PATHOPHYSIOLOGY OF BONES AND JOINTS

GENERAL MEDICINE
2023/2024

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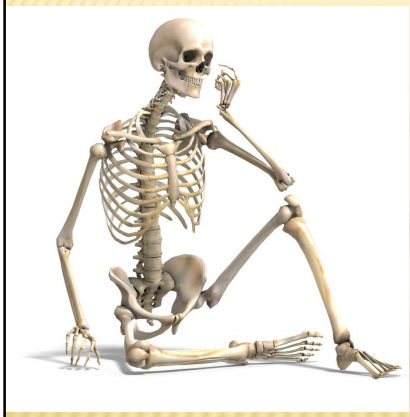
DEFINITION OF BONE TISSUE



- 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 tissue. Throughout life, it is continually being broken down and formed.

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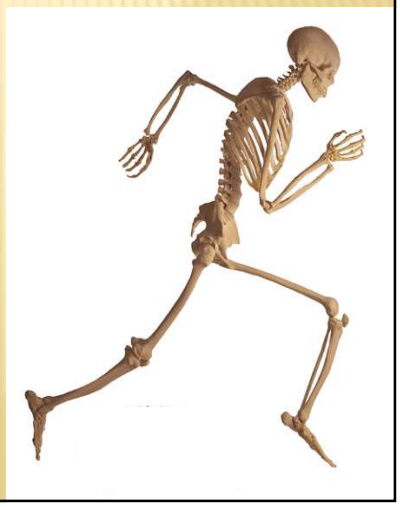
FUNCTIONS OF BONE TISSUE

- 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



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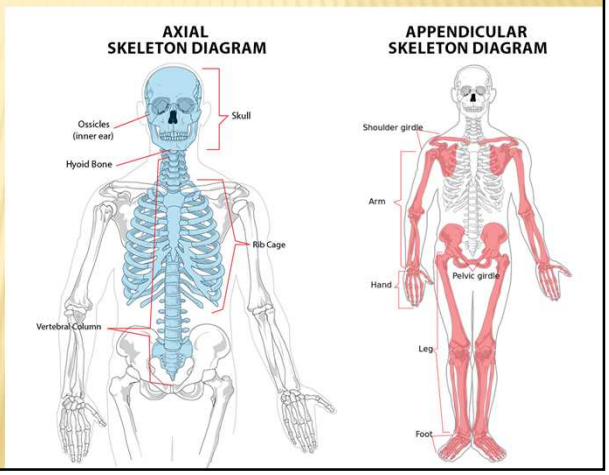
CLASSIFICATION OF BONES

ACCORDING TO POSITION

- Axial skeleton
  - Skull, vertebral column, ribs, sternum
- Appendicular skeleton
  - Skeleton of limbs



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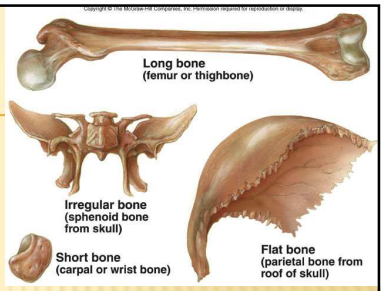
CLASSIFICATION OF BONES
ACCORDING TO SHAPE



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

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CLASSIFICATION OF BONES
ACCORDING TO MATURITY

Woven bone
- Immature bones
  - Fetal bones
  - Fracture healing
  - Areas surrounding tumors or inflammation
- Collagen fibers lay in disorganized manner

Lamelar bone
- Mature bone
- Regular parallel alignment of collagen fibers organized into sheets (lamellae)

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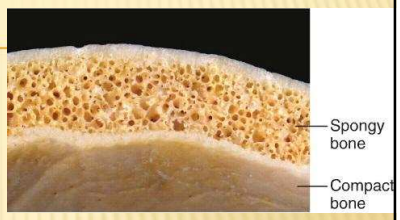
CLASSIFICATION OF BONES
ACCORDING TO STRUCTURE



- Compact bone
  - 85% skeleton
  - surface layer of short and flat bones and diaphysis of long bones
  - concentrically arranged bone lamellae - give the bone strength
  - between the lamellae in the cavities (lacunae) are bone cells osteocytes
- Spongy bone
  - 15% skeleton
  - a main part of the flat and short bones and epiphysis of the long bones
  - lamellae arranged in trabecules, between which there are cavities, filled with red bone marrow

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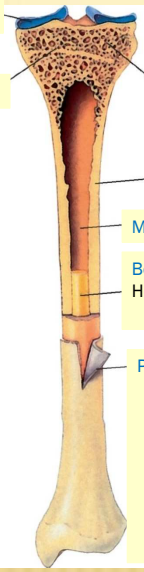
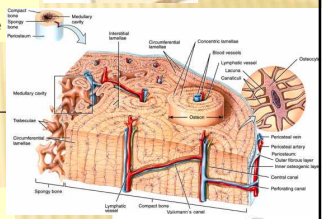
ANATOMY OF BONES

Epiphysis
Metaphysis
Diaphysis
Metaphysis
Epiphysis

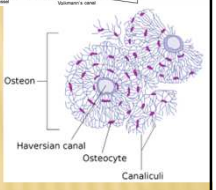
Cartilage
Trabeculae



Sponge bone
formed by trabeculae
more elastic, more durable



Compact bone
Medullary cavity
Bone marrow
Hematopoietic stem cells
lymphoid/myeloid



Periosteum
Outer fibrous layer
Bone protection
Bone attachment to tendons and ligaments
Inner cell layer
Progenitor stem cells from which osteoblasts and chondroblasts are formed

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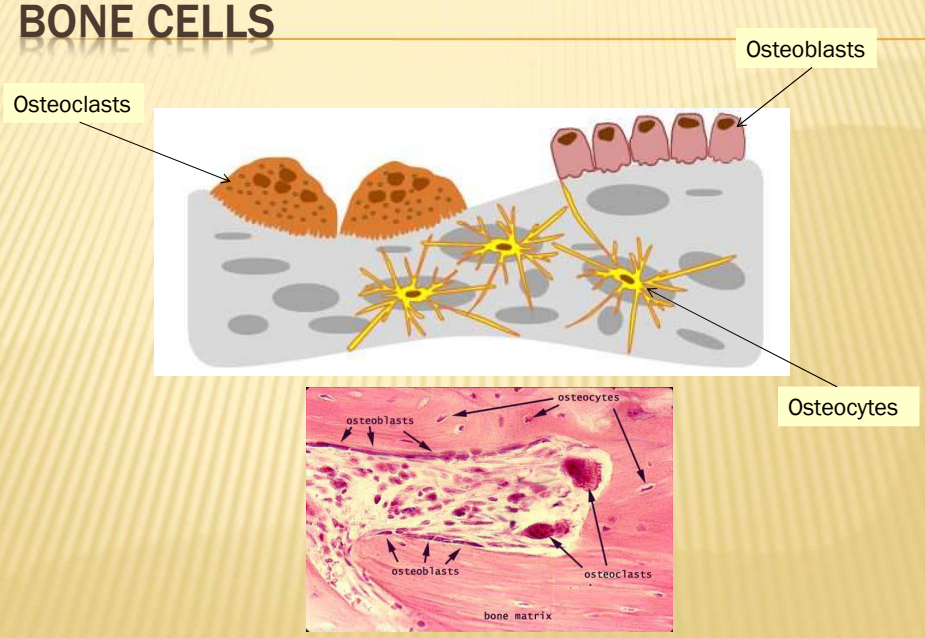
BONE CELLS



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BONE CELLS

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 accelererated by skeletal growth factors

Functions

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

Osteoprogenitor cells

- Osteoblast precursors (preosteoblasts)
- Unspecialized cells derived from mesenchyme
- Undergo mitosis and develop into osteoblasts
- They also play a role in bone growth and healing, they can also differentiate into chondroblasts or fibroblasts.
- They are involved in the nutrition of bone tissue
- They are found in the periosteum, endosteum and in canals that contains blood vessels

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BONE CELLS

Osteoblasts

- They synthesize the bone matrix - collagen
- Role in the deposition of inorganic substances in the bone matrix - calcification
- They synthesize growth factors - TGFb, GM-CSF, ...
- They produce enzymes - ALP

- They synthesize regulatory factors for remodeling
  - RANKL (RANK ligand) → binds to the RANK receptor (receptor activator of nuclear factor kappa B), which is found on osteoclast precursors → osteoclast precursors change into mature osteoclasts
    → **ACTIVATION OF BONE RESORPTION**
  - Osteoprotegerin (OPG) - prevents the binding of RANKL to the RANK receptor on osteoclasts → **INHIBITION OF BONE RESORPTION**
    (it is also the RANK receptor)

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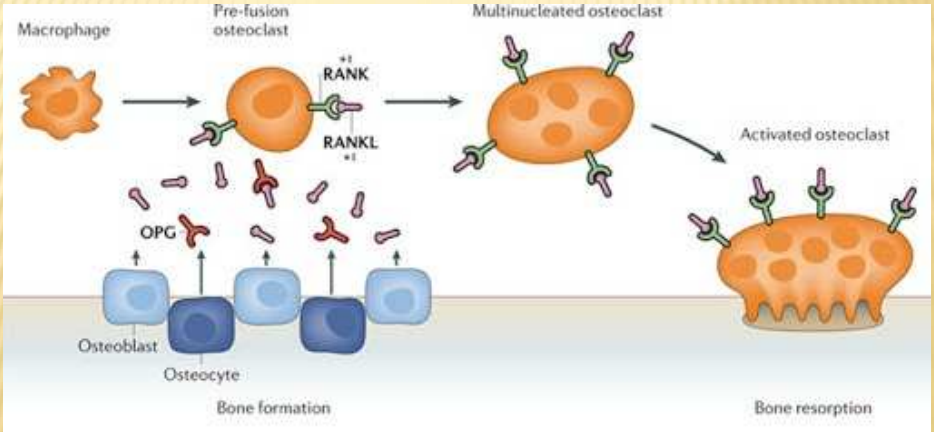
RANKL/RANK/OSTEOPROTEGERIN



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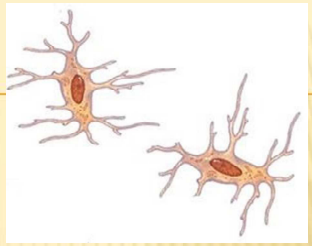
BONE CELLS



Osteocytes

- Bone maintenance
- Small star-shaped cells placed in lacunae communicating with each other through protrusions
- Derived from mature osteoblasts
- Produced by RANKL and OPG
- Important for the existence of the extracellular matrix, they have a low synthetic capacity, they also participate in resorption
- maintain the bone matrix, regulate bone metabolism, participate in the transport of substances, especially ions (calcium, phosphates) between the bone and blood plasma
- their protrusions serve as mechanoreceptors, transmit mechanical stimulation from the bone surface to osteocytes, which on the basis of this information in cooperation with osteoblasts and osteoclasts activate bone formation or resorption

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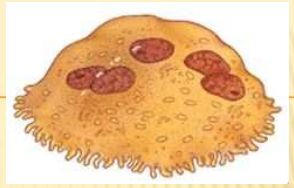
BONE CELLS



Osteoclasts

- Large multinucleated cells
- They are involved in bone resorption
- Derived from the same hematopoietic lineage as monocytes and macrophages
- They contain a large number of lysosomes filled with hydrolytic enzymes
- They bind to the bone surface via receptors for adhesive molecules. At the point of contact, the membrane osteoclasts form a typical wavy edge by which they adhere to the bone surface. This increases the size of the contact cells and determines the area of bone resorption and protects the surrounding tissue.
- Formation of hydrochloric acids (HCl), which acidifies the area of resorption, and breaks down the mineral matrix
- They release the protease cathepsin K from lysosomes, which breaks down bone matrix proteins, especially collagen I.
- Ions formed by the decomposition of hydroxyapatite (calcium, phosphate) and collagen fragments are absorbed by osteoclasts (endocytosis), transported in vacuoles to the opposite pole of the cell (transcytosis) and excreted into the extracellular fluid.

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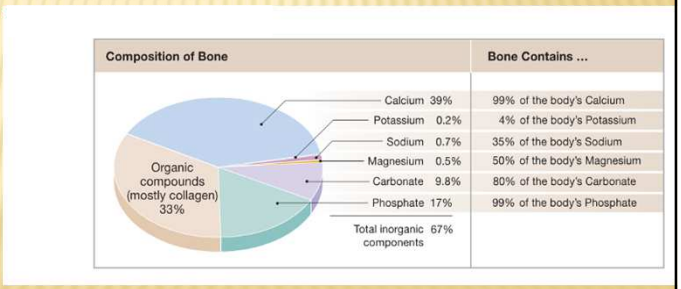
BONE MATRIX

- Inorganic components (cca 70 %)
  - Hydroxyapatite $Ca_{10}(PO_4)6(OH)_2$ (99 %)
  - Other - $CaHPO_4$, $MgHPO_4$, $CaCO_3$
- Organic components (cca 25 %)
  - Collagen 1 (90 – 95 %)
  - Osteocalcin (protein)
  - Osteonectin
  - Proteoglycans
  - Glykoproteins
  - Sialoproteins
  - Lipids
- Water (cca 5 %)



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OSTEOGENESIS (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
     - *Perichondrial ossification - on the surface of the cartilage model*
     - *Enchondrial ossification - inside the cartilaginous model*

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

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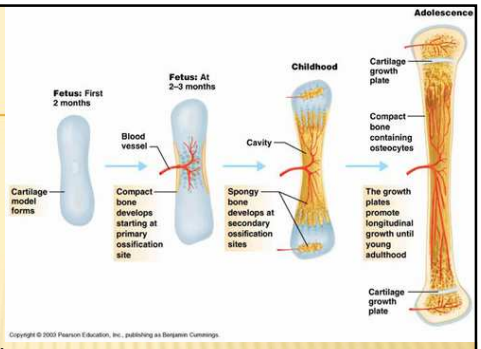
ENDOCHONDRAL OSSIFICATION



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.

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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

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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 RANKL/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.

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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 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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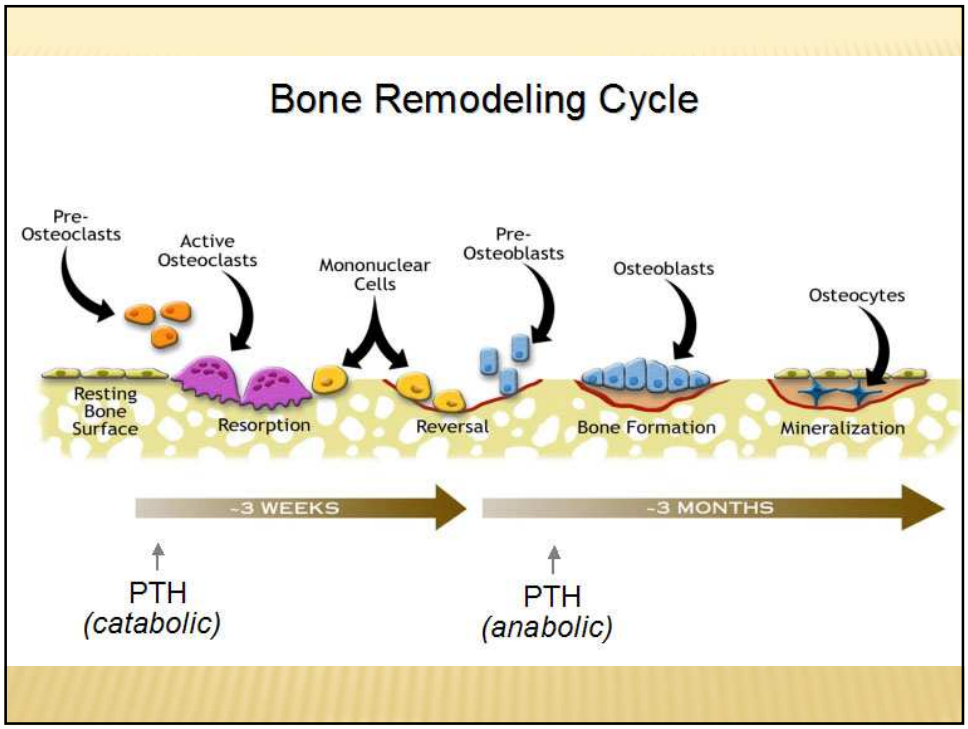

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REGULATION OF SKELETAL METABOLISM

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 parafolicular C-cells of thyroid gland
- inhibit osteoclast-mediated bone resorption

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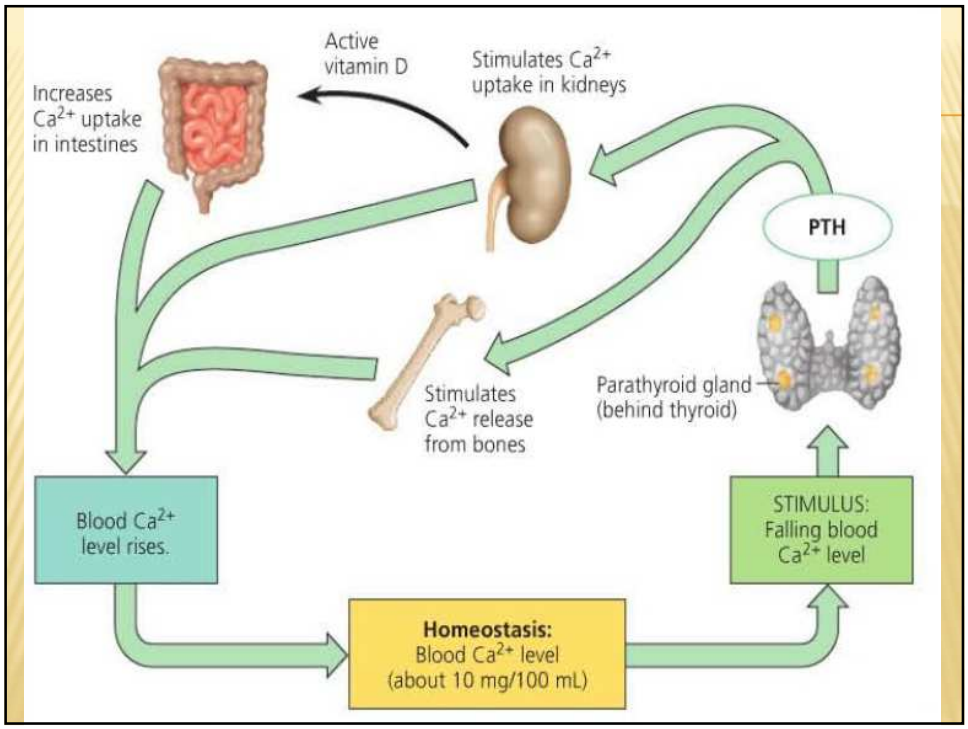

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REGULATION OF SKELETAL METABOLISM

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

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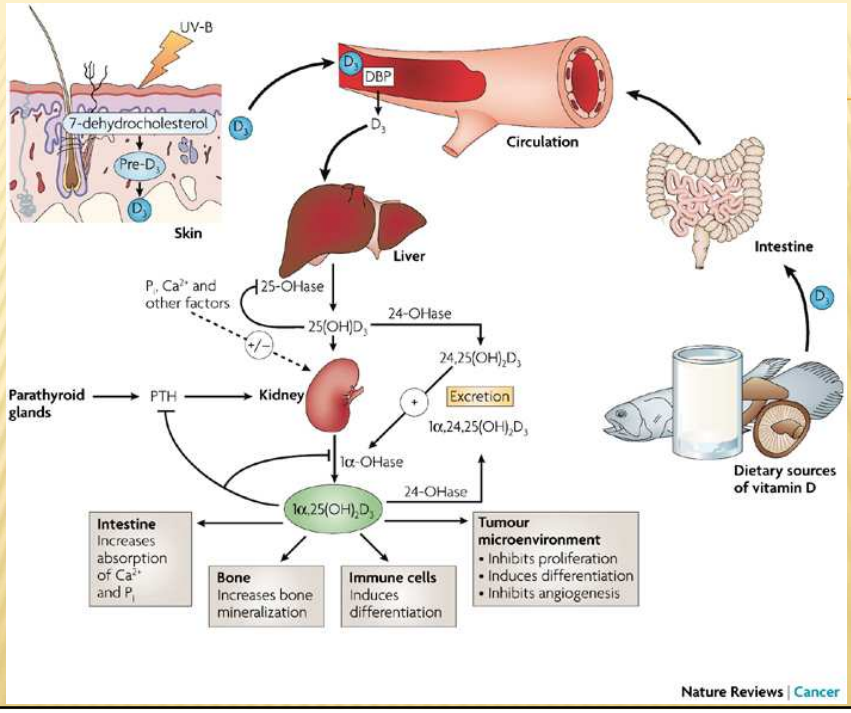

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REGULATION OF SKELETAL METABOLISM

Other hormons

Parathyroid hormone-related protein (PTHrP)
- Function as parathyroid hormone, produced by cancers but also physiologically
- E.g. tooth eruption - local bone resorption

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 diferentiation 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)

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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

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REGULATION OF SKELETAL METABOLISM

Other factors

Growth factors and cytokines

- Insulin-like growth factors I and II (IGF-I and II) - Increase osteoblast number and activity, increase collagen synthesis
- Interleukin 1 (IL-1) - Increases bone resorption

Other factors

- Genetic predisposition - The amount of bone tissue is partially inherited. The difference is between the races, black people have a stronger skeleton than whites, the lowest bone tissue amount have Asians.
- Movement - Lack of exercise increases bone breakdown, while regular movement promotes bone formation
- Nutritional factors - Malnutrition leads to bone loss. Calcium in the diet is essential for bone mineralization. Smoking, coffee, alcohol, lots of salt in the diet increase the risk of osteopenia

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ANATOMY AND PHYSIOLOGY OF JOINTS

Joint (articulation) - the place of connection of two or more bones.

The role of the joints is to allow movement and support the stability of the skeleton.

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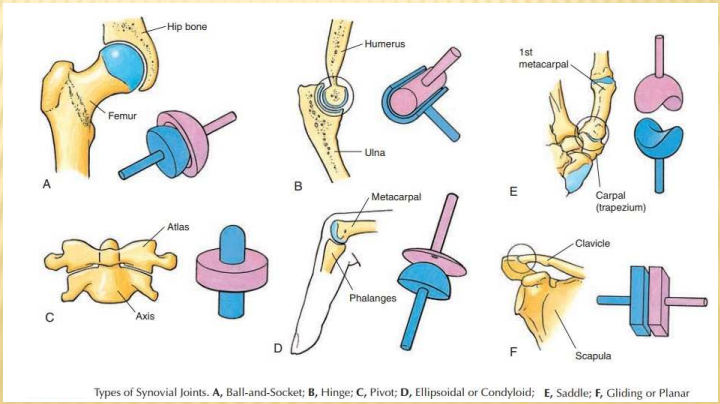
CLASSIFICATION OF JOINTS

ACCORDING TO MOBILITY

- *immovable (synarthrosis)*
- *slightly movable (amphiarthrosis)*
- *Freely movable (joints, diarthrosis)*



Types of Synovial Joints. **A,** Ball-and-Socket; **B,** Hinge; **C,** Pivot; **D,** Ellipsoidal or Condyloid; **E,** Saddle; **F,** Gliding or Planar

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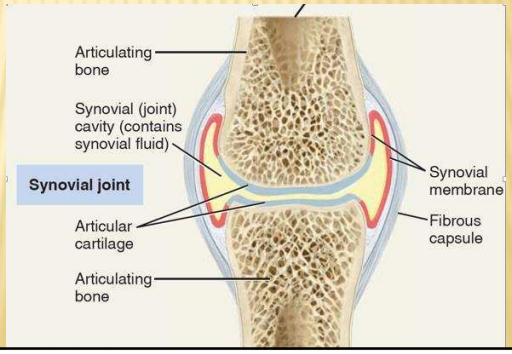
CLASSIFICATION OF JOINTS

Movable (synovial) joints

- They are formed by articulating bones
- The surfaces of the bones that are in contact are covered with hyaline cartilage, which exactly copies the shape of the joint. Its thickness is 0.5 to 6 mm.
- Between the joint surfaces - cavity filled with synovial fluid. The cavity can be divided into two parts using the so-called articular disc (meniscus).
- The whole joint is surrounded by a fibrous capsule, the inner layer - synovial membrane produces synovial fluid and the outer layer, the fibrous membrane, strengthens the joint.



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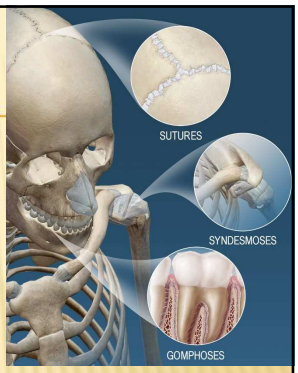
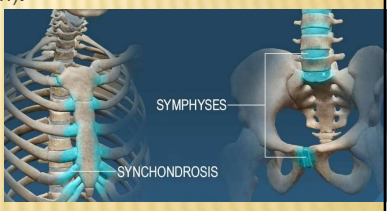
CLASSIFICATION OF JOINTS



Immovable joints

- *Fibrous*
  - Syndesmosis - bones held together by an interosseous membrane. The middle radioulnar joint and middle tibiofibular joint are examples of a syndesmosis joint
  - Sutura - is a junction of flat bones, e.g. skull bones in children
  - Gomphosis - where the teeth articulate with their sockets in the maxilla (upper teeth) or the mandible (lower teeth).
- *Catilaginous*
  - Synchondrosis - the bones are connected by hyaline cartilage - the joint between the diaphysis and epiphysis of a growing long bone
  - Symphysis - pubic symphysis



- *Bone*
  - Synostosis - fusion of two or more bones - e.g. the connection of the five sacral vertebrae forming the sacrum

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PATHOPHYSIOLOGY OF BONES

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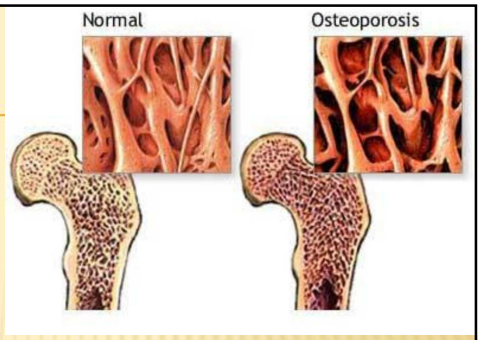
OSTEOPOROSIS



- 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, idiopatic juvenile, senile
- Secondary – nutrition (anorexia), endocrine (Cushings, hyperprolacinemia), drug (corticoids), malignancy, chronic diseases (diabetes mellitus), genetic (Klinefelter sy., Turner sy.), idiopathic

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PRIMARY 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

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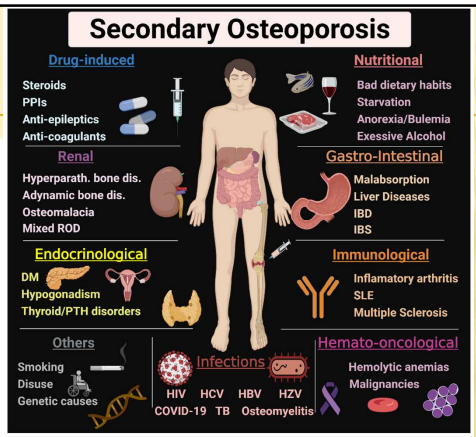
SECONDARY OSTEOPOROSIS



Endocrine diseases
- Diabetes mellitus
- GH deficiency (rare)
- Acromegaly (rare)
- Hypercortisolism
- Hyperparathyroidism
- Hyperthyroidism
- Premature menopause
- Male hypogonadism

Gastrointestinal disorders
- Gastrectomy
- Celiac disease
- Inflammatory bowel disease
- Liver cirrhosis
- Chronic biliary tract obstruction
- Chronic therapy with proton pump inhibitors

Hematologic diseases
- Myeloma
- Monoclonal gammopathy of undetermined significance
- Lymphoma/leukemia
- Systemic mastocytosis (rare)
- Disseminated carcinoma
- Chemotherapy

Rheumatological diseases
- Rheumatoid arthritis
- Ankylosing spondylitis
- Systemic lupus erythematosus

Connective tissue diseases
- Osteogenesis imperfecta
- Marfan's syndrome (rare)
- Ehlers–Danlos syndrome (rare)
- Pseudoxanthoma elasticum (rare)

Other
- Anorexia nervosa

Nutritional deficiencies
deficiency of vitamins D, K, C, calcium, proteins

Drugs
- Glucocorticoids
- Heparin
- Anticonvulsants
- High doses of thyroid hormones
- Cytostatic drugs
- Aluminum-containing antacids
- Some diuretics
- Lithium containing drugs (e.g. psychoactive drugs)

Other
- Transplantation
- Immobilization
- Smoking
- Alcohol
- Weightless state

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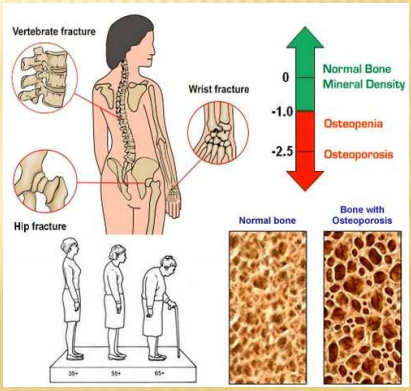
OSTEOPOROSIS

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



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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
- In the beginning - non-specific symptoms: muscle weakness, fatigue, muscle, bone and joint pain
- Diffuse joint and bone pain - lumbosacral spine, pelvis, ribs, forelegs and plexus areas of the limbs. Pain most often occurs with movement
- Bones are sensitive to touch.
- Later - deformities, mainly in the area of the chest and lower limbs
- Fractures - less common than in osteoporosis
- In the advanced stage of the disease - immobility, pain and hypersensitivity to touch

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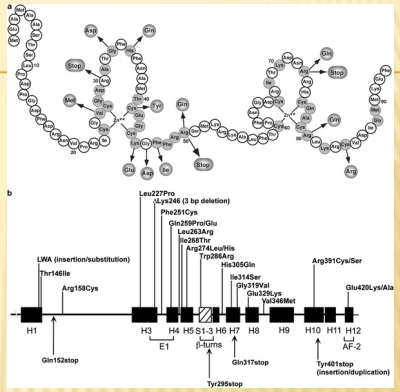
RICKETS



- 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
  - In newborns – deformation of skull
  - In older children - the lower limbs
  - As a result of insufficient mineralization, the growth plates are widening, which is manifested by swelling most often on the ankles, wrists and sternal ends of the ribs Growth is slowed, muscles are hypotonic, gait is slow "duck"

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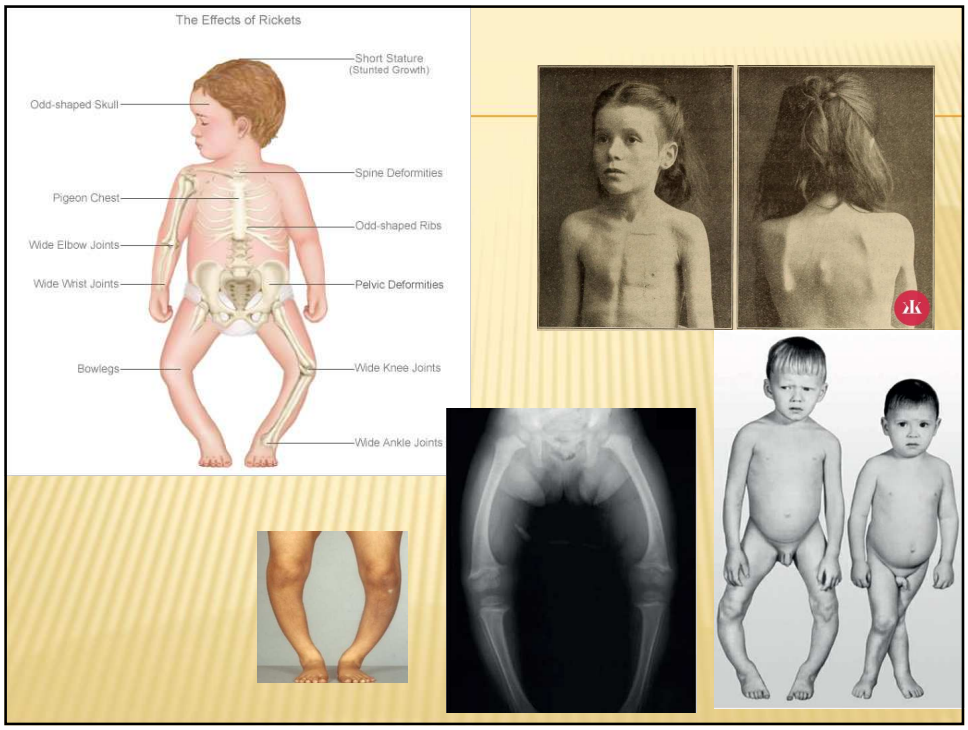

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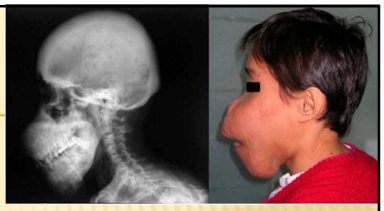
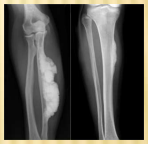


PAGET´S DISEASE

- 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

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

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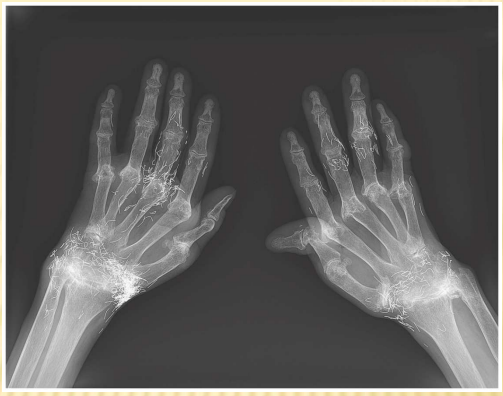

PATHOPHYSIOLOGY OF JOINTS

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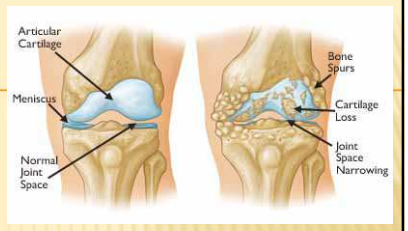
OSTEOARTHRITIS



- Degenerative changes of joints

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

Classification
- Primary arthrosis
  - causes are unknown
  - genetic predisposition (quality of cartilage, strength of ligaments)
  - risk factors - obesity, uneven loading of joints (incorrect footwear), long-term mechanical stress (sports, dancing).
- Secondary arthrosis
  - the consequence of another primary joint disorders, e.g. in some metabolic diseases (alkaptonuria, hemochromatosis), in some congenital disorders (dysplasia of the hip joint, hypermobility of the joints), after injuries (fractures, bleeding in the joint), in inflammatory diseases (rheumatoid arthritis).

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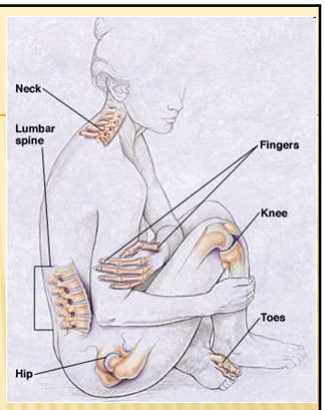
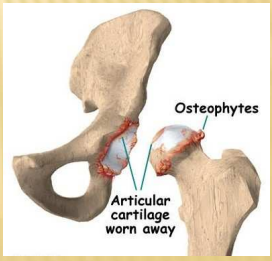
OSTEOARTHRITIS



Pathogensis

Slow progressive degeneration of articular cartilage, cartilage is damaged, loses elasticity, thins, joint space narrows, bones come into contact, causing pain and limitation of movement. Outgrowths (osteophytes) form on the edges of the joints. Synovial fluid production increases. Although arthrosis is not primarily an inflammatory disease, due to changes and increased irritation in the joint, local inflammation occurs secondary to it, which contributes to pain and limitation of movement.



Clinical signs

- Pain
- Difficulty to initiate movement - morning stiffness
- Joint crepitation

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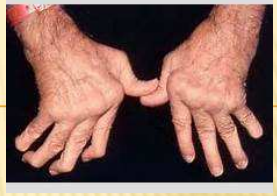
RHEUMATOID ARTHRITIS



- 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

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RHEUMATOID ARTHRITIS

Mechanism

- The process starts with the activation of T helper cells → they produce cytokines and activate B cells to produce antibodies → autoantibodies bind to a fragment of immunoglobulin G (rheumathoid factor, antibody against antibody) and together form immunocomplexes in blood, synovial membrane and synovial fluid → neutrophils and macrophages are attracted to inflammation site, absorb immunocomplexes and in the process of phagocytosis release lysosomal enzymes that damage the synovial membrane and joint cartilage.
- T-lymphocytes, cytokines (TNFα, IL-1), macrophages ...
- The cytokines activate osteoclasts

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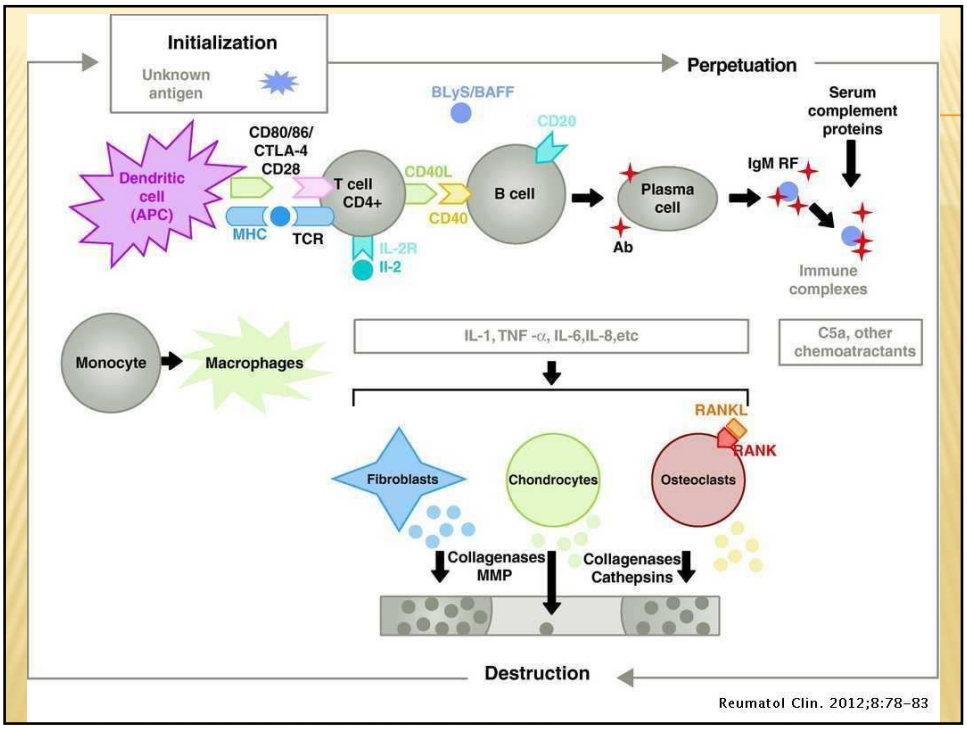

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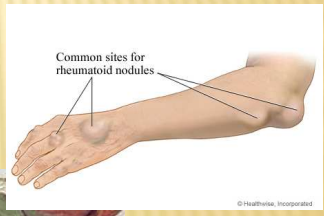
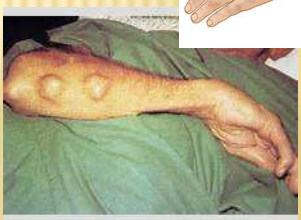
RHEUMATOID ARTHRITIS

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 sign
  - Fatigue, weakness, anorexia, weight loss
  - Rheumatoid nodules
  - Fibrosis of lungs
  - Atherosclerosis





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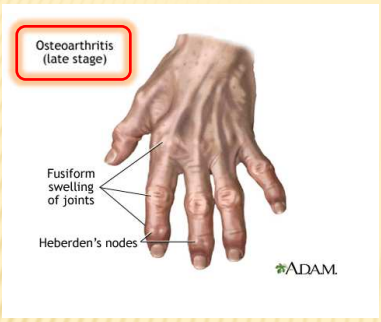

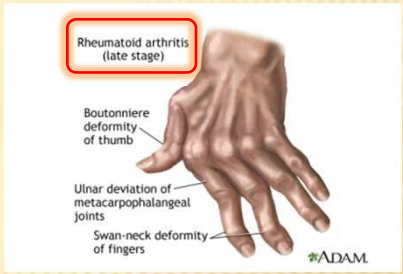

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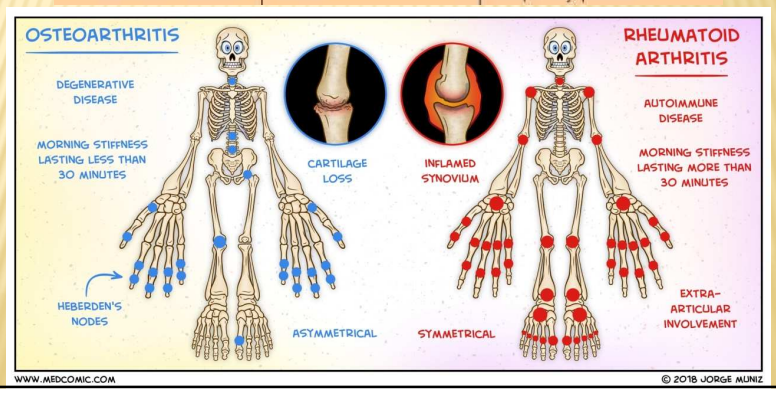
	Osteoarthritis	Rheumatoid Arthritis
Site(s) affected	Localized to joint	Articular, systemic and extra-articular manifestation
Pathogenesis	Biomechanical, leads to loss of cartilage matrix	Autoimmune response leads to joint destruction
Symptoms	Pain Stiffness <20 minutes Limited motion	Pain Joint swelling Stiffness >1 hour Limited motion
Inflammation	Usually limited, may be present in advanced disease	Chronic
Osteophytes	Usually present	Absent
Rheumatoid factors	Absent	Frequently present



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ANKYLOSING SPONDYLITIS

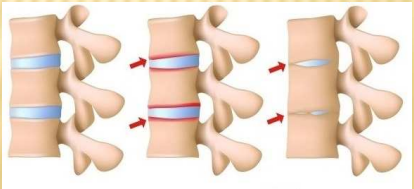
- Systemic inflammatory disease of the joints characterized by stiffness and fusion (ankylosis) of the joints of the spine
- Especially in young people, men> women

Causes

- Autoimmune disease ?? with a genetic predisposition (HLA-B27).

Patogenesis

- Inflammation affects the ligament-cartilage, cartilage and bone parts of vertebrae → erosions, especially in the cartilage, are compensated by proliferation of fibroblasts, which synthesize collagen, whose fibers fill erosions, which subsequently calcify and ossify → joints fuse and lose mobility.



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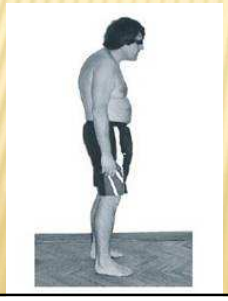
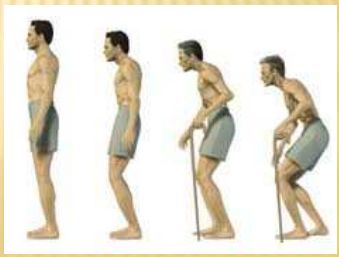
ANKYLOSING SPONDYLITIS

Clinical signs

- Initially pain in the lumbar-sacral region, stiffness and pain when breathing, pain in the lower back is typical in the morning, or after a long rest, the movement is relieved
- Later, the patient has trouble sitting upright and turn. The spine changes shape, the typical lower curvature of the spine disappears and the upper part of the spine is tilted forward → breathing problems
- Sometimes the joints of the limbs (more often in women)
- Extra-articular manifestations - lung fibrosis, cardiomegaly, amyloidosis and others.





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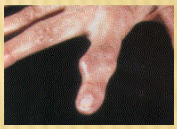
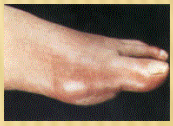
GOUT (ARTHRITIS URICA)

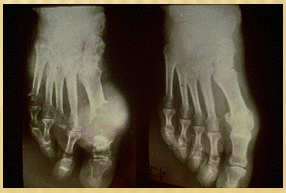
- cause - ???
  - congenital - ↑ production of uric acid - enzyme defects
  - ↓ excretion of uric acid - defect of renal transporters
  - acquired - ↑ production of uric acid - obesity, alcohol high intake of food containing purins, leukaemia, haemolysis, cytostatic drugs, Gierke's disease
  - ↓ excretion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





Clinical symptoms

- hyperuricemia
- arthritis - acute arthritis
  - chronic arthritis - tophi
- chronic uric acid intestitial nephropathy
- uric acid nephrolithiasis (kidney stones



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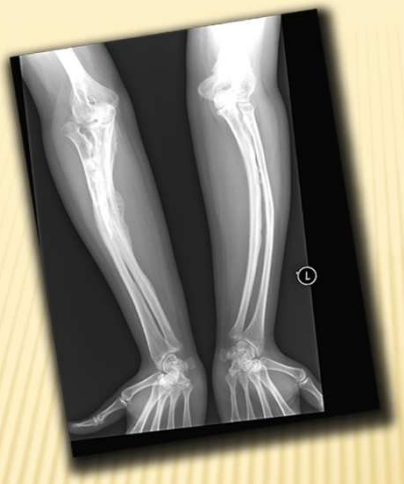

RARE SKELETAL DISEASES

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ACHONDROPLASIA

Disease with impaired bone growth, manifested by disproportionate short stature with short limbs. The most con form of dwarfism.

Cause

- AD inherited mutation of the FGFR3 gene (fibroblast growth factor receptor 3)
- Endochondrial ossification disorder of bones
- More than 80% - neomutation

Clinical signs

- Disproportionately low stature, short limbs, normal torso, large head
- Reduced range of joint movement, deformation - legs to O
- Scoliosis, lordosis - ventilation disorders
- Brachydactylia, the position of the fingers in the shape of a trident
- Macrocephaly, prominent forehead - neurological symptoms
- Intelligence normal

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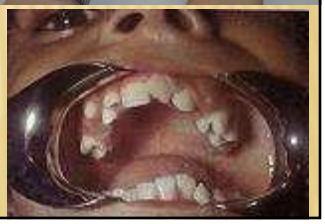
OSTEOPETROSIS

- Osteosclerosis , stone bones, Marble bone disease
- Rare hereditary disorder
- Osteoclast activity disorder – bone resorption disorder
- Impaired bone remodeling, defective bone architecture
- 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 –

Clinical signs
- Fragility and bone deformities
- Insufficient growth
- Defects of teeth
- Deformations of the spine - scoliosis
- Disorder of hematopoiesis (the medullary cavity of the bone is filled with bone tissue) - anemia
- Blindness
- Deafness
- Hepatosplenomegaly



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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

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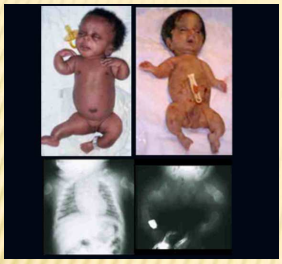
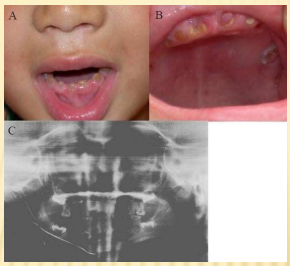
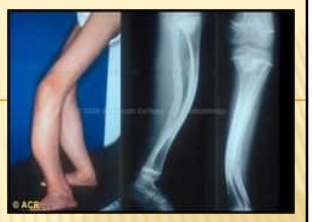
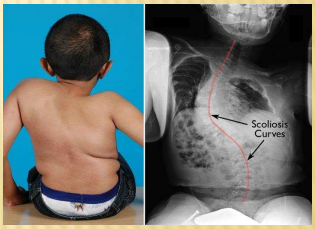
OSTEOGENESIS IMPERFECTA

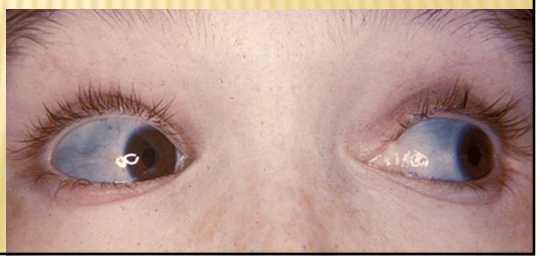








Atticus Shaffer



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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, PLOD1…

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

Garry Turner

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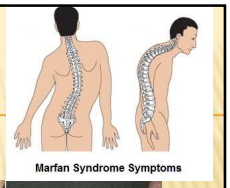
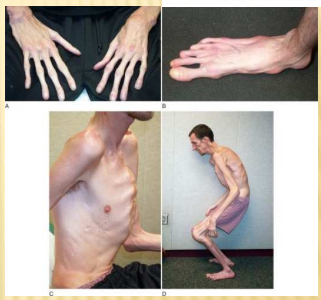
MARFAN SYNDROME


Marfan Syndrome Symptoms

- 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.

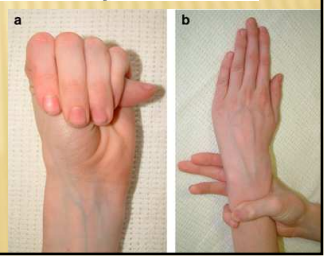


Clinical signs

- 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, Michael Phelps



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THANK YOU FOR YOUR ATTENTION

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