

# ENDOCRINE SYSTEM

## Pharmacology

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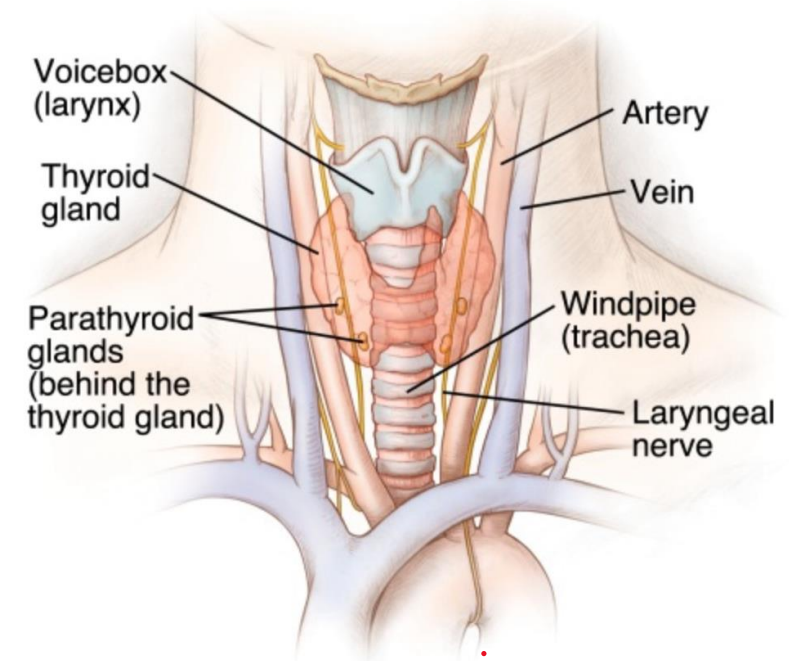
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ما ينطق به الدكتور من شرح سيكون باللون **الاحمر**  
وما يكون مهم في شرح الدكتور يكون باللون **البنفسجي**  
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# Parathyroid Gland & Calcium Metabolism

Remember that : we have 4 parathyroid glands that lie posterior to the thyroid gland, in fact they are embedded in the posterior wall of the thyroid gland



- A 70-kg person has approximately 1.2 kg of calcium in the body, more than 99% of which is stored as hydroxyapatite in bones. Less than 1% (5-6 g) is located in the intracellular and extracellular compartments, with only 1.3g located extracellularly
- The total calcium concentration in the plasma is 4.5-5.1 mEq/L (9-10.2 mg/dL). Fifty percent of plasma calcium is ionized or in free form (which is the active form of calcium), 40% is bound to proteins (mainly to albumin), and 10% circulates bound to anions (e.g., phosphate (mainly), carbonate, citrate, lactate, sulfate)

- Functions of calcium

It is important element (the 5<sup>th</sup> important element in our bodies) for :

- Maintaining the integrity and solidity of bones and teeth
- Contraction of muscles (voluntary and smooth)
- Blood coagulation or blood clotting
- Neurotransmitters and hormones release
- Nerve impulse and transmission
- Mediating effects of neurotransmitters and hormones (second messenger)...

The major manifestation of hypercalcemia is generalized muscle weakness while in case of hypocalcemia, the main general symptom is tetanic attack

**3 factors PTH, Vitamin D, Calcitonin**

**3 tissues Bone, Intestine, Kidneys**

**Parathyroid Hormone (PTH)**

**84 a.a peptide translated as a pre-prohormone (so it originates from a large precursor)**

**Regulation of synthesis & release (regulated by Calcium blood level):**

**↓ [Ca<sup>++</sup>] (Hypocalcemia) → ↑ PTH; ↑ [Ca<sup>++</sup>] (Hypercalcemia) → ↓ PTH**

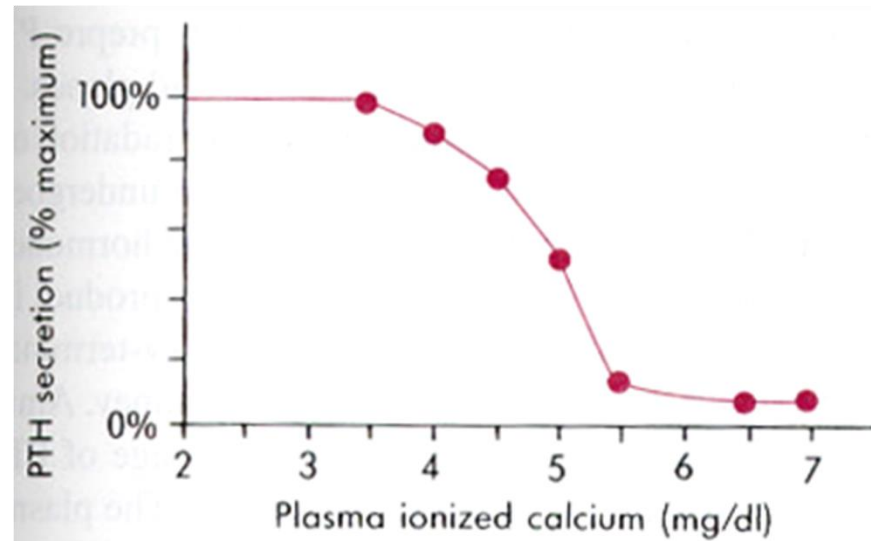
**Little if any regulation by PO<sub>4</sub><sup>--</sup>**

Calcium is regulated by 3 major factors :

- PTH (Parathyroid hormone)
- Vitamin D
- Calcitonin (which is produced by Parafollicular cells (C-cells) in the thyroid gland)

Each one of these factors acts on three different tissues : Bone, Intestine, kidneys

- **Maximum secretion of PTH occurs at plasma  $\text{Ca}^{++}$  below 3.5 mg/dl**
- **At  $\text{Ca}^{++}$  above 5.5 mg/dl, PTH secretion is maximally inhibited**



This slide shows the action of PTH on different tissues, notice that the bone is the primary target tissue

notice that the effect of PTH on bone & intestine is to increase calcium and phosphate blood level

- **On bone (1<sup>o</sup> target tissue):**

**PTH ↑ resorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^-$**

**Increase resorption of bone means increase the movement of calcium and phosphate from the bone back to blood**

**(cAMP (a 2<sup>nd</sup> messenger)) mediated effect**

- **On intestine:**

**↑ absorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^-$**

**Increase absorption from the intestine to the blood**

**An indirect effect through ↑ vitamin D synthesis**

- **On kidneys:**

**↑ reabsorption of  $\text{Ca}^{++}$ , ↑↑↑ excretion of  $\text{PO}_4^-$**

**(cAMP mediated effect)**

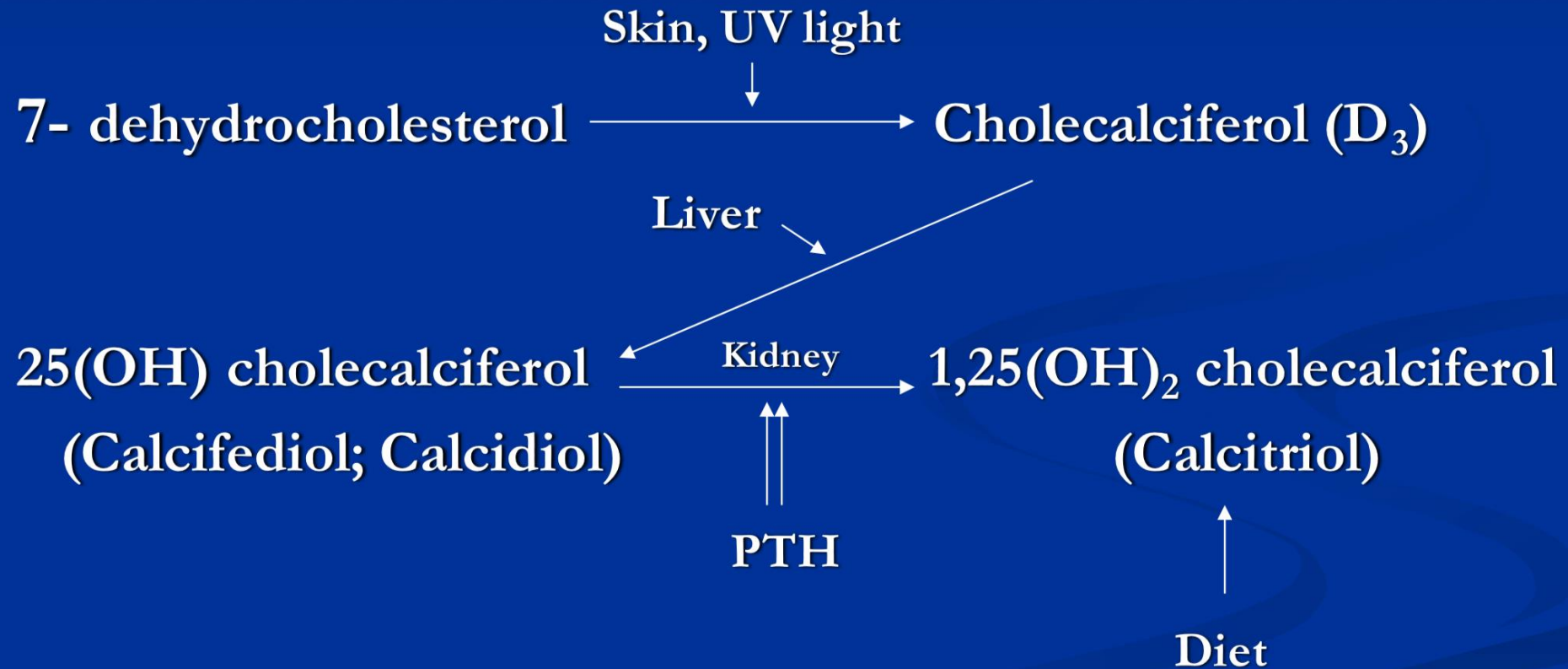
The amount of phosphate excreted from the kidney usually overcomes the amount of phosphate absorbed from the intestine and the amount moved from the bone, so the net effect of PTH on calcium and phosphate blood level is to :

Increase calcium blood level

Decrease phosphate blood level



## ■ Synthesis of vitamin D



The previous slide shows the steps of vitamin D synthesis and its activation

Notes : The synthesis of vitamin D begins in the skin under the presence of UV light by converting 7-dehydrocholesterol to cholecalciferol or (Vitamin D<sub>3</sub>) which is inactive....cholecalciferol is carried by a specific protein to the liver where the 1st step in activation of vitamin D occurs by formation of calcifediol or calcidiol.....the final step of vitamin D activation occurs in the kidney by forming **calcitriol which is the most active form of vitamin D**

PTH increases the synthesis of vitamin D by stimulating the conversion of (calcidiol → calcitriol)

Note: Calcitriol (vitamin D) can be obtained from diet

People are advised to expose themselves to sun for at least 15 minutes everyday...by this, no one will have the problem of vitamin D deficiency which could result in Paget disease in children or Osteomalacia in adult  
Vitamin D deficiency is very common in our country

## **Vitamin D (Normal daily requirement 400 IU/day)**

- **On intestine (1<sup>o</sup> target tissue):**
  - ↑ **absorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^{--}$**
- **On bone:**
  - ↑ **bone resorption**
- **On kidney:**
  - ↑ **reabsorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^{--}$**

The net effect of vitamin D on calcium and phosphate blood level is to :  
Increase calcium and phosphate blood level

## Calcitonin (32 a.a peptide)

Synthesized and released from parafollicular cells of the thyroid

- Regulation of synthesis & release (**regulated by calcium blood level**):

↑  $[Ca^{++}]$  (**hypercalcemia**) → ↑ calcitonin; ↓  $[Ca^{++}]$  (**hypocalcemia**) → ↓ calcitonin

- Effects:

On bone: ↓ bone resorption (↓  $Ca^{++}$  &  $PO_4^{-}$  movement) **keep calcium and phosphate in bone**

On kidneys: ↑  $Ca^{++}$  &  $PO_4^{-}$  excretion **or inhibits calcium and phosphate reabsorption**

? On intestine: ↓  $Ca^{++}$  &  $PO_4^{-}$  absorption

So by the measurement of calcium and phosphate blood level, we can differentiate the differences in the action of the 3 hormones

- **Calcitonin** May be more important in regulating bone remodeling than in  $\text{Ca}^{++}$  homeostasis:

**Evidence: Chronic excess of calcitonin does not produce hypocalcemia and removal of parafollicular cells does not cause hypercalcemia**

- **PTH and Vitamin D<sub>3</sub> regulation dominate**

PTH

Vit. D

Calcitonin

[Ca<sup>++</sup>]

↑

↑

↓

[PO<sub>4</sub><sup>--</sup>]

↓

↑

↓

- **Disorders affecting the parathyroids:**

- 1- Hyposecretion (hypoparathyroidism):**

- **Causes:**

- Thyroidectomy (**most common cause**)

- Idiopathic (**unknown cause**)

- ↓ sensitivity of target tissues to PTH (**PTH blood level is normal**)  
(pseudohypoparathyroidism)

Thyroidectomy: surgical removal of the thyroid gland

Most of endocrine surgeons prefer whenever they perform a surgery on the thyroid gland to remove all parathyroid glands along with the thyroid.....some surgeons prefer to keep at least one parathyroid gland

- **Symptoms of hypoparathyroidism:**

**Are those of hypocalcemia:**

**Parasthesia, tingling lips, fingers, and toes,  
carpopedal spasm, muscle cramps, tetanic contractions,  
convulsions (seizures)**

**Bronchospasm**

**Depression, anxiety, abdominal pain**

**Cataract...**



- **Lab. Tests (hypoparathyroidism):**

- ↓ **blood [Ca<sup>++</sup>]**
- ↑ **blood [PO<sub>4</sub><sup>--</sup>]**
- ↓ **urinary [cAMP]**
- ↓ **urinary [PTH]**
- ↓ **urinary [Ca<sup>++</sup>]**
- ↓ **urinary [PO<sub>4</sub><sup>--</sup>]**

Measurement of levels of cAMP in the urine are used in order to assess the function of the parathyroid gland as follows :

- Decreased levels of cAMP in urine —> Hypoparathyroidism
- Normal levels of cAMP in urine —> normal parathyroid gland function
- Increase levels of cAMP in urine —> Hyperparathyroidism

- **R<sub>x</sub> of hypoparathyroidism:**

- **Vitamin D**

Calcifediol, Calcitriol, Ergocalciferol, α-Calcidol, Dihydrotachysterol...

**Vitamin D replacement therapy is the Drug of choice for chronic cases**

- **Ca<sup>++</sup> supplement**

Ca<sup>++</sup> rich diet

Ca<sup>++</sup> salts (carbonate, gluconate, chloride...)

**Calcium salts is considered the Drug of choice in acute cases**

- **Thiazide diuretics could help, they inhibit excretion of Ca<sup>++</sup>**

- **Teriparatide (synthetic rPTH (**recombinant PTH**))-recently approved in the management of osteoporosis; given SC (**Subcutaneously**)**

- Chronic cases of hypoparathyroidism are more common than acute cases
- Vitamin D is available in many dosage forms include the oral dosage
- Drug of choice for most cases of hypoparathyroidism (are best treated or controlled) is vitamin D replacement therapy (oral administration)
- Small or low dose of PTH usually increases bone formation therefore, it could be effective in management of osteoporosis

## 2- Hypersecretion (hyperparathyroidism):

- **Causes:**

- 1° hyperparathyroidism (adenomas) **characterised by excessive synthesis and release of PTH into the bloodstream**

- 2° hyperparathyroidism

2° to any cause of hypocalcemia

e.g. malabsorption syndrome, renal disease...**(they decrease blood levels of calcium and that leads to excessive synthesis & release of PTH from the parathyroid gland)**

- 3° hyperparathyroidism

**Results from hyperplasia of the parathyroid glands and a loss of response to serum calcium levels; this disorder is most often seen in patients with chronic renal failure**

- **Symptoms of hyperparathyroidism:**

**Are those of hypercalcemia:**

**Generalized weakness and fatigue**

**depression, bone pain, muscle pain (myalgias), decreased appetite, feelings of nausea and vomiting, constipation, polyuria, polydipsia, cognitive impairment, kidney stones and osteoporosis...**

Excessive or large doses of PTH could lead to osteoporosis BUT small doses are found to be effective in the management of osteoporosis  
(because they increase bone formation)

- **Lab. Tests (hyperparathyroidism):**

- **↑ blood [Ca<sup>++</sup>]**
- **↓ blood [PO<sub>4</sub><sup>-</sup>] (due to the tremendous excretion of phosphate by the kidney)**
- **↑ urinary [cAMP]**
- **↑ urinary [PTH]**
- **↑ urinary [Ca<sup>++</sup>]**
- **↑ urinary [PO<sub>4</sub><sup>-</sup>]**

**Bone x-ray → bone decalcification**

- **R<sub>x</sub> of hyperparathyroidism:**

- **Low Ca<sup>++</sup> diet**

- **Na<sup>+</sup> phosphate because they have very low levels of phosphate**

- **Steroids e.g. Prednisolone or synthetic analogues to cortisol ... ↓ Ca<sup>++</sup> absorption from the intestine**

- **Calcitonin reduces blood calcium level**

- **Surgery (best Rx) surgical removal of parathyroid gland**

- **Cinacalcet (calcimimetic) (oral tab) is used to treat secondary hyperparathyroidism in patients with end-stage(chronic) renal disease who are on dialysis & also used to treat patients with 1<sup>o</sup> hyperparathyroidism & cancer of parathyroid gland**

- Hypophosphatemia could lead to confusion, alterations in mental status, and even a very severe breakdown of muscles a condition known as (Rhabdomyolysis)
- Calcimimetic have a (mimic) or a similar action to calcium with respect to its negative effects on synthesis and release of PTH from the Parathyroid gland, in other words they inhibit the synthesis and release of PTH from the parathyroid gland without further increase in calcium blood levels



- **Other drugs effective in the management of hypercalcemia:**

- **Diuretics**

e.g. Furosemide ( $\uparrow$   $\text{Ca}^{++}$  excretion)

- **Plicamycin (anti-cancerous agent); inhibits bone resorption**

- **Biophosphonates (widely used in the management of osteoporosis and highly effective orally)**

**Etidronate, Pamidronate...**

**$\uparrow$  bone formation and  $\downarrow$  bone resorption**

Any drug that inhibits or decreases bone resorption (keep calcium in bones) could benefit such patients

## Paget's disease

Rare bone disorder characterized by demineralization of bone **or loss of calcium**, disorganized bone formation, ↑ bone resorption, fractures, spinal cord injuries, deafness...

- R<sub>x</sub>:
  - Salmon calcitonin (was considered drug of choice) whether extracted from salmon fish or synthetic, **S.C(subcutaneously)**, **I.M(Intramuscularly)**. Also effective in the management of osteoporosis in postmenopausal women
  - **Biophosphonates (Orally)**

Etidronate, zoledronate, alendronate, residronate, pamidronate... (most preferred drugs in the management of paget's disease). Such drugs are known as antiresorptive agents

اللهم إنا نستودعك  
غزه وأهلها، اللهم  
أنصرهم وثبت  
أقدامهم، اللهم كن  
لهم نصراً ومعيناً.

