MSS

pathology

LEC no.2

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MUSCULOSKELETAL PATHOLOGY-2 METABOLIC DISEASES

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In this lecture, we moved to metabolic diseases which are more common in clinical practice and more important, so yalla!

هشاشة العظام

OSTEOPENIA AND OSTEOPOROSIS

- Osteopenia: decreased bone mass
- Osteoporosis (OP): severe osteopenia that predisposes to fracture

The radiologist measures the bone mass by an instrument, and the s.d we got will give a result if the patient had already the disease or not

This is very common
If patient had osteopenia , then it might be developed to osteoporosis. (Osteoporosis is an advanced stage of osteopenia)

Radiologically:

- Osteopenia: bone mass is 1-2.5 standard deviation below mean normal
- Osteoporosis: <2.5 SD of normal bone mass
- Normally, maximum bone density is reached in second decade of life, then an annual loss of 0.7% of mass takes place

العشرينات

- Maximum mass depends on genetic factors, diet and exercise

We can increase our maximum body mass, but couldn't decrease the annual loss (0.7%)

CLINICAL TYPES OF OSTEOPOROSIS

- Might be localized to certain bones (disuse of limbs)

Like in fractured bones or paralyzed ones.(now we are not intrested in this point, the following ones are much important)

- Generalized OP is mostly primary, seen is two settings:
- Senile
- B) Post-menopausal

Means old aging , mainly after 70s, and this for both genders.
But this Only for women, means in 50th بعد انقطاع الطمث

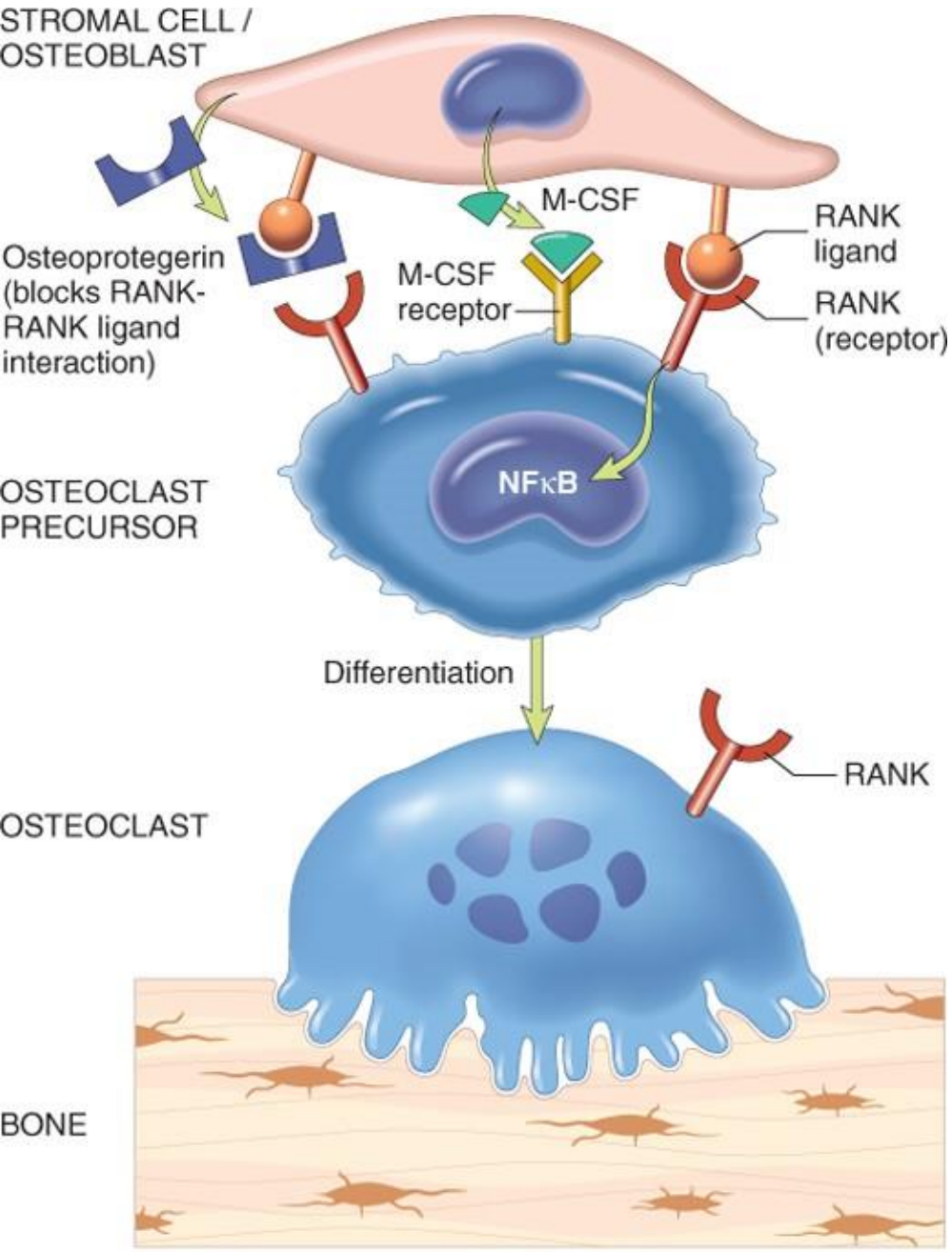
Generalized means in all body bones, and primary means the problem (OP) started in the bone itself, not as a complication for other diseases.

- Secondary OP is rare, associated with:

A) Endocrine diseases (hyperthyroidism)
B) Gastrointestinal diseases (malnutrition)
C) Exposure to drugs (corticosteroid, heparin)

Secondary means other problem in the body leads to OP

A) The most common
B) while the patient can't absorb calcium and vitamins, so he will have weak bones as well
C) Cortisone and heparin lead to bone resorption, thus weaker bones



- Paracrine mechanisms regulating 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

Let me tell you the story simply,
Osteoclasts are cells responsible for bone resorption, its precursor is macrophage and the precursor of macrophages are stem cells.
Stem cells have a protein molecule called RANKL, the receptor of this ligand is found on macrophages or monocytes, when they are bound to each other, they lead the activation of osteoclast's differentiation. This pathway can be blocked by OPG.

SENILE OP

- Occurs due to:

1. Age-related cellular changes (low replication rate of cells, less biosynthesis)
2. Reduced physical activity (resistance training > endurance)
3. Genetic factors: polymorphism in RANK, RANKL, OPG, HLA, estrogen receptors
4. Calcium deficiency in adolescence (especially in girls) and vitamin D deficiency are risk factors for senile OP

- Called: low-turn over OP

Osteoclasts will not function well

Endurance like walking or bicycling.. Doesn't resist OP like resistance training that builds the bones.

بـ معنى أن الرياضات التي يمارسها غالبًا كبار السن مثل المشي مثلًا، ليست من النوع الذي يقوي العظام فـ رح تزيد احتمالية المرض

Polymorphism: refers to the occurrence of multiple forms or variations of a gene (alleles) or a trait within a population.(it's common unlike mutations (rare/acquired))

over means (شغل) ,
so senile OP is low turn overTurn due to less use of bones

هذا فقط مسمّى ثاني للحالة

POST MENOPAUSAL OP

Happens earlier, in women

- Under normal conditions, estrogen:

a) Inhibits apoptosis of osteoblasts

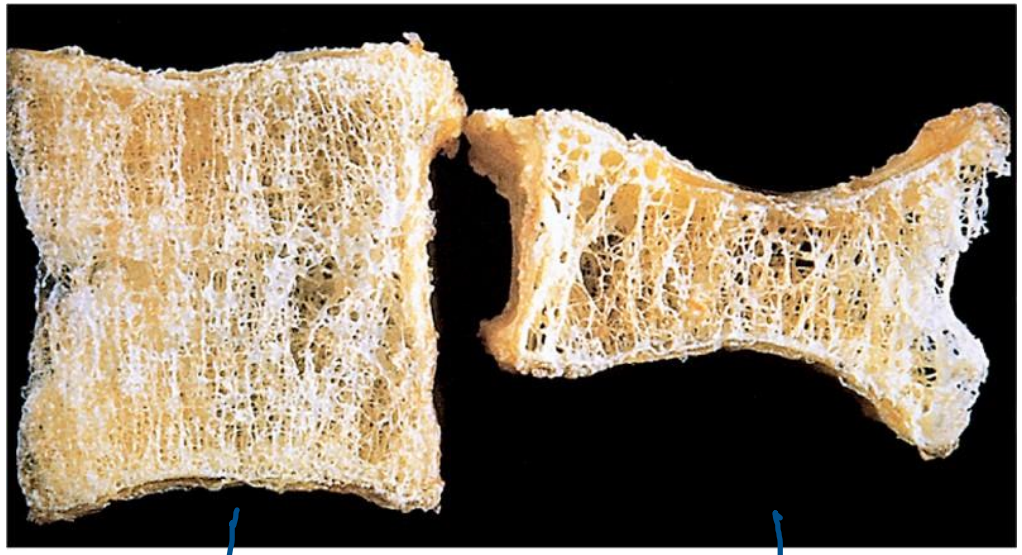
b) Increases apoptosis of osteoclasts

c) Inhibits RANKL (by suppressing cytokines)

- The rate of bone loss in postmenopausal women is 2% every year
- 40% of postmenopausal women suffer from osteoporosis
- For unknown reasons, estrogen deficiency causes increase in serum cytokines (IL-1, IL-6, TNF) **which all activate RANKL**
- Called: high-turn over OP

Because it's accelerating

MORPHOLOGY: GROSS

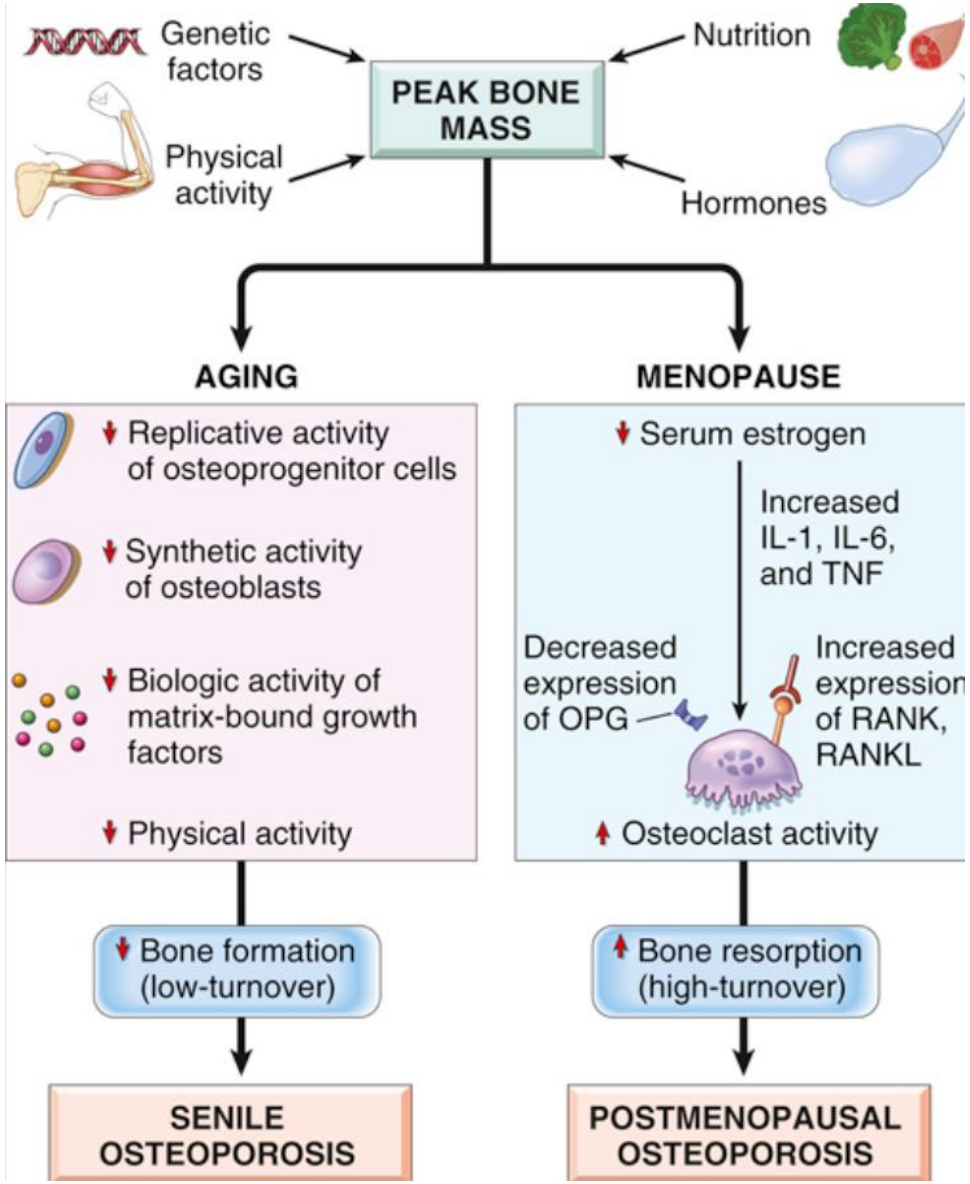


- Grossly: decreased interconnections, more porous
- Most prominent regions: cancellous bones of vertebrae, femur neck

Because they carry the weight of the body

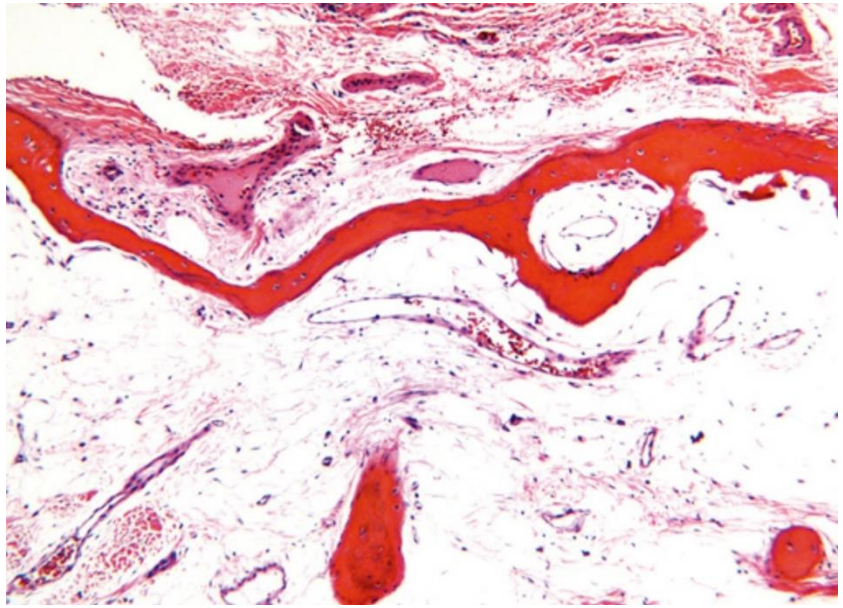
Normal vertebrae
Dense, bone trabeculae in all directions

OP
Thinner, less amount of bone trabeculae so the bone is porous



- IL, Interleukin;
- OPG, osteoprotegerin;
- RANK, receptor activator of nuclear factor kappa-B;
- RANKL, receptor activator of nuclear factor kappa-B ligand;
- TNF, tumor necrosis factor

MORPHOLOGY: MICROSCOPIC



- Normal morphology, but less tissue
- Bone trabeculae becomes thin ⇒

The only thing which can be distinguished by morphology

CLINICAL COMPLICATIONS

- Fracture is painful, causes significant morbidity

Needs more recovery time, significant morbidity means not fetal but make it hard to deal with

- Fracture of spine causes deformity, lordosis, kyphoscoliosis

Lordosis= Lateral movement (left or right). While kypehoscoliosis means تحدب

- Fracture of femur neck or pelvis may cause fat embolism, pneumonia

Fat embolism could be fatal, which is the flow of fat out of the bone marrow.

- A few patients are asymptomatic

RICKETS AND OSTEOMALACIA

- Bone disease secondary to vitamin D deficiency or its abnormal metabolism
- Rickets: occurs in children, abnormal deposition of bone in the growth plates

Because they're still growing, so their skeletal is affected with vit D deficiency

- Osteomalacia: occurs in adults, bone has less minerals, prone to fractures

Unlike adults who stopped growing, only they are exposed more to fractures

- Vitamin D deficiency is caused by limited sun exposure, inadequate dietary vitamin D, malabsorption disease, renal disease (no conversion to the active form: 1,25-dihydroxyvitamin D)

90% of vit D from sun exposure, 10% from diet (fish+milk)

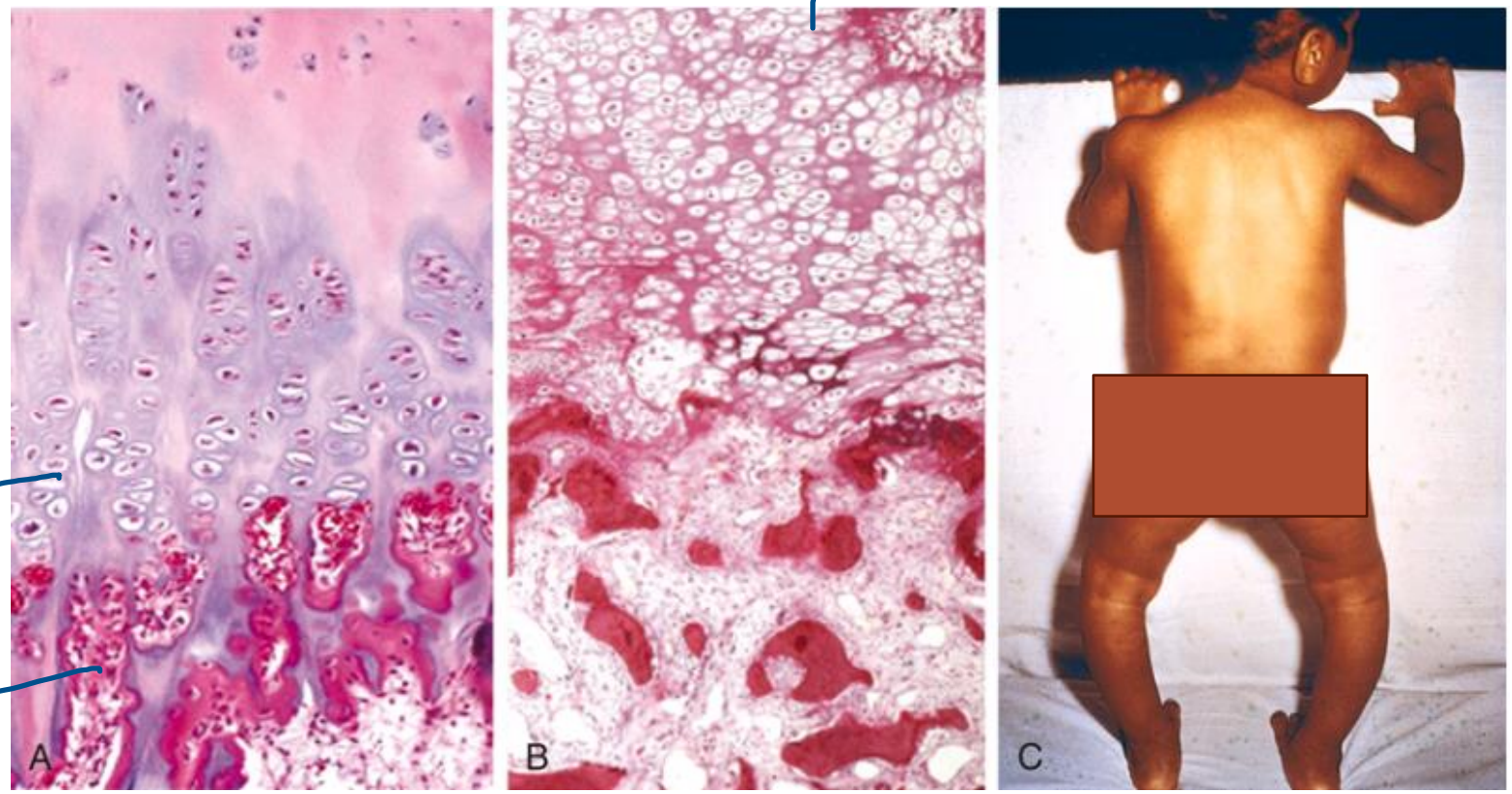
- Vitamin D deficiency results in hypocalcemia, which activates secretion of parathyroid hormone, aggravating bone resorption

Parathyroid hormone activates osteoclasts which causes bone resorption

RICKETS

- Growth of long tubular bones occur through endochondral ossification
- The cartilage of epiphysial plate is provisionally mineralized, then reabsorbed and replaced by osteoid matrix, which undergo mineralization to create bone.
- In rickets, epiphyseal cartilage appears large and distorted due to inadequate calcification and failure of maturation, may protrude into bone marrow cavity
- There is deposition of osteoid matrix on this cartilage, but the replacement is disordered, and show lateral expansion of the osteochondral junction

Briefly, the cartilage cannot be replaced by a bone , so we have large amounts of cartilage .. which leads to weaker bones and disorderd ones



- Rickets. (A) Normal costochondral junction of a young child. Note cartilage palisade formation and orderly transition from cartilage to new bone. (B) Rachitic costochondral junction in which the palisade of cartilage is absent. Darker trabeculae are well-formed bone; paler trabeculae consist of uncalcified osteoid. (C) Note bowing of legs as a consequence of the formation of poorly mineralized bone in a child with rickets.

MORPHOLOGIC CHANGES OF RICKETS

Infants:

- Craniotabes: flattened soft skull bone
- Frontal bossing
- Chest deformity: large costochondral junction appears as nodules. Inward bending of ribs due to pull of respiratory muscles and diaphragm (Harrison groove)

Toddlers

- Deformity of pelvis, spines (lordosis)
- Bowing of lower limbs

MORPHOLOGY OF OSTEOMALACIA

- Grossly, bone has normal contour, but fragile
- Histologically: abundant osteoid matrix deposition, but appears eosinophilic (not mineralized), in contrast to normal basophilic osteoid (well-mineralized)

HYPERPARATHYROIDISM

Parathyroid hormone is essential for homeostasis of calcium.
When this hormone increases, the bone resorption increase.

- PTH causes osteoclast activation, through increased RANKL expression on osteoblasts
- Increased reabsorption of calcium by renal tubules
- Increased urinary excretion of phosphates
- Increased synthesis of active vitamin D
- End result: generalized bone osteopenia, hypercalcemia and hypophosphatemia
- Small bones of phalanges, vertebra and proximal femur show the most prominent changes

ETIOLOGY

- Mostly secondary to parathyroid gland adenoma, called "primary hyperparathyroidism"
- Most cases are sporadic (middle age adults)
- Sometimes syndromic (multiple endocrine neoplasia syndrome), appears early in life
- Secondary hyperparathyroidism: seen patients with renal failure (no active vitamin D → hypocalcemia → increased PTH)

Primary hyperparathyroidism —> the problem is in parathyroid gland

Secondary hyperthyroidism—> there are problem in another organ that affects PTH level

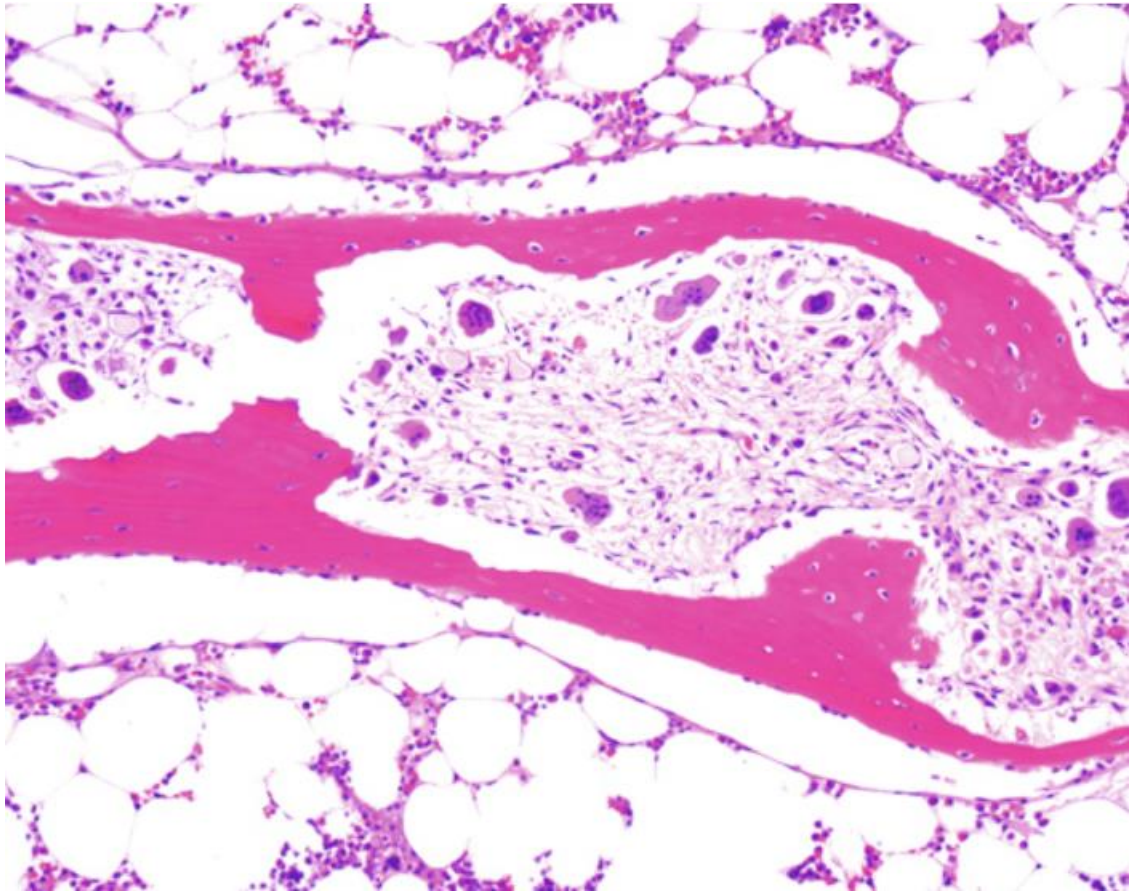
MICROSCOPIC CHANGES

- Thin bone trabeculae (similar to **osteoporosis**)
- **Dissecting osteitis** (railroad appearance of bone trabeculae)

  Dissecting means to separate into pieces

- **Brown tumor**: due to repeated microfractures, the bone marrow is replaced by macrophages, fibroblasts, blood vessels and hemorrhage. Hemosiderin appears brown in color.
- In advanced stage, cysts and cavities develop, a condition called: **osteitis fibrosa cystica**

  Large cavity inside the bone



- Hyperparathyroidism with osteoclasts boring into the center of the trabecula (dissecting osteitis)

PAGET DISEASE

- Also called Osteitis Deformans
- Characterized by increased bone formation, that is disordered and abnormal
- Repetitive episodes of severe, regional osteoclastic activity and bone resorption *(osteolytic stage),* followed by exuberant bone formation *(mixed osteoclastic-osteoblastic stage),* and finally by an apparent exhaustion of cellular activity *(osteosclerotic stage)*
- The net effect of this process is *gain in bone mass;* however, the newly formed bone is disordered and lacks strength
- Does not occur until mid-adulthood but becomes progressively more common thereafter
- White population

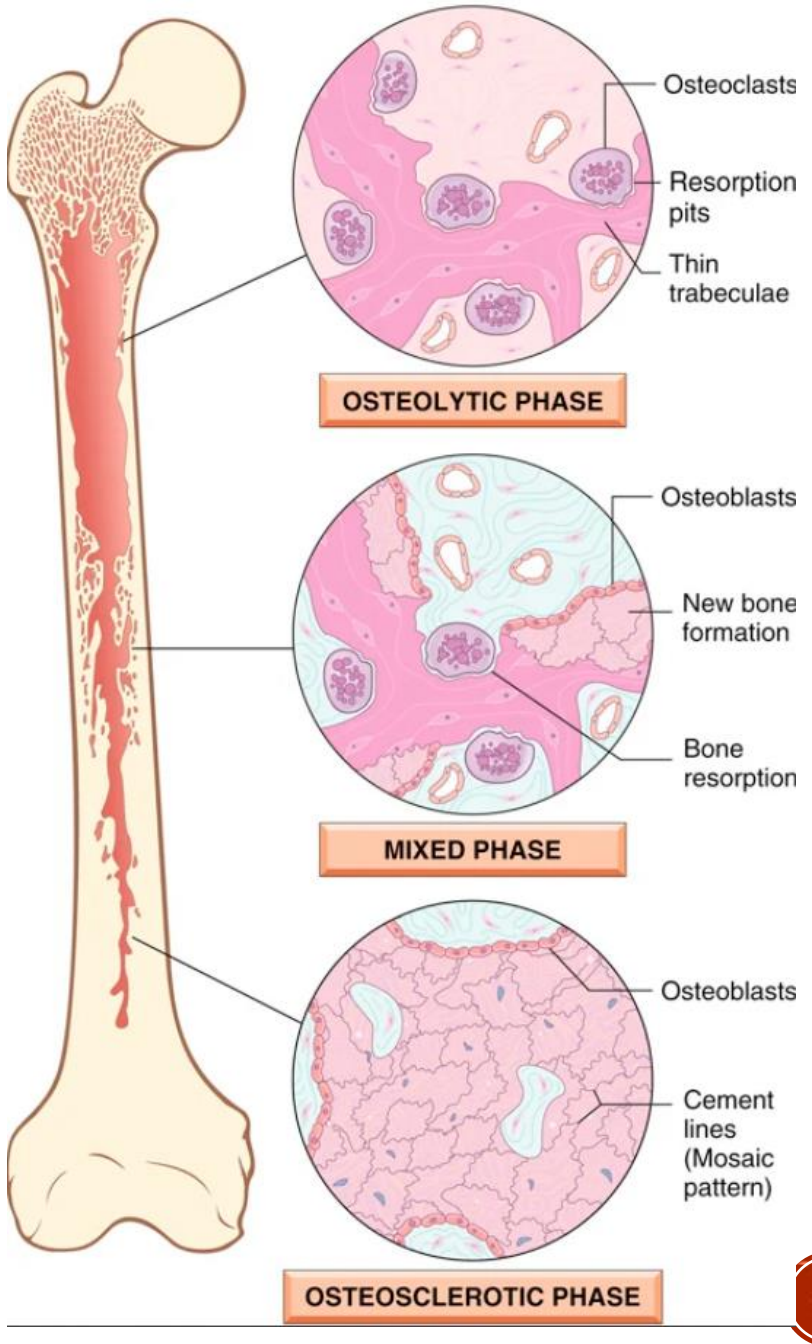
PATHOGENESIS

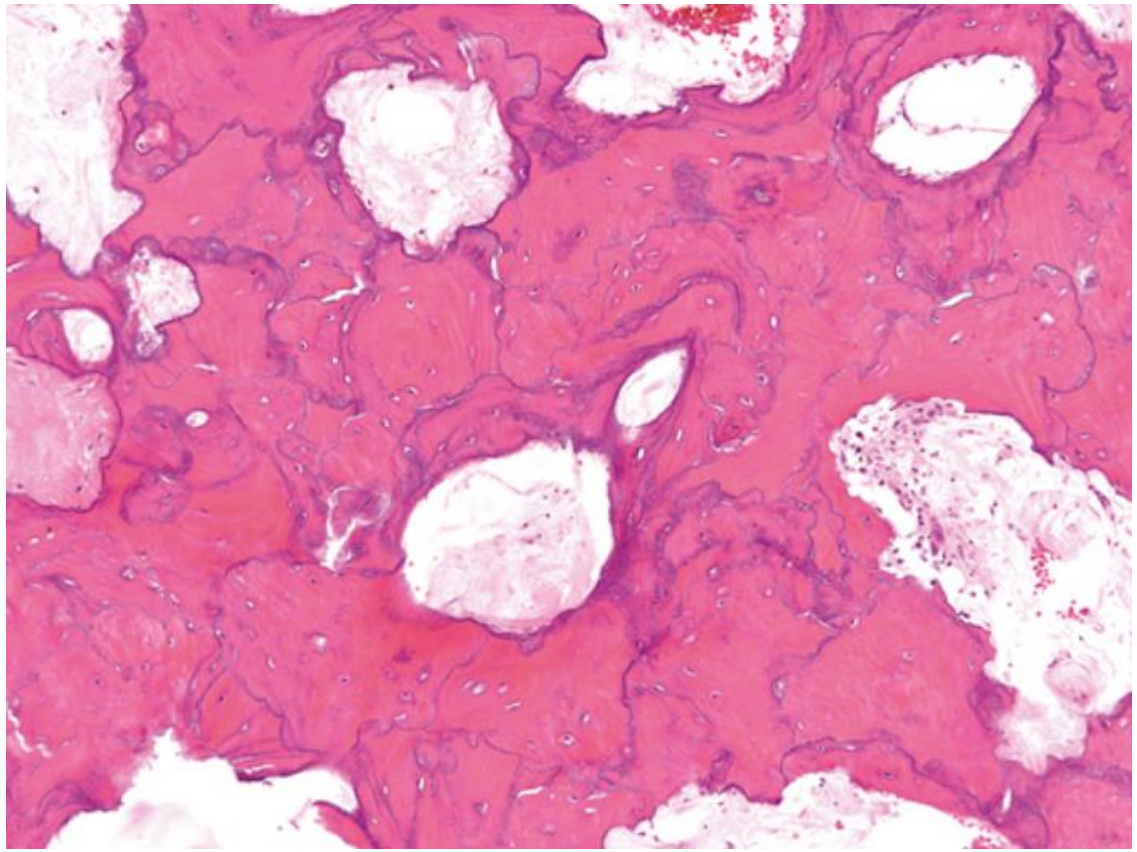
- Familial cases of Paget disease are present
- Sequestosome-1 mutation (SQSTM1) occurs in 50% of familial cases and 10% of sporadic cases **The most important mutation**
- It activates NF-kB, which activates osteoclasts
- Activating mutations in RANK gene and inactivating mutations in OPG result in juvenile-onset Paget disease
- Environmental factors: osteoclasts precursors are infected by measles, paramyxovirus

MICROSCOPIC FINDINGS

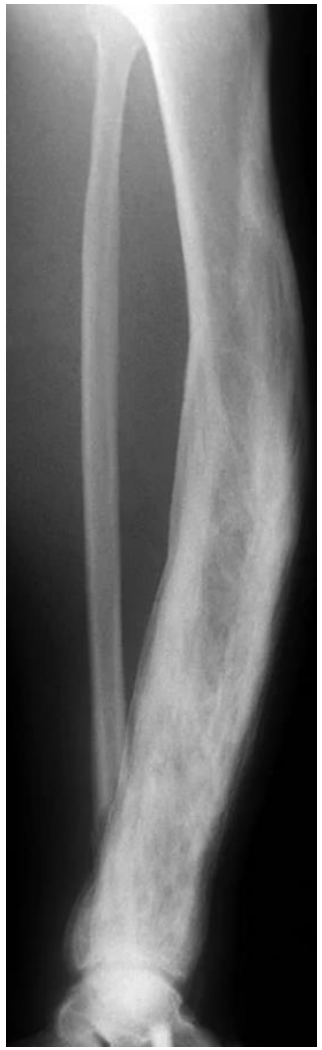
- Initial lytic phase: numerous large osteoclasts, some have >100 nuclei
- Mixed phase: osteoclasts persist, osteoblasts increase in number
- Sclerotic phase: mosaic pattern and jigsaw-puzzle of lamellar bone

In this phase There is large amount of osteoid





- Mosaic pattern of lamellar bone pathognomonic of Paget disease



- Severe Paget disease. The tibia is bowed. The affected portion is enlarged and sclerotic, and it exhibits irregular thickening of both cortical and cancellous bone

CLINICAL FINDINGS

Polyostotic: more than one bone are affected
Monoatomic: one bone are affected

- 85% are polyostotic, 15% monostotic
- Spine and proximal femur are involved in 80% of cases
- Most cases are asymptomatic
- Localized pain is the most common symptom (microfracture, nerve compression)
- Leontiasis ossea (lion face): enlargement of craniofacial bones, heavy skull
- Platybasia: base of skull is flattened and compress against posterior fossa.
- Bowing of femur and tibia, Secondary osteoarthritis
- Kyphosis, spinal cord injury
- Increased vascularity in bone: warm skin, heart failure

Because bone synthesis is a process that needs a lot of blood.

- Secondary osteosarcoma