Hormonal regulation of blood calcium

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Learning outcomes:

- **At the end of the lecture, you will be able to:**

1. Explain the significance, distribution, requirement, absorption and excretion of calcium .
2. Explain the hormonal regulation of calcium metabolism.
3. Explain the hypoparathyroidism and hyperparathyroidism.
4. Explain the causes, manifestations and treatment of tetany.

Calcium metabolism

♦ Significance of Ca:

1. Blood **clotting**.
2. Muscle **contraction**.
3. Release of **neurotransmitters**.
4. Formation of **bone** and **teeth** and production of **milk**.
5. Mechanism of **hormone secretion** and mediator of **hormonal effects**.
6. Participate in numerous **enzymatic reactions**.

♦ Distribution of Ca in body

Skeleton

- Contain **99%** of total body ca (**1 kg** in young adult)
- **After the 3rd decade of life**, bone resorption exceeds bone formation ➔ slow and progressive **bone loss** (♀>♂)

Plasma

Ca^{2+} = 9 – 11 mg%

Non diffusible (40%)

↓

bound to **plasma proteins** mainly **albumin**

Diffusible (60%)

Ionized (50%)

Complexed

in non ionic form with citrate, & HCO_3 **(10%)**

♦ Requirements of Ca^{2+}:

- **400 mg/day** for adults.
- **↑ needs** occur in childhood, pregnancy and lactation.

♦ Intestinal absorption:

- **Site:** from all parts of small intestine.
- **Mechanism:**

*i.**Active transport:*** In duodenum (controlled by **vit D3 & PTH**).

*ii.**Passive or facilitated diffusion:*** in jejunum & ileum.

Calcium absorption decreases in:	*Calcium absorption enhanced by:*
1- Vitamin D deficiency. 2- Renal failure. 3- Intestinal malabsorption. 4- Intake of phytate, phosphates or oxalates. 5- Excess unabsorbed fatty acids in the intestine. 6- Advancing age.	1- Parathyroid hormone. 2- Growth hormone. 3- Vitamin D3

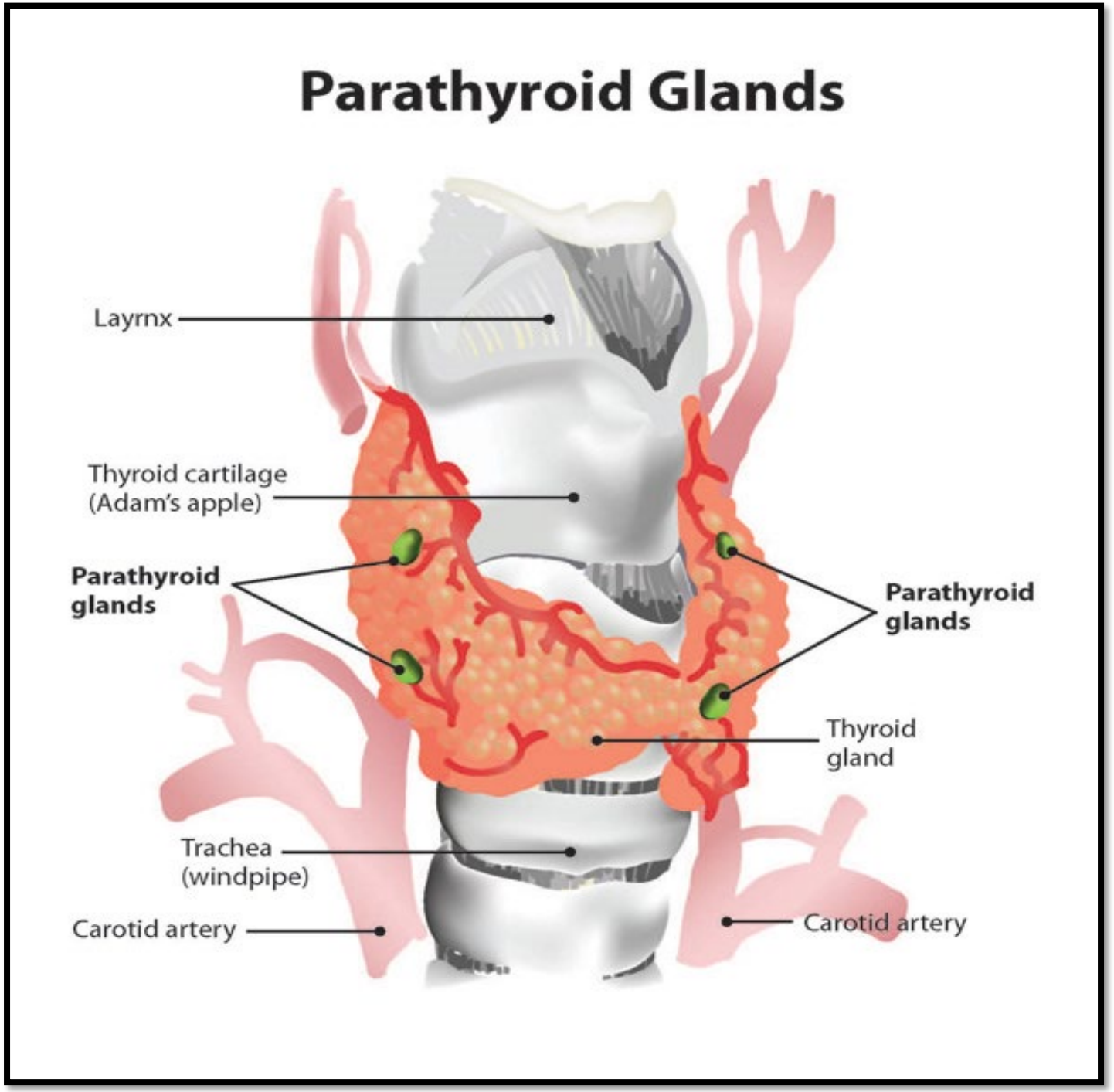
♦ Urinary excretion of Ca^{2+}:

80-400 mg/day.

Parathyroid glands

*Parathyroid glands are **4** glands on **posterior** aspect of **thyroid** gland, **120 mg** combined weight, **3-5mm** diameter.

*Parathyroid glands contain **chief** cells & **Oxyphil** cells (little & represent inactive chief cells).



Hormonal regulation of calcium metabolism

	Parathormone (essential for life)	Calcitonin	Vit. D
- **Nature**	Polypeptide (84aa)	Polypeptide (32aa)	Steroid
- **Site of release**	**Chief** cells of parathyroid glands.	**Parafollicular or C** cells of thyroid gland.	• **Vit D_2:** (ergocalciferol) formed in plants from ergosterol. • **Vit D_3:** (cholecalciferol) formed by ultraviolet irradiation of 7-dehydrocholesterol present in skin • **Vit D_3** is activated in liver & kidney to **1-25 DHCC**

	Parathormone	Calcitonin	Vit. D
- **Actions**	↑ plasma Ca^{2+} & ↓ plasma $PO^{=}_{4}$ to maintain **solubility product constant**.	↓ plasma Ca^{2+} & ↓ plasma $PO^{=}_{4}$	↑ plasma Ca^{2+} & ↑ plasma $PO^{=}_{4}$
1) Small intestine	• PTH indirectly stimulate Ca absorption from small intestine by ↑ formation of 1-25 DHCC in kidney. • ↑ Mg & PO_4 absorption.	• Calcitonin inhibits intestinal absorption of Ca and PO_4.	• Vit D increases intestinal absorption of Ca & PO_4

	Parathormone	Calcitonin	Vit. D
2) Kidney	• ↑ Ca & Mg reabsorption from renal tubules •↑ $PO^{=}_{4}$ excretion.	• ↑ excretion of Ca^{+2} & $PO^{=}_{4}$ • inhibit renal α1 hydroxylase enzyme which activate vit D	•↑ renal tubular reabsorption of Ca^{2+} and $PO^{=}_{4}$

	Parathormone	Calcitonin	Vit. D
3) Bone	• ↑ **Ca permeability** of bone cells. • ↑ **number & activity of osteo-clast** ➔ ↑ bone resorption ➔ release of Ca to blood. • ↓ **osteoblast activity**. • ↑ **activity of collagenase enzyme** of osteoclast ➔ breakdown of bone collagen.	•↓ **Ca permeability** of bone cells. •↓ **number & activity of osteo-clast** ➔ ↓ bone resorption ➔ ↓ mobilization of Ca from bone to blood. • ↑ **osteoblast activity** ➔↑ bone formation.	• In the presence of PTH, it increase Ca and PO_4 mobilization from bone. • **Paradoxically**, by increasing serum Ca^{2+} and $PO^{=}_{4}$, it stimulate calcium deposition in bone.

	Parathormone	Calcitonin	Vit. D
- Mechanism of action	• ↑ intracellular cAMP • ↑ intracellular Ca^{2+}	• ↑ intracellular cAMP	• Stimulating ribosomal protein synthesis.
- Control of secretion	**(1) <u>pl Ca^{2+}</u>:** ↓ plasma Ca ➔ ↑ PTH. **(2) <u>pl $PO^{=}_4$</u>:** ↑ plasma $PO^{=}_4$ ➔ ↑ PTH. **(3) <u>pl Mg^{2+}:</u>** ↓ plasma Mg^{++} ➔ ↑ PTH	**(1) <u>pl Ca^{2+}:</u>** ↑ plasma Ca ➔↑ calcitonin. **(2) <u>GIT hormones:</u>** (as gastrin, CCK, secretin…, **<u>mainly gastrin</u>**).	

Other hormones that affect calcium metabolism

(1) Estrogens and androgens:

- ***In adult ♀*** → **estrogen protect skeleton from osteoporosis by:**

1. ***Inhibiting PTH mediated bone resorption*** Osteoblasts (have estrogen receptors) → release factors which inhibit osteoclast resorption.
2. ***↓bone resorbing cytokines*** as IL-1 and 6 in bones.

3. ***↑serum PTH***, due to **hypocalcemic** effect of **inhibition of bone resorption**. It also **facilitate PTH action on kidney** ➔ ↑ $PO^{=}_{4}$ excretion, ↑ Ca absorb & vit D_3 activation.

- **Similarly**, **androgens protect men from osteoporosis** as evidenced by excess bone loss in **hypogonadal conditions** as Klinefilter syndrome (47, XXY) & castration.

(2) glucocorticoids:

- ***At physiological levels*** ➔ necessary for skeletal growth.
- ***Chronic ↑*** ➔

(1) ↓ **renal tubular** Ca reabsorption.

(2) ↓ **intestinal** ca absorption.

(3) **Stimulating PTH release** due to low Ca level.

(4) **Inhibiting osteoblastic bone formation**.

(5) **Inhibiting gonadal estrogen & androgen** production.

(3) Thyroid hormones:

- ***Important for*** the **development** and **growth** of **skeleton** in infants and childhood.
- ***Hypothyroidism*** ➔ **Retarded bone growth**.
- ***Hyperthyroidism*** ➔ **↑ bone resorption**.

(4) Growth hormone:

- ***Stimulate bone growth*** by **somatomedins** (IGF-1).
- ***↑ intestinal Ca absorption*** by **Vit D – dependent mechanism**.
- ***↑ renal tubular PO_4 reabsorption.***

Disorders of parathyroid gland

Hypoparathyroidism

- **Causes:** Accidental removal of parathyroid glands or damage to their blood supply during surgical operation on thyroid.
- **Characters:**
  - **Hypocalcemia** ➔ ↑ neuromuscular excitability due to ↑ neuronal membrane permeability to Na^+.

- **Nerve Fibers:** ➔

  - Hyperexcitable.
  - Spontaneously depolarized.
  - Initiate nerve impulses to skeletal muscles ➔ titanic contraction.

Tetany

- **Def:** A disease manifested by **↑ neuromuscular excitability due to ↓ plasma Ca^{2+} concentration**.

- **Causes:**

1) **Hypoparathyroidism**.

2) **Alkalemia**.

3) **Renal failure** due to phosphate retention.

4) ↓ Ca^{2+} absorption from small intestine due to:

a) ↓ Ca^{2+} intake.

b) ↑ antacid intake (as in peptic ulcer) ➔ ↑ alkalinity of intestine ➔ Ca^{2+} precipitation ➔ ↓ absorption.

c) Steatorrhea ➔ Ca^{2+} loss in stool.

d) Vitamin D deficiency.

• **Manifestations:** Depend on the **degree of lowering of plasma Ca^{2+} level:**

	Manifest Tetany	Latent Tetany
Plasma Ca+2 level	**below 7mg%.**	**7-9 mg%.**
Manifestations	***1-Muscular spasm in hand and feet (carpopedal spasm):*** **Hand** ➔ -Flexion of wrist & metacarpo-phalangeal joints. -Extension of interphalangeal joints. -Adduction of thumb. **Foot** ➔ -Dorsiflexion of ankle. -Planter flexion of toes. ***2-Generalized convulsions***. ***3-Laryngeal spasm*** ➔ difficult breathing.	- **No manifestations.** - **Muscle spasm** occurs only when the patient is exposed to **stress**. **- Patients may have:** *Tingling. *Sensation of heat and flushing (parathesia).

• Treatment:

(1)Intra venous **ca gluconate** stops immediately tetanic spasm.

(2)Ca level is maintained by: **Vit D & Oral ca**.

(3)Acidifying salts as NH_4 Cl (ammonium chloride) ➔ ↑ Ca^{2+} ionization ➔ ↑ Ca absorption.

(4)In hypoparathyroidism ➔ PTH administration ➔ antihormone formation, which antagonize its action. So, **dihydrotachysterol (AT_{10})** (synthetic steroid) is used as it has similar effects as PTH but not produce anti-hormones.

Hyperpararthyroidism

- Causes: Parathyroid tumour → ↑ PTH → hypercalcemia (**20mg%**).

- Manifestations:

1) On the bone:

* **Bone resorption:** due to ↑ osteoclastic activity → Ca mobilization from bone.

* **Bone ache & bone collapse** due to formation of fibrous masses & cysts in bone **(Ostitis fibrosa cystica).**

* **This may lead to** ↑ bone fragility & spontaneous fracture.

2) On the kidney:

a) ↑ Ca in glomerular filtrate → precipitation of Ca compounds → calculi formation → renal failure.

b) Polyurea due to:

a. Excess excretion of Ca and PO_4 in urine → osmotic diuresis.

b. Renal damage (from calculi).

3)**Hypotonia of muscles** → muscular weakness and sensation of tiredness.

4)**Vomiting, diarrhea, and intestinal pain**.

5)**Cardiac irregularities, mental confusion, coma, and death**.

- **Treatment:** Surgical removal of parathyroid tumour.

References

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