

Biochemistry 2 :- Dr. Odeh :-

⊕ Bone disorders

① Osteoporosis → thin bone disease.

② Osteopetrosis → thick bone disease.

③ Rickets / Osteomalacia → nutritional bone disorders.

↳ ↓ level of vitamin D and calcium.

④ Paget's disease → ↑ bone turnover.

thickening يصير أكثر جوا لـ B.M الـ bone صلبا الـ periosteum وكذا الـ
 subperiosteum بغير عظام الـ cortical bone جوا الـ trabecular الـ spongy bone
 وداخلها جوا لـ trabeculae - spongy bone الـ B.M
 ↑ to bone density يصير عظم

Osteopetrosis

- Defective **osteoclast activity** → defective bone resorption → buildup to bone ↑
 ↳ Thick bone
- Osteoblastic activity >> osteoclastic activity
- **Increased** bone density

autosomal dominant variant

autosomal recessive variant

balance بين الـ thickness العظم

Fracture بغير الـ resiliance العظم بظهوره على حساب الآخر بغير

osteopetrosis الـ thickness الـ bone عظم الـ risk to fracture لك الاثنين

pathological thickening

⊛ Autosomal recessive → بغير أكثر بغير في العظام

Osteopetrosis

Autosomal recessive (infantile) form

- Most severe form
- Presents in infancy
- Mutations in carbonic anhydrase type II gene
- Also may have renal tubular acidosis
- Children may have seizures, intellectual disability

لا يستطيع إنتاج osteoclast
عشيرة يصير يطفئ acid
عاشق - defective
فان osteoclast يتكون - defective

Autosomal dominant form

- Albers-Schönberg disease
- Presents in adolescence
- Milder form of disease
- May be asymptomatic - identified by x-ray

تتراكم عندكم acid
لا يستطيع osteoclast
بتفئة بشكل أساسي
acid
ويكون defective

دهار
severe form
في الصغار

يمكن يصير fracture أولاً
الأول مرة يجي accidentally وينمو x-ray

التي تأتي سنالتي عنده صورة صرفة 6 لك واحد يمكنها لتتأخذ

85% يتبين في x-ray بنالتي bone عنه في
kidney stones
الصورة

بعض يمكن يجي لادامة بالaccidentally
يتصور لاني تأتي 6 أو لادامة صوته
وكا - في
pathological fracture

Osteopetrosis

- Bones prone to fracture
- Excess bone → loss of bone marrow →

دست به خطه spongy
B.M و invasion

• Pancytopenia

- Enlarged liver and spleen (extramedullary hematopoiesis) → secondary.

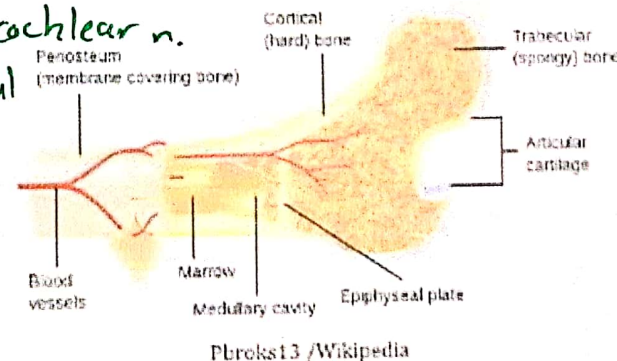
- Excess bone in skull → **cranial nerve compression**

- Vision loss → optic n.
- Deafness → vestibulo cochlear n.
- Facial paralysis → Facial n.

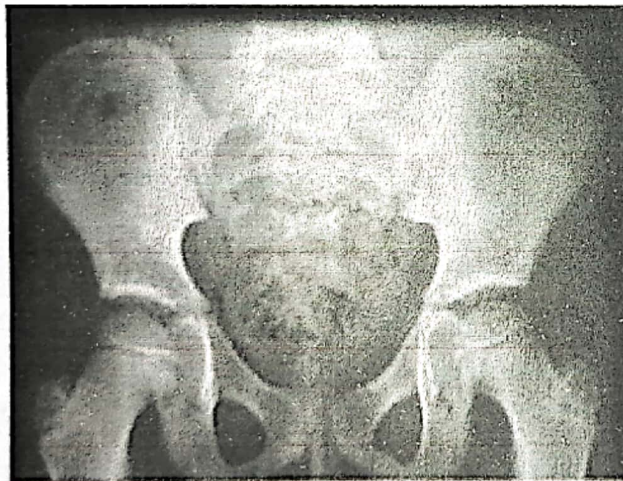
- Hydrocephalus

↳ ↑ ICP.

cranial nerves و
Foramina ص
بنا skull
في skull
بنا cranial n.
بنا Foramen
و thickening
compression



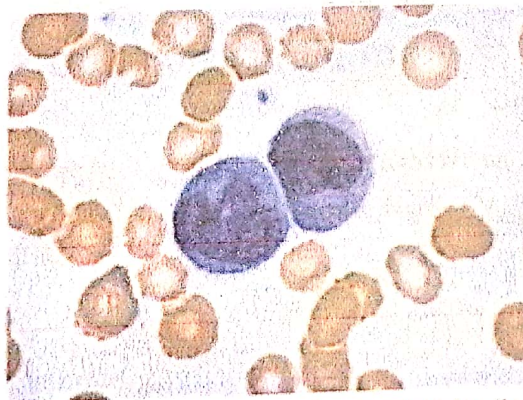
Osteopetrosis



④ ١٠ origin ١٢٠ osteoclasts ١٣٠ monocytes ١٤٠ macrophages ١٥٠ B.M transplant ١٦٠ macrophages ١٧٠ monocytes ١٨٠

Osteopetrosis

- Potentially curable with **bone marrow transplant**
- Used for infantile form *not in adult form.*
- Osteoclasts derived from monocytes/macrophages



Dr Graham Beards/Wikipedia

→ children

→ children and adolescent

Rickets and Osteomalacia

- Nutritional bone disorders
- Low calcium or vitamin D intake

↓ Ca^{+2} low

دائماً يظهر بسبب

low vitamin D intake

very rare نادر

↓ Ca^{+2} نادر

with normal vitamin D

فدائماً ↓ vitamin D

↓ Ca^{+2} هو الذي يولد



① bone لا يتكثف في عظام osteoid الموجود (موجود في مشكلة في الـ osteoporosis) + الـ mineralization بالـ vitamin D , Ca^{+2} .

Rickets and Osteomalacia

- Poor mineralization of **osteoid**
 - Non-mineralized bone matrix
 - Mostly proteins → without calcification [No Ca^{+2} or phosphate]
 - Laid down by osteoblasts
 - Later mineralized with calcium and phosphate
- Sites of osteoid and new bone growth:
 - Children: Growth plates
 - Children and adults: Bone turnover



growth بصير في الـ plate
diaphysis الـ
epiphysis في المنطقة
التي بصير فيها bone
resorption . بصير في bone resorption
تكون الـ bone

- Sites of mineralization

① end plate between diaphysis and epiphysis

مشكلة في الـ rickets.

② Osteoporosis → osteomalacia.

rickets في الـ osteomalacia في (التي) الـ bone resorption بصير في (التي). الـ growth plate بصير في الـ bone

Growth Plates

- Found at ends of long bones in children → between diaphysis and epiphysis.
- Contains hyaline cartilage
- Chondrocytes grow toward epiphysis
- Osteoblasts lay down matrix toward diaphysis

Failure of elongation.



Gae1969/Wikipedia

Rickets

- Growth plate thickens [widening and fraying]
 - Chondrocytes expand (disorganized growth)
 - Osteoblasts lay down **osteoid only** → osteoid without mineralization.
- Bone thickening from **osteoid accumulation**
- Distorted bone growth

most common cause of rickets → nutritional deficiency.

Chronic - celiac disease & malabsorption (e.g. Crohn's) &
absorption liver disease - chronic pancreatitis
of fat soluble vitamins.



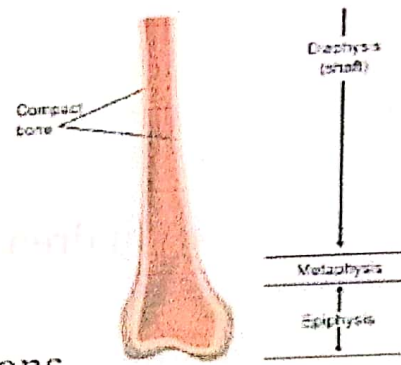
So malabsorption whatever the cause → rickets.
one of the fat soluble vitamins is vitamin D
soluble vitamins.

Rickets

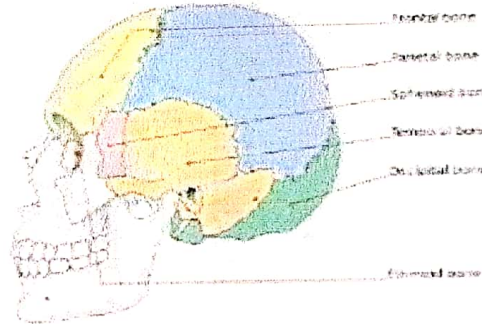
في الكبار رickets كائنة

- Epiphyseal widening
- Bowed legs (genu varum)
- Swelling at costochondral junctions
 - Rachitic rosary
- Craniotables (soft skull)
 - Occipital/parietal bones
 - Collapse with pressure

بنضض لوبه حل الجوازي ماسي
reconerter.



BruceBlair / Wikipedia



subcostal + بار
rib كسار
الاضغني
sulcus groove
داخلجا
اعنه

harrison groove
لهودار

rachitic rosary

cheil manifestation

* Craniotabes

- ① Rickets
- ② Delivery [pre mature]
- ③ Syphilis.
- ④ Thalassaemia
- ⑤ Osteogenesis imperfecta.

اکثر ایسی ہی ۱۱
wrist

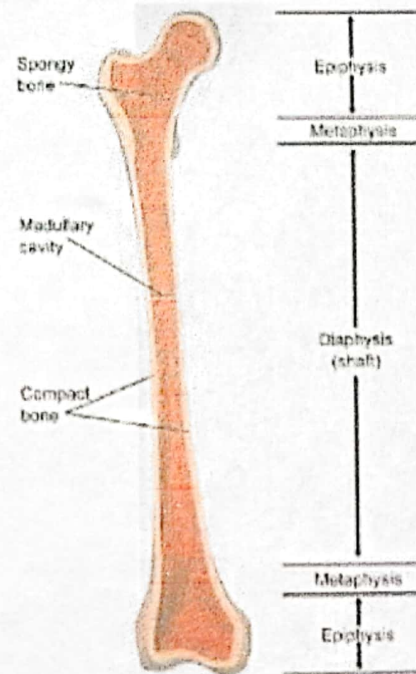
[radius and
ulna]

۱۱ کے دو لمبے ہڈی
ہیں۔

Epiphyseal Widening

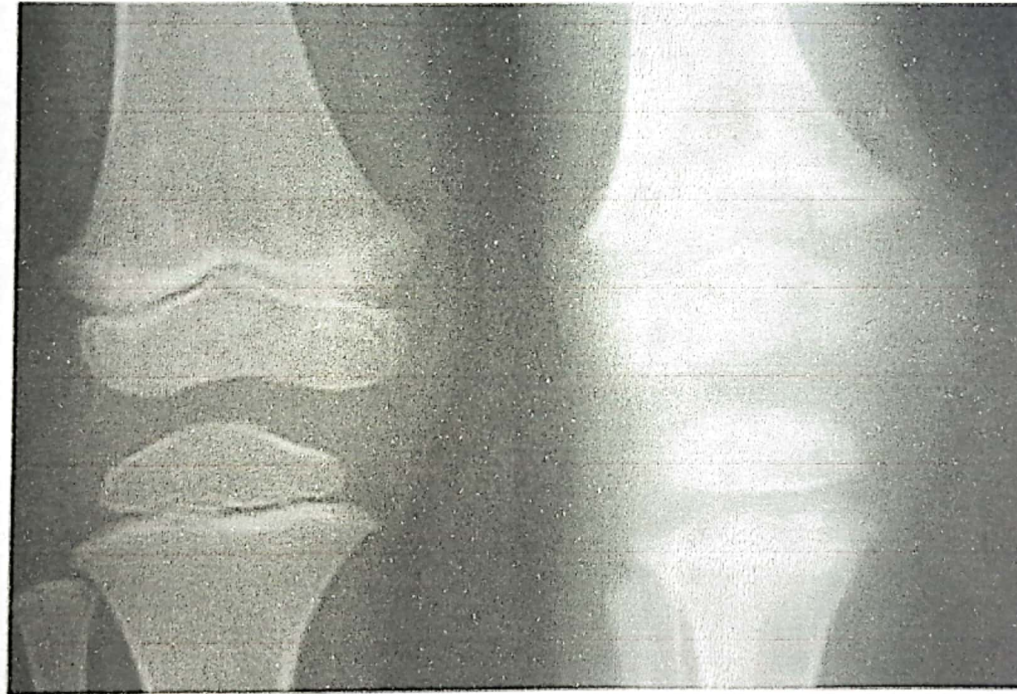


Wikipedia/Public Domain



BruceBlaus /Wikipedia

Growth Plate Fraying + widening.



Normal

Rickets

Pro Faather/Slideshare

So, widening and fraying to growth plate are specific to rickets.

Genu Varum [Bowling legs]

لہ داخلین لہوا.

① genu valgus → لہوا.

① genu varum in adults
can be due to
Paget's disease.

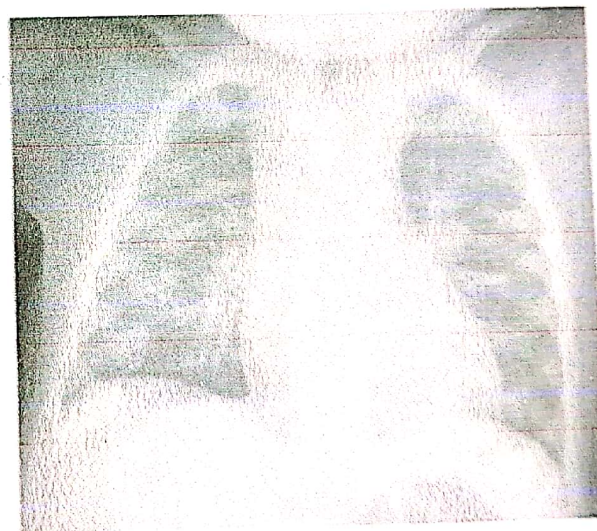


Michael L. Richardson, M.D./Wikipedia

Rachitic Rosary



Ma Wady/Public Domain



Frank Gallard/Wikipedia

① Osteoporosis - osteopetrosis - osteomalacia - rickets → systemic diseases.

② Paget's disease → localized disease.

Osteomalacia

- Children and adults
- Occurs in areas of bone turnover / resorption
- **Bone pain/tenderness** → most common 1st presentation
- Most often spine, pelvis, and legs
- Fractures

المرض يصيب
العظام
وخصوصاً
الوركين

Fracture
(hip)

ألم في العظام
والألم في الوركين
Common
pain و tenderness

Osteomalacia

Two classic x-ray findings:

- Pseudofractures
- Looser Zones

Caused by:

- Repaired stress fractures, inadequately mineralized
- Erosion of bone by arterial pulsations

X-ray [بسیفخار]

Fracture دینفر ایچ

لگن و مش

هیک

ولا

Fracture

قدیم

major or minor

of bone

pulsation

صغیر و pulsation

cavity

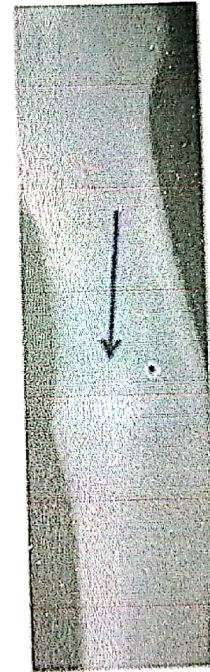
منطقه عین

[pseudofracture - looser zone]

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Pseudofracture

Fracture ما انشجوة بنفكره
injury قديم ما لكنا صحتك يكو -
healing وصلا لهاله

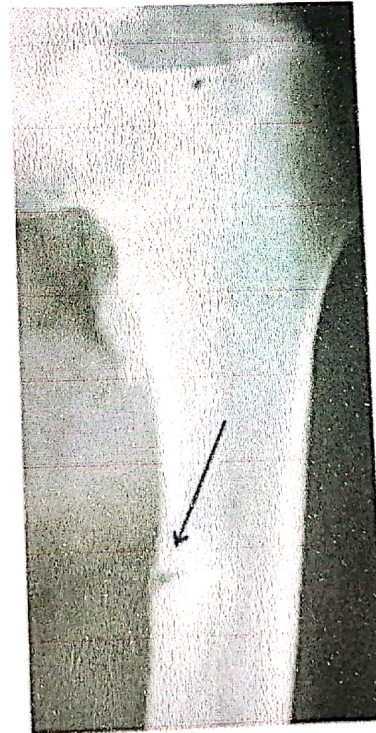


Calgary Centre / Sideshare

Looser Zone

green-stick ^ق
Fracture

Failure of ^{فشل}
bone resorption



Pinterest/Public Domain

backwards ileitis ulcerative colitis ileum (الجزء) حالة ١

↳ 10% → due to incompetent valve.

⊗ Chronic pancreatitis can cause malabsorption → pancreatic secretions defect.
[exocrine duct].

Rickets and Osteomalacia

Causes

• Vitamin D deficiency

- Maternal deficiency during pregnancy ← pregnant lady needs vitamin D
- Reduced sun exposure → Female
- Fat malabsorption → most common cause.
- Cystic fibrosis, pancreatitis, Celiac disease, IBD → cystic fibrosis → pancreatitis is obstructive jaundice.
- Liver and renal failure (both activate vitamin D) ← liver and kidney produce vitamin D

• Calcium deficiency (rare)

- Only seen with severe dietary deficiency

• Treatment: **Vitamin D and Ca supplementation**

↳ very rare in the absence of vitamin D ↓

Rickets and Osteomalacia

Lab Findings

- ↓ Calcium
- ↓ Vitamin D

↑ alkaline phosphatase.

cholecalciferol $\rightarrow$ activation in liver by ~~25~~ 25-hydroxylase

Vitamin D

- Liver: 25-OH Vitamin D (calcidiol)
- Kidney: 1,25-OH₂ Vitamin D (calcitriol; active form)

sub best $\leftarrow$ 25-OH Vitamin D = storage form $\rightarrow$ calcidiol [inactive form]

test of measurement $\leftarrow$ Constantly produced by liver
Available for activation by kidney as needed

to vitamin D $\leftarrow$ Serum **25-OH VitD** best indicator vitamin D status

synthesis

ii calcidiol.

بالا زنجیر ال $\leftarrow$ vit. D $\leftarrow$ skin $\leftarrow$ nutrition $\leftarrow$ liver $\leftarrow$ calcidiol $\leftarrow$ activation

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PTH $\rightarrow$ calcitriol $\leftarrow$ calcidiol

Rickets and Osteomalacia

Lab Findings

- ↑ Parathyroid hormone (PTH) → due to ↓ vitamin D and Ca^{2+}
 - Normal response of parathyroid gland
- ↓ Phosphate
 - Excretion promoted by PTH
- ↑ Bone alkaline phosphatase
 - ↑ osteoblast activity

hypophosphatemia (في حالة نقص) secondary hyperparathyroidism (في حالة زيادة)

hyperparathyroidism → hyperphosphatemia → renal failure

→ no ability to excrete phosphate

(HAGMA)

→ AG > 10-12.

Paget's Disease → localized disease.

Osteitis Deformans

- **Focal** disorder
- Common in **older patients**
 - Average age at diagnosis: 70

Paget's Disease

Osteitis Deformans

- Excessive bone remodeling
- Overgrowth of bone at focal sites of bone → subperiosteal necrosis.
- New bone: abnormally large, deformed ← مناطق خضفا
- Exact cause unknown
- Believe to be due to abnormal **osteoclasts**

osteoclast
زيادة و مناطق
osteoblast
عالية وفي
الاستن.

osteoclastoma (Brown tumor) → osteoclastoma
bone lytic lesion. ← انسحبا Ca^{+2} plus

Paget's Disease

Osteitis Deformans

- Evolves through phases/stages
- Initial phase: **osteolytic**
 - Osteoclasts breakdown bone
 - Bizarre shape, numerous
 - Multi-nucleated
- Mixed phase: osteolytic-osteoblastic
- Final phase: Osteosclerotic → osteoblastic activation.
 - Bone formation dominates
 - **Hypervascularity** of bone occurs

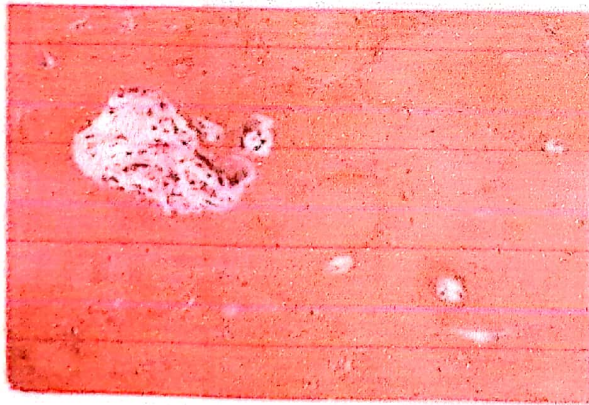
↳ high cardiac output HF
[rarely]

Paget's Disease

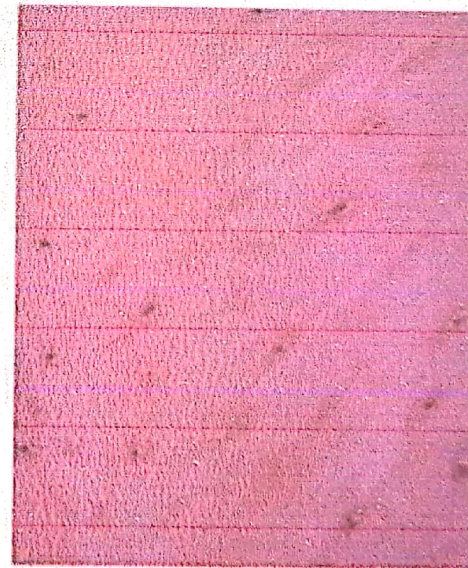
Bone Morphology

- Hallmark: mosaic pattern of lamellar bone
- Cement lines

Paget's



Normal



Paget's Disease

Clinical Features

- May be asymptomatic
- Often affects long bones, skull, spine
- Pathologic fractures (most common complication)
 - "Chalkstick" fracture → *کانه طبرستور*
- Bone pain (microfractures) *بسنکسر*
- Bowing of legs

Fragile fracture

Chalkstick Fracture



Hellerhoff/Wikipedia

Boards & Beyond

علاج D1AS

[dynamic hip
screw]

أو البلاستيك.

Paget's disease is a rare cause of radiculopathy.

Paget's Disease

Clinical Features

- Enlarged skull (increased hat size)
- Cranial nerve compression (deafness) → vestibulocochlear n.

← متلازمة عار → Radiculopathy at spine → Compression on spinal cord.

- Erythema may occur over affected bone area
 - Due to hypervascularity

↳ high cardiac output failure.

lambosacral
plexus

بجسر

limbing →

بشيء عجيب

due to fragility of bone.

Paget's Disease

Clinical Features

- **High output heart failure** → (rare)
 - AV fistula in new bone
- Osteosarcoma
 - Increased risk in Paget's disease

mechanism of high CO & HF

arterioles, AV shunt, artery, venule, vein, (highly resistance)

Boards & Beyond, arterioles, artery, venule, vein, network, arterioles, venule, vein

① diameter of arteriole, resistance, artery, capillary meshwork, highly resistance



paget's disease, AV shunt, artery, vein, heart

→ preload of heart, HF

high cardiac output, HF

* Causes of high cardiac output HF

- ① AV shunt → patent foramen ovale.
- ② Hyperthyroidism.
- ③ Anemia.
- ④ Pregnancy
- ⑤ Aortic regurgitation
- ⑥ Fever.
- ⑦ Beriberi disease.

* Beriberi disease

vitamin B $\rightarrow$ B₁-12.

B₁ $\rightarrow$ thiamine.

B₂ $\rightarrow$ riboflavin.

* B₆-9-12 $\rightarrow$

الحصين.

* vitamin B₁ deficiency / thiamine deficiency
beriberi disease. لـ بـ ١

pulmonary edema
ولا
← جـب الرئـة حـاد
wet beriberi $\rightarrow$ pulmonary edema.
dry beriberi $\rightarrow$ cough.

Paget's Disease

Clinical Features

- Increase **bone alkaline phosphatase** → ↑ osteoblastic activity.
- Treatment: bisphosphonates and calcitonin

management
osteoporosis.

hypercalcaemia
[hyperPTH]

side effects

① drug-induced esophagitis

التي يتسببها دواءنا
لهذا نلزم أن نرتب

doxycycline
ويشربوا ماء بعده وهو واقف زيار

② Joint necrosis.

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⊕ Furosemide [Lasix] → ↑ Ca^{+2} .

⊕ Tacrolimus and cyclosporine → hyperuricemia.
alopecia
hypertrichosis.

Osteitis Fibrosa Cystica

- Classic bone disease of **hyperparathyroidism**
- Clinical features: Bone pain and fractures
- Parathyroid adenoma
 - ↑ PTH
 - Hypercalcemia
 - ↓ Phosphate

↑ PTH ~ ٢٠-٤٠%
secondary ١٠-١٥%
~ ١٠%

normal Ca^{+2} level,

primary - tertiary → hypercalcemia.



↑ PTH ١٠-٢٠%
~ ١٠% hypophosphatemia
renal failure
[secondary]

75% single adenoma
20% hyperplasia
4% multiple adenoma
1% malignancy.

→ primary - secondary - tertiary.

→ osteoclastic activation.

[Osteoclastoma - brown tumor] → osteitis fibrosa cystica.

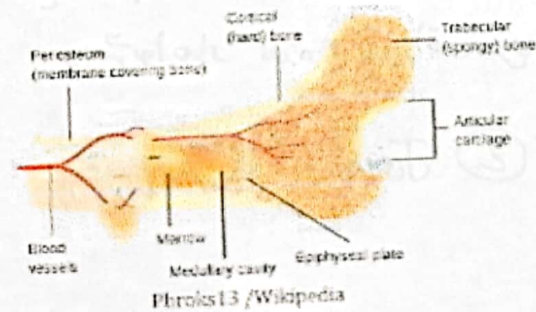
Osteitis Fibrosa Cystica

- **Subperiosteal** bone resorption [hard / cortical bone].

- Commonly seen in bones of fingers
- Irregular or indented edges to bones

- **Brown tumors** (osteoclastoma) → accumulation of osteoclasts → bone resorption

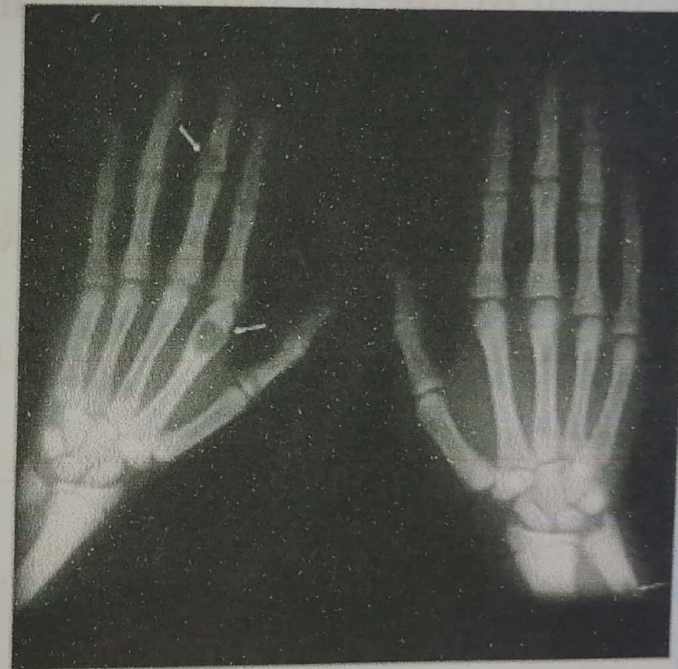
- Collections of giant osteoclasts in bone
- Mixed with stromal cells and matrix proteins
- Appear as black spaces in bone on x ray



lung

دبره موجود بنی ار
bone

Osteitis Fibrosa Cystica



Frank Gaillard/Wikipedia

PIP / DIP /
metacarpals

Boards & Beyond

bone lytic lesion.

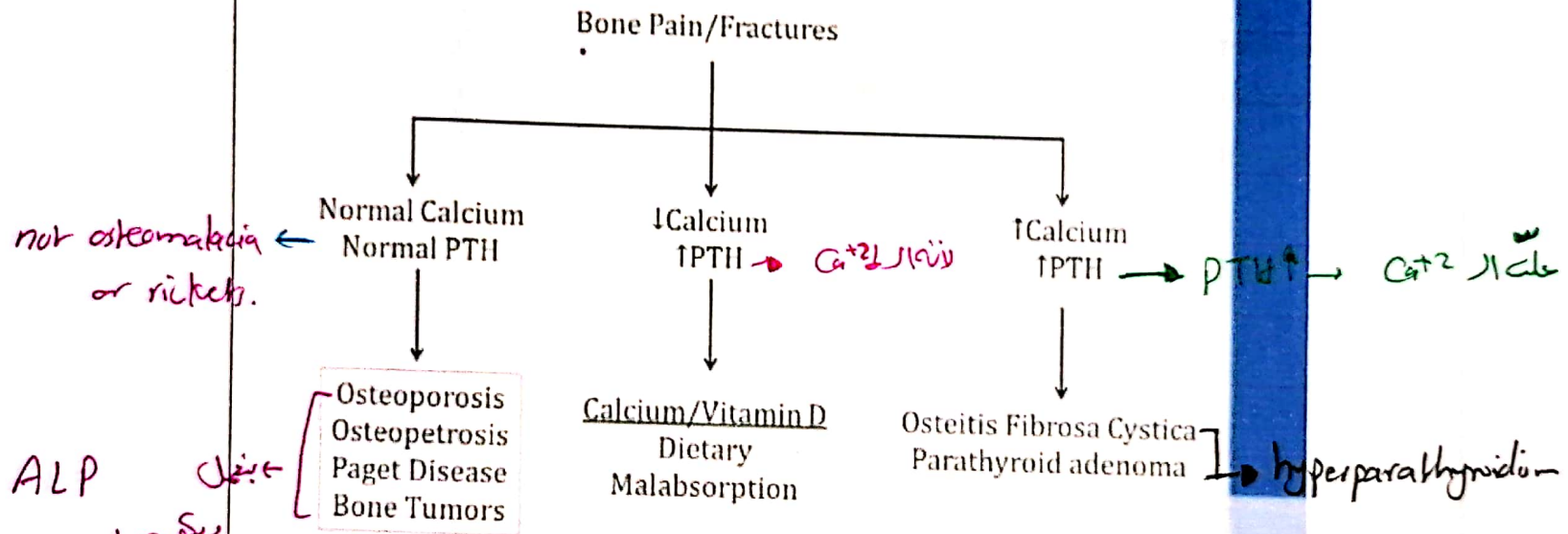
* Differential diagnosis of hyperthyroidism

- ① Multiple myeloma.
- ② Follicular thyroid carcinoma.
- ③ Bone tumors.
- ④ Histocytosis.

patients who are fragile/pathological fracture from minor trauma
 approach to trauma.

tests, Ca^{2+} and PTH

Bone Pain/Fractures



ALP
 normal ~
 osteoporosis
 osteopetrosis
 Paget disease

Boards & Beyond

① Paget disease of bone → isolated elevated alkaline phosphatase level. → normal calcium.

embolization
 Paget's disease of bone → Ca^{2+} low
 hypercalcemia → Ca^{2+} high

Osteoporosis → common in elderly

- Porous bone → disease of elderly / estrogen deficient females.
- **Weak bones** prone to fracture
- No clinical symptoms until fracture



Normal bone



Osteoporosis

Terminology

- Osteopenia: ↓ bone mass
- Osteoporosis: markedly ↓ bone mass
- Osteoporosis associated with ↑ fracture risk

[advanced stage of osteopenia].

Osteoporosis

ileum - femur

Trabecular bone > cortical bone

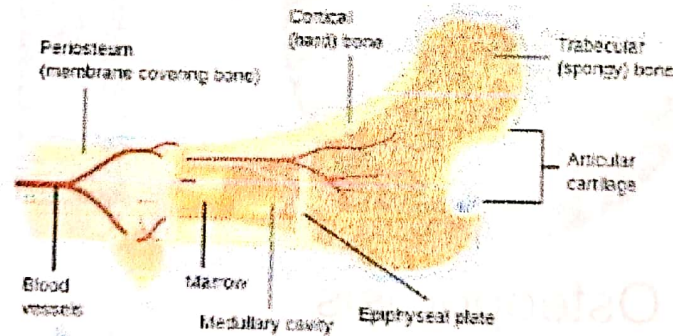
- Trabecular bone: high surface area →
- Osteoblasts/osteoclasts found on surface

نصف مساحتی

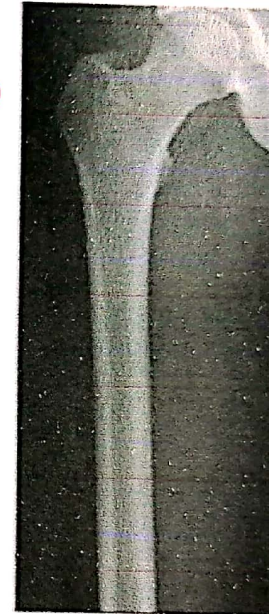
High trabecular bone content:

- Spine
- Head of femur (hip)
- Wrist (distal radius)

جوشن لار
osteoporosis.



Phroks13 / Wikipedia



Boards & Beyond

Osteoporosis

- Common in elderly, white women

سفي انك في ال black في الـ

- Peak bone mass
في عمر 30

dexascan لذكور

30 highest peak bone mass.



30-40 years.

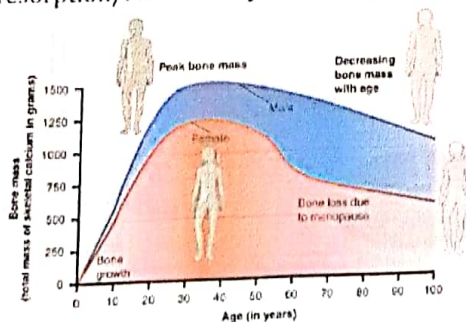
male 7 female →

decelation ال female ال

Peak incidence 51.8 year old. menopause
Peak bone mass male ال female ال

Bone Mass

- Peak bone mass occurs in young adulthood
- Many influences: gender, genetics, diet - ethnicity [black < white].
- Decreases slowly thereafter
- Each resorption/formation cycle → some bone loss



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OpenStax College/Wikipedia

Female → osteoporosis.

Male → thrombosis (الجلطات)

weight bearing activities $\rightarrow$ $\uparrow$ bone mass - $\downarrow$ risk of osteoporosis.

لذلك female أكثر عرضة لـ osteoporosis لأنهن male في هياكل activities أكثر.

Bone Loss

$\rightarrow$ $\uparrow$ bone resorption.

- Males achieve higher peak bone mass
- Bone loss less likely to lead to osteoporosis
- **Weight-bearing activity** $\rightarrow$ $\uparrow$ bone mass



Everkinetic/Wikipedia

Boards & Beyond



Menopause

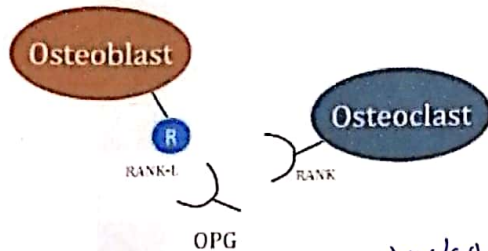
- Accelerates bone loss in women

تسبب في حالة الـ
steroids/
glucocorticoids.

Caused by **estrogen deficiency**

- Increased osteoclast activity
- Increased levels of RANK-L
- Decreased osteoprotegerin (OPG)

steroid excess =
estrogen $\downarrow$



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الـ $\downarrow$ estrogen يجل العكس.
 $\uparrow$ osteoclastic activity.

② $\downarrow$ RANK receptor.

① خلل في estrogen في الـ
Fracture
في الـ osteoblast على الـ
[RANK-L]
① osteoclast على الـ receptor الـ RANK-L
② OPG لا يوجد.
الـ RANK-L اذا ارتبط بالـ osteoclast
يسبب الـ activation في الـ
RANK receptor أكثر $\leftarrow$ osteoclast $\uparrow$
osteoporosis $\uparrow$
OPG كـ يـ أكثر $\leftarrow$ osteoclast
ربط الـ RANK-L

① $\uparrow$ OPG $\leftarrow$ الـ estrogen $\downarrow$

Osteoporosis

- Most osteoporosis: ^{elderly.} senile/postmenopausal
- **Calcium, PTH, Alkaline phosphatase all normal**
- Less commonly: **secondary** osteoporosis

^{late stages} ^{bone} ^{abnormal} ^{PTH} ^{abn}
↳ in children.

secondary to steroids -

hyperthyroidism hyper PTH ^{dim} - heparin-

anti-convulsant.

Osteoporosis

- Most osteoporosis: senile/postmenopausal
- **Calcium, PTH, Alkaline phosphatase all normal**
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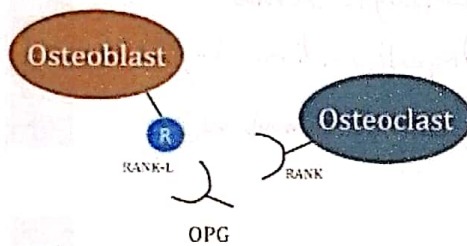
Osteoporosis

Secondary Causes

Glucocorticoids

- Increase bone resorption
- Reduce bone formation
- Suppress synthesis of OPG
- Increase RANK production

[Cushing's - idiogenic - Rheumatoid arthritis - immunosuppressant (auto-immune disease).]



Boards&Beyond

مقبول
estrogen
بمقابل OPG
مقبول
RANK
receptor.

Osteoporosis

Secondary Causes

Alcohol

- Heavy use associated with osteoporosis
- Often leads to falls/hip fracture
- Moderate use effects not clear

Smoking

- Accelerates bone loss



Pixabay/Public Domain



Pixabay/Public Domain

Boards&Beyond

alcohol abstinence
and smoking
cessation
are lines of management
of management of
osteoporosis.

+ Drugs.
as anti-convulsants

⊕ Indications for using steroids →

① IBD.

② Rheumatoid arthritis

③ Auto-immune diseases.

④ Transplantation.

⑤ Addison.

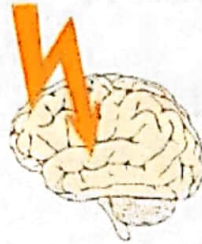
⑥ Asthma.

⑦ Glomerulonephritis.

Anticonvulsants

→ Tegretol.

- Phenobarbital, Phenytoin, Carbamazepine
- Used to treat seizures/epilepsy
- Risk of osteoporosis with long term therapy
- Increase activity of **P450 enzymes**
- Increases breakdown of vitamin D
- Less calcium → increased PTH → bone loss



Osteoporosis with ↑ PTH.

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Pixabay/Public Domain

Anticoagulants

لذلك نستعمل الـ

dexan

long-term

management

unfractionated

ما يستعمله الـ

long term

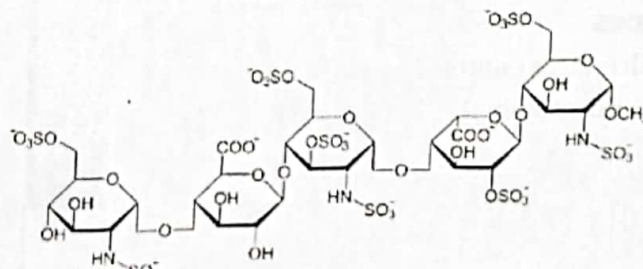
side

side effects

أو

• Unfractionated Heparin

- Decreases bone formation
- Increases resorption
- Only with long term use
- Low molecular weight heparin: unclear bone effects



Unfractionated Heparin

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lyt - osteoporosis - Addison - bleeding.

Thyroid Replacement

- **Hyperthyroidism** → osteoporosis/fractures
- Levothyroxine (T4) used in **hypothyroidism**
- Too high dose → **iatrogenic hyperthyroidism**
 - If mild may produce no symptoms
- Key test: TSH
- If TSH is low ("suppressed") need to lower dose
- Many elderly, post-menopausal women take T4

$TSH \downarrow \rightarrow T_3-T_4 \uparrow$

~2% levothyroxine next dose

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osteoporosis

hyperthyroidism

Osteoporosis

Secondary Causes

- Hyperparathyroidism
- Hyperthyroidism
- Multiple myeloma
 - Myeloma cells → Increase osteoclast activity
 - Results in "lytic" bone lesions of MM
- Malabsorption syndromes
 - Celiac disease, Crohn's, Ulcerative Colitis
 - Poor absorption calcium and vitamin D

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Osteoporosis

Diagnosis

- **Fragility fracture** [clinically]
 - Fall from standing height or less
 - Not from major trauma (i.e. MVA) or RTA
 - Spine, hip, wrist, humerus, rib, or pelvis
 - Also a spontaneous vertebral "compression" fracture
- **T score of -2.5 or lower**

↳ DexaScan.

minor trauma.

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DXA

Dual-energy X-ray absorptiometry

- Two X-rays of different energy levels aimed at bones
- **T score:** patient BMD vs. healthy 30-year-old BMD
- Normal: -1.0 or higher (least fractures) → O = الطبي
- Osteopenia: -1.0 to -2.5 ← لا يحتاج
- Osteoporosis: -2.5 or lower (most fractures) ← يحتاج
- Recommended for **screening in women >65**



Nick Smith photography/Wikipedia

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بصورة دورية للمريض عنده عدد ال bone mineral density DXA عن 30 years. of age
 T-score. ال
 ال Peak. ال

Fractures

- Hip
 - Weight-bearing joint
 - Easily injured from fall
- Spine
 - Lower thoracic/lumbar spine
 - "Compression" fractures
 - Often occur slowly over time
 - Minor trauma of daily activities
 - **Loss of height**
 - Kyphosis (forward curved spine)
 - Back pain



James Heilman/Wikipedia

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اکتے ایسی موجود ہیں
Femur →
spongy bone.