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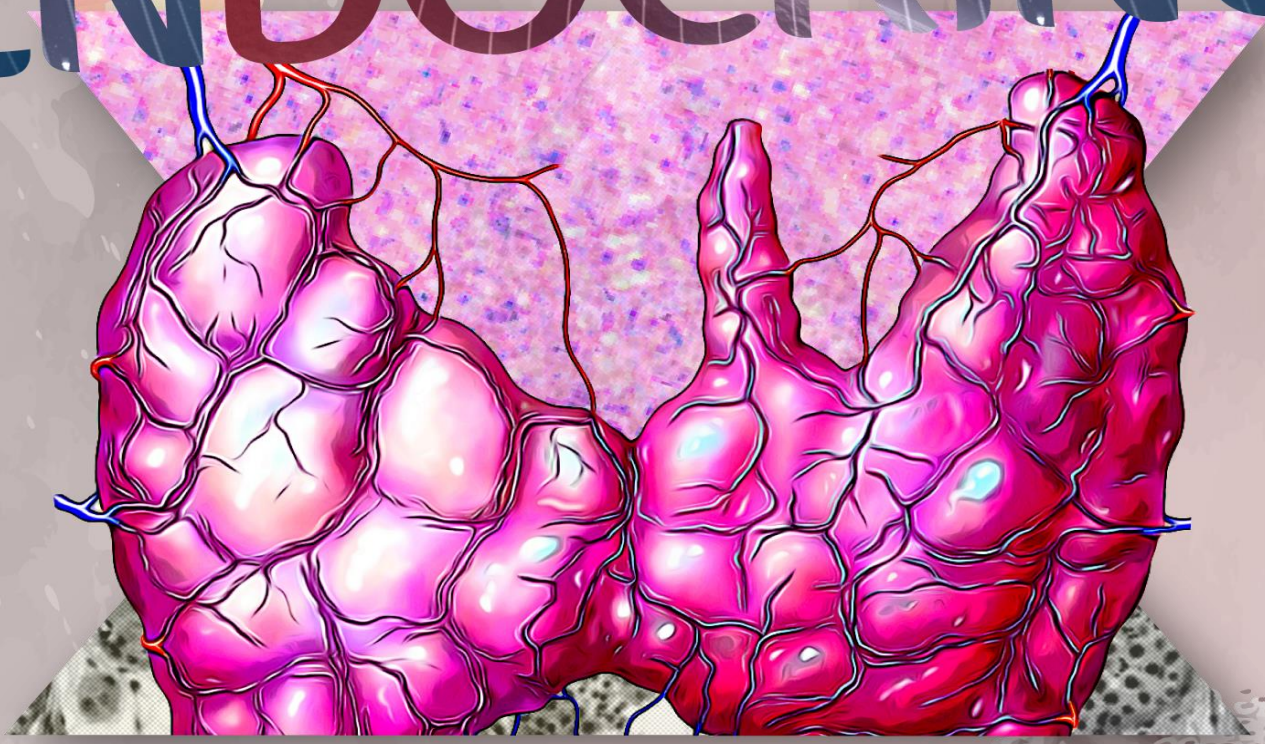
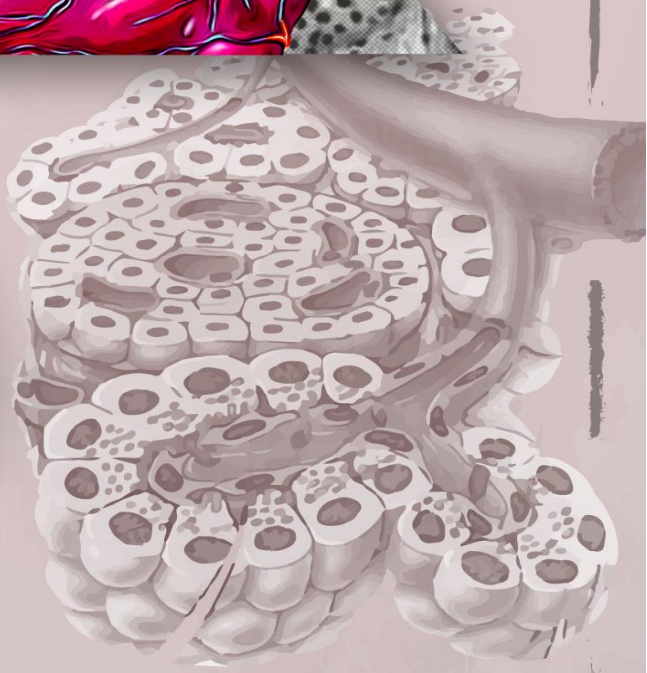
ENDOCRINE





SUBJECT: Physiology

DONE BY: 2016

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Review

In the previous lecture we started talking about vitamin D and calcium:

- **Hypocalcemia** causes **tetany**, where low ionized calcium levels in the extracellular fluid increase the **permeability** of neuronal membranes to **sodium** ion, thus causing progressive depolarization, which increases the possibility of action potentials.

  If this tetany reaches the **lungs**, the patient **dies**. However, if it reaches the **heart**, the patient wont die; because cardiac muscle cells' **refractory period** doesn't end until the muscle is relaxed preventing the summation of action potentials and tetanus from occurring.

- Vitamin D has 3 derivatives, all present in the plasma, bound to proteins, and having the same function:

  'follow on the graph in the next page'

  1- 25(OH)-D → Processed in the **liver** from D2 or D3, transferred to the **kidney** for hydroxylation by the **1-α-hydroxylase** enzyme forming 1, 25$(OH)_2$-D.

  2- 1, 25$(OH)_2$-D → The **most potent** derivative, it works mainly on the intestine, kidneys, and bones for mineral homeostasis. It is also transferred to the mammary glands, placenta, skin, and Avian-shell glands where it is important for mineral transfer.

  3- 24,25$(OH)_2$-D → The **24-hydroxylase** enzyme breaks down the active form of vitamin D, 1, 25$(OH)_2$-D, to an **inactive** form when the vitamin is no longer needed in certain conditions such as: calcium or phosphate excess.

- The **potency** of the 3 derivatives: 1, 25$(OH)_2$-D > 24, 25$(OH)_2$-D > 25(OH)-D.

- **Stimulators** of 1, 25$(OH)_2$-D production:

  1- Pituitary through Prolactin (**PRL**) and Growth Hormone (**GH**) .

  2- Parathyroid through **PTH**.

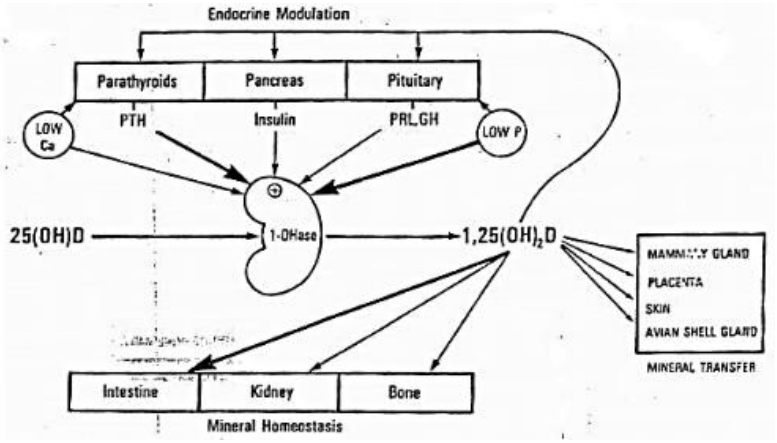
  3- Pancreas through **Insulin**.

  ⇨ The later 3 stimulate the production through affecting the **1-α-hydroxylase enzyme**.

  4- Low **Ca^{+2} / low phosphate**.

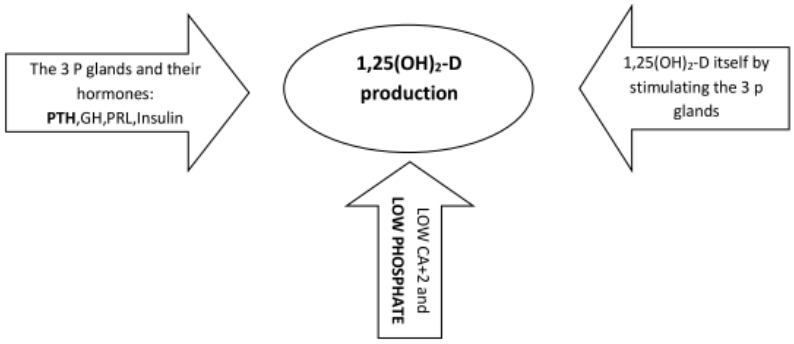
  ⇨ Stimulates the production either **directly** by acting on the **enzyme** or **indirectly** by stimulating the **secretion** of hormones from the 3 P-glands mentioned above.

- The **thick** arrows in the figure indicate that **PTH** and **low phosphate** levels are the **major** factors affecting **1-α-hydroxylase** enzyme, while the rest are minor factors.



- 1, 25$(OH)_2$-D itself can stimulate the 3 P-glands producing PTH, insulin, prolactin, and GH which in turn stimulates its **own** synthesis as seen in the figure.

Summary:

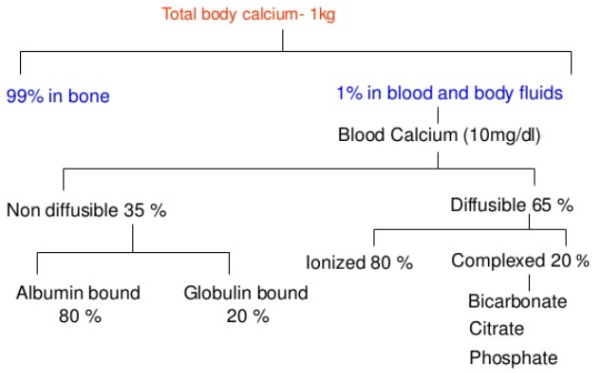


- In the previous lecture we said that 99% of Ca^{+2} is in the **bones**, the remaning 1% is found in the **plasma** where they are either:

1- **Diffusible**: ionized or complexed to HCO3-, citrate, etc.

2- **Non-diffusible** (protein bound): bound to albumin or globulin.

⇨ The **diffusable ionized** form Ca^{+2} level is what affects **PTH** secretion.



Calcium Homeostasis

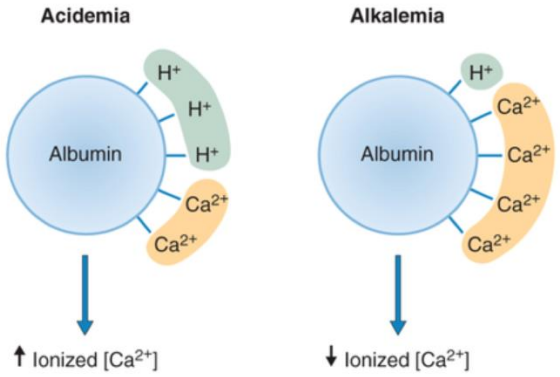
- Factors affecting calcium ions concentration in plasma:
  1- **PTH**: which **increases** plasma calcium levels when it drops low.
  2- **Vitamin D: increases** plasma calcium.
  3- **Blood pH:** pH affects the concentration of Ca^{+2} in plasma.
  4- **Calcitonin**: **decreases** plasma calcium.

We will discuss the last 2 points:

- **Blood pH:**

  a. **In alkalosis**, more calcium ions are **bound** to protein. Therefore, the concentration of the diffusible ionized form **decreases**.

  b. **In acidosis**, calcium is replaced by H^+, thus less calcium ions are bound to the protein having more **free** ions in the plasma. Therefore, the concentration of the diffusible ionized form **increases**.



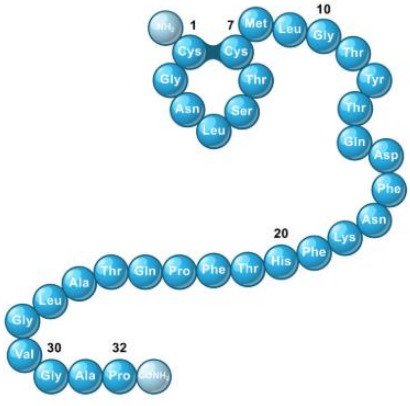
- **Calcitonin**:

  a. It is a straight-chain peptide of 32 amino acids with a molecular weight of 3400.

  b. The biologically active core of the molecule probably resides in its central region.

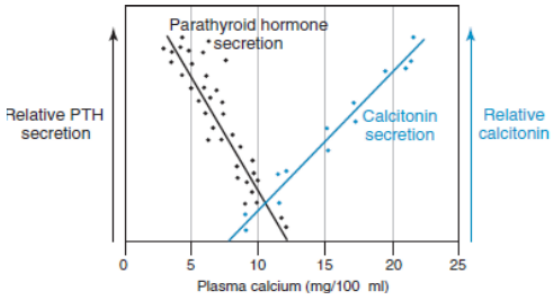
  c. It is secreted by the **thyroid parafollicular** cells known as "C" cells.

  d. Calcitonin, also abbreviated CT, is degraded within the **liver** and **kidney**, like other hormones, with a half-life of 30-60 minutes.



Functions of calcitonin:

1. Calcitonin (CT) **decreases** plasma calcium levels by **antagonizing** the actions of **PTH** on bone; by promoting Ca^{+2} deposition into bones **decreasing** its concentration in the plasma. It inhibits both, osteocytic osteolysis and osteoclastic bone resorption particularly when these are stimulated by PTH.
2. When **Ca^{+2}** plasma levels increase, PTH level decreases while calcitonin level **rises**, and vice versa.



> ***Note 1:*** *Calcitonin **deficiency** does not lead to **hypercalcemia**, and Calcitonin **hypersecretion** does not produce **hypocalcemia**. This may be due to the fact that abnormal CT secretion is easily **compensated** for by adjustment in **PTH** and **vitamin D** levels.*
>
> ***Note 2****: The major **stimulus** of CT secretion is a **rise** in plasma calcium concentration, opposite to the major stimulus of PTH secretion which is a fall in plasma calcium concentration.*

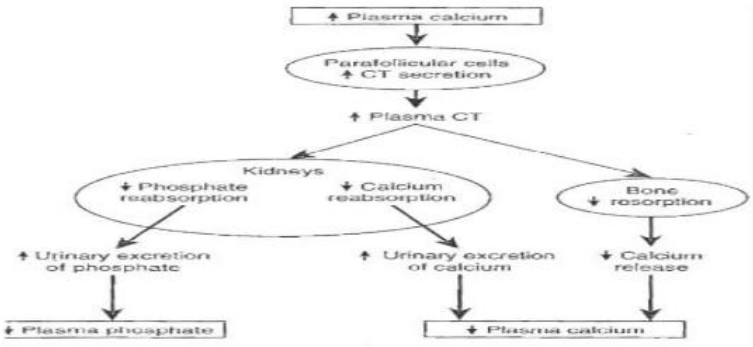
3. Calcitonin's effect on **calcium** is **opposite** to PTH's effect but both of them have the **same** effect on **phosphate** (they decrease phosphate levels).
4. Calcitonin is also present in nervous tissue, where it may function as a neurotransmitter.

Mechanism of action of Calcitonin:

- **On the bone:** CT **inhibits** bone resorption, via the inhibition of osteoclastic, and accordingly, calcium release from the bone is **decreased**. (Opposite to the effect of PTH).
- **On the kidneys:** CT **decreases** calcium and phosphate reabsorption, resulting in **increased** urinary excretion of both **Ca^{+2}** and **phosphate**, thus **decreasing** their concentrations in the plasma.

⇨ CT **decreases** Ca^{+2} plasma concentration (**opposite** to PTH).

⇨ CT **decrease** phosphate plasma concentration (**similar** to PTH).



Phosphate Functions and Homeostasis

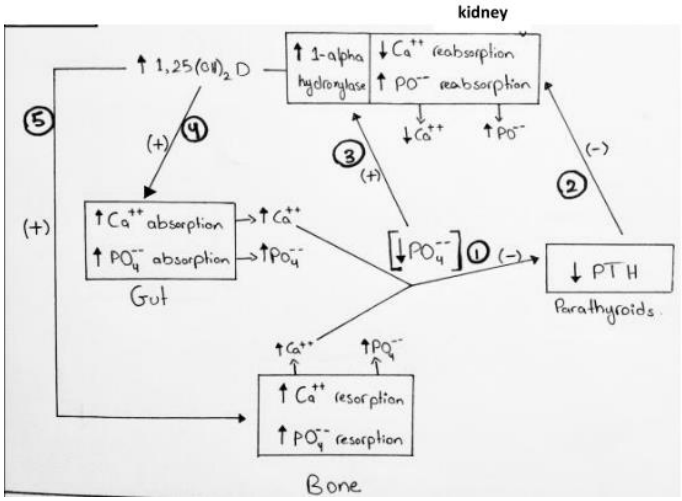
- **Physiological actions of phosphate:**

  a. Constituent of bone: 85 % of phosphate in the body is found in bones. Mineralization does not occur without phosphate.

  b. Important constituent of a variety of **macromolecules**, such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins.

  c. Functions as part of the **intracellular buffer system**; it has a role in pH regulation.

- **Phosphate Homeostasis**: the figure shows the responses to a marked **decrease** in serum phosphate concentration, opposite responses occur to marked increase in serum phosphate concentration.



'Numbers correspond to the numbers on the graph'

1. **Decreased** plasma phosphate concentration **inhibits** the secretion **of** PTH.
2. Therefore, the action of PTH on the **kidneys** will be **inhibited** resulting in a **decrease** in the excretion of **phosphate** and **increase** in **phosphate** reabsorption.
3. Decreased plasma phosphate concentration **stimulates** 1-α-hydroxylase in the **kidney** to produce 1,25 (OH)2-D. 1,25 (OH)2-D acts on both the:
4. Intestines, **increasing** the **absorption** of both Ca^{+2} and phosphate.
5. Bones, **increasing** the **resorption** of both, Ca^{+2} and phosphate.

   ⇨ As a consequence, plasma phosphate concentration will **rise**.

In summary: the body's response to decreased phosphate levels is **stimulating** the production of **1,25(OH)** and **inhibiting PTH** secrtetion.

- Notes mentioned by the doctor:

  1. Homeostasis of Ca^{+2}, phosphate ($PO4^{-3}$), Mg^{+2}, is essential for health and life.
  2. A complex system acts to maintain normal healthy concentrations of these minerals in the ECF and the whole body in the face of environmental and internal changes.
  3. The major elements in this system are:
     a. PTH.
     b. Vitamin D.
     c. Calcitonin.
     d. Other hormones (Growth Hormone, Insulin, and Prolactin).
  4. The GIT, kidneys, skeleton, skin, and the liver are all involved in the homeostasis of the previously mentioned three minerals.

Abnormalities of Calcium Homeostasis

1- **Rickets**: caused by vitamin D deficiency.

- We said earlier that vitamin D in adults is stored in **lipids** and it would be sufficient for many months *(more than 6 months)*, but children do **not** have such store or supplement.

  Rickets occurs mainly in children as a result of calcium or phosphate deficiency in the extracellular fluid, which mainly happens due to the **lack of vitamin D**, rather than a dietary lack of calcium or phosphate.

  If the child is properly exposed to **sunlight**, the 7-dehydrocholesterol in the skin becomes **activated** by the ultraviolet rays and forms vitamin D3, which **prevents** rickets by promoting calcium and phosphate **absorption** from the intestines, as discussed earlier.

- Rickets tends to occur especially in the late spring months, because:

  a- Vitamin D formed during the preceding summer is **stored** in the **liver** and available for use during the **early** winter months.

  b- Calcium and phosphate mobilization from the bones can prevent clinical signs of rickets for the first **few months** of vitamin D deficiency.

> ***Note:*** *Poor diet and inadequate skin exposure to sunlight are the **two main** contributors to rickets in children. Healthy diet and adequate exposure to sunlight are both important as two different sources of vitamin D for the human being; each one alone is **not** sufficient.*

2- Osteomalacia (adult rickets)

- Normal adults **rarely** have a serious dietary deficiency of vitamin D or calcium, because large quantities of calcium are not needed for bone growth as in children. However, a serious deficiency of both, vitamin D and calcium, occasionally occurs as a result of **steatorrhea** (failure to absorb fat); because:

  a- Vitamin D is **fat soluble**.

  b- Calcium tends to form **insoluble** soaps with fat. Consequently, in steatorrhea, both vitamin D and calcium tend to pass with the **feces**.

  ⇨ Under these conditions, an adult occasionally has **poor** calcium and phosphate **absorption** where **rickets** can occur, though this almost never proceeds to the stage of tetany, but very often, is a cause of severe **bone disability**.

3- Osteoporosis (decreased bone matrix)

- Osteitis fibrosa cystica is the **softening of the bone**, whereas **Osteoporosis** is different, it is the most common of all bone diseases in adults, especially in old aged, particularly in old women after **menopause**. 1 out of 10 old women in the USA suffer from osteoporosis which is a very **high** percentage.
- It is different from osteomalacia and rickets because it results from **diminished** organic bone matrix; a problem in the **metabolism** of all bone constituents (Ca^{+2}, Phosphate, Mg^{+2}, proteins, etc.) rather than abnormal bone **calcification** (mineralization).
- **Causes of osteoporosis:**

  1. Lack of physical stress on the bones because of inactivity. Being inactive will:

  a. Decrease the turn-over rate of the bones.

  b. Inhibits the **mineralization** of bone as well as **Ca^{+2} deposition** in bones.

  > ***Note:*** *This is **most common** cause of osteoporosis of young ages.*

  2. Malnutrition (poor diet) to the extent that sufficient protein matrix cannot be formed. This cause is rare nowadays.

  3. Lack of vitamin C, which is necessary for the secretion of intercellular substances by all cells, including the formation of osteoid by the osteoblasts. All vitamins are important but vitamin C is the most important in our body.

  4. Postmenopausal **lack of estrogen** secretion because estrogens decrease the number and activity of osteoclasts.

5. **Old age**, in which growth hormone and other growth factors **diminish** greatly, plus the fact that many of the protein anabolic functions also **decline** with age, so bone matrix cannot be deposited satisfactorily.
6. **Other causes**: Cushing's syndrome and Arcomegaly.

- To sum up the causes, ordered from the most to the least affecting:

1- Postmenopausal lack of estrogen secretion.
2- Lack of vitamin C.
3- Inactivity.

Prevention and treatment of osteoporosis:

- The **major** risk factor for osteoporosis is the **decline of estrogen level** in aging women. Strategies to prevent the development of osteoporosis begin in the Premenopausal period. Osteoporosis in old women is known as "The silent killer".
- High Ca^{+2} intake and consistent program of weight lifting exercises are widely recommended for both, males and females.
- Pharmacological agents are now available for **preventing** or at least delaying the development of osteoporosis or for treating the disease once it has become established. These pharmacological agents are classified into **two** groups:

a- **Anti-resorptive drugs.**

b- Agents which are able to **stimulate bone formation**.

- Among the anti-resorptive drugs group, **estrogen** is by far the most widely used therapy. It is most effective when started at the onset of menopause, it's even better to start it 2-3 years before menopause. Calcitonin used to be given, but it's controversial now

> ***Note:*** *Males **cannot** use estrogens, and even if they do, the estrogen they take will be converted in the body into **testosterone**, and the other way around applies in females.*

- **Bisphosphonates** are powerful **inhibitors** of bone **resorption**, however, some of them in higher doses might affect mineralization. The ideal way for the treatment of osteoporosis is Estrogen, Vitamin D and Ca^{+2}.

Good Luck