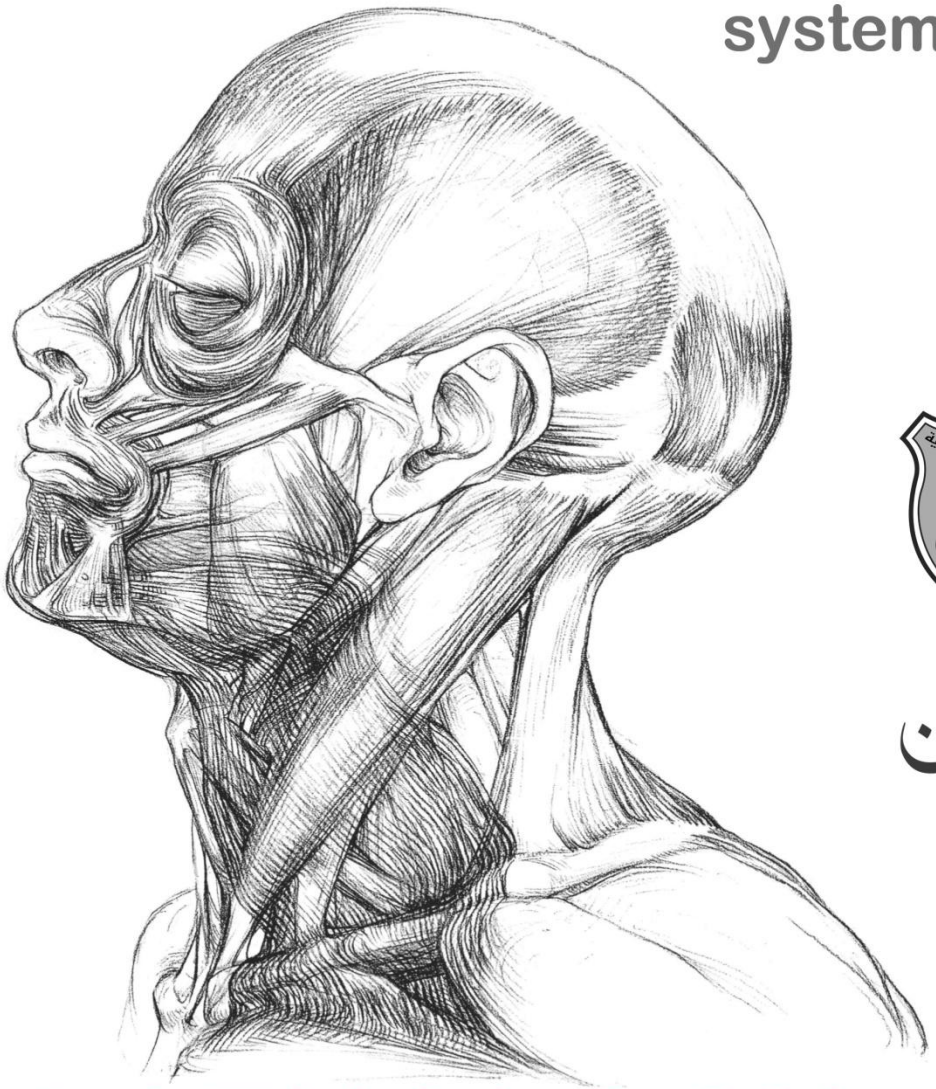
The skin & Musculoskeletal system



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 1

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- **Congenital Bone diseases**

• Range from localized malformations to generalized hereditary disorders

• Can be isolated, or part of a more complex syndrome (with other systems defects)

• are Mostly the result of mutations in the homeobox gene

• Result from abnormal migration and development of mesenchymal cells, or from abnormal bone & cartilage growth and maintenance of normal matrix components
Abnormal migration and development.

Before we start discussing bone malformations, we should be familiar with these words:

- **Dysostosis**: localized abnormal bone formation, commonly occurs in the craniofacial area.
- **Bone aplasia**: (no bone formation). Commonly occurs in long bones and ribs resulting in absence of bone(s) in the digits (fingers) or missing ribs.
  Side note: remember Anatomy, long bone is a bone with proximal end, distal end and a shaft, so digits are long bones!!
- **Supernumerary** (extra bone formation) occurs in the digits or ribs.
- Abnormal bone fusion or **synostosis** (rib fusion or sometimes occurs in the skull which called craniosynostosis), the sutures of the skull are not fused until the skull is fully grown. If they fused earlier the skull won't grow normally (this will result in abnormal skull shape, usually the skull is relatively long).
- **Phocomelia:** (multiple bone deformations in different places) multiple absent or short, fused bones in the limbs. Sometimes there are fingers in unusual places such as the shoulder. The cause might be:
  1) genetic (isolated)
  2)Thalidomide (a drug found to cause phocomelia when given to a pregnant woman.)

Osteogenesis Imperfecta

This means that the formation of the bone isn't typical or perfect (systematic)

• Group of hereditary disorders caused by defective synthesis of **type I collagen**

• Gene mutations in the coding sequences for α1 or α2 chains

• Mutant type 1 collagen is defective and prematurely degraded

• Bone matrix amount is too little, results in bone fragility, deformity.

• Different types of mutations, range in severity

  - **Type 1:** most common, normal life expectancy, higher chance of getting fractures and abnormal skeleton shape sometimes (but does not differ very much from the original shape)
  - **Type 2**: most sever, death early in life (shortly after birth) or in utero (severe fractures, ribs aren't formed well, so the body cannot do respiration normally which results in death)

• Collagen type 1 is present in other tissues, so this disease affects **skin**, **joints**, and the **eyes** (blue sclera, sclera is the white area in the eye, it becomes thinner and appear darker), **hearing loss** (conduction defects in the middle and inner ear bones), and **small misshapen teeth** are a result of this deficiency.

Achondroplasia (problem in the cartilage formation)

· Major cause of dwarfism

• Point mutation in the **fibroblast growth factor receptor 3 (FGFR3)** that results in **permanent activation**

• Activated FGFR3 inhibits chondrocyte proliferation (inhibits cartilage formation); as a result, the normal epiphyseal growth plate of the long bones is suppressed.

• Patients have **normal head and trunk** (because they don't depend on the same type of growth that long bones use), but **short limbs** (upper and lower limbs)

• mode of inheriting: **Autosomal-Dominant**, transmission, most cases represent **new acquired mutation.**

• The affected individuals are typically heterozygotes, since homozygosity leads to abnormalities in chest development and death from respiratory failure soon after birth

Osteopetrosis

(the bone is thicker than normal and looks like a stone)

· Rare genetic disorders characterized by **reduced activity of osteoclast mediated bone resorption** and therefore defective bone remodelling **bone forms faster than the resorption**.

*It is **not** transferred vertically (from parents to children)

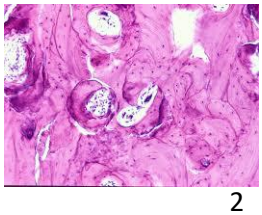
• Normally, bone matrix degradation requires first **acidification** of contact site

• Multiple mechanisms, one is known as; deficiency in enzyme **Carbonic Anhydrase II**, which is required for the osteoclast **hydrogen ion excretion** that is important for acidification, when this enzyme is defected it cannot perform its function -> the bone is not acidified -> cannot be degraded easily.

• The affected bone is grossly dense and stone-like. Paradoxically, the architecture is not normal and fractures are common (thickening decrease the flexibility of bones so they can be fractured easier.

The **systematic complications** of the disease are:

- Cranial nerves compressions because of the thickened bone around them, resulting in deafness in some cases.
- Decreased hematopoiesis due to the compression of the bone marrow by the thickened bone resulting in anemia (no enough RBCs), infections (no enough WBCs) and bleeding (no enough platelets).
- *the body can compensate this loss by producing blood outside the bone marrow (extramedullary haematopoiesis), where the body can produce blood from the liver and spleen as in embryonic life.
- Hepatosplenomegaly (extramedullary hematopoiesis)



• Treatment: bone marrow transplant

• Osteopetrosis: markedly thickened bone trabeculae, marrow spaces are minimal

- **Acquired (metabolic) diseases of bone development**

• Osteoporosis

• Paget disease

• Vitamin D deficiency

• Hyperparathyroidism

None of these diseases is inherited

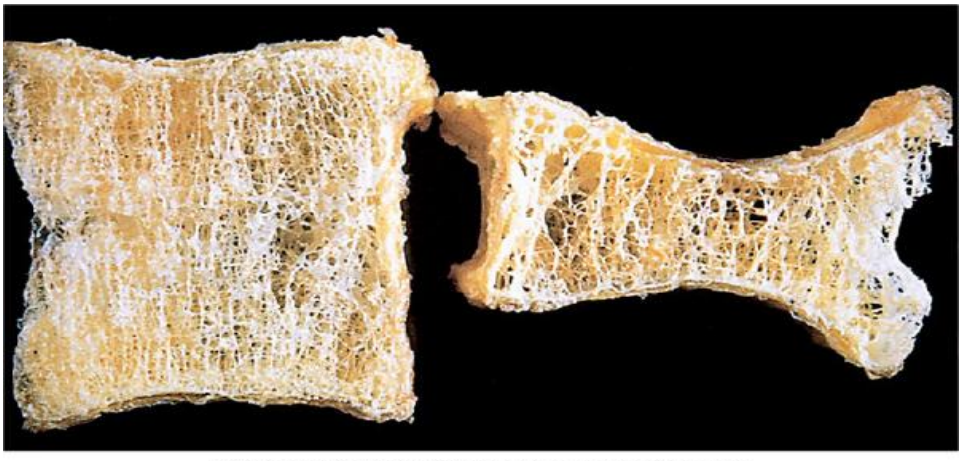
Osteoporosis

"porous": means having big holes; osteoporosis: bone becomes thin and has big holes.

- the most common acquired disease
- Decreased bone mass, prone to fracture:

  Both parts of the bone mass (osteoid and cellular part (osteoclast, osteoblast, stroma)) decrease and change the bone to become thin thus making it easily fractured.

- Grossly: bone appears porous and spongy.
- occurs localized or generalized:
  - Localized: common in disused limbs (fractures, paralysis)
  - Generalized: more common than localized; in the entire skeleton, its either
    - primary: most common, problem begins with the bone itself with no previous problems with the patient
    - secondary: there's a disease that causes osteoporosis



Osteoporotic vertebral body (right) shortened by compression fractures (it is compressed because it is weak) and has bigger holes, compared with a normal vertebral body. Note that the osteoporotic vertebra has a characteristic loss of horizontal trabeculae and thickened vertical trabeculae (we see only vertical osteoid, compared to normal where there is osteoid in all directions)

- how to diagnose osteoporosis? how to see these changes? by **radiology**.

- Primary Osteoporosis:
  - The most common and most important form of osteoporosis
  - has two conditions:
    - senile: means old age, affects both genders (males and females) when they become very old (after the age of 70).
    - postmenopausal: in women only, appears earlier (at the age of 50) and it follows the time of menopause.
  - Peak bone mass is achieved during young adulthood, then in the third or fourth decade in both sexes, bone resorption begins to outpace bone deposition:

    both of them (senile and postmenopausal) are almost a normal physiological process, but why some people develop osteoporosis while others don't depends on the bone development earlier in life.

    the maximal bone density mass (the maximum amount of bone that you get in your life) that any person has forms at the 20s of age, after that there's no bone synthesis. So, if a person developed a good amount of bone, he won't develop osteoporosis and vice versa.

    this depends on many nutritional or environmental factors (sun exposure, exercise which is very important, and smoking which inhibits bone synthesis).
  - Such losses generally occur in areas containing abundant cancellous(trabecular) bone and are therefore more pronounced in the spine and femoral neck
  - The rate of loss can be accelerated by the postmenopausal state.
  - Osteoporosis-related fractures cause significant morbidity and mortality.

    osteoporosis generally causes significant morbidity NOT mortality (it doesn't kill). It could cause mortality indirectly through following conditions like fractures that can cause heart clots and problems.

    Osteoporosis is a very "expensive" disease because it needs continuous care as fractures in elderly are very bad condition.

✓ **Pathogenesis:**

- there are molecules that increase and others that decrease:
  1. Receptor Activator for Nuclear factor κB(RANK)- ligand
  2. Macrophage colony-stimulating factor (M-CSF)

  } increase

  3. Osteoprotegerin(OPG) → decrease
- Together, RANK ligand and M-CSF activate the formation of osteoclast:

  first, they come from the osteoblast and stromal cells (fibroblast and endothelial cells that exist in any tissue in the body) and they transform **<u>monocytes</u>** into osteoclast. So, more RANK-ligand and M-CSF…. more Osteoclast which dissolves the bone.
- OPG blocks RANK-ligand

functions as the opposite of the above factors, ending up with a higher number of Osteoblasts that resolves the bone morrow.

Paracrine mechanisms regulate osteoclast formation and function.

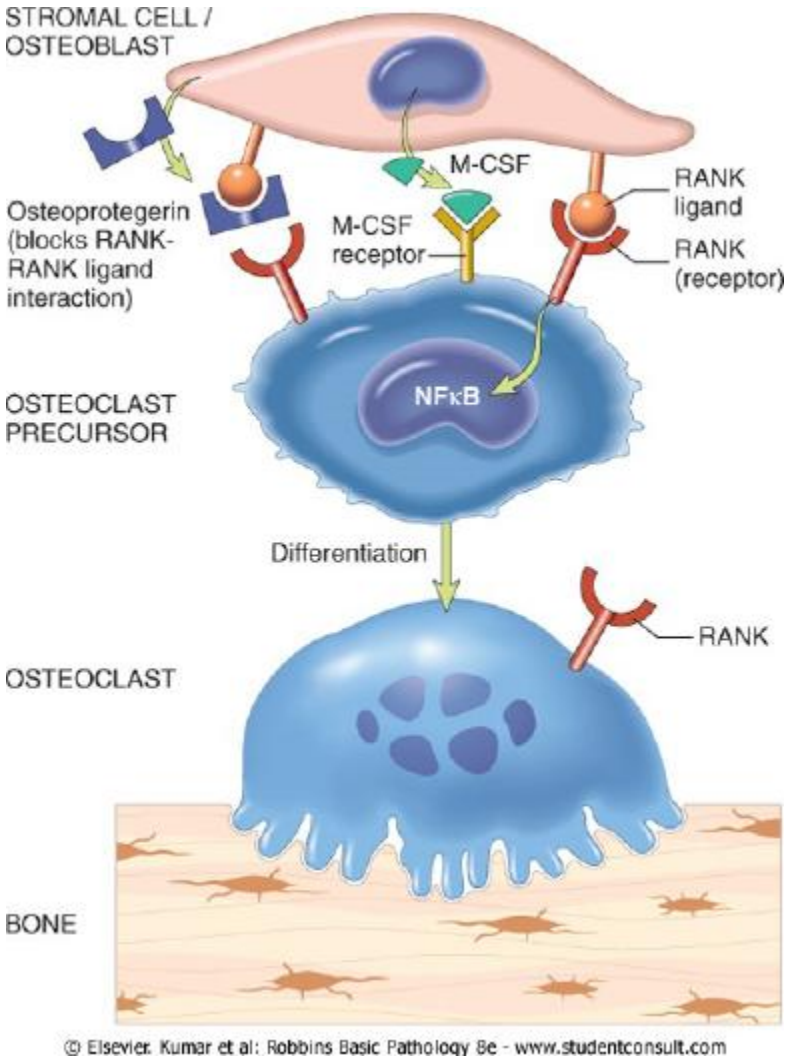
Osteoclasts are derived from the same stem cells that produce macrophages.

RANK (receptor activator for nuclear factor-κB) receptors on osteoclast precursors bind RANK ligand (RANKL) expressed by osteoblasts and marrow stromal cells.

Along with macrophage colony-stimulating factor (M-CSF), the RANK-RANKL interaction drives the differentiation of functional osteoclasts.

Stromal cells also secrete osteoprotegerin (OPG) that acts as a decoy receptor for RANKL, preventing it from binding the RANK receptor on osteoclast precursors. Consequently, OPG prevents bone resorption by inhibiting osteoclast differentiation.

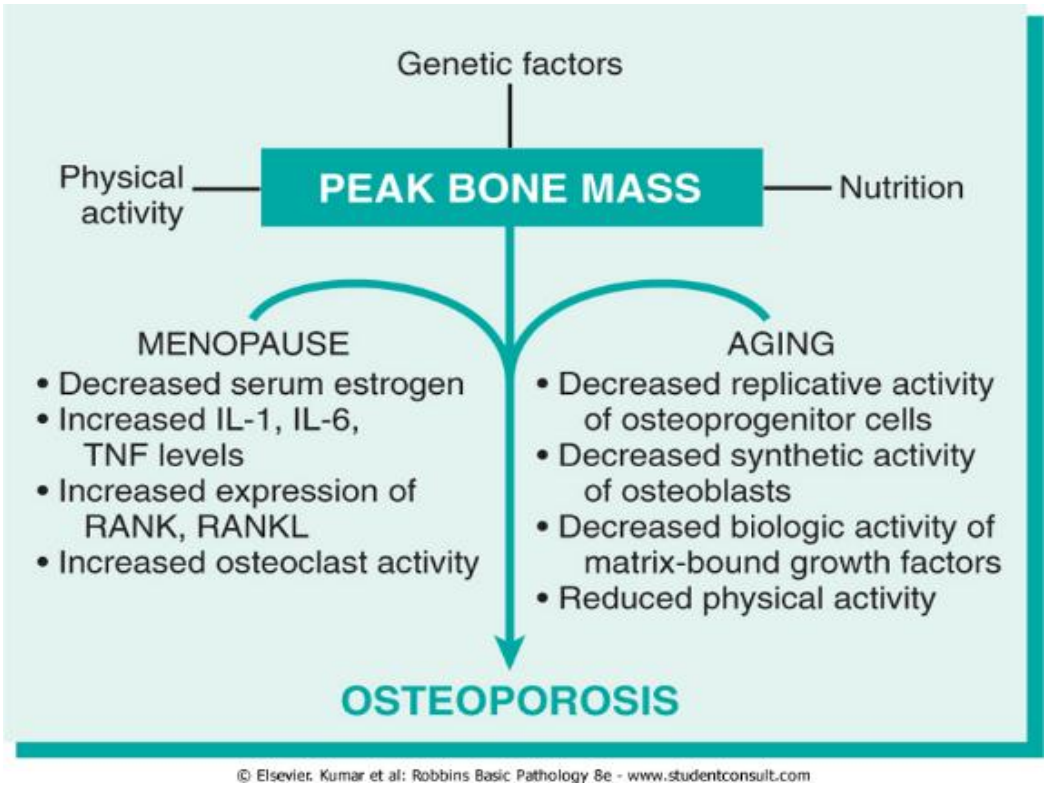
most affected bones are: spine and femur



- Dysregulation of these interactions occur with aging**(senile):** here changes are not obvious mostly dependent on the decreased function of osteoblast activity with time, and decreased estrogen: (in case of **postmenopausal**) resulting in increased amount of cytokines (IL-1, IL6, TNF), resulting in relative increased osteoclast activity compared to osteoblast function.

- secondary osteoporosis: they are a few diseases, mostly endocrine ones: (high cortisol level, hyperthyroidism, hyperparathyroidism, drugs)

Study the following comparison carefully, the doctor mentioned it!!



Paget disease

• Repetitive episodes **of severe, regional osteoclastic activity and rapid bone resorption** (osteolytic stage), **followed by exuberant bone formation** (mixed osteoclastic-osteoblastic stage), and finally by an **apparent exhaustion of cellular activity** (osteosclerotic stage) – starts as osteoporosis, but ends up as a thicker bone.

* **Osteosclerosis** is a type of osteopetrosis that involves abnormal hardening of bone and an elevation in bone density.

• The net effect of this process is gain in the bone mass; however, the newly formed bone is **disordered and lacks strength**

• Does not occur until mid-adulthood (does not occur in children) but becomes progressively more common thereafter

• White population, common in Europe.

✓ **Pathogenesis:**

• Original name (osteitisdeformans)

•In some cases – not in all cases- paramyxo virus antigens (not the true virus) can be demonstrated in osteoclasts (but the virus is not isolated from tissue) activating osteoclasts

• IL-1 and M-CSF are secreted in large amounts from infected cells, activating other osteoclasts

•In the other cases – rather than paramyxo virus antigens- the responsible factor is Genetic background: osteoclasts in Paget disease appear to be intrinsically **hyper-responsive to activating agents such as vitamin D and RANK ligand**

- ✓ **Morphology:**

• Paget disease can be monostotic or polyostotic (more common)

- if it affects one bone -> monostotic

-affects more than one bone -> polyostotic

• Axial bones and proximal femur most commonly affected (like osteoporosis)

Morphology

• In the **initial lytic phase**, osteoclasts (and their associated Howship lacunae which are prominent and empty) are numerous and abnormally large, osteoclasts are lying on the **peripheral edges** of the osteoid.

• **Mixed phase**: persistent osteoclasts, but the bone surfaces become lined by prominent osteoblasts. The marrow is replaced by loose connective tissue containing osteoprogenitor cells, as well as numerous blood vessels needed to meet the increased metabolic demands of the tissue. The newly formed bone may be woven or lamellar. The final product is a thick osteoid.

• The pathognomonic histologic feature is a mosaic pattern of lamellar bone (appears like a jigsaw puzzle), this feature is used to differentiate between this disease and osteopetrosis.

• As the osteoblastic activity burns out, the resulting cortex is softened and prone to deformation and fracture under stress.

• Sarcoma may complicate the disease in 1% of patients (like in any chronic disease)- the cancer of the bone tissue is called osteosarcoma-.

• Mosaic pattern of lamellar bone pathognomonic of Paget disease: