Bone Pathology

Lecture: 2 (for females)/ 1 (for males)

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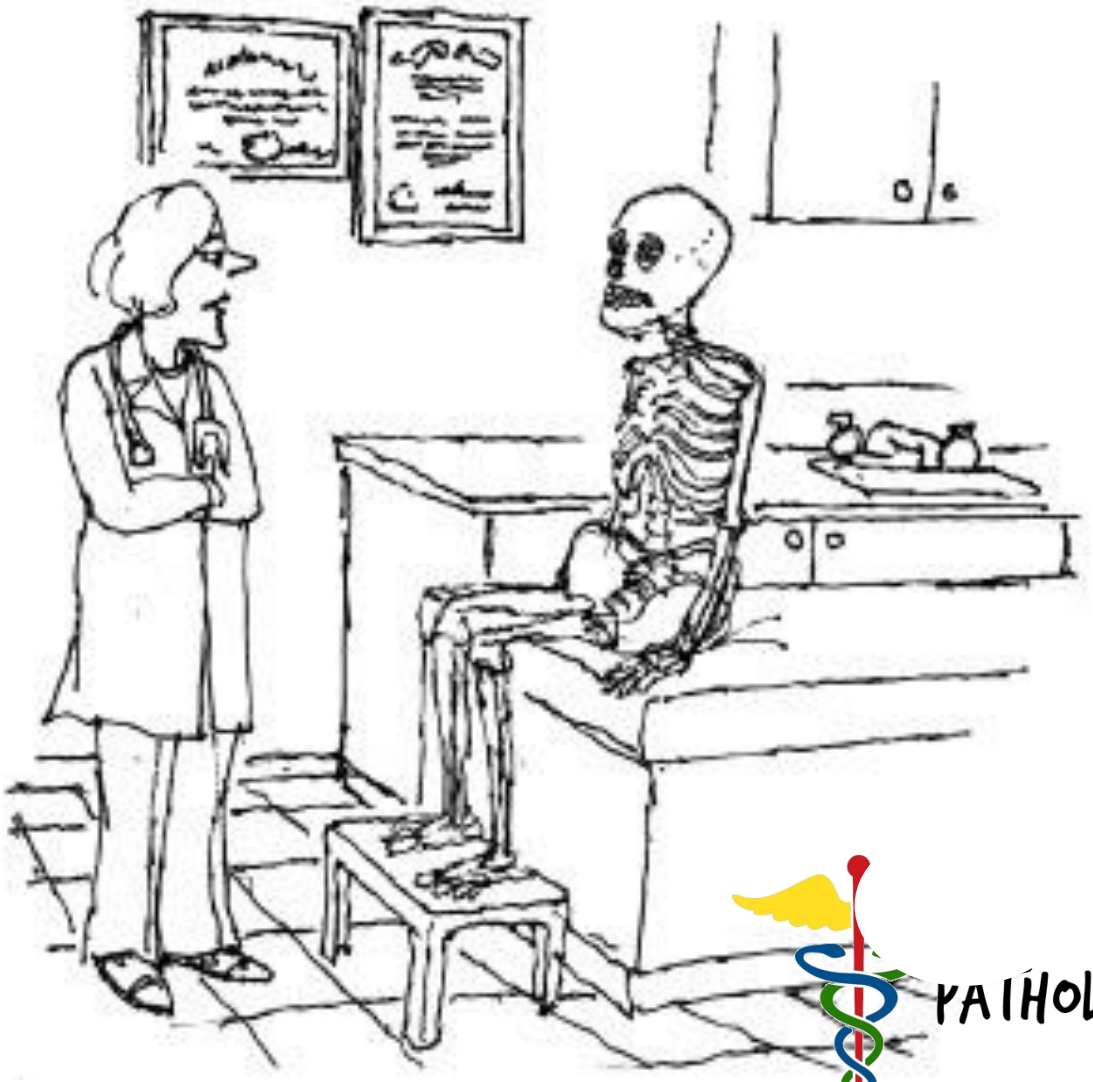


Objectives:

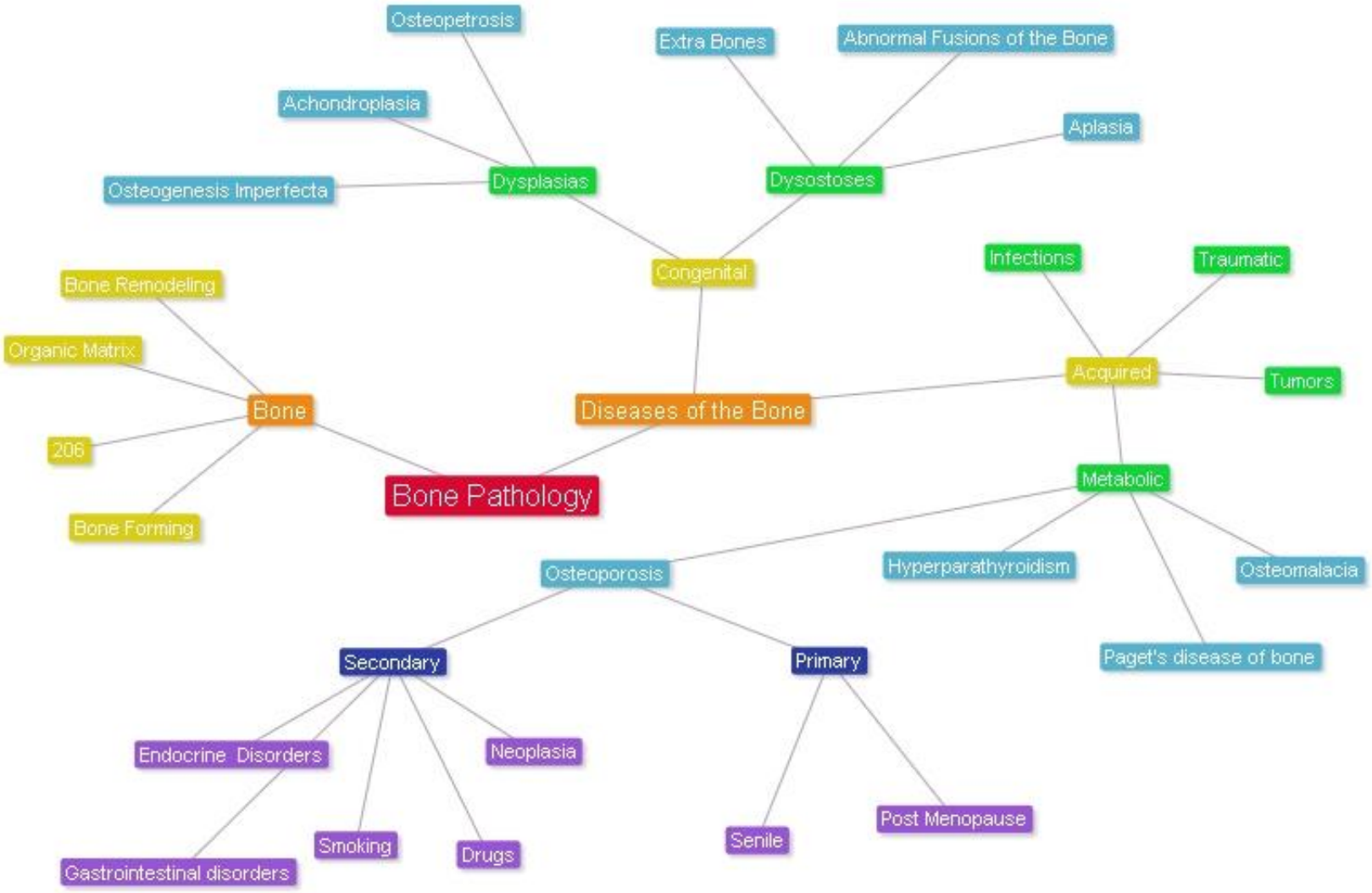
- Be aware of some important congenital and developmental bone diseases and their principal pathological features.
- Be familiar with the terminology used in some important developmental and congenital disorders.
- Understand the etiology, pathogenesis and clinical features of osteoporosis.

Videos to Watch:

- Bone Modelling, Remodelling, and Peak Bone Mass
http://www.youtube.com/watch?v=GenafQna0J4

- Developmental Abnormalities in Bone Cells, Matrix, and Structure
http://www.youtube.com/watch?v=p8UYRhs76F4&list=PLfefVARFaHqUsQuEHGx8iVcHhjwvMPFFK

- Fractures - Robbins Pathology Audiobook
http://www.youtube.com/watch?v=daEqlRtbFkc&list=PLfefVARFaHqUsQuEHGx8iVcHhjwvMPFFK

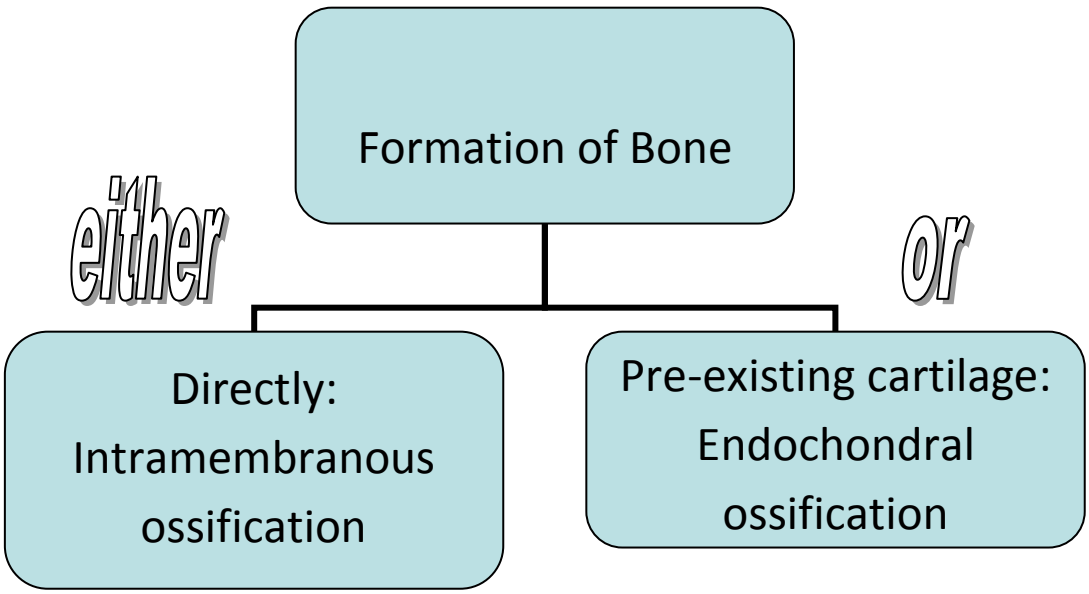

Bone Pathology
Bone
Bone Remodeling
Organic Matrix
206
Bone Forming
Diseases of the Bone
Congenital
Osteopetrosis
Achondroplasia
Osteogenesis Imperfecta
Dysplasias
Extra Bones
Abnormal Fusions of the Bone
Aplasia
Dysostoses
Acquired
Infections
Traumatic
Tumors
Metabolic
Hyperparathyroidism
Osteomalacia
Paget's disease of bone
Osteoporosis
Secondary
Endocrine Disorders
Neoplasia
Smoking
Drugs
Gastrointestinal disorders
Primary
Senile
Post Menopause

Bone:

- 206 bones
- Organic matrix (35%) and inorganic elements (65%): calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]
- The bone-forming cells include osteoblasts and osteocytes, while cells of the bone-digesting lineage are osteoclasts
- In bone development, action of osteoblast predominates. When the skeleton reaches maturity, actions of osteoblast and osteoclast are equal (remodeling). By the third decade, the action of osteoclast predominates.

Is very dynamic and subject to constant breakdown and renewal: Remodeling

Development and Growth of the skeleton:



First: Intramembranous ossification:

Bone is laid down as woven bone that matures into lamellar bone, e.g. (skull and clavicles)

Second: Endochondral ossification:

The cartiladinous template undergoes ossification at ossification centers. As in long bones, the cartilages at the epiphysis ossify after puberty and the area is called growth plate.

IMPORTANT SCHEDULE HERE!!!!!!

sease	Achondroplasia &Thanatophoric (Dwarfism القزامة)	Osteogenesis Imperfecta (brittle bone disease) (OI)	Osteopetrosis
Types	Congenital disease. Many of its types transmitted as an autosomal dominant. • Achondroplasia (most common form of dwarfism) • Thanatophoric (lethal variant of dwarfism)	It is Congenital disease and it is also inherited autosomal dominant disease. Type I OI & Type II OI. Type III OI's , type IV OI	There are several forms of it. It is a Congenital and rare diseases

Cause	**Defect in the cartilage synthesis at growth plates due to mutation on gene FGFR3 is on the short arm of chromosome 4 (4p16.2 or 4p16.3). Resulting in failure of longitudinal bone growth and subsequent short limbs.**	**Many genes may be mutated.** **Mutations occur in genes that encode for collagen type1 production, cause deficient or abnormality in collagen type1 leading to t*oo* little bone resulting in extreme skeletal fragility with susceptibility to fractures**	**Dysfunction of osteoclasts (Decreasing in turnover rate).** **And it is unknown in many cases,**
Mechanism	**FGFR3 is a receptor with tyrosine kinase that transmits intracellular signals. Signals that transmitted by FGF3 inhibit the proliferation and function of growth plate chondrocytes. Therefore, the growth of normal epiphyseal plate is suppressed**	**Defect in α_1 or $\alpha_2$chains of type I collagen.** **Most of the fractures happens in the Diaphysis**	**failure of normal bone resorption by osteoclasts results in uniformly thickened, dense bones due to abnormal function of osteoclasts (deficiency of carbonic anhydrase) leads to an abnormal environment around the osteoclast, resulting in defective bone resorption**
	Normal intelligence, Abnormal height, short arms and legs. The trunk and head are almost	**1-Normal Life Span.** **2-Increase proclivity**	**1- increased tendency to fractures and**

Features	of normal size (the head may look larger but it is not large it only looks large because his limbs are short) with depression of the nasal bridge. General health is not affected, and life expectancy is normal Thanatophoric dwarfism Features: Thanatophoric means (death-loving). 1-Lethal. 2-Extreme shortening of the limbs. 3-Extreme frontal bossing. 4-Extreme small thorax, which will be the cause of fatal respiratory failure.	for fractures during childhood (decrease after puberty) from any minor trauma. 3-Blue Sclera (مسحة زرقاء في بياض العين) 4-Small misshapen teeth. 5-Hearing loss (sometimes). 6-In addition, other tissues contain collagen type I are affected such as: tendons, ligaments, skin and dentine. Type II OI's Features: Uniformly fatal in utero or immediately postpartum because of multiple fractures during pregnancy. Type 1 Features: blue sclera in both eye, deformed teeth and hearing loss	osteomyelitis 2-Recurrent infections because of the reduced bone marrow size and activity. 3-anemia and extramedullary hematopoiesis

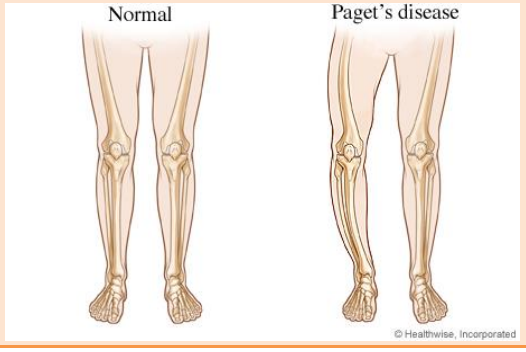
Notes:

- Achondroplasia can occurs as a sporadic mutation in approximately 80% of cases (associated with advanced paternal age)
- People with Achondroplasia, their Membranous ossification are not affected, so that the skull, facial bones, and axial skeleton develop normally.
- The Four main types of Osteogenesis Imperfecta occur with different clinical manifestations classified according to the severity of bone fragility, the presence or absence of blue scleras, hearing loss, abnormal dentition, and the mode of inheritance.
- FGFR3 : Fibroblast growth factor receptor 3
- Sclera appears blue because it is thin that the underlying uveal pigment becomes visible.

Metabolic bone disease

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

- Hyperparathyroidism
- Osteoporosis
- Paget's disease of bone
- Osteomalacia

OSTEOMALACIA AND RICKETS,	PAGET'S DISEASE OF BONE	HYPERPARATHYROIDISM
Osteomalacia and rickets are the same, but <u>osteomalacia occur in adult and rickets occur in children .</u> Bone biopsy taking from osteomalacia patient shows: Black area: calcified bone Red area: osteoid (Uncalcified bone) Space: bone marrow with progenitor cells The main pathology of osteomalacia is: 1. Abnormal calcification 2. Mineralization due to deficiency vitamin D **Causes:** **1.Malnutrition** **2.Malabsorbtion** **3.Renal diseases** **Symptoms of rickets are:** big head, frontal bone is fosselated, opened gap in skull suture. One of fractures of osteomalacia is pseudofracture (rupture of cortical bone)	Excessive uncontrolled destruction of bone <u>by abnormally large and active osteoclasts</u>, with concurrent inadequate attempts at haphazard new bone formation by osteoblasts, producing physically weak woven bone. It may result from a paramyxovirus infection in genetically susceptible persons. 	Excessive secretion of PTH ☐ produces <u>increased osteoclastic activity</u>. There is excessive ☐ destruction of cortical and trabecular bone, with inadequate compensatory osteoblastic activity.

OSTEOMALACIA AND RICKETS:

They are characterized by defective mineralization of osteoid matrix with lack of vitamin D which maintains the serum calcium and phosphorous levels. In osteomalacia, lack of vitamin D impairs normal mineralization of osteoid laid down in the remodeling of bone. In children, lack of vitamin D leads to inadequate mineralization of the epiphyseal cartilage and the osteoid (rickets).

Osteoporosis:

Osteoporosis is an acquired condition characterized by reduced bone mass, leading to bone fragility and susceptibility to fractures.

-Trabecular bone ("large amount" in vertebral bodies and pelvis) is affected before cortical bone ("large amount" in long bones).

- **There is a slowly progressive increase in bone erosion**

It may be:

	localized	generalized
cause	disuse osteoporosis of a limb	a metabolic bone disease
types	----------	primary or secondary

(Primary forms of osteoporosis are most common and may be associated with aging (senile osteoporosis) or the postmenopausal state in women. The drop in estrogen following menopause tends to exacerbate (يفاقم) the loss of bone that occurs with aging, which means women are more likely to get this disease more than men.

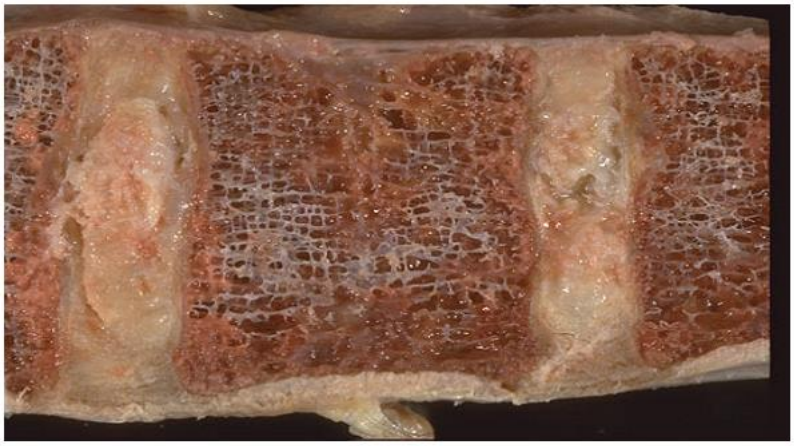
The risk of osteoporosis with aging is related to the maximum of bone mass earlier in life, the greater the peak bone mass, the greater the delay in onset of osteoporosis.)

More info about Osteoporosis:

The main pathology of Osteoporosis is slim and slender Trabeculae (Woven). Osteoporosis shows normal calcification. Alkaline Phosphatase Isoenzymes: can be in the liver, placenta and bone. Alkaline Phosphatase of the bone is really high in Paget's disease of the bone.

- **Osteoporosis fractures** are neck of femur, wrist (Coles fracture), vertebrae. Kyphosis is due to Osteoporosis and shows compression fracture in vertebrae, in Kyphosis (التحدب) the elbow becomes in the level of hip. Scliosis (الالتواء) shows deviation in vertebrae taking S shape.

- **Morphology:**



The hallmark of osteoporosis is a loss of bone. The cortical bone is thinned, with dilated haversian canals, and the bone trabeculae are reduced in thickness and lose their interconnections. Osteoclastic activity is present but is not dramatically increased, and the mineral content of the bone tissue is normal. Once enough bone is lost, susceptibility to fractures increases.

	Primary	Secondary
cause	- Post-menopausal probably a consequence of declining levels of estrogen. - Senile. Environmental factors may play a role in osteoporosis in the elderly: 1-Decreased physical activity. 2- Nutritional protein or vitamin deficiency (1, 25-dihydroxycholecalciferol). -Women are at higher risk than men. White people are at higher risk than black people.	- Endocrine Disorders: such as Cushing's syndrome, hyperthyroidism, and acromegaly (Pituitary tumors), Hypo or hyperthyroidism, Hypogonadism, Diabetes type 1, Addison disease. - Gastrointestinal disorders : Malnutrition, Malabsorption, Hepatic insufficiency, Vitamin C, D deficiencies, Idiopathic disease. - Neoplasia: Multiple myeloma, Carcinomatosis. - Drugs: Anticoagulants, Chemotherapy, Corticosteroids, Anticonvulsants, Alcohol. - Miscellaneous (others): smoking, Osteogenesis imperfect, Immobilization, Pulmonary disease, Homocystinuria, Anemia. - Reduced mobility. - Obesity. - Corticosteroid therapy.

Note:

-Post- menopausal women lose up to 2% of cortical bone per year and up to 9% of trabecular bone per year for 8-10 years with declining to the normal loss after that.

Pathophysiology:

Osteoporosis occurs when the dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts tilts in favor of resorption.

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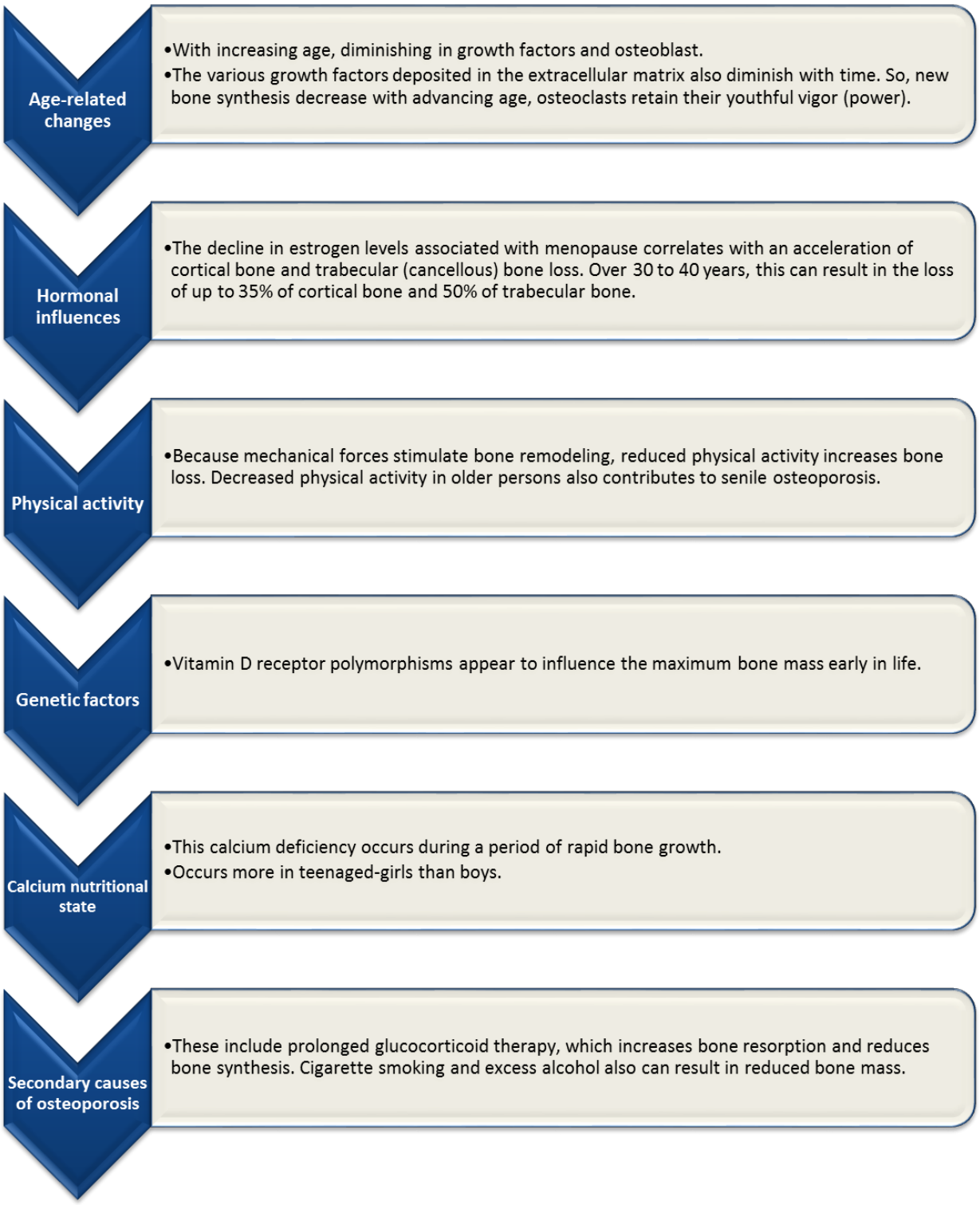
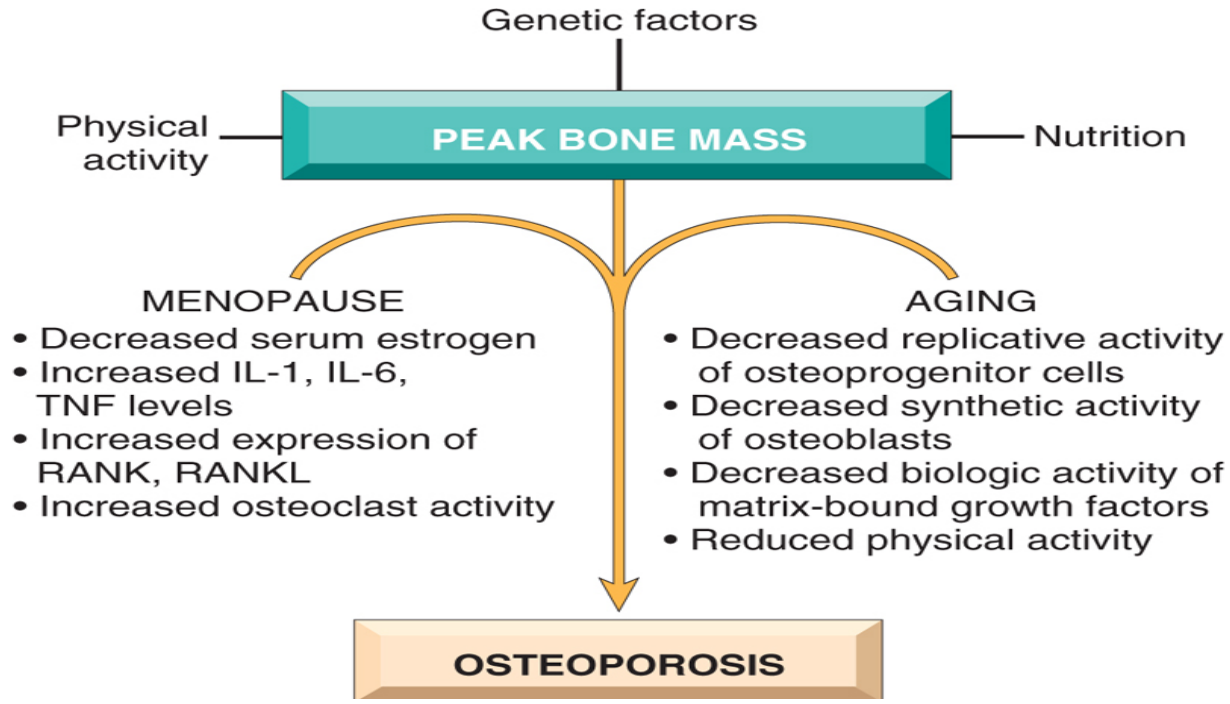

Age-related changes
•With increasing age, diminishing in growth factors and osteoblast.
•The various growth factors deposited in the extracellular matrix also diminish with time. So, new bone synthesis decrease with advancing age, osteoclasts retain their youthful vigor (power).
Hormonal influences
•The decline in estrogen levels associated with menopause correlates with an acceleration of cortical bone and trabecular (cancellous) bone loss. Over 30 to 40 years, this can result in the loss of up to 35% of cortical bone and 50% of trabecular bone.
Physical activity
•Because mechanical forces stimulate bone remodeling, reduced physical activity increases bone loss. Decreased physical activity in older persons also contributes to senile osteoporosis.
Genetic factors
•Vitamin D receptor polymorphisms appear to influence the maximum bone mass early in life.
Calcium nutritional state
•This calcium deficiency occurs during a period of rapid bone growth.
•Occurs more in teenaged-girls than boys.
Secondary causes of osteoporosis
•These include prolonged glucocorticoid therapy, which increases bone resorption and reduces bone synthesis. Cigarette smoking and excess alcohol also can result in reduced bone mass.

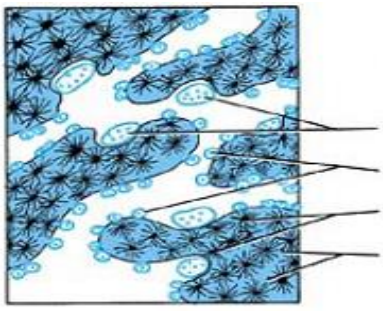


Clinical features:

- **Difficult to diagnose**
- **Remain asymptomatic ---- Fracture**
- **Fractures**
  - **Vertebrae**
  - **Distal radius (Cole's fracture)**
  - **Hips**
  - **Femoral neck**
- **Patients with osteoporosis have normal serum levels of calcium, phosphate, and alkaline phosphatase.**

OSTEOPOROSIS

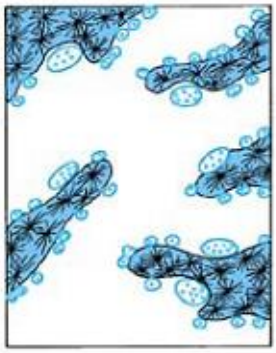
Diagnosis	Prognosis	Prevention strategies
1. Plain X ray: cannot detect osteoporosis until 30% to 40% of bone mass has already disappeared. 2. Dual-emission X-ray absorptiometry (DXA scan): is used primarily to evaluate bone mineral density, to diagnose and follow up pt. with osteoporosis.	• Osteoporosis 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, pulmonary embolism and pneumonia --vertebral bodies fractures may lead to progressive loss of height and pain or may cause deformity of the spine(kyphosis)	• 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 • Taking hormonal replacement therapy.



Normal
Normal trabeculae and calcification

Osteomalacia
- Trabeculae normal in size but only partially calcified
- Surface shows "seams" of uncalcified osteoid
- Often increased osteoblasts
- Results:
  - Soft bones
  - Weakness
  - Deformity
  - Fracture

Hyperparathyroidism
- Increased osteoclasts erode bone
- Compensatory increase in osteoblasts insufficient to restore trabeculae
- Normal calcification of residual bone
- Fibrosis of marrow spaces with giant cells



Osteoporosis
- Thin, sparse trabeculae
- Calcification normal
- Normal osteoblasts, osteoclasts
- Results:
  - Weakness
  - Fractures

Laboratory Findings in Metabolic Bone Disease

	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Parathyroid Hormone (PTH)
Osteoporosis	N	N	N	N
Osteomalacia (rickets)	↓	↓(↑)[1]	↑	N(↑)
Primary hyperparathyroid bone disease	↑	↓	N↑	↑
Bone disease in renal failure—with secondary hyperparathyroidism	N↓	↑	↑	↑
Lytic bone neoplasms	N↑	N↑	N↑	N
Paget's disease of bone	N	N	↑	N

MCQs

1- Which of following strategies can provide the best overall long-term reduction in risk of fracture from osteoporosis in women? Page 278 Q 27

(A) Supplement the diet with calcium and vitamin D after menopause.

(B) Begin estrogen replacement therapy after a fracture.

(C) Increase bone mass with exercise in childhood and young adulthood.

(D) Limit alcohol use and avoid use of tobacco

2- After a minor fall, a 63 year old woman sustains a complete right femoral neck fracture. Of the following conditions, the most significant contributing factor for this fracture is Page 276 Q 13

(A) Multiple myeloma

(B) Vitamin D deficiency

(C) Chronic osteomyelitis

(D) Postmenopausal bone loss

3- In a 75 year old male, which of the following processes contributes to the occurrence of osteoporosis?

(A) Decreased production of osteoid by osteoblasts.

(B) Increased resorption of bone by osteoclasts.

(C) Synthesis of chemically abnormal osteoid.

4- A 2-year-old child has a history of multiple bone fractures with minor trauma. Radiographs reveal diffusely and symmetrically sclerotic bones with poorly formed metaphysis. He is treated with bone marrow stem cell transplantation. Which of the following cells in his bones was most likely functionally deficient and replaced following transplantation?

(A) Chondroblast

(B) Chondrocyte

(C) Osteoblast

(D) Osteoclast

(E) Osteocyte

5- A 5 year old child has a GI tract problem that causes malabsorption of a certain substance. The same disease seen in adults is known as osteomalacia. What condition is also associated with the deficiency?

A. Osteoporosis
B. Osteopetrosis
C. Scurvy
D. Cushing's syndrome
E. Pneumonia of the Lung

6- A 15 year old boy has shortened limbs and ribs, frontal bossing of the forehead, bowing of the limbs, his IQ however is normal. The cells that are affected in his disorder are:

A. Osteoclasts
B. Chondrocytes
C. Osteoblasts
D. Macrophages
E. Osteocytes

7- A patient presents with multiple fractures and blue sclera of the eye. The same disease in infants would result in:

A. Death
B. Tumor of the bone
C. Fractures
D. Blue sclera
E. A C and D

1 C, 2 D, 3 A, 4 D, 5 A, 6 B, 7 E