DISEASES WITH ABNORMAL MATRIX

MSK-1 FOR 2ND YEAR MEDICAL STUDENTS

Dr. Nisreen Abu Shahin

CONGENITAL DISEASES WITH ABNORMAL MATRIX

OSTEOGENESIS IMPERFECTA (OI):

- **also known as "*brittle bone disease*"**
- **a group of genetic disorders caused by defective synthesis of type I collagen.**

- **also numerous extraskeletal manifestations**

(affecting skin, joints, teeth, and eyes, etc).

- **Mutations: the coding sequences for α_1 or α_2 chains of type I collagen ➔ most defects manifest as autosomal dominant disorders.**
- **a broad spectrum of severity**

- ***The fundamental abnormality in all forms of OI is too little bone,* resulting in extreme skeletal fragility**.

- Four major subtypes are recognized:
- **Type** II : uniformly fatal in utero or immediately postpartum as a consequence of multiple fractures that occur before birth.
- **Type** I :

- have a normal lifespan
- increased tendency for fractures during childhood (decreasing in frequency after puberty)
- ***blue sclerae*** (due to decreased scleral collagen content) → relative transparency that allows the underlying choroid to be seen.
- ***Hearing loss*** **(due to** conduction defects in the middle and inner ear bones)
- ***small misshapen teeth*** → dentin deficiency (also composed of collagen type I)

ACHONDROPLASIA

- *is the most common form of dwarfism.*
- *Have a normal lifespan.*
- caused by **activating** point mutations in FGFR3.
- **FGFR3➔** *inhibits* the proliferation and function of growth plate chondrocytes (result= the growth of normal epiphyseal plates is suppressed, and the length of long bones is severely stunted).
- Can be inherited as AD, but many cases → new spontaneous mutations.
- Affects all bones that develop by endochondral ossification.
- **Clinical picture**: short stature, disproportionate shortening of the proximal extremities, bowing of legs, and frontal bossing with midface hypoplasia.
- **Microscopically**: the cartilage of the growth plates is disorganized and hypoplastic

THANATOPHORIC DWARFISM

- *Thanatophoric* = "death-loving".
- is a lethal variant of dwarfism, affecting 1 in every 20,000 live births
- Also caused by missense or point mutations most commonly located in the extracellular domains of **FGFR3**. ((also results in FGFR3 activation)).

- Clinical features: extreme shortening of limbs, frontal bossing of skull, and small thorax (the cause of **fatal respiratory failure** in the **perinatal** period)

OSTEOPETROSIS

- *Osteopetrosis* (literally= "bone-that-is-like-stone disorder")
- *is a group of rare genetic disorders characterized by* ***defective osteoclast-mediated bone resorption****.*
- the bones are dense, solid, and stone-like. Paradoxically, because turnover is decreased, the persisting bone tissue becomes weak over time and predisposed to fractures like a piece of chalk.
- Several variants are known, the two most common being:

1- an autosomal dominant adult form: mild

2- autosomal recessive (infantile) form: severe/lethal

- The defects that cause osteopetrosis are categorized into:

- defects that disturb osteoclast function (the ability of osteoclasts to resorb bone). some of the identified abnormalities include:

1- carbonic anhydrase II deficiency

2- proton pump deficiency

3- chloride channel defect

- defects that interfere with osteoclast formation and differentiation.

- **Complications**:
- fractures
- cranial nerve palsies (due to compression of nerves within shrunken cranial foramina)
- recurrent infections (reduced bone marrow size and activity)
- Hepato-splenomegaly (caused by extramedullary hematopoiesis due to reduced marrow space).

- **Morphology:**

  the primary spongiosa persists, filling the medullary cavity, and bone is deposited in increased amounts woven in architecture.
- **Treatment= hematopoietic stem cell transplantation**

- **osteoclasts** are derived from B.M. monocyte precursors
- many of the skeletal abnormalities may be reversible

ACQUIRED DISEASES WITH ABNORMAL MATRIX

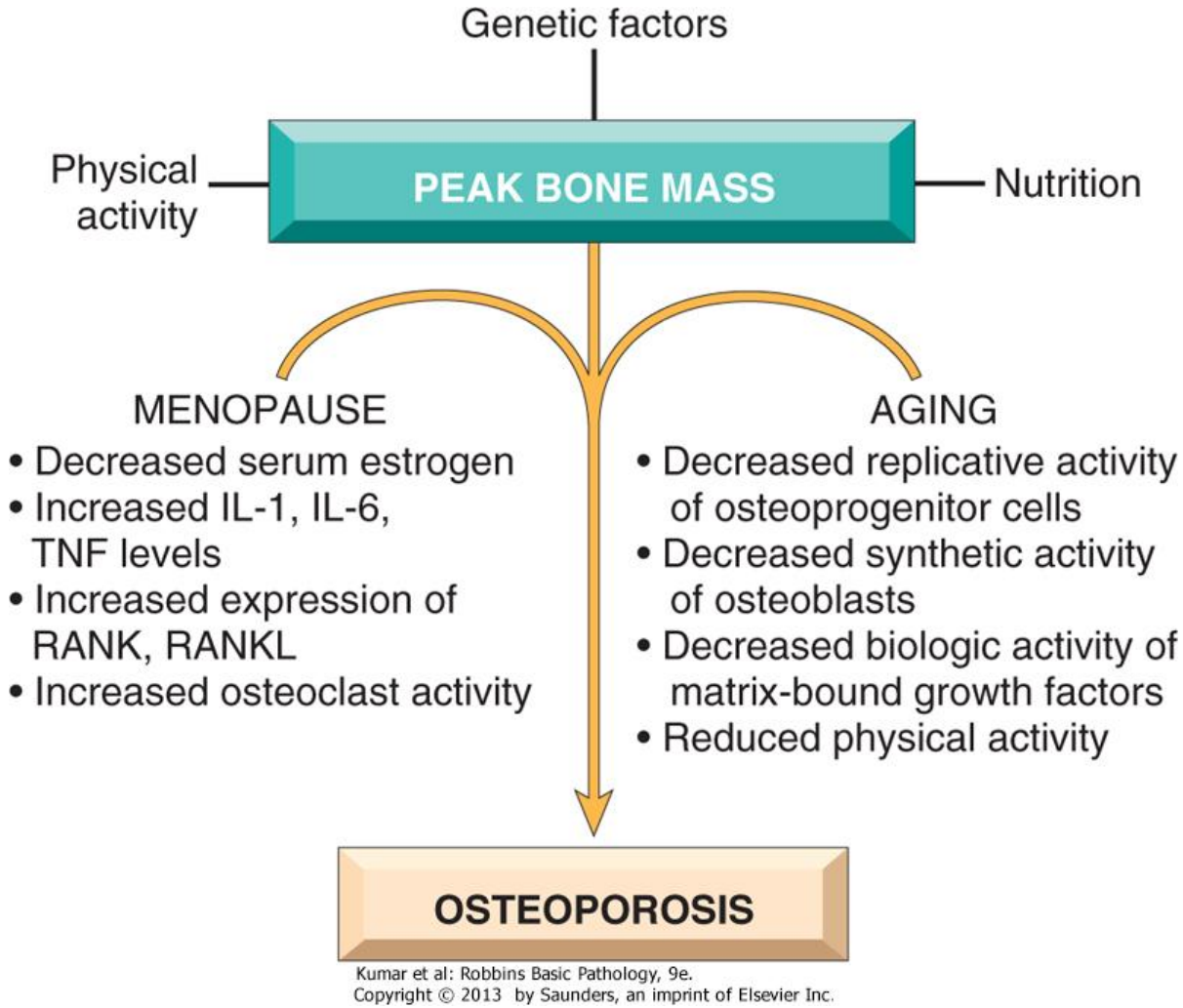
OSTEOPOROSIS

- *increased porosity of the skeleton resulting from reduced bone mass.*
- It is associated with an increase in bone fragility and susceptibility to fractures.
- Causes of osteoporosis:

1- Primary : (most common)

- Postmenopausal
- Senile

PATHOPHYSIOLOGY OF POSTMENOPAUSAL AND SENILE OSTEOPOROSIS



Kumar et al: Robbins Basic Pathology, 9e.

CAUSES OF SECONDARY OSTEOPOROSIS

2- Secondary

1-ENDOCRINE DISORDERS

- **Hyperparathyroidism**
- **Hypo or hyperthyroidism**
- **Hypogonadism**
- **Pituitary tumors**
- **Diabetes, type 1**
- **Addison disease**
- **Multiple myeloma**
- **Carcinomatosis**

2-GASTROINTESTINAL DISORDERS

- **Malnutrition**
- **Malabsorption**
- **Hepatic insufficiency**
- **Vitamin C, D deficiencies**
- **Idiopathic**

3-DRUGS

Anticoagulants
Chemotherapy
Corticosteroids
Anticonvulsants
Alcohol

4-MISCELLANEOUS

- **Osteogenesis imperfecta**
- **Immobilization**
- **Pulmonary disease**
- **Homocystinuria**
- **Anemia**

Morphology

- The cortices are thinned, with dilated haversian canals
- The trabeculae are reduced in thickness and lose their interconnections.
- Osteoclastic activity is present but is not dramatically increased
- the mineral content of the bone tissue is normal

OSTEOPOROTIC VERTEBRAL BODY (*RIGHT*) SHORTENED BY COMPRESSION FRACTURES, COMPARED WITH A NORMAL VERTEBRAL BODY. THE OSTEOPOROTIC VERTEBRA EXHIBITS A CHARACTERISTIC LOSS OF HORIZONTAL TRABECULAE AND THICKENED VERTICAL TRABECULAE

CLINICAL COURSE

- The patient is asymptomatic until he comes with a fracture
- **The most common= Thoracic and lumbar vertebral fractures**

- produce loss of height
- various deformities, including kyphoscoliosis
- can compromise respiratory function.

Diagnosis :

- The best is bone scan→ very sensitive
- x-rays: cannot be reliably detected until 30%-40% of bone mass has already disappeared.
- serum levels of calcium, phosphorus, and alkaline phosphatase are **not** sensitive.

COMPLICATIONS

- 1-Fractures of the femoral neck, pelvis, or spine.
- 2- bone deformities (kyphoscolyosis)
- 3-Pulmonary embolism
- 4-Pneumonia

- **Osteoporosis prevention and treatment:**
- adequate dietary calcium intake
- vitamin D supplements
- regular exercise
- Calcium and vitamin D supplements later in life can also modestly reduce bone loss.
- Pharmacologic treatments include use of antiresorptive and osteoanabolic agents