CALCIUM HOMEOSTASIS

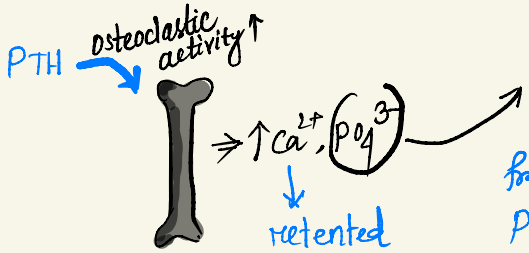
Hormones in charge of Calcium Homeostasis

→ **parathyroid hormone** - peptide
low MW
$t_{1/2}$ → ~ 25 min
↳ no binding protein

① maintain normal serum Ca^{2+} level
↳ Bone: ↑ osteoclastic activity ⇒ ↑ Ca^{2+} mobilisation
Kidney: ↑ Ca^{2+} reabsorption
GIT: ↑ Ca^{2+} absorption

② ↓ Serum PO_4^{3-} level
↳ inhibit Na^+-PO_4^{3-} co-transporter
⇓
↓ PO_4^{3-} reabsorption from PCT
⇓
↓ PO_4^{3-} serum level
potentially wastes PO_4^{3-} in urine

③ Act on **both** Osteoblastic & osteoclastic activity
↓ marker - ALP
↓ marker - urinary hydroxyproline (degradat^n product of collagen)



→ excreted through kidney
⇓
free Ca^{2+} never deposits on kidney
PO_4^{3-} excreted → No $Ca_3(PO_4)_2$ formed
↓
No chance of deposition

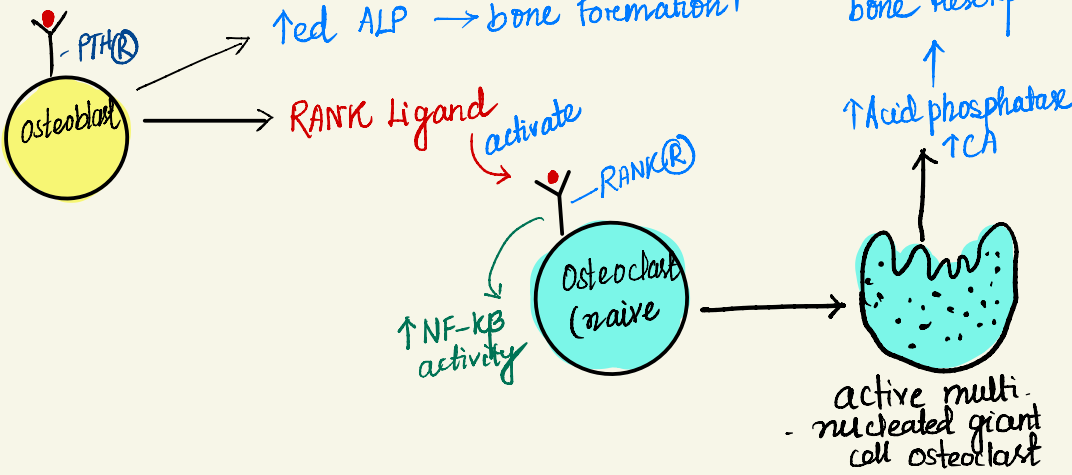
- thus PTH → hypercalcemic hypophosphatemic

→ normally 4 parathyroid gland
supernumerary glands upto 9 may be +nt

↳ consists **calcium sensitive receptores** (CASR)
(also +nt in kidney)

Note: In hyperepareathyroidism, ↑PTH → ↑serum Ca^{2+}
↓
sensed by CASR
↓
Protective mechanism → ↑ Ca^{2+} excretion

thus, ↑PTH can not cause (generally) hypercalcemia and in hyperepareathyroidism, urinary Ca^{2+} level ↑es although PTH ↑es Ca^{2+} reabsorptn (due to CASR in kidney)



PTH level	actn on Osteoblast	actn on osteoclast	funcn
physiological/ normal	⊕	⊕	bone remodelling
hyperparathyroidism (↑↑level)	⊕⊕	⊕⊕⊕⊕	bone destruction
Intermittent low dose of PTH (teriparatide)	⊕⊕⊕	⊕	bone protection

→ Vit D → can stimulate osteoblast → ↑bone formation

→ don't produce RANK Ligand → No Osteoclastic activity

→ ↑ Ca^{2+} absorption from GIT

→ ↑ Ca^{2+}, PO_4^{3-} reabsorption

↓

serum ↑ Ca^{2+}, ↑ PO_4^{3-} level

→ Calcitonin → inhibit osteoclastic activity

↓

↓ Serum Ca^{2+} level

also ↓ PO_4^{3-} level

	Ca^{2+} (serum	PO_4^{3-}
PTH	↑	↓
Vit D	↑	↑
Calcitonin	↓	↓

Osteoclast have only calcitonin receptores.

↳ No PTH & Vit D receptore.

Directly acting on Osteoclast → (Inhibition)

- Calcitonin
- Bisphosphonates (drug)
- Osteoprotogenin (natural)

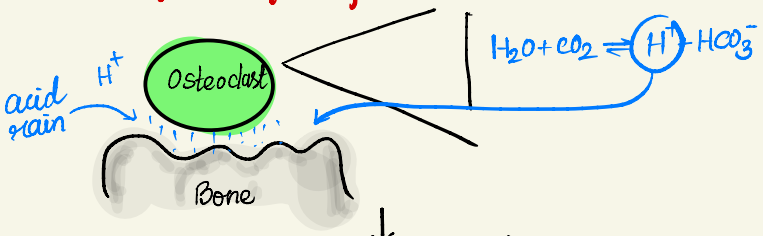
(bind to RANK (R)eceptor and inhibit binding of RANK Ligand
↓
do not stimulate osteoclast
↓
bone protection)

IL-6, Microphage activating protein (MAP) ↑ Multiple myeloma
↓
can directly activate osteoclast
↳ lytic lesions

* Denosumab (monoclonal antibody drug similare to osteoprotogenin)

Only substance directly activating osteoblast and inhibiting Osteoclast is- Strontium

Action of Bisphosphonates



↓
bone degradation
⇓
Ca^{2+}, PO_4^{3-}, collagen
↑
Normal Osteoclast bone resorption function

↓ Carbonic anhydrase → ↓ osteoclastic activity → thick, weak bone
⇓
Osteopetrosis

↓ bone matrix → Osteoporosis

1st generation bisphosphonate ⇒ gets incorporate in bone matrix

↓

osteoclast can't identify bone

- camoflage effect

Etidronate

Tiludronate

not used anymore

2nd generation / NO_3^- containing bisphosphonate

↓

encourage osteoclast to take up the bisphosphonate

↓

Inhibit & becomes toxic to osteoclast

↓

osteoclast lifespan reduces

Pamidronate (i.v./oral)

↳ needs no dose adjustment ∈ renal failure

Risedronate (oral)

3rd generation bisphosphonate

↳ highly potent

Alendronate (oral)

Zoledronate (i.v.)

} - needs dose adjustment ∈ renal failure

S/E of bisphosphonate- hypocalcemia
pill induced Esophagytis
(C/I- GERD)
Kidney Injury - nephropathy
CKD
(C/I- Renal failure)
Aseptic osteonecrosis of jaw
⊛ femur fracture (Paradoxical)
↳ subtrochanteric
(on longterm use)

uses of Bisphosphonate-, Osteoporosis
- Hypercalcemia of malignancy
- Bone metastasis.

Advise-
- lot of water ⊼ pills to avoid sticking at GIT
- do not lie down for 1-2 hrs.

CALCIUM

Ⓝ level 9-11 mg%.

- Ionised (45%) active 4.5-5.5 mg%.
- Inactive (55%)
  - albumin (45%)
  - anions (10%)

1g albumin binds to 0.8 mg of calcium.

Corrected calcium = Serum Ca^{2+} + 0.8 [4 - albumin]

Example ➤ serum Ca^{2+} = 7.5 mg%.
albumin = 2 g/dL

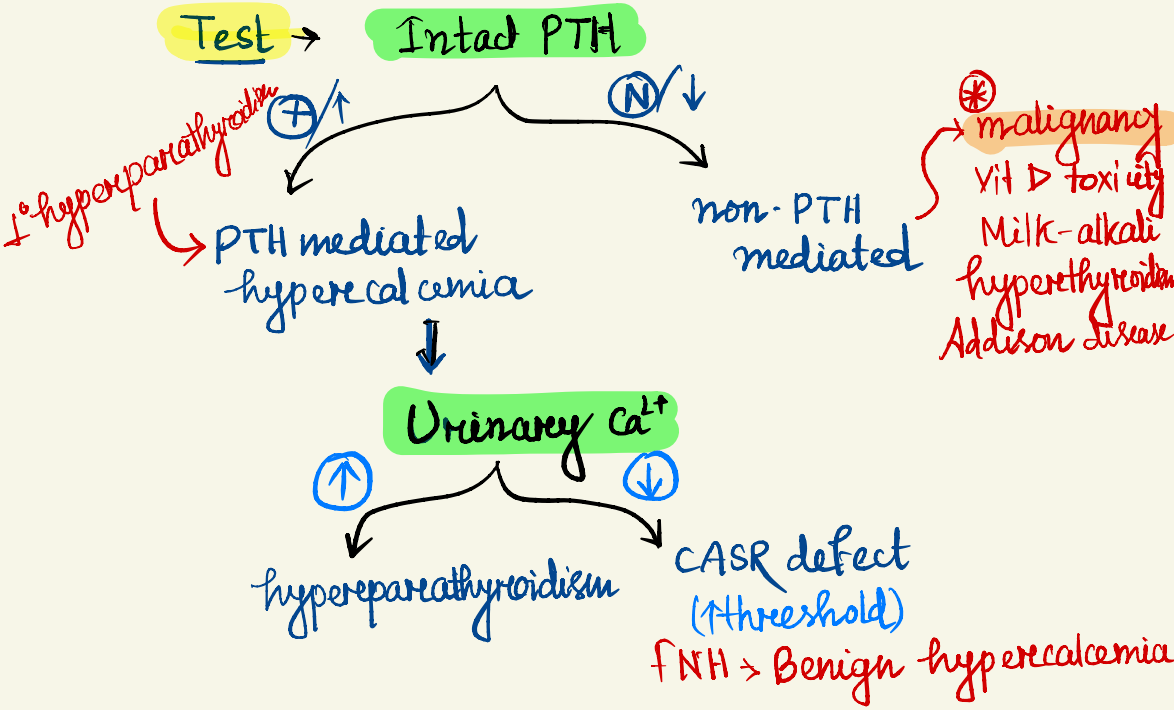
calcium = 7.5 + 0.8 × [4 - 2]

= 9.1 mg%.

↳ normal but appear hypocalcemic due to low albumin

Hypercalcemia

Mild 10.5/11 - 12 mg%.
moderate 12 - 13.5 mg%.
Severe > 13.5 mg%.
↳ M/C cause - malignancy



Mechanism Hypercalcemia of Malignancy

- PTH related Peptide (80%)
  - → work like PTH
  - → suppress endogenous PTH
- direct activation of osteoclast via MAP (20%)
- Others (<1%)

In lymphoma, sarcoidosis
activation of 1α-OHase in macrophage (normally +ntin ⊖)
that helps in ↑ 1,25-cholecalciferol
↳ ↑ Ca^{2+} absorpt^{n} from gut

dietary vit D → (N)
active vit D → (↑)

TREATMENT of Hypercalcemia

i.V. fluid (hypercalcemia induce dehydration, kidney injury, polyuria)

A
B
C

TOC → Bisphosphonate (i.v.) (to reduce calcium level)

pamidronate
↳ at emergency condition because requires no dose adjustment

Zoledronate
↳ c/I - CKD

other options - Calcitonin
Denosumab

Adjuvant therapies - steroids
↳ lymphoma, granulomatous condition

useful in PTH mediated → cinacalcet → calcimimetic
↓
stimulate CASR
↓
reduce PTH

↓

if cancer is diagnosed, then propere therapy should be done

Primary Hyperparathyroidism

Cause → parathyroid adenoma
↳ parathyroid carcinoma (very rare)

- sporadic
  - m/c site → (R) inferior parathyroid gland
- familial
  - MEN1
  - MEN2A
  - (multiglandular)

clinical features · commonly asymptomatic
if symptomatic · m/c · renal stones
→ abdominal groans
Peptic ulcer
→ psychic moans.

Investigation → ↑ Ca^{2+} → ↑ iPTH → urinary Calcium ↑

supports ∴ hyperparathyroidism

4DCT, USG, MIBI scan to localise which gland is problematic

Uniglandular

Observe or surgery

Indication

age < 50y

serum Ca^{2+} > 11 mg/dL

Renal failure (eGFR - 60ml/min)

Osteoporosis (Tscore -2.5)

Minimally invasive parathyroidectomy

Multiglandular

[test for MEN]

surgery is only option

Total/subtotal parathyroidectomy

if +nt, treatment extend.

little part of gland can be implanted in forearm - under brachioradialis muscle

leg - tibialis anterior muscle

X-Ray - lytic lesion - m/c - radial side of middle phalanx

- 24 hr urinary Ca^{2+} - >100 mg/dL
- FECA <0.01 → FHH

ECG change in hypercalcemia-

- shorted QT
- ± J waves (Osbourne waves)
- ST change

Hypocalcemia

↓

↑PTH

↓ → 1° hypoparathyroidism

cause- parathyroidectomy

Auto-immune disease

↳ APS-1

↑ → 2° hyperparathyroidism

(can occure in Vit D def.)

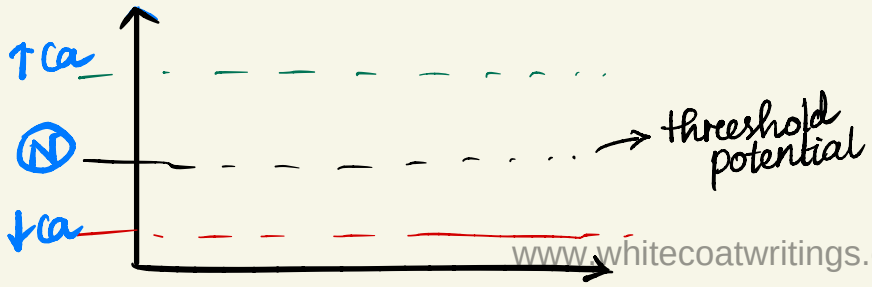
Rickets

Clinical feature- Neuromuscular irritability

Bone problems

↳ trousseau sign

tetany



ECG change - long QT
(can lead to torsade de's pointes)

Treatment - i.V. Calcium gluconate (1-2g) stat in CODE situation, Calcium chlorate
↑ central line has to be chosen

↳ fore severe patient

fore mild/moderate case - oral Calcium carbonate citrate

Vit D

Disease	$S.Ca^{2+}$ ↑	$S.PO_4^{3-}$ ↓	ALP ↑	PTH ↑
1° HPT	↑	↓	↑	↓
Malignancy (PTH rP)	↑	↓	↑	↓ (PTH related peptide ↑) (m/c - squamous cell cancer of lung)
Malignancy (lytic)	↑	↑/N	N	↓ (m/c - breast & lung cancer)
Dietary Vit D toxicity	↑	↑/N	(N)/↑	↓ (25Hcc ↑)
Sarcoidosis	↑	N	N	↓ (↑ 1-α-OHase) (1,25-HCC ↑, 25HCC N)

↓ hypoPTH	↓	↓	N	↓
Vit D def. simple	↓	N/↓	N	↑
Vit D def. complicated	↓	↓	↑↑	↑↑ - Rickets Osteomalacia
Vit D resistance Rickets	↓	↓↓	↑↑	↑

hypophosphatemic Rickets

N - 25-HCC (Vit D Normal)

Problem - PHEX gene ↓⊗ FGF 23 metabolisation ↓ ↑FGF ← ↑ lysis of 1,25-DHCC

pseudohypoparathyroidism	↓	↑/N	N	↑

↳ due to PTH receptor defect.

Clinical feature - short stature, round face, brachydactyly (4th-5th metacarpal)

↳ Knuckle knuckle dimple dimple sign

100 %

Pseudopseudohypoparathyroidism (N) (N) (N) (N)

↳ Normal biochemical profile

abnormal bone remodelling

↳ Basal ganglia calcification

differentiating c/ Vit D def.

CKD (↓) (↑) (↑↑) (↑↑)

(↓ 1,25 DHCC)

Osteoporosis (N) (N) (N) (N)

(matrix deficiency)

DXA scan req