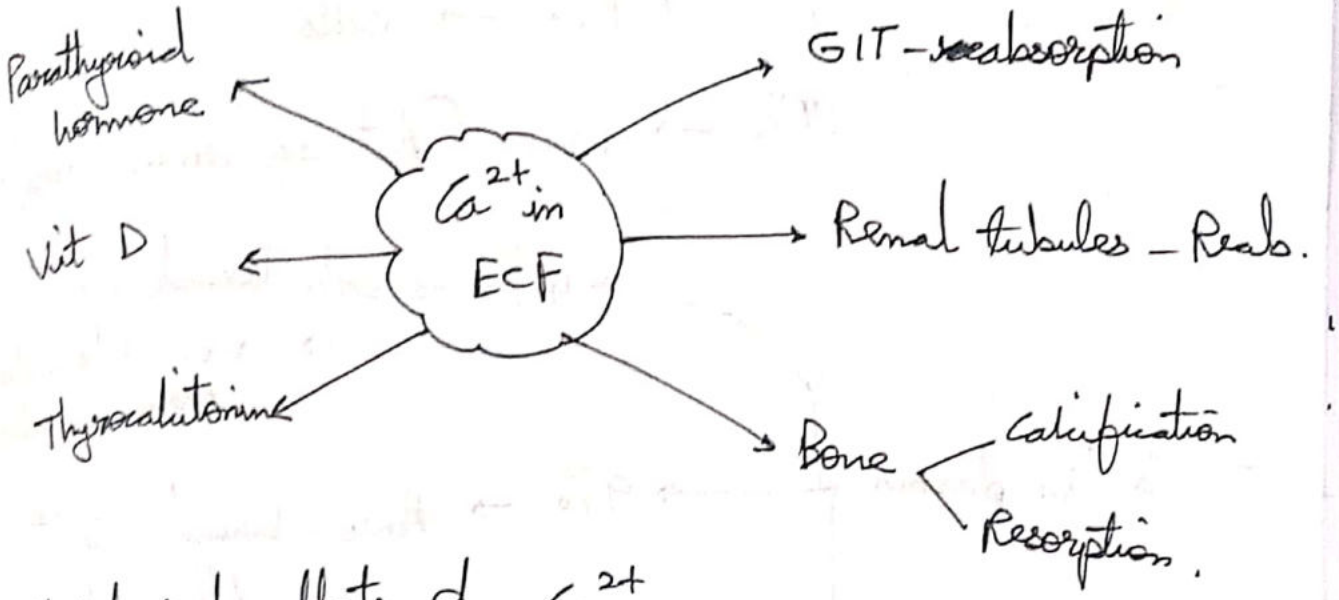
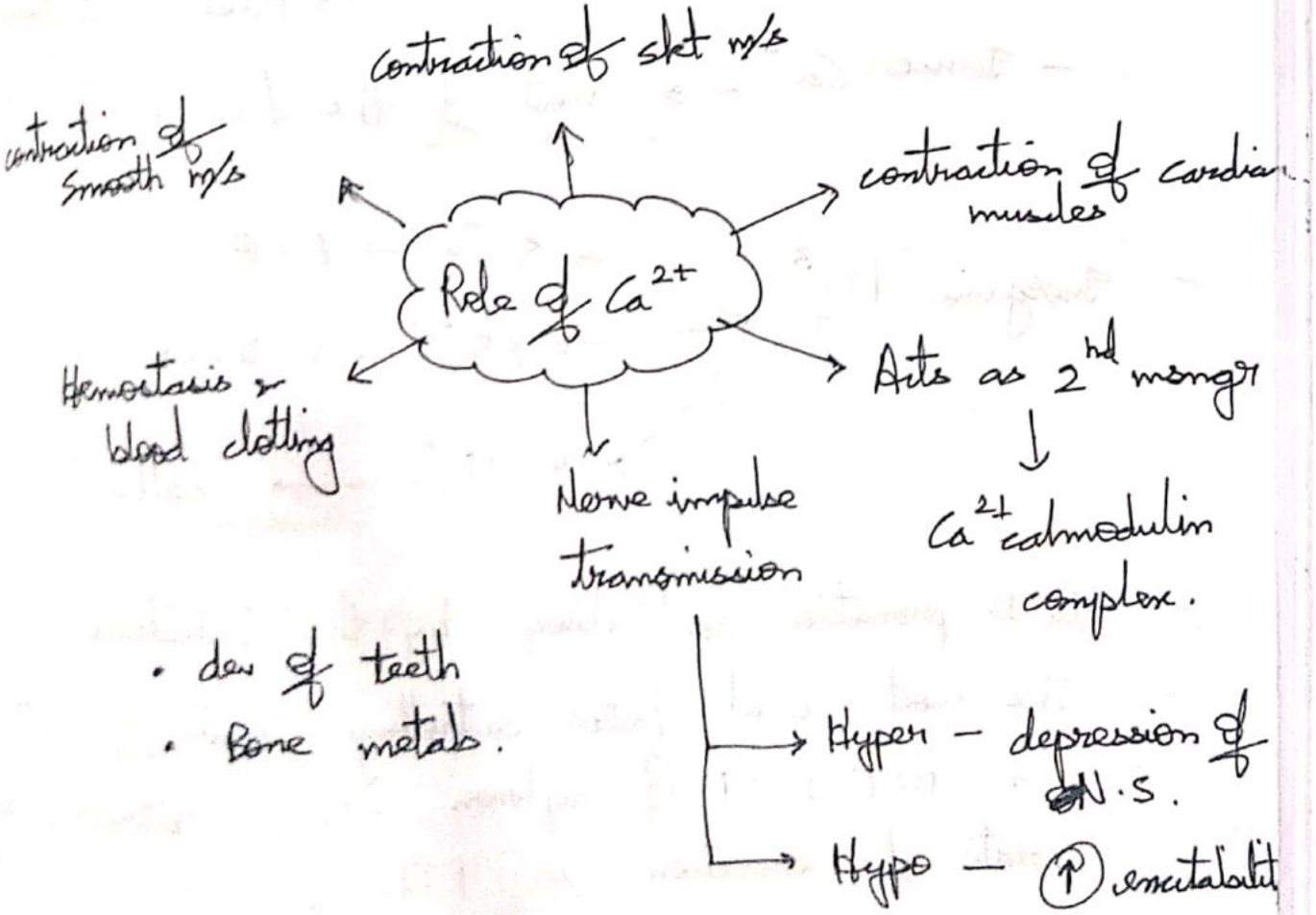


⇒ Physiological effects of Ca^{2+} :-

- Normal value — 9.4 mg/dL
- Regulated precisely as it plays an ☆ role.



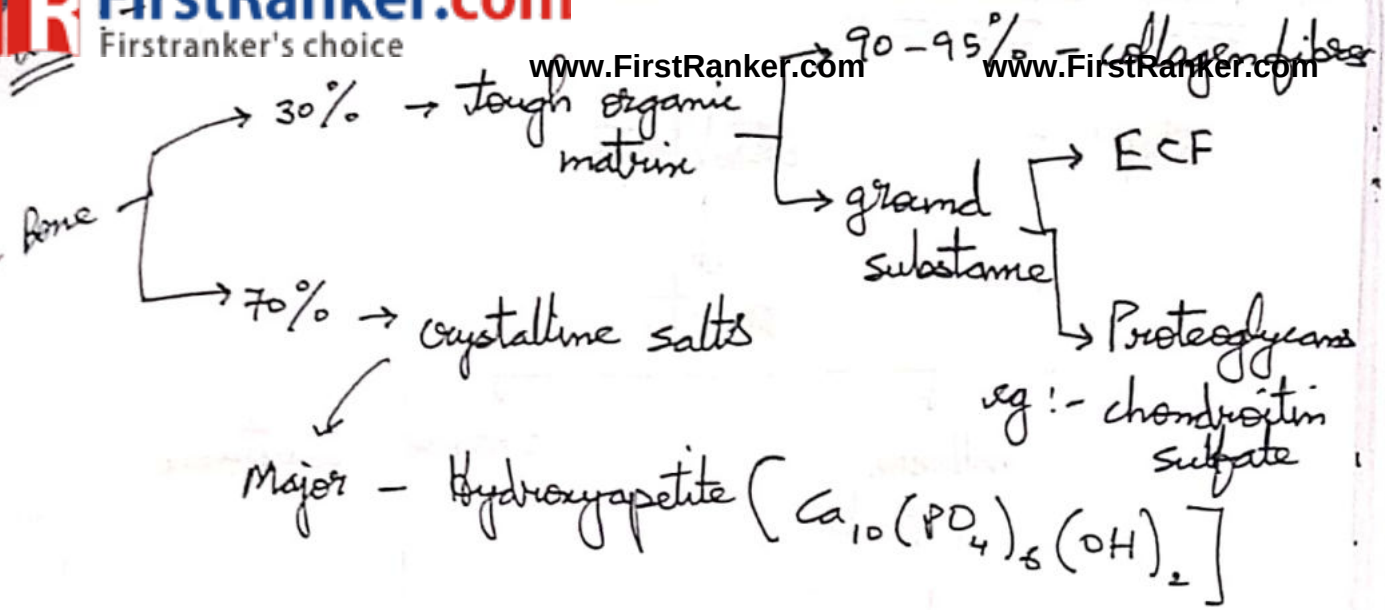
Total body Ca
- 0.1% → ECF
- 1% → cells
- 99% → Bones [Act as reservoirs]

- Ca^{2+} in plasma
  - 41% → prtn bound Ca^{2+} → non diffusable thru capillary mb...
  - 9% → Anion bound Ca^{2+} → diffusable
  - 50% → Ionic Ca^{2+} → diffusable. → Most impt form

- Ionic Ca^{2+} → most of the form of Ca^{2+}

- Inorganic PO_4^{3-}
  - <1% → ECF
  - 85% → Bones
  - 14-15% → cells.

- Vit D promotes Ca^{2+} absorp by the intestines
- The most impt factor controlling reab of Ca^{2+} in DCT & CT of nephron & ∴ controlling the rate of excretion is PTH.



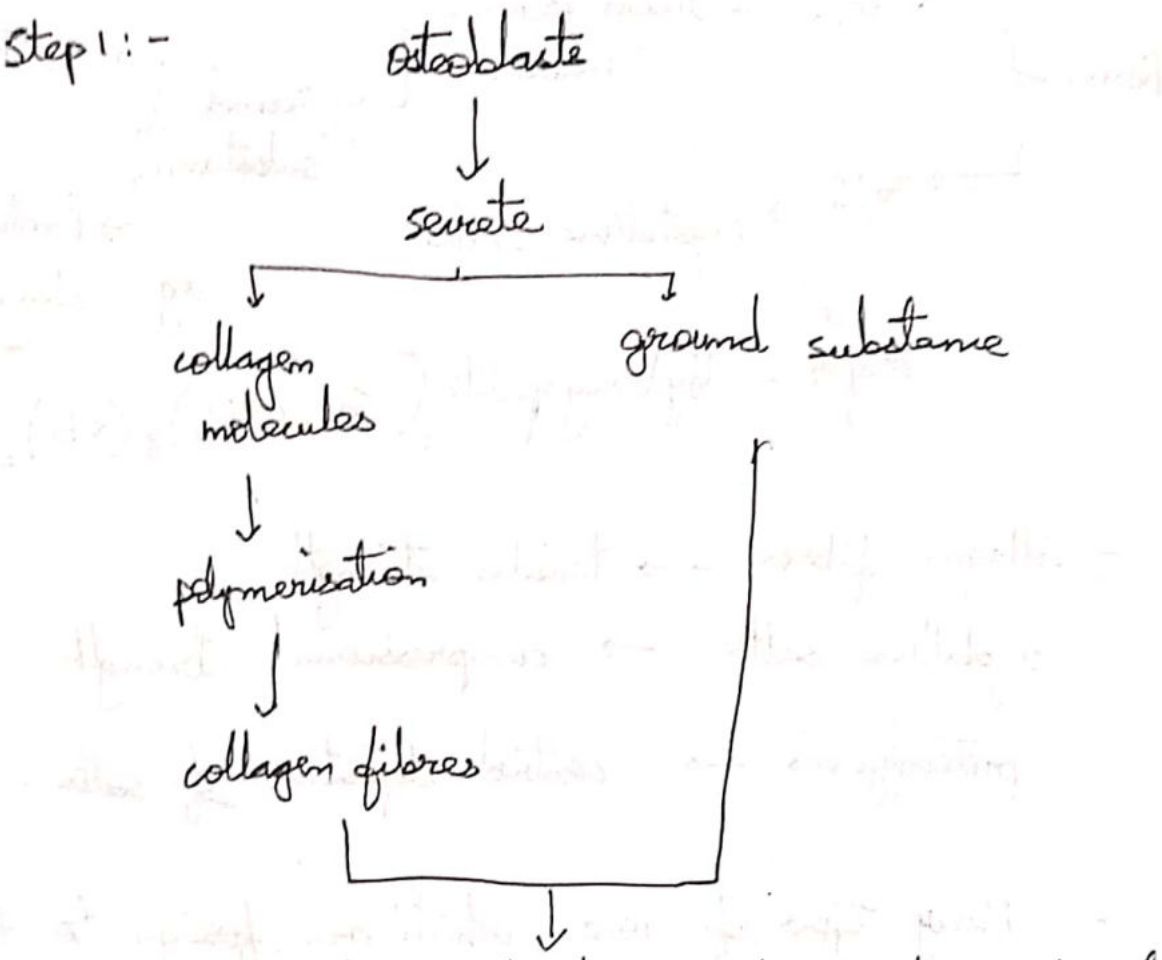
- collagen fibres → tensile strength
  crystalline salts → compressional strength.
  proteoglycans → control deposition of salts.

- Many types of ions which are foreign to the bone can combine with bone crystals.
  eg:- strontium, uranium, plutonium and other transuranic metals.
  Pb, Au, heavy metals.

  Deposition of radioactive subs in bone can cause prolonged irradiation → osteogenic sarcoma.

Bone calcification :-

Step 1 :-



Step 2 :-

[Within a few days] Ca^{2+} salts precipitate on the surface of collagen fibres

↓

These precipitates rapidly multiply & grow to form hydroxyapatite.

- Deposition of Ca^{2+} salts regulated by pyrophosphate which inhibits hydroxyapatite crystallisation. and thus calcification of bone.

Regulation of pyrophosphate levels in ECF

↓ d by

↓

Tissue Nonspecific alkaline phosphate (TNAP)

↓

promotes calcification

genetic defiency ⇒ soft bones

↑ d by 2

↓ ↓

NPP1 — Nucleotide pyrophosphatase phosphodiesterase

ANK — Ankylosis protein

Genetic defiency of these two

↓

↓ ECF pyrophosphate

↓

↑ bone calcification.

↓

Bone spurs or calcification of tendons or ligaments.

0.4 - 1% of Tot bone Ca^{2+}

- bone contains a type of exchangeable Ca^{2+} that is always in equilibrium with ECF Ca^{2+}

This Ca^{2+} is deposited in the bones in a form of readily mobilised salt such as $CaHPO_4$

Provides rapid buffering mech → prevents fluctuation in plasma Ca^{2+} levels.

Bone Remodelling :-

- Deposition of bone → osteoblasts
  Resorption of bone → osteoclasts
- Except in growing bones the rates of bone deposition and resorption are normally equal so that the total bone mass remains const.
- Osteoclasts → large phagocytic multi nucleated cells [>50 nuclei] → derivatives of monocyte like cells in bone marrow.
- Mech of Resorption :-

  Osteoclast send out villi like projections towards the bone

  ↓

  Villi secrete two types of subst.

  ↓

  - Proteolytic enzymes from lysosomes → digest organic matrix
  - Acids from mito eg:- citric acid, lactic acid → dissolution of bone salts.

Stimulation of osteoclast by PTH :-

PTH binds to receptors on osteoblasts

(+) Synthesis of RANK ligand → Binds to RANK on preosteoclast

(+) Rly of M-CSF → Binds to its receptor on preosteoclast

(−) Syn of osteoprotegerin which inhibits differentiation of pre-osteoclast by binding to RANK.

Pre osteoclast differentiates to form mature osteoclast

Note :-

RANK → Receptor activator for nuclear factor

RANKL → Receptor activator for nuclear factor K-B Ligand

M-CSF → Macrophage colony stimulating factor.

OPG → osteoprotegerin → also called osteoclastogenesis inhibitory factor.

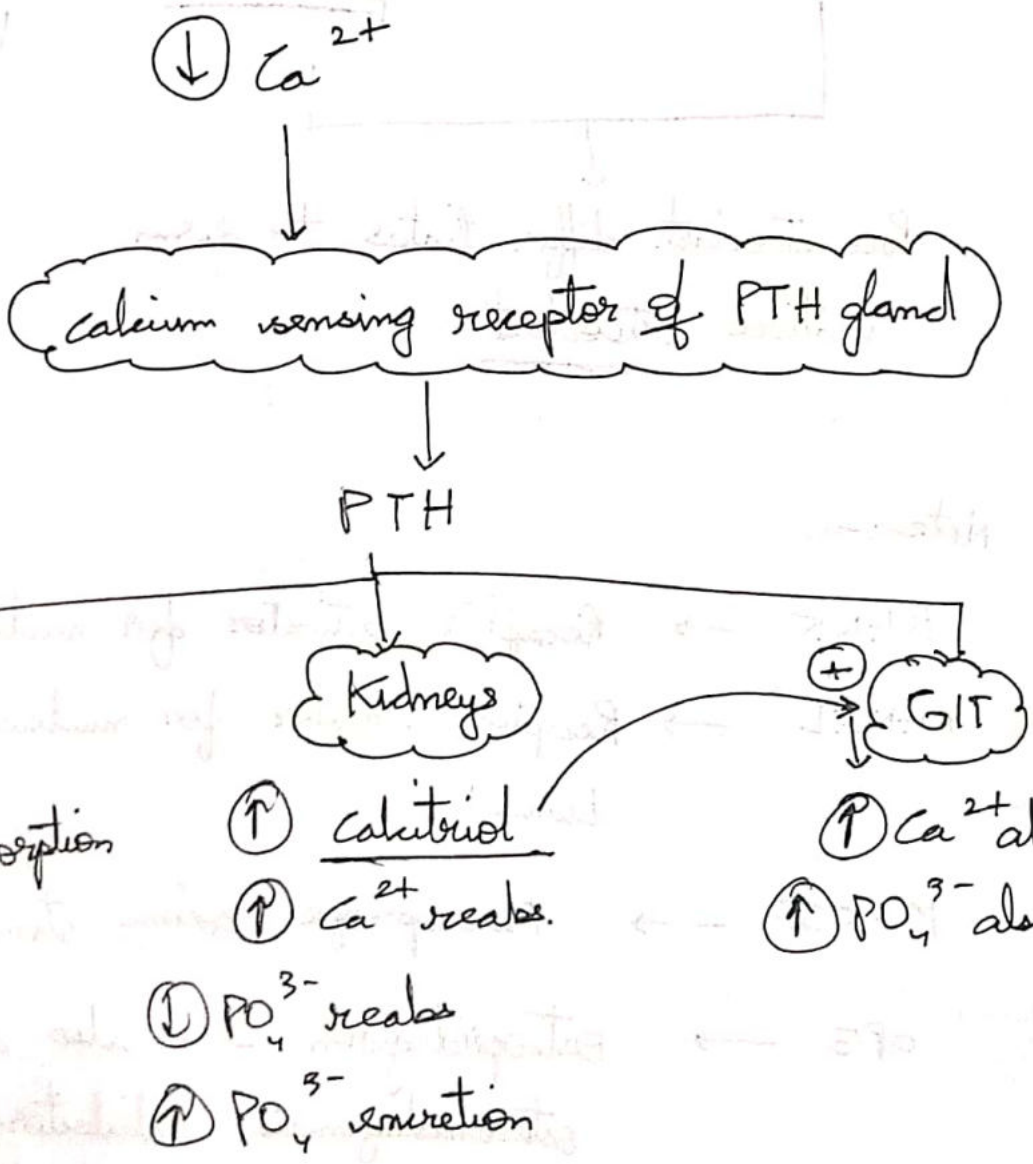
- ↑ Ca^{2+} conc in plasma

↑ Ca^{2+} & PO_4^{3-} reabs from bone

Rapidly ↓s excretion of Ca^{2+} by kidney

- However PTH ↓s PO_4^{3-} conc in plasma
  ↳ strong effect of PTH to ↑ renal PO_4^{3-} excretion → overrides ↑d PO_4^{3-} absorpt from bone.

-



PO_4^{3-} from Bone

Rapid phase

Rapid removal of Ca^{2+} & PO_4^{3-} from amorphous bone crystals that lie near the cells. This is called osteolysis & there is no resorption of organic matrix

Slow phase

Activation of osteoclasts.

- Activation of pre formed osteoclasts
- Formation of new osteoclasts

- Action on Kidneys

1. ↑ Ca^{2+} reabsorption :- ↓ loss of Ca^{2+} in urine
   ↳ from late distal tubules & collecting tubules
2. ↑ PO_4^{3-} excretion in urine → ↓ reabsorption
   ↳ from PCT.

- Action on GIT:-
  ↑ formation of 1,25 - dihydroxycholecalciferol in kidneys
  ↓
  ↑ absorption of Ca^{2+} & PO_4^{3-} from GIT.

→ Acts thru GPCR → cAMP.

⇒ Control of PTH secretion :-

- By Ca^{2+} conc → Ca^{2+} sensing receptor.
  ↳ even slight ↓ → ↑ rate of PTH secretion in min.

- Prolonged ↓ Ca^{2+} conc → hypertrophy of PTH gland
  eg :- rickets
  pregnancy
  lactation.

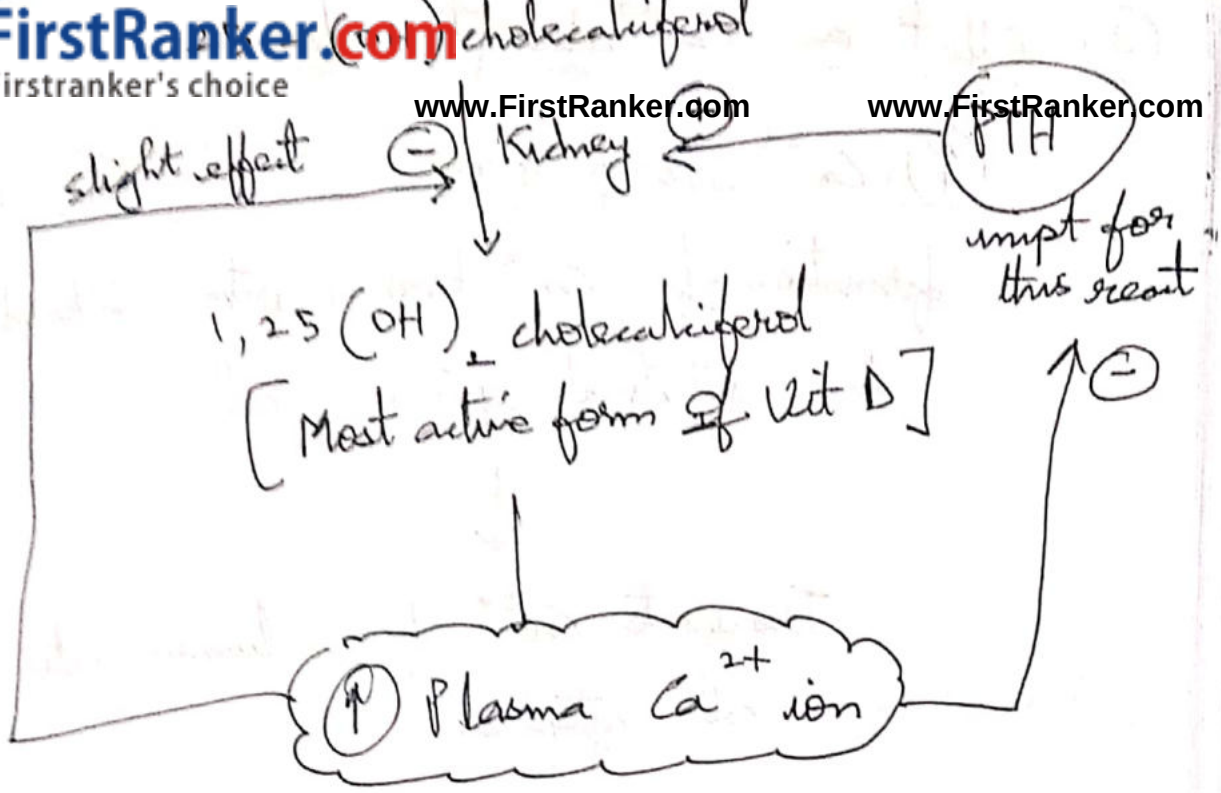
- Prolonged ↑ Ca^{2+} conc → ↓ size of PT gland.

⇒ Vitamin D_3 :- [cholecalciferol]

Active form is 1,25 - dihydroxycholecalciferol.
[$1,25(OH)_2 D_3$]

7 - dehydrocholesterol in skin
↓ UV rays
cholecalciferol [Vit D_3]
↓ Liver
25 - hydroxy cholecalciferol

(−) feedback inhibition prevents excess & conserves Vit D_3 for future use in Liver



- slight (↓) in Ca^{2+} conc below normal causes (↑)d formation of activated Vit D.

- Actions of Vit D :-

① Effect on bone

↓ Excess quantity → ↓ Bone resorption

↓ Slight quantity → ↓ Bone calcification

② Effect on Kidney :-

(↑) reab of Ca^{2+} & PO_4^{3-} from renal tubules.

Effect on Ca^{2+} absorption from GIT :-

(1) Ca^{2+} absorp from GIT by (4) the formation of Ca^{2+} binding prtn Calbindin in the intestinal epithelial cells

↓

Transports Ca^{2+} from lumen into cell cytoplasm.

↓

Ca^{2+} moves thru basolateral mem into plasma by facilitated diffusion.

other effects :-

- formation of Ca^{2+} stimulated ATPase
- formation of Alkaline phosphatase

- calbindin remains for a longer time even if D_3 has been removed.

(2) (1) PO_4^{3-} absorption from GIT :-

- ↑ plasma Ca^{2+} conc stimulates calcitonin secretion.
- Action :- ↓s plasma Ca^{2+} conc
  ↳ opp effect of PTH
- Actions :-
  Bone – inhibits osteoclasts bone resorption.

⇒ Control of Ca^{2+} conc

1st line of defense
↓
exchangeable Ca^{2+} in bones
↳ in into of Liver ↳ intestine

2nd line of defense
↓
Hormones.

⇒ Hypocalcemia :- 9.4 to 6 mg/dL
↳ [redacted] – N.S becomes more excitable as neuronal membrane permeability for Na^+ ↑s.
↳ occasionally seizures.
↳ Tetany.

⇒ Hypercalcemia → depresses N.S & m/s activity.
>12 mg/dL.
↳ ↓ QT interval of Ht ↓ motility of GIT.

~~Thyroid Hormones~~

(1) Hypoparathyroidism :-

- osteocytic resorption of exchangeable Ca^{2+} (↓)
- osteoclasts become inactive.
- Plasma Ca^{2+} (↓) but bones remain strong.

- Removal of PT glands
  9.4 ⟶ 6 mg/dL
  bld phosphate doubles

- Tetany develops
- m/s sensitive to tetanic spasm are laryngeal m/s ⟶ obstruction to respiration.

(2) ~~Hyperparathyroidism~~ :-

Treatment :- with PTH ~~+~~ Vit D + Ca^{2+}.

but this is expensive
Heme not usually preferred

I Primary :- excess PTH with hypercalcemia

- common cause → tumour
  more frequent in women → pregnancy & lactation stimulate parathyroid gland.
- There is extreme osteoclastic activity

↓

↑↑ plasma Ca^{2+} conc.

- (↑↑) Renal excretion of PO_4^{3-}

↓

(↓) Serum PO_4^{3-}.

- severe hyper → osteoclastic resorption >> osteoblastic calcification.

↓

Multiple fractures with mild trauma

Radiographs of such bones → extensive decalcification
large punched out cystic areas filled with osteoclasts

This dzz is called osteitis fibrosa cystica.

↓ compensation osteoblasts activity ↑↑ greatly in vain

↓

↑↑ secretion of Alk. phosphatase

↓

(↑) Serum. Alk phosphatase.

- Hypercalcemia :- 12 - 15 mg/dL

  - → depression of CNS & PNS
  - → muscle weakness
  - → constipation
  - → abdominal pain
  - → peptic ulcer
  - → Lack of appetite
  - → (↓) relaxation of hrt during diastole.

- Parathyroid poisoning :-

When blood Ca^{2+} levels > 17 mg/dL

↓

metastatic $Ca(HPO_4)$ crystals deposition

- → Alveoli
- → Renal tubules
- → Thyroid gland
- → Stomach mucosa
- → arterial walls.

formed

II Secondary :- excess PTH due to hypocalcemia

↳ causes → Vit D def

→ chronic renal dzz which interferes with calcitriol formation.

(3) Vitamin D deficiency

I Rickets in children :-

- plasma Ca^{2+} → slight ↓ [compensated by PTH]

plasma PO_4^{3-} → great ↓.

- marked compensatory ↑ PTH → ↑↑ osteoclastic activity

Bone becomes weak

- when bones Ca^{2+} is finally exhausted

↓

Plasma Ca^{2+} begins to fall rapidly

< 7 mg/dL → Tetany → death due to respiratory tetanic spasm.

① dietary Ca^{2+} PO_4^{3-} & Vit D

II Osteomalacia in adults :-

- No dietary def
- serious def of Vit D & Ca^{2+} due to steatorrhea [failure to absorb fat]
  both Vit D which is fat soluble & Ca^{2+} are lost in feces
- Poor Ca^{2+} & PO_4^{3-} absorp occurs.
- Never proceeds to stage of tetany
  But severe bone disability.

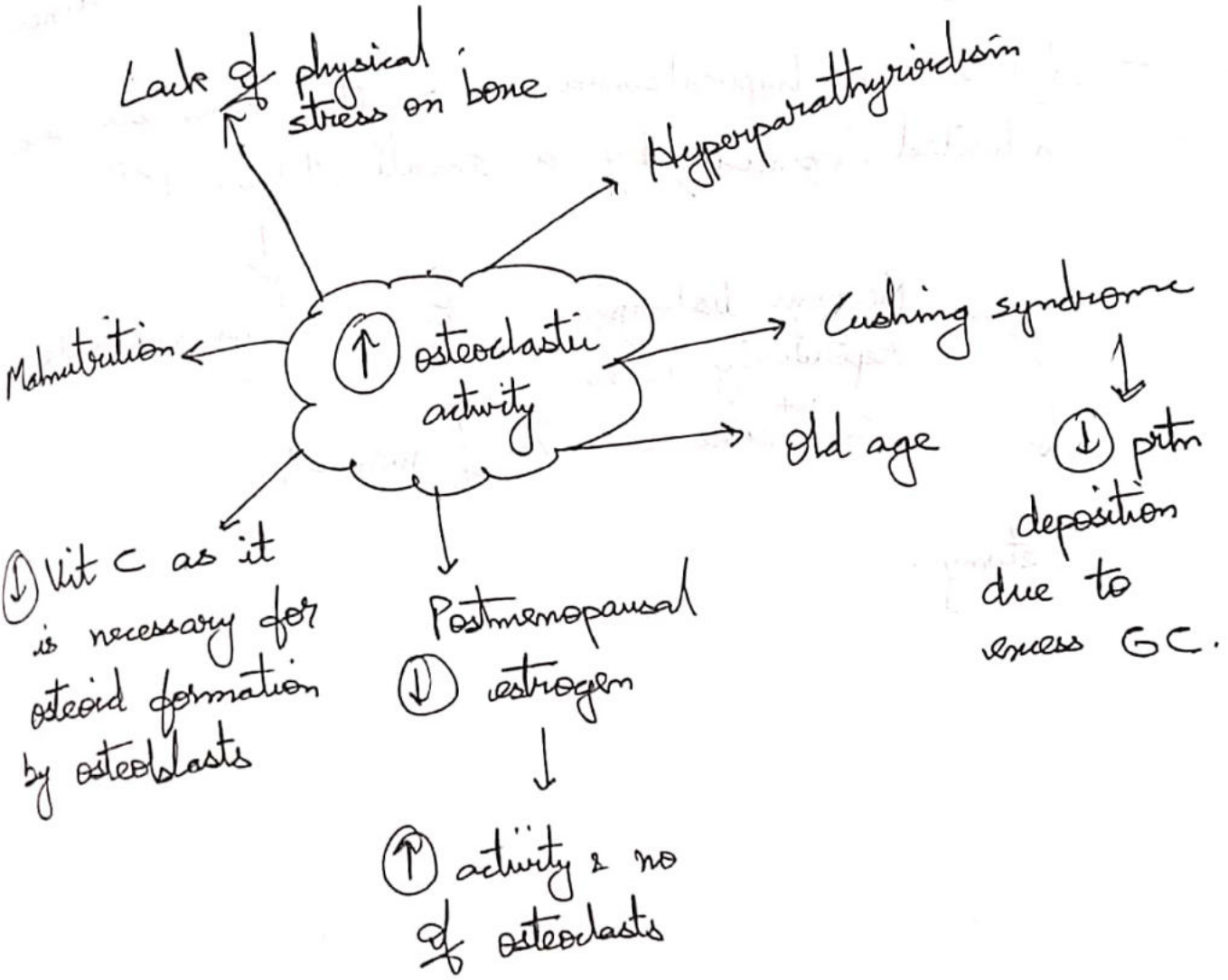
III Vit D deficiency due to Renal disease :-

Renal rickets

↳ damage kidneys → fail to form $1,25(OH)_2 D_3$.

Note :- congenital hypophosphatemia / Vit D resistant rickets
↳ reduced reab of PO_4^{3-} by renal tubules
Must be treated with PO_4^{3-}

(4) ↓ organic matrix due to excessive osteoblastic activity
osteoblastic activity is also unusually ↓.



Why does hypocalcemia cause Tetany?

- Ca^{2+} in ECF has a stabilising effect on voltage gated Na^+ channel.

  Ca^{2+} ions bind to exterior of these channels altering the electric state of the Na^+ channel.

- (↓) Ca^{2+} ie hypocalcemia ⟶ Na^+ channels become activated (opened) by a small (↑) in MP

  ↓

  Become hyperexcitable. ⟵ Neurons discharge repetitively when Ca^{2+} conc < 50% of normal

Tetany.