# MSK block

## BONE DISEASES

## 1- Congenital/Developmental

## 2- Metabolic

Afaf AlSolami

Bone and Soft tissue Pathologist

aalsolami1@ksu.edu.sa

# Objectives

- Be aware of some important congenital and developmental  bone diseases and their principal pathological features
- Be familiar with the terminology used in some important developmental and congenital disorders.
- Understand  the etiology, pathogenesis and clinical features of osteoporosis

CONGENITAL/DEVELOPMENTAL:

Localized or
Involve the entire skeleton

ACQUIRED:

**1- Metabolic**
2- Infections
3- Traumatic
4- Tumors

# 1) Congenital

**Osteogenesis Imperfecta (OI)**

**Achondroplasia**

Thanatophoric dysplasia

Osteopetrosis “Marble bone disease”

# Congenital..

**Dysostosis:**
localized abnormalities in the migration and condensation of mesenchyme
1- Aplasia: complete absence of a bone or a digit
2- Supernumerary digit: extra bones or digits
3- Syndactyly, Craniosynostosis: abnormal fusions of bones.

**Dysplasia (not related to neoplasia):**
global disorganization of bone and/ or cartilage

# Osteogenesis Imperfecta (OI)

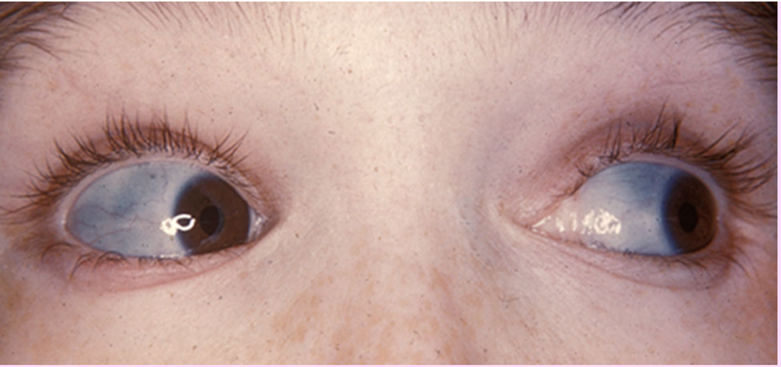
- Most common inherited disorder of connective tissue.
- Brittle bone disease.
- Diverse phenotype.
- Affects the synthesis of type I collagen (autosomal dominant mutation in the genes $\alpha1$ and $\alpha2$ chains of type I collagen).
- Can be AR
- Affect bone and organs rich in type I collagen.

Type I collagen

- Bone → Fragile bone → ? Child abuse
- Eye → Blue sclerae
- Ear → Hearing loss → Affect bones in middle ear
- Teeth → Small, misshapen, blue-yellow teeth → Dentin

# Diverse phenotype…

- E.g. type 2 variant is FATAL in utero or during peri-natal period, while Type 1 have normal life span but with more susceptibility to fractures (especially during childhood).




L
L

# Achondroplasia..

# Achondroplasia..

- The most common skeletal dysplasia and a major cause of dwarfism.
- Autosomal dominant disorder resulting from retarded **cartilage** growth (but 90% arise from New mutation in the Paternal allele).
- Caused by **gain-of-function** mutation of **FGFR3.**
- A receptor with tyrosine kinase activity that transmits intracellular signals. Signals transmitted by FGFR3 *inhibit* the proliferation and function of growth plate chondrocytes; consequently, the growth of normal epiphyseal plates is suppressed.

- It is characterized by failure of cartilage cell proliferation at the epiphysial plates of the long bones, resulting in failure of longitudinal bone growth and subsequent short limbs.

- Membranous ossification is not affected, so that the skull, facial bones, and axial skeleton develop normally.

- Affected individuals have shortened proximal extremities, a trunk of relatively normal length, and an enlarged head with bulging forehead and conspicuous depression of the root of the nose.
- Longevity, intelligence, or reproductive status are <u>not affected</u>, and life expectancy is <u>normal</u>

CONGENITAL/
DEVELOPMENTAL:
Localized or
Involve the entire
skeleton

ACQUIRED:

1. **Metabolic**
2. Infections
3. Traumatic
4. Tumors

# 2) Metabolic bone disease

- Comprises four fairly common conditions in which there is an imbalance between osteoblastic (bone forming) and osteoclastic (bone destroying) activity:

**OSTEOPOROSIS** /Osteopenia
- Decreased bone mass.
- Primary or secondary.
- Senile and postmenopausal.

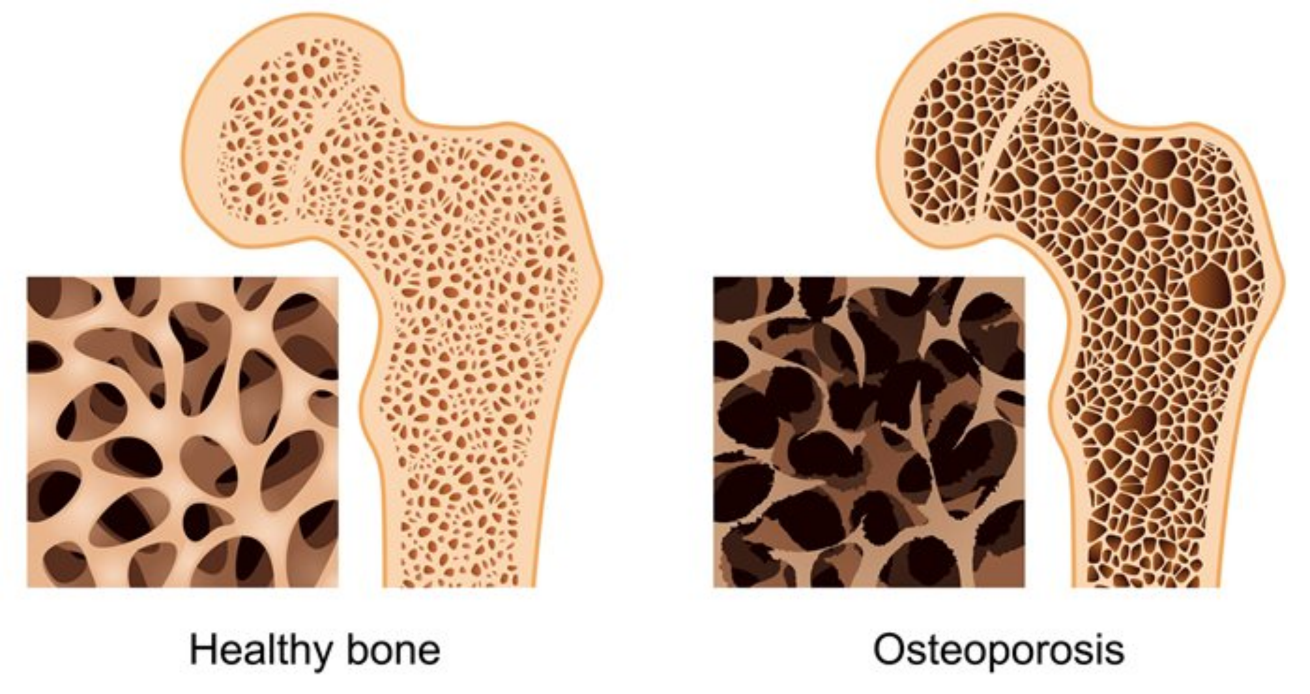
**OSTEOMALACIA** /Rickets
- Impaired mineralization.
- Vitamin D deficiency or abnormal metabolism

PAGET DISEASE **OF BONE**
- 3 phases
- Risk of secondary osteosarcoma

HYPERPARATHYROIDISM
- High PTH.
- Brown tumor of bone and osteitis fibrosa cystica

# OSTEOPOROSIS

- Osteoporosis is an acquired condition characterized by **reduced bone mass**, leading to bone fragility and susceptibility to fractures. Occur when the balance between bone formation and resorption tilts in favor of resorption
- The hallmark of osteoporosis is a loss of bone.
- The cortices are thinned, with dilated haversian canals, and the trabeculae are reduced in thickness and lose their interconnections.
- The mineral content of the bone tissue is normal.
- Once enough bone is lost, susceptibility to fractures increases
- In **postmenopausal** osteoporosis, trabecular bone loss often is severe, resulting in compression fractures and collapse of **vertebral bodies**.
- In **senile** osteoporosis, cortical bone loss is prominent, predisposing to fractures in other weight-bearing bones, such as the **femoral neck**


Healthy bone
Osteoporosis

# OSTEOPOROSIS

- **Involvement**
  - Localized → Disuse of a limb
  - Diffuse → The entire skeleton
- **Cause**
  - Primary (most common)
  - Secondary
    - Endocrine
      - Thyroid
      - Adrenal
      - DM
      - Acromegaly
    - GI
      - Malnutrition
      - Malabsorption
      - Vit. C and D insufficiency
      - Hepatic insufficiency
    - Drugs
      - Steroids
      - Chemotherapy
      - Anticoagulant
      - Anticonvulsant
    - Neoplasia
      - MM
      - Carcinoma
    - Others :
      Smoking, immobilization, anemia, pulmonary diseases

# Primary osteoporosis

- Idiopathic
- Post menopausal probably a consequence of declining levels of estrogen (In the decade after menopause, yearly reductions in bone mass may reach up to 2% of cortical bone and 9% of cancellous bone).
- Women may lose as much as 35% of their cortical bone and 50% of their cancellous bone by 30 to 40 years after menopause).
- Senile (Environmental factors may play a role in osteoporosis in the elderly: decreased physical activity and nutritional deficiency)

# Pathogenesis

Age-related changes
Osteoblasts have reduced proliferative potential and reduced response to growth factor.
Senile osteoporosis ( **low turnover osteoporosis**).

Reduced physical activity
Senile, immobilized or paralyzed.
Weight training more effective than bicycling (resistance)

Genetic factors

Calcium nutritional state
PTH and vitamin D

Hormonal influence
Estrogen
Decreased estrogen levels after menopause increase both bone resorption and formation but the latter does not keep up with the former, leading to ***high-turnover*** **osteoporosis.**

# Estrogen..?

- $\downarrow$ Estrogen $\rightarrow$ $\uparrow$ secretion of inflammatory cytokines by monocytes $\rightarrow$ ++osteoclast recruitment and activity by $\uparrow$ level of RANKL and $\downarrow$ expression of OPG and prevent osteoclast apoptosis.
- IL-1, IL-6, TNF-α

# Estrogen..?

- ↓ Estrogen ⟶ ↑secretion of inflammatory cytokines by monocytes ⟶ ++osteoclast recruitment and activity by ↑ level of RANKL and ↓expression of OPG and prevent osteoclast apoptosis.
- IL-1, IL-6, TNF-α

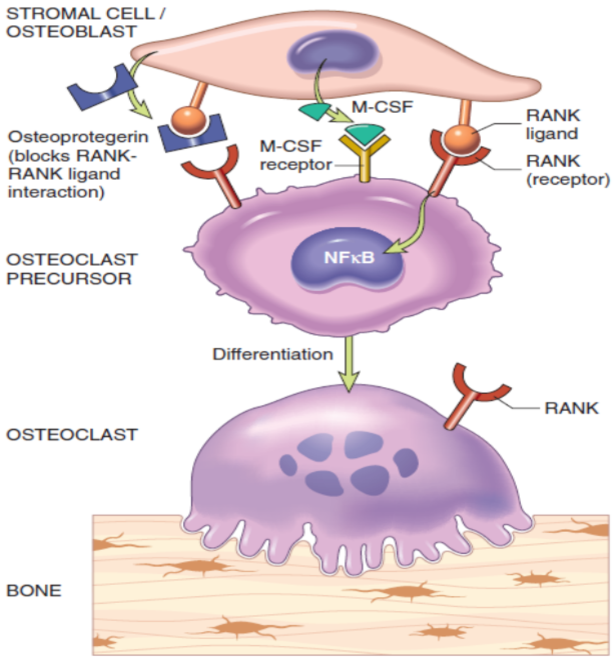
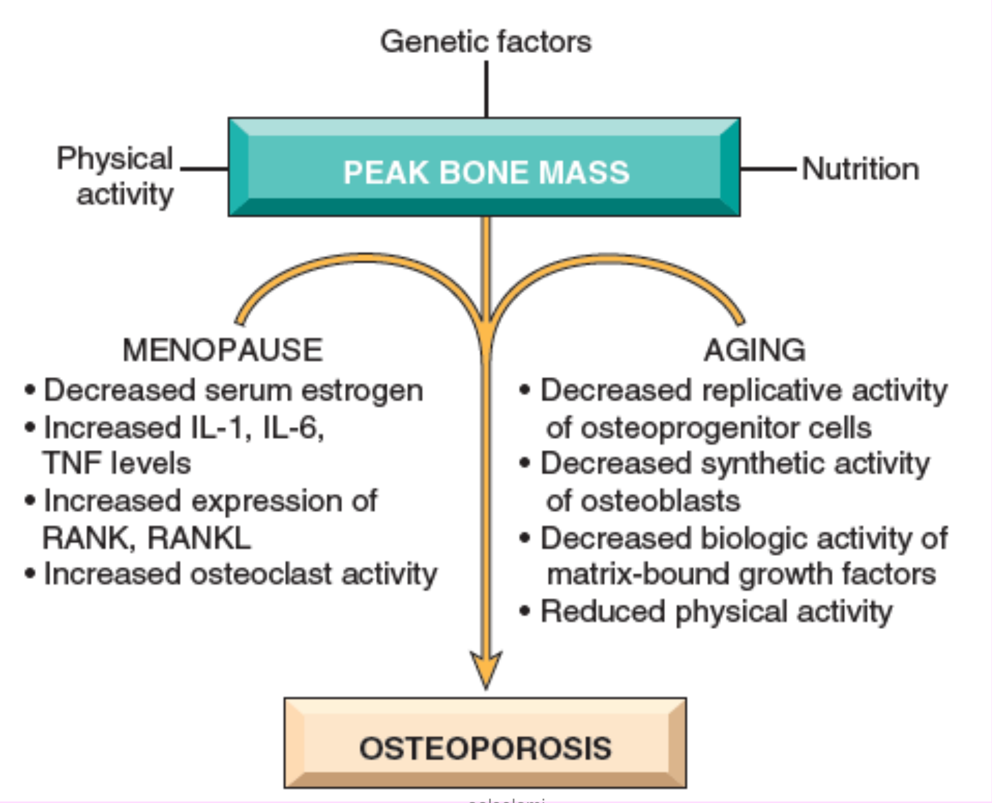
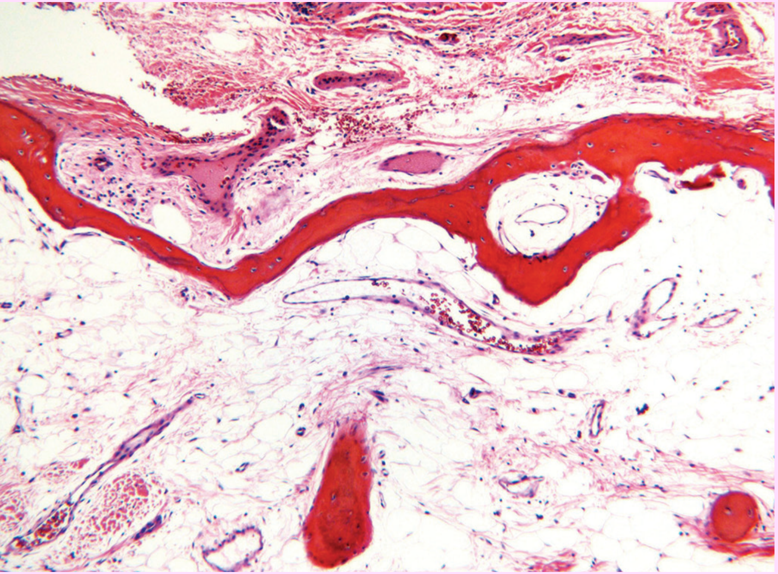
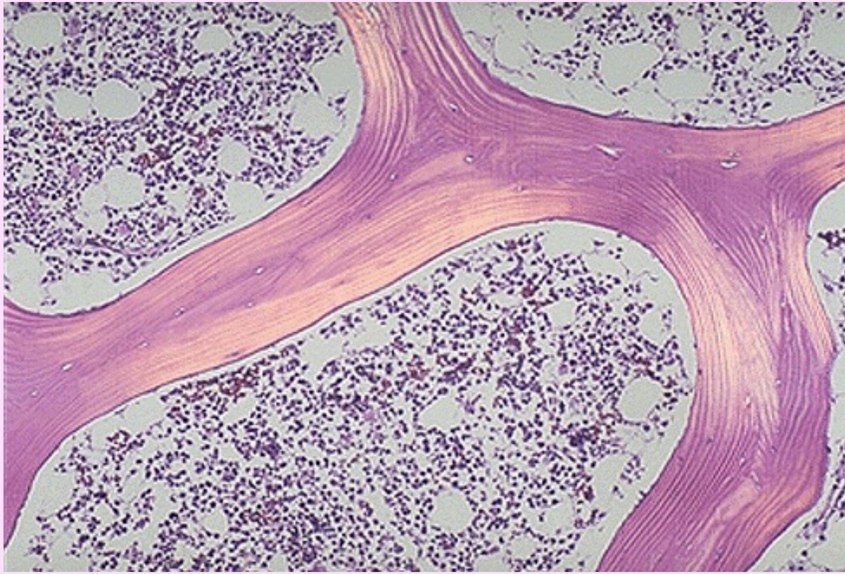



Fig. 21.4 Paracrine molecular mechanisms that regulate osteoclast formation and function. Osteoclasts are derived from the same mononuclear cells that differentiate into macrophages. Osteoblast/stromal cell membrane-associated RANKL binds to its receptor RANK located on the cell surface of osteoclast precursors. This interaction in the background of macrophage colony-stimulating factor (M-CSF) causes the precursor cells to produce functional osteoclasts. Stromal cells also secrete osteoprotegerin (OPG), which 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.

- Bone mass peaks during young adulthood; the greater the peak bone mass, the greater the delay in onset of osteoporosis. In both men and women, beginning in the third or fourth decade of life, bone resorption begins to outpace bone formation.


Genetic factors
Physical activity
PEAK BONE MASS
Nutrition
MENOPAUSE
• Decreased serum estrogen
• Increased IL-1, IL-6, TNF levels
• Increased expression of RANK, RANKL
• Increased osteoclast activity
AGING
• Decreased replicative activity of osteoprogenitor cells
• Decreased synthetic activity of osteoblasts
• Decreased biologic activity of matrix-bound growth factors
• Reduced physical activity
OSTEOPOROSIS





# Clinical course

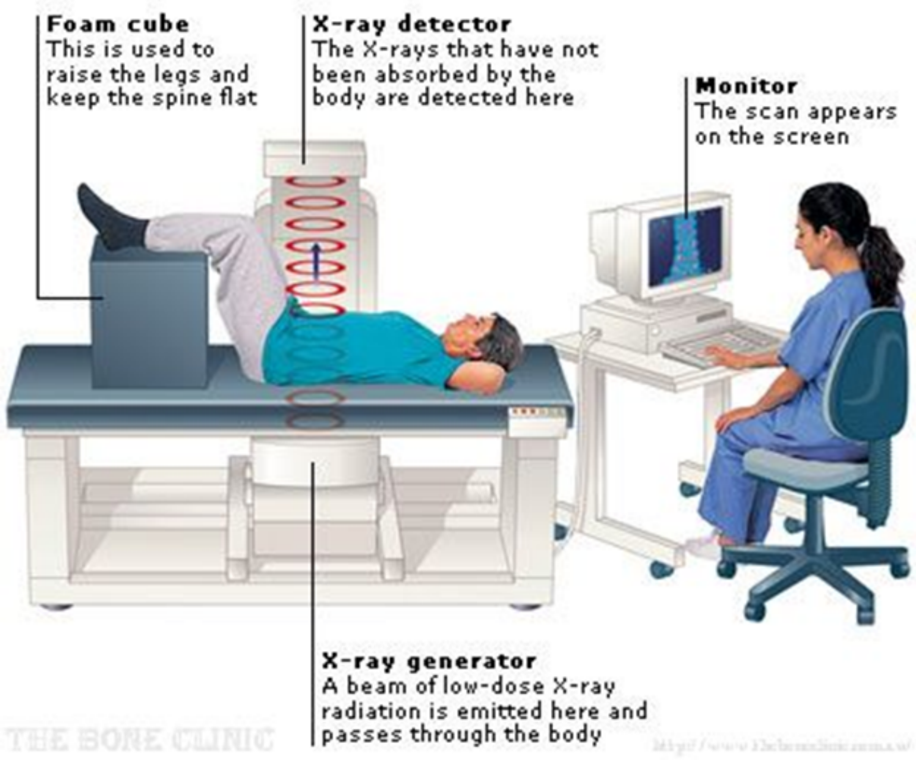
- Difficult to diagnose
- Remain asymptomatic … FRACTURE!.. Vertebra and femoral neck.
- Patients with osteoporosis have normal serum levels of calcium, phosphate, and alkaline phosphatase

# Diagnosis

- Bone density by radiographic measures

PLAIN X-RAY:
- cannot detect osteoporosis until 30% to 40% of bone mass has already disappeared.

DXA SCAN (Dual-emission X-ray absorptiometry):
- used primarily to evaluate bone density, to diagnose and follow up pt. with osteoporosis.


Foam cube
This is used to raise the legs and keep the spine flat
X-ray detector
The X-rays that have not been absorbed by the body are detected here
Monitor
The scan appears on the screen
X-ray generator
A beam of low-dose X-ray radiation is emitted here and passes through the body
THE BONE CLINIC

# Prognosis

- Osteoporosis is rarely lethal.
- Patients have an increased mortality rate due to the complications of fracture. e.g. hip fractures can lead to decreased mobility and an additional risk of numerous complications: deep vein thrombosis (DVT), pulmonary embolism (PE) and pneumonia.

- Prevention Strategies
- The best long-term approach to osteoporosis is **prevention.**
- Children and young adults, particularly women, with a good diet (with enough calcium and vitamin D) and get plenty of exercise, will build up and maintain bone mass.
- This will provide a good reserve against bone loss later in life. Exercise places stress on bones that builds up bone mass

# Rickets and osteomalacia

- In **Osteomalacia and Rickets**, osteoblastic production of bone collagen is normal but **mineralization is inadequate**. It is a manifestations of vitamin D deficiency
- Impairment of mineralization and a resultant accumulation of unmineralized matrix.

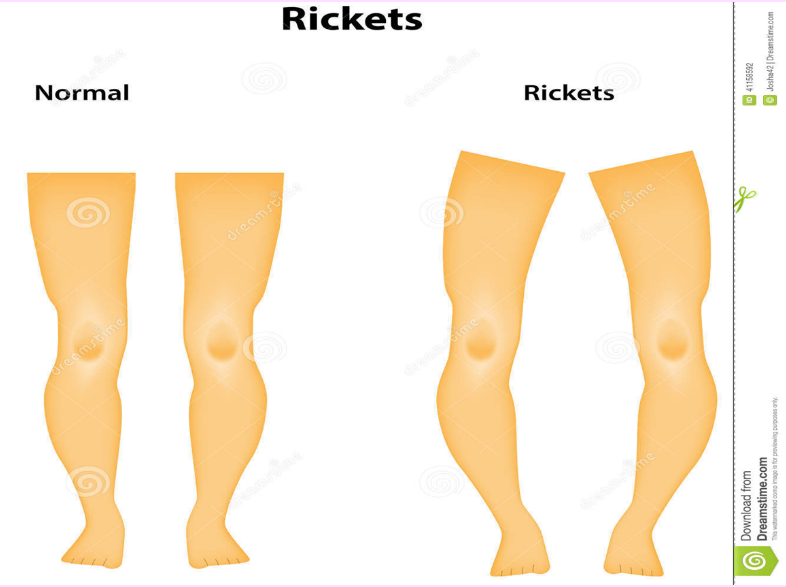
Rickets

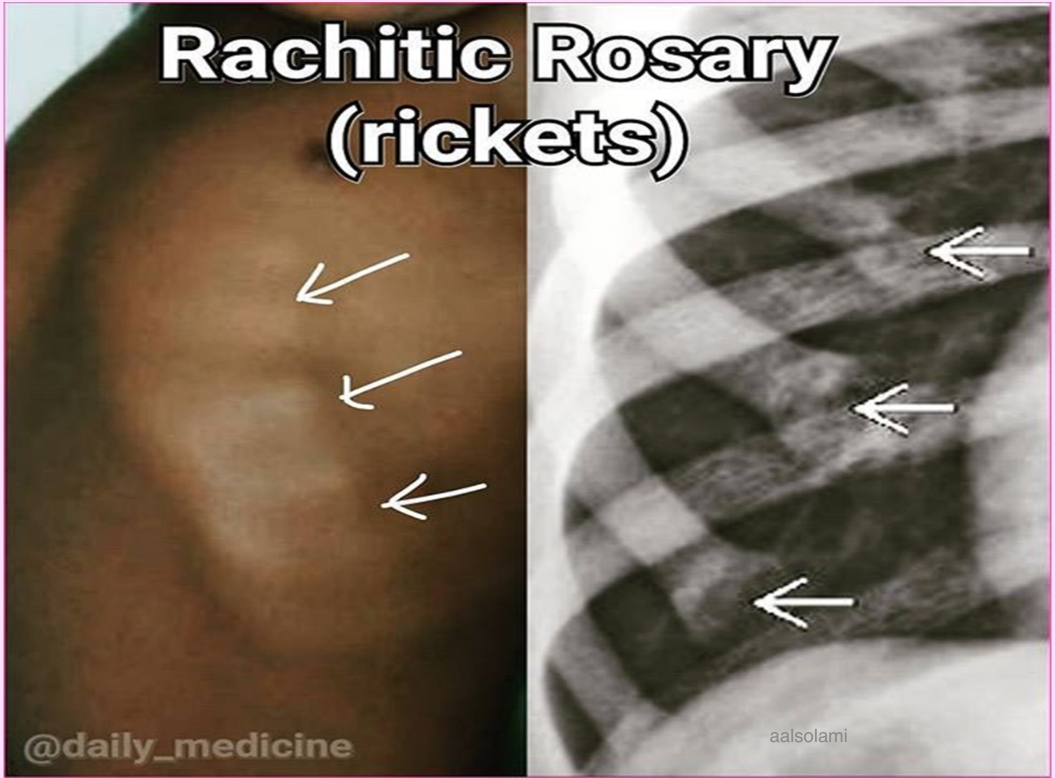
- Disorder of **children**
- It interferes with deposition of bone in growth plate.

Osteomalacia

- **Adults**
- bone formed during remodeling is undermineralized, resulting in a predisposition to fractures

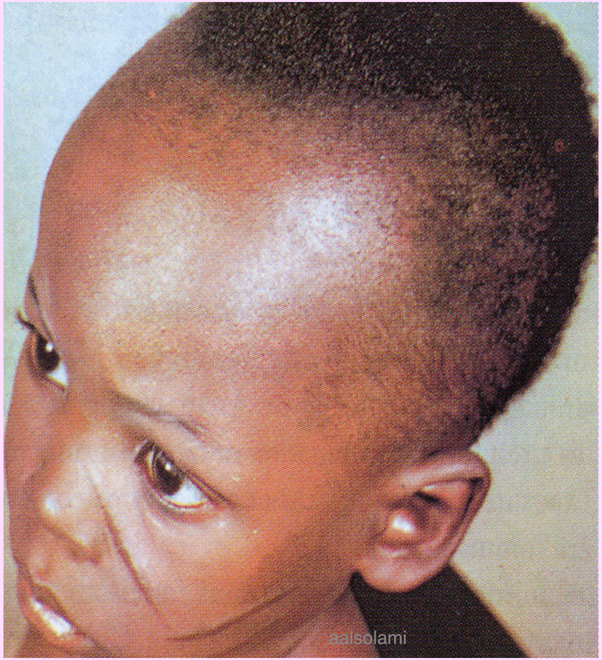
# Leg bowing


Rickets
Normal
Rickets
41158592
Josha42 | Dreamstime.com
Download from
Dreamstime.com

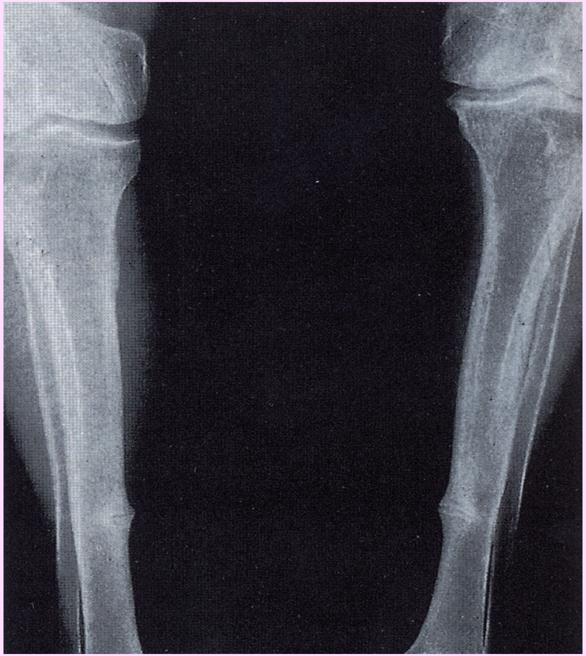



Catholic rosary

# Frontal bones are prominent and bossed

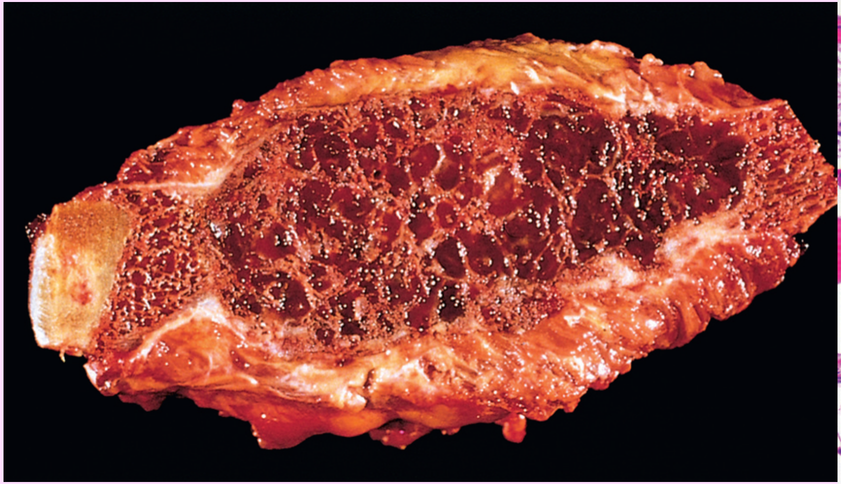


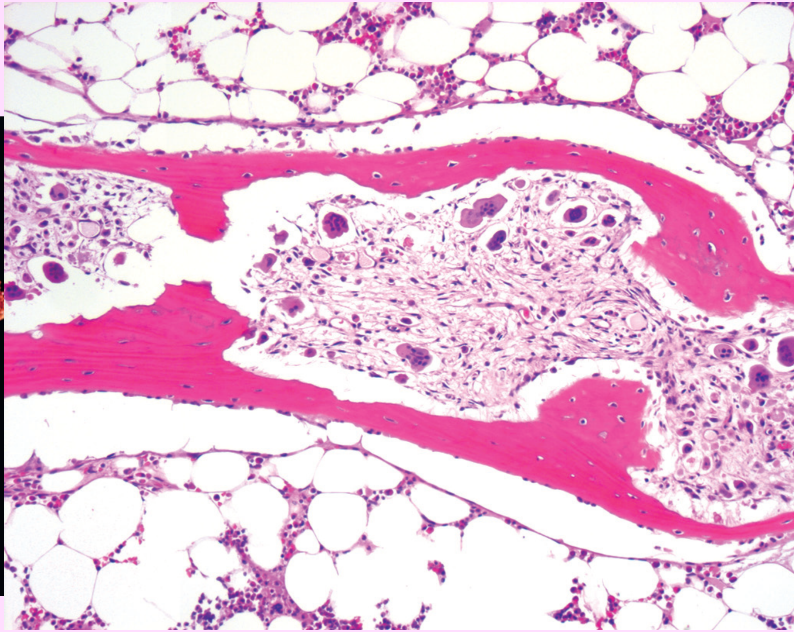
# Looser's zone (cortical infarctions, milkman lines, pseudofractures)



# Hyperparathyroidism (PTH)

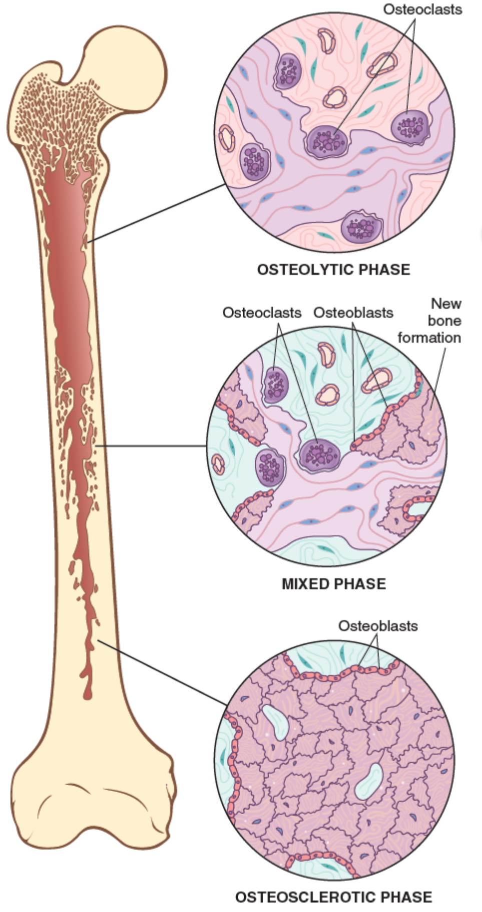
- Result in increased osteoclast activity, bone resorption, and osteopenia.
- Primary, secondary, or tertiary
- As component of multiple endocrine neoplasia (MEN, types I and IIA).
- Osteoporosis, brown tumor, osteitis fibrosa cystica





# Paget disease **of bone**

- A condition of increased, but disordered and structurally unsound, bone.
- Common in whites.
- Risk of fracture and malignancy.



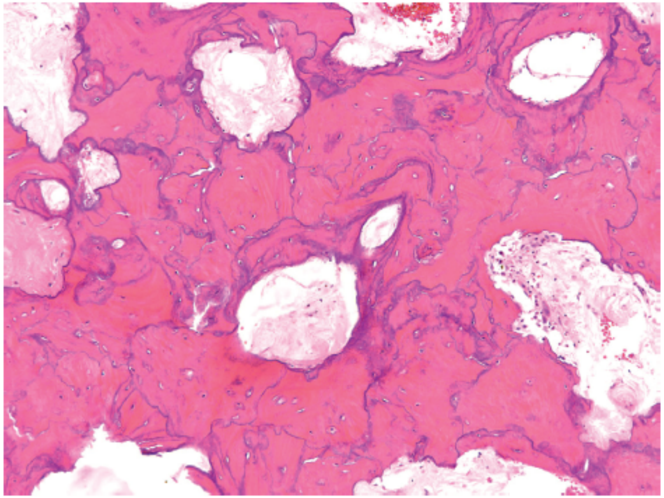



Fig. 21.11 Mosaic pattern of lamellar bone pathognomonic of Paget disease.

# Reference

Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Elsevier; 2017. Philadelphia, PA.
p. 799-805.

aalsolami1@ksu.edu.sa