CONGENITAL DISORDERS

DYSOSTOSIS

- Abnormal condensation & migration of mesenchyme
- Genetic abnormalities of homeobox genes, cytokines and its receptors
  - Aplasia
  - Supernumerary digit
  - Syndactyly & craniosynostosis

DYSPLASIA

- Disorganized bone & cartilage
- Gene mutations that control development and remodeling
- Dysplasia here: not premalignant

Dysostosis refers to a group of disorders caused by abnormalities in the condensation and migration of mesenchymal cells during bone formation. These abnormalities result in congenital bone defects, which can vary depending on the genetic issue and the type of malformation.

Dysostosis: A defect in the formation or development of bones in specific areas, such as missing bones, extra bones, or fused bones.

Dysplasia: The problem in dysplasia is in the organization of bone and cartilage. There is an abnormality in the organization of the structure of the bone and the cartilage.

Genetic mutations play a role in these conditions. There are genetic mutations that control the proper development and remodeling of bones. It is important to remember that dysplasia in the bone **does not mean a premalignant condition.**

Examples of ***Dysostosis***

1. Aplasia:
Complete absence of a bone or group of bones due to failure of mesenchymal condensation and migration.

Example: Missing bones in the hand or leg, such as the tibia or fibula.

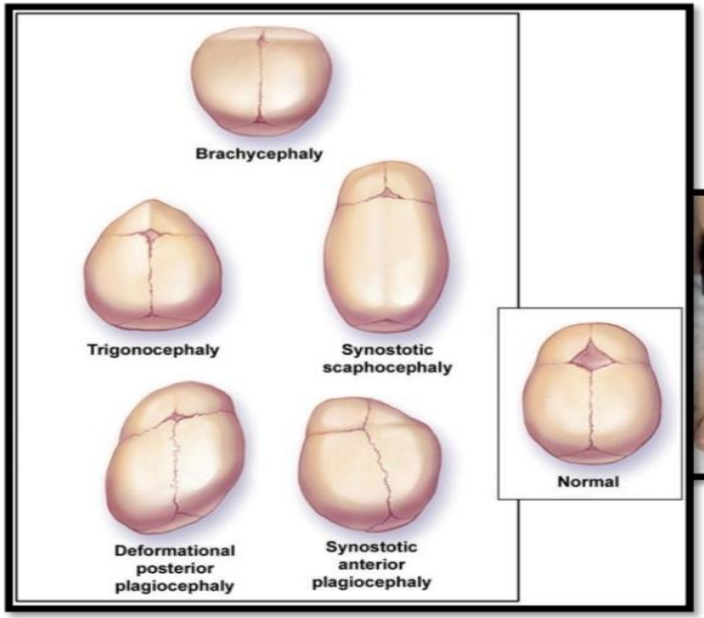
2. Supranumerary Digits*:*
Extra fingers or toes caused by genetic mutations in specific genes, such as Homeobox genes.

Example: The presence of an additional digit on the hand or foot.

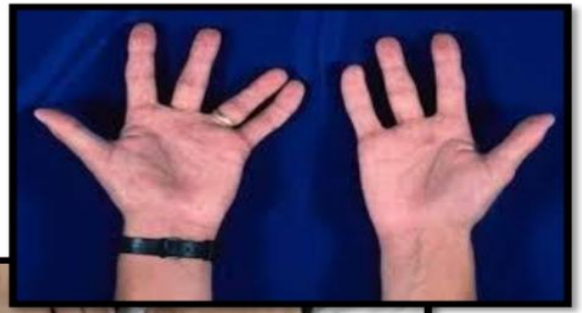
3. Syndactyly:
Fusion of fingers or toes due to failure in the separation process during embryonic development.

4. Craniosynostosis:
Premature fusion of cranial sutures, leading to abnormal skull shape and growth patterns.

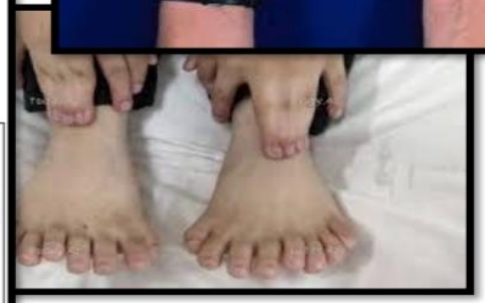
DYSOSTOSIS



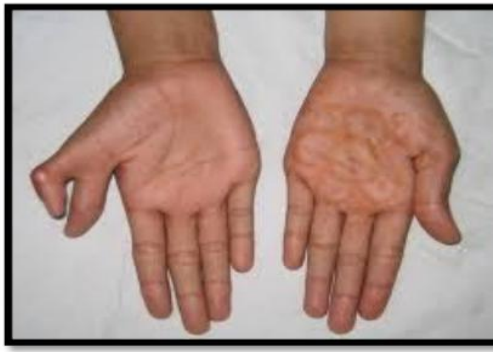
Aplasia

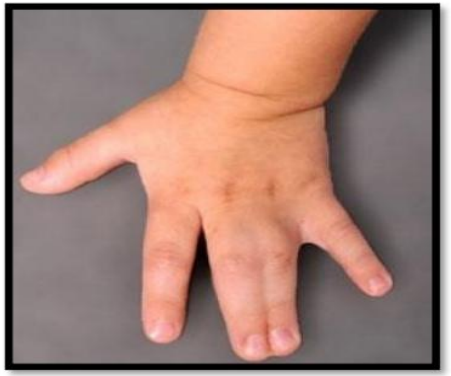


Supranumerary Digits+Syndactyly



Supranumerary Digits

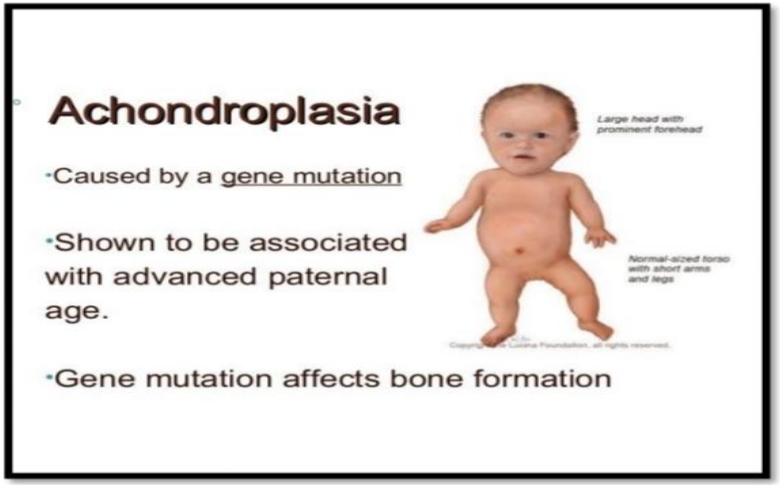




Syndactyly

DYSPLASIAS

- **Achondroplasia (dwarfism): most common**
- **Mutations in FGFR3**
- **No impact on longevity, intelligence or reproductive status**



Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey
"Game of thrones"

Achondroplasia is the most common cause of dwarfism worldwide.

It is classified under ***skeletal dysplasias*** and results from a mutation in a specific gene.

Achondroplasia is caused by mutations in the fibroblast growth factor receptor 3 (FGFR3) gene.

FGFR3 plays a critical role in regulating bone growth. The mutation causes ***overactivation*** of the receptor, leading to impaired growth of long bones.

Physical Features

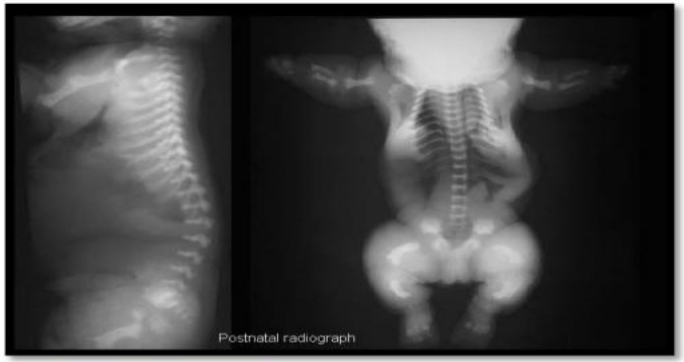
Head: Enlarged head with prominent forehead (frontal bossing).

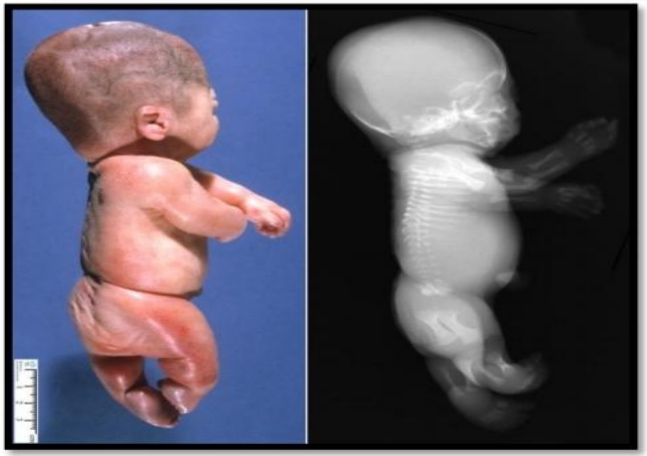
Limbs: Short arms and legs (short-limbed dwarfism).

Trunk: Normal-sized torso.

THANATOPHORIC DYSPLASIA

- Most common lethal form of dwarfism
- FGFR3 mutations (different from Achondroplasia)
- Die at birth or shortly after (small chest leading to resp. insufficiency)





Thanatophoric dysplasia

This disease is the most common cause of **lethal** dwarfism

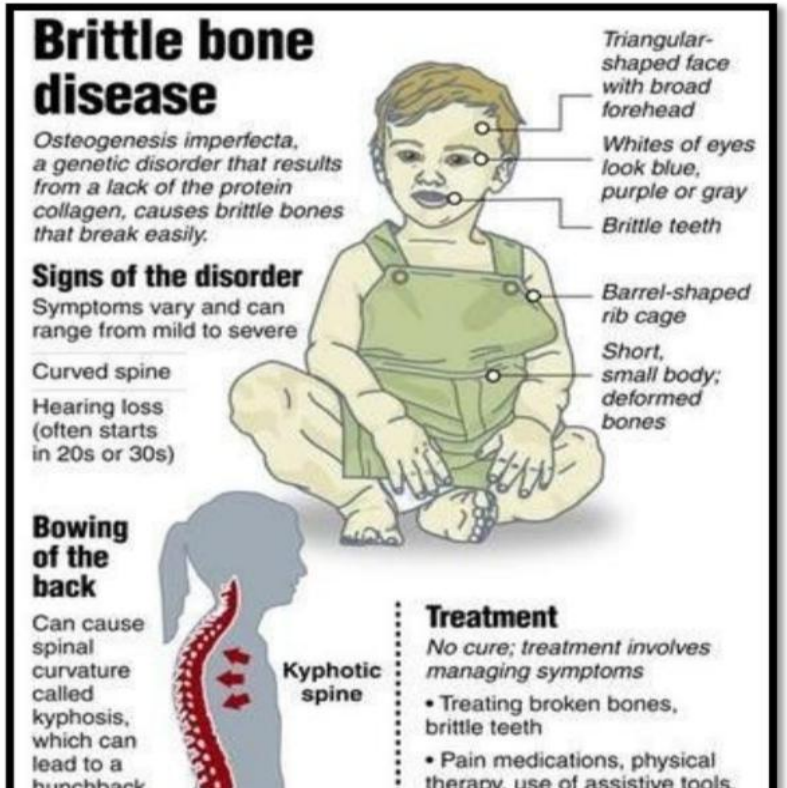
Most cases result in **death in utero or shortly after birth** due to an inability to maintain normal respiration

The chest wall collapses, leading to **severe respiratory insufficiency.**

Thanatophoric dysplasia

This condition is a severe form of dwarfism caused by a mutation in the **FGFR3** gene, but it affects a **different location on the receptor compared to achondroplasia**. Unlike achondroplasia, which does not impact life expectancy, thanatophoric dysplasia is **almost always fatal**. If presented with a clinical scenario where a baby dies in utero or shortly after birth, the correct diagnosis would be thanatophoric dysplasia, not achondroplasia.

OSTEOGENESIS IMPERFECTA



- Most common inherited disorders of connective tissue
- Group of disorders; AD; deficiency of type I collagen synthesis
- Too little bone; fragility
- Blue sclera; hearing loss; teeth abnormalities
- Type 2 (lethal) and type I (relatively normal life)

Blue sclera: Due to thin sclera from defective Type I collagen, making underlying choroidal veins visible.

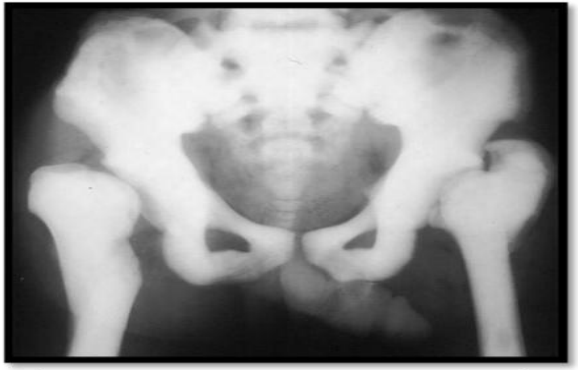
Hearing loss: Fragile middle ear bones (ossicles) cause conductive hearing loss, often in adulthood.

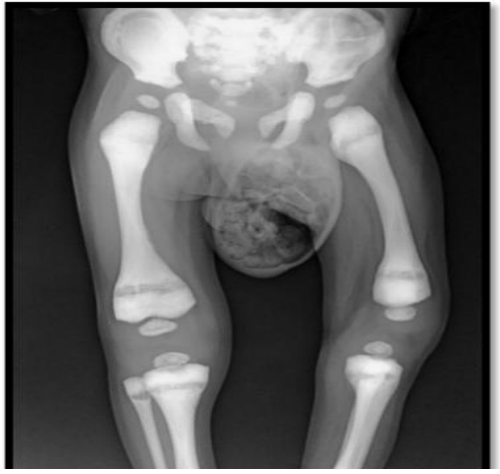
Teeth abnormalities: Weak dentin (dentinogenesis imperfecta) leads to brittle, discolored, and easily fractured teeth.

👀**The doctor did not state these reasons himself but asked us to research them.**

OSTEOPETROSIS

- Marble bone disease “stone bone” (group of disorders); rare
- Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis
- Dx: X-ray
- Fractures and leukopenia in severe forms





METABOLIC DISORDERS

- Osteopenia: decreased bone mass (1-2.5 SD below the mean).
- Osteoporosis: severe osteopenia; > than 2.5 SD below the mean with increase risk for fractures
- Generalized (much more common) or localized

PRIMARY OSTEOPOROSIS

Much more common
Senile (aging) & postmenopausal

SECONDARY OSTEOPOROSIS

Much less common
Hyperthyroidism, malnutrition, steroids

1. Osteopenia (Low Bone Density):

"Osteo" means bone, and "penia" means deficiency.

Defined as a decrease in bone mass between 1 and 2.5 standard deviations below the mean.

2. Osteoporosis (Severe Bone Loss):

A more severe form of osteopenia.

Occurs when bone mass decreases by more than 2.5 standard deviations below the mean.

Increases the risk of fractures and other complications.

Osteoporosis can be classified in different ways:

1. Generalized vs. Localized Osteoporosis:

Generalized Osteoporosis: The most common form, affecting the entire skeleton.

Localized Osteoporosis: Affects a specific area, such as an upper limb, due to conditions like trauma, fractures, or immobility.

2. Primary vs. Secondary Osteoporosis:

Primary Osteoporosis:

The most common type, increasing with age.

Mostly affects postmenopausal women, especially those who have had multiple pregnancies, as each pregnancy further reduces bone mass.

All individuals begin to experience some degree of bone loss after age 40, ranging from mild to severe.

Secondary Osteoporosis:

Less common and caused by specific medical conditions or medications rather than natural aging or pregnancy.

Causes include **hyperthyroidism**, **malnutrition**, **chronic steroid use** (for cancer or autoimmune diseases), which activate osteoclasts and accelerate bone loss.

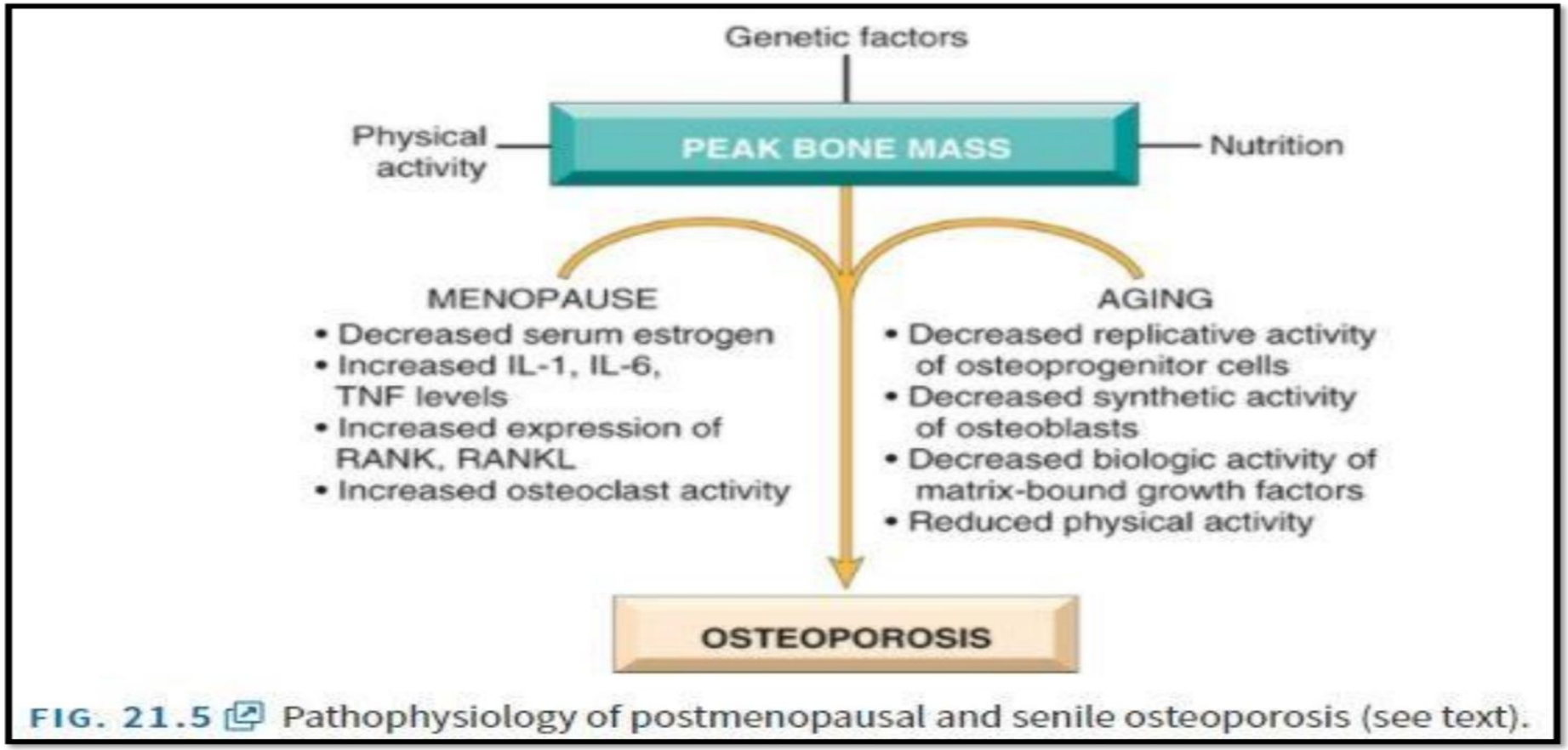


FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

Impact of Menopause on Osteoporosis:

1. Decline in Estrogen and Progesterone:

After menopause, the drop in estrogen levels increases the risk of osteoporosis.

2. Increase in Inflammatory Mediators:

Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF) rise, stimulating **osteoclast** activity, which leads to bone loss.

3. Increased Expression of RANK-L Protein:

This protein enhances **osteoclast** activation, accelerating bone resorption after menopause.

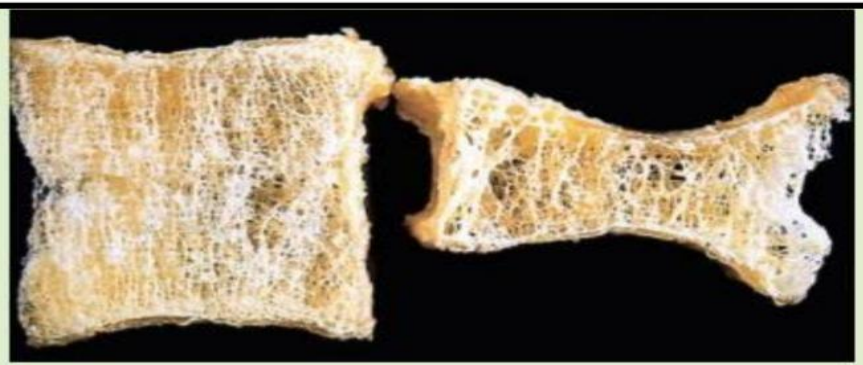


FIG. 21.6 Osteoporotic vertebral body *(right)* shortened by compression fractur.

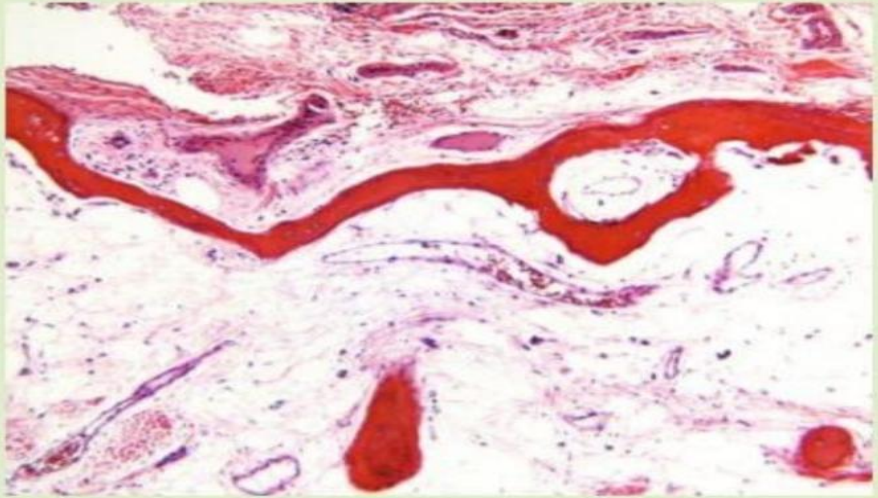


FIG. 21.7 In advanced osteoporosis, both the trabecular bone of the medulla *(b.*

1. Osteoporotic Vertebra:

The image shows a vertebra with severe osteoporosis and a compression fracture.

The measured distance between the fractured parts has doubled or tripled due to the fracture.

There are multiple micro-fractures at all levels, weakening the bone structure.

The vertebra bears the entire body weight, and with these fractures, it undergoes compression.

Complications:

Micro and macro fractures lead to compression fractures, one of the major complications of severe osteoporosis.

Comparison with a Normal Vertebra:

A normal vertebra has dense, intact bone, whereas the osteoporotic vertebra is weak and fragile.

Histological (Microscopic) Findings:

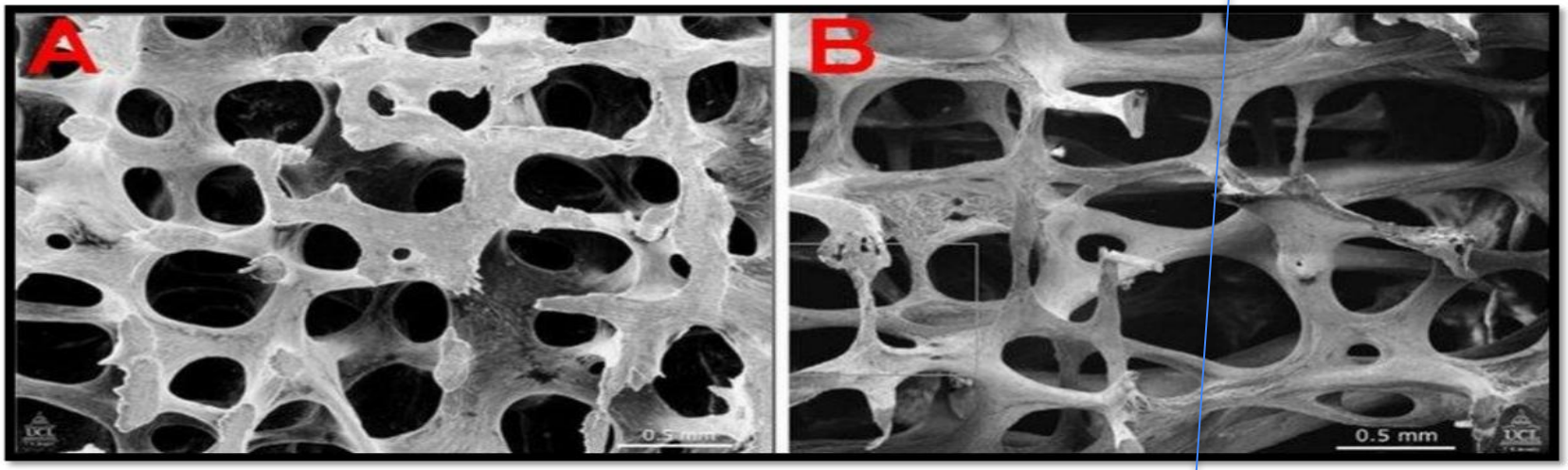
Severe bone thinning with very thin trabeculae.

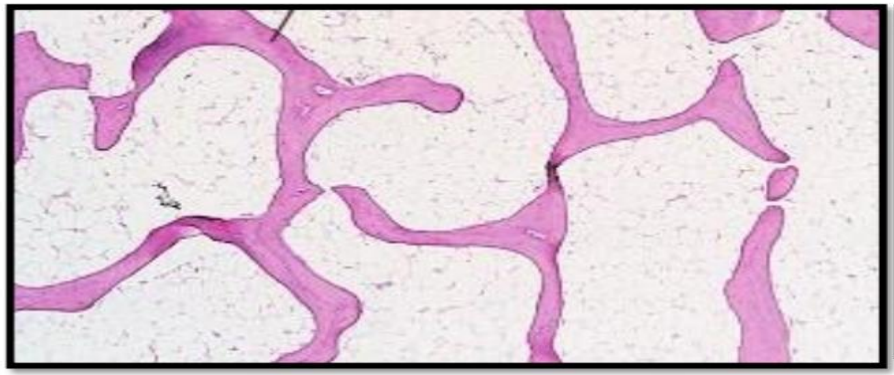
Reduced number of trabeculae, leading to an increased amount of bone matrix with inadequate support.

The bone appears pale and extremely thin, reflecting significant structural loss.

Normal bone : Osteoporosis

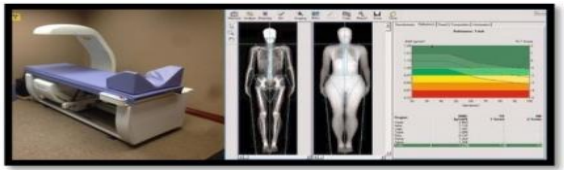
"Thinner trabeculae, more matrix, and multiple microfractures."





OSTEOPOROSIS CLINICALLY

- Vertebral fractures
- Femur and pelvic fractures: immobility, PEs, 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

- Exercise
- Calcium & vitamin D
- Bisphosphonates: reduce osteoclast activity and induce its apoptosis
- Denosumab: anti-RANKL; blocking osteoclast activation (new expensive potent)
- Hormones (estrogen): risking DVT and stroke