

# Congenital Diseases

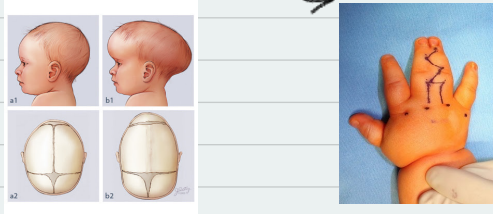
① **Dysostosis** → localized abnormal bone formation

\* Examples:- 1) aplasia → absence of bone or digit

2) Supernumerary digits or ribs

3) abnormal fusion of bones (craniosynostosis, syndactyly)

ازواجية (ارتفاق) الأصابع → تقادم درزات الجمجمة المبكر



\* Results of mutation in → homeobox genes which affect inflammatory cytokines, & it's receptors

② **Bone Dysplasia** → abnormal growth

\* Generalized abnormality (affecting the entire skeleton)

\* Mutations in genes that control the development or remodeling of the entire skeleton

\* Types of bone dysplasia:

1) osteogenesis/ 2) achondroplasia/ 3) thanatophoric dysplasia/ 4) Osteopetrosis



## A) Osteogenesis Imperfecta

\* Most common inherited disorder of connective tissue

\* Bone is abnormal, weak, and prone to fractures (simple trauma can cause a fracture)

\* Mutation in type-1 collagen gene (autosomal dominant)

\* it results in little bone, & fragility

\* Symptoms & types: →

\* **Osteogenesis Imperfecta symptoms:-**

① Bowing in the back

② Repeated fractures

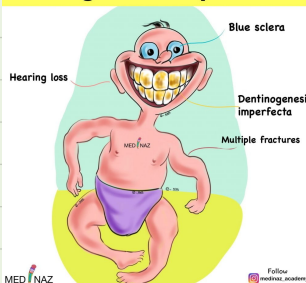
③ Also affects (skin, joints, and eyes)

④ Hearing loss

blue sclera ←

⑤ Brittle, misshapen teeth

### Osteogenesis Imperfecta



\* Type 1 → most common (normal life expectancy)

\* Type 2 → severest, death early in life (after 6 months or 1 year of life)

# Congenital Diseases

B) Achondroplasia: most common cause of dwarfism

\* Gene mutation affects bone formation

\* mutation in the fibroblast growth factor receptor 3 (FGFR 3), shown to be associated with advanced paternal age.

\* Patients have a big head, but short bowing limbs, also they have normal life expectancy and mental functions.



## C) THANATOPHORIC DYSPLASIA

\* Most common lethal form of dwarfism

\* FGFR3 mutations (different location from Achondroplasia)

\* Most patients die at birth / in utero or shortly after (small chest leading to respiratory insufficiency)

\* Features: 1. Big head / 2. Short limbs / 3. Very severe restriction on the chest wall

## D) OSTEOPETROSIS: (rare)

\* Marble bone disease "stone bone" (rigid)

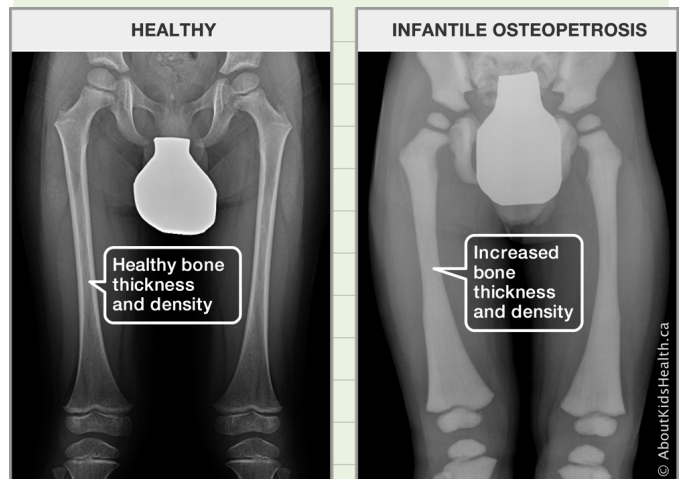
\* Basic etiology: Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis, diffuse formation of marble bone or stone bone.

\* Diagnose: X-ray

\* Prone to multiple fractures and leukopenia in severe forms



If the bone is closed, even if the bone is open, the hematopoiesis will be impacted. these are severe forms of leukopenia, also may lead to immune deficiencies and they will be exposed to more opportunistic bacterial infection





## Summary

### Congenital Disorders of Bone and Cartilage

Abnormalities in a single bone or a localized group of bones are called **dysostoses** and arise from defects in the migration and condensation of mesenchyme. They manifest as absent, supernumerary, or abnormally fused bones. Global disorganizations of bone and/or cartilage are called **dysplasias**. Developmental abnormalities can be categorized by the associated genetic defect.

- FGFR3 mutations are responsible for achondroplasia and thanatophoric dysplasia, both of which manifest as dwarfism.
- Mutations in the genes for type I collagen underlie most types of osteogenesis imperfecta (brittle bone disease), characterized by defective bone formation and skeletal fragility.
- Mutations in *CA2* and *TCIRG1* result in osteopetrosis (in which bones are hard but brittle) and renal tubular acidosis.

# Metabolic Disorders

\*What's the difference between osteoporosis & osteopenia?

## 1. Osteopenia (decreased bone mass):

- It is the first stage before osteoporosis, it's between (1 and -2.5) below the mean.

## 2. Osteoporosis (osteoporosis):

- It is a more severe stage of osteopenia, making the bones weak and easy to break (easy to be fractured) even with minor injuries.

Osteoporosis classification:

1) **Generalized** (more common)

2) **Localized** → In some cases, osteoporosis may affect only a specific region of the body, such as the right upper limb. This can occur due to a previous injury, fracture, trauma, or prolonged immobilization, leading to decreased bone density in that area while the rest of your bones are completely healthy. This condition is referred to as localized osteoporosis.

Another classification:

## 1) PRIMARY OSTEOPOROSIS

(Much more common)

- \*Increasing with senile (aging)

- \*usually occurs in postmenopausal women, especially who has been pregnant many times

\*All of us, after the age of 40, we will start having a certain element of osteoporosis

## 2) SECONDARY OSTEOPOROSIS

(Much less common)

- \*Caused by: Hyperthyroidism, malnutrition, steroids

→ These causes stimulate the activation of osteoclasts leading to secondary osteoporosis.

normal vertebra ↗      ↖ severe osteoporotic

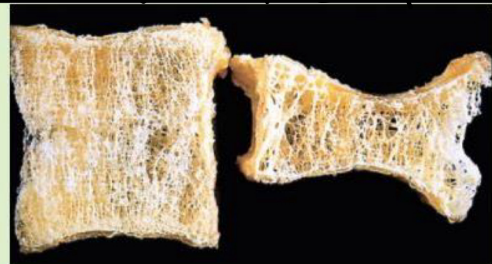


FIG. 21.6 Osteoporotic vertebral body (right) shortened by compression fracture.



\*decreased No. of trabecular bone

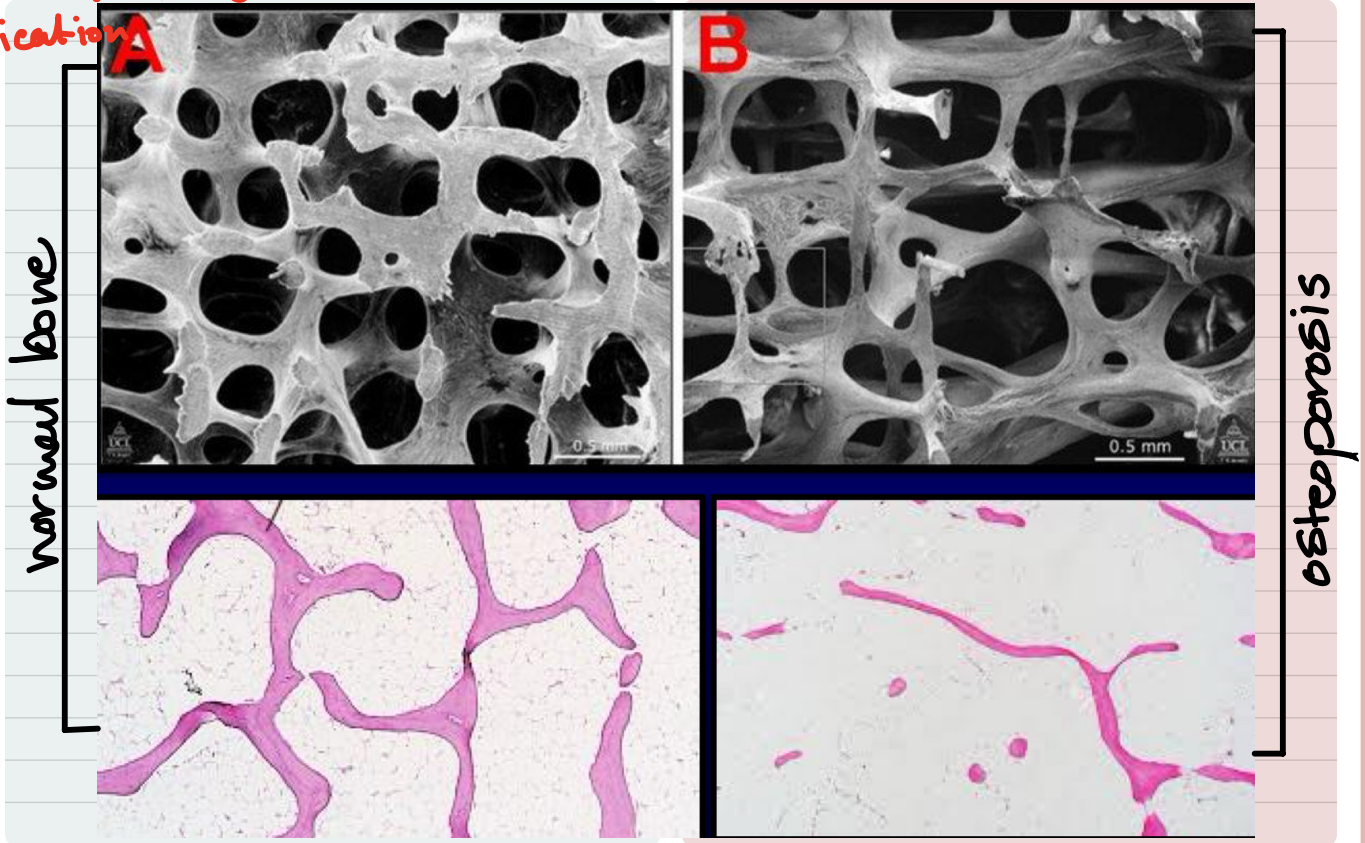
\*increased matrix

FIG. 21.7 In advanced osteoporosis, both the trabecular bone of the medulla (b).

advanced osteoporosis ↖

# Metabolic Disorders

\*check the modified for more  
clarification ↵

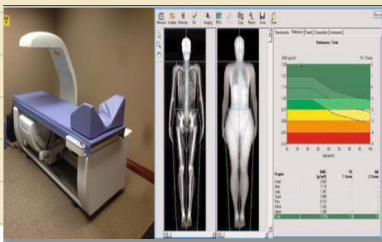


## OSTEOPOROSIS CLINICALLY

\*vertebral fractures (especially compression fractures)

\*Femur and pelvic fractures:  
immobility, PEs (pulmonary embolus: is a blockage of a pulmonary artery by a blood clot), pneumonia (40-50K death/yr in USA)

• Diagnosis: special imaging technique, bone mineral density (BMD scan): dual-energy X-ray absorptiometry (DXA or DEXA scan) or bone densitometry



## PREVENTION AND TREATMENT

(We mainly care about prevention not treatment)

1. Exercise
2. Calcium especially females approaching menopause and vitamin D
3. Bisphosphonates: drugs work on reducing osteoclast activity and inducing its apoptosis
4. Denosumab (a drug): anti-RANKL; works on blocking osteoclast activation
5. Hormones (estrogen) → exogenous estrogen replacement therapy.

Side effects: risking DVT (deep vein thrombosis), stroke and endometrial hyperplasia

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