTEOPOROSIS

Clinical signs
- „silent killer of bones“ – long time without signs, pain
- decrease of height
- fractures of bones – hip, humerus,...
- wedging and collapse of vertebrae
- kyphosis
- hump
OSTEOMALACIA

- inadequate mineralization of bones

**Causes**
- deficiency of vit. D - ↓ absorption of calcium from the intestine
- phosphate deficiency due to renal diseases or ↓ of intestine absorption

**Clinical signs**
- pain, tenderness and fracture of bones

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RICKETS

- inadequate mineralization of bones in children whose epiphyses have not yet fused

**Causes**
- deficiency of vit. D
- Vit. D resistant rickets
  - phosphate deficiency
  - mutation of vit. D receptor

**Clinical signs**
- deformation, widening of the bones
PAGET’S DISEASE
- Osteitis deformans
- disorder of bone remodeling
- the osteoclasts become abnormally activated, and produce a bizarre and irregular pattern of resorption, to which there is usually an intense osteoblastic response with irregular new bone formation often in the form of woven bone
- increased bone density, but because of the irregular architecture, bone strength is decreased and pathologic fractures may occur.

Causes
- hereditary?
- environmental factors – virus infection

Clinical signs
- enlargement and deformation of bones – face, long bones
- CVS disorders
- teeth loosing
- Pain
- Hearing loss

RHEUMATOID ARTHRITIS
- Chronic autoimmune systemic disease
- Synovial inflammation and destruction of the bone architecture
- Women vs. Men 3 : 1

Causes
- Autoimmune
  - Seropositive form – rheumatoid factor (antibody)
  - Seronegative form
  - T-cells, B-cells, antibodies, macrofages, cytokines (TNFα, IL-1),
  - Genetic predisposition – HLA-DR4-Dw4 alleles
  - Production of cytokins – activate osteoclasts
  - Trigger factor – infection (virus, bacteria, fungi)
  - Chronic parodontitis is risk factor
RHEUMATOID ARTHRITIS

Clinical signs
- Joints
  - Attacks of symmetric joint pain and morning stiffness
  - Inflammation and later fibrosis cause movement limitation
  - Later deformation, dislocation of joints
- Extra-articular signs
  - Fatigue, weakness, anorexia, weight loss
  - Rheumatoid nodules
  - Fibrosis of lungs
  - Atherosclerosis

OSTEOPOROSIS

- Degenerative changes of joints

Causes
- Unknown
- Genetic predisposition
- Environmental factors
- Obesity
- Mechanical stress

Mechanisms
- Inflammation produces cytokines that activate production of proteases – damage of cartilage

Clinical signs
- Pain
- Difficulty to initiate movement
- Joint crepitation
GOUT (ARTHITIS URICA)

- cause - ???
  - congenital - ↑ production of uric acid - enzyme defects
  - congenital - ↓ excretion of uric acid - defect of renal transporters
  - acquired - ↑ production of uric acid - obesity, alcohol
  - acquired - high intake of food containing purins, leukaemia, haemolysis
  - acquired - cytostatic drugs, Gierke’s disease
  - acquired - ↓ excretion of uric acid - kidney disease
  - acquired - drugs

Clinical symptoms
- hyperuricemia
- arthritis - acute arthritis
- chronic arthritis - tophi
- chronic uric acid intestinal nephropathy
- uric acid nephrolithiasis (kidney stones)

RARE SKELETAL DISEASES
OSTEOPETROSIS

- osteosclerosis, stone bones, Marble bone disease
- too dense - “stone” bones
- bone resorption is defective because of impaired formation of osteoclasts or loss of osteoclast function
- bone modeling as well as remodeling is impaired, and the architecture of the skeleton can be quite abnormal – deformities of bones

OSTEOGENESIS IMPERFECTA

- Brittle bone disease

**Cause**
- AD disorder of collagen type 1 (8 types)
- AR types

**Mechanisms**
- Mutation of COL1 A1 or COL1 A2 genes - abnormal collagen structure

**Clinical signs**
- Fractures of bones
- Bone deformity
- Short stature
- Damage of joints
- Blue colour of sclera
- Loss of hearing
EHLERS-DANLOS SYNDROME

- a group of genetic connective tissue disorders

**Cause**
- AD or AR inherited mutation of one of group of genes – result: defect in synthesis or function of collagen or proteins that interact with collagen
- Affected genes: COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, and TNXB, ADAMTS2, PLOD...

**Clinical signs**
- Hyper-flexible joints, luxation and dislocation of joints, swan neck deformity of the fingers, deformities
- Osteoarthritis
- Hyperelastic skin, fragile skin, bruising
- Valvular disorders, aneurysm, varices

MARFAN SYNDROME

- a genetic connective tissue disorder

**Cause**
- AD inherited mutation in the FBN1 gene on chromosome 15, which encodes fibrillin-1, a glycoprotein component of the extracellular matrix.

**Clinical signs**
- Tall, long limbs, long fingers – arachnodactyliy
- Increased joints flexibility
- Scoliosis, lordosis
- Lens dislocation – fibrillin is one protein of apparatus that fix sclera in position
- Valvular disorders, aneurysm, varices

Abraham Lincoln, Nicolo Paganini
LITERATURE SOURCES
