The Endocrine System

PHYSIOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	7
Subject:	PTH, Vitamin D & Calcium homeostasis
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Review:

●**Hypothyroidism** means under activity of thyroid gland, it causes cretinism in children and myxedema in adults. On the other hand **Hyperthyroidism** occurs due to hypersecretion of thyroid hormone, characterized by exophthalmos, goiter and hyperthermia.

●**Hypopituitarism** means under activity of pituitary gland, it's classified into four groups; panhypopituitarism, severe Hypopituitarism, moderate Hypopituitarism and mild Hypopituitarism. In all four groups Gonadotropins are deficient.

Hypersecretion of Pituitary gland

As you know, pituitary gland has very important effect in controlling other glands activates. However, symptoms of overactive pituitary results mainly from hypersecretion of growth hormone. The most common disorders associated with hypersecretion of pituitary gland are Giantism and Acromegaly.

● ***Giantism or gigantism***, If the over-secretion occurs before being adult (during the childhood), almost all the organs will be affected & become larger than normal.

- These individuals will be 8-9 feet (~ 2.5 meters) height.
- These giants will have hyperglycemia, 10% are going to develop diabetes mellitus eventually.
- If the giants remain without treatment, they'll develop panhypopituitarism.
- All parts of the body develop in appropriate proportion.
- Also the organs will be enlarged.

●***Acromegaly***, If the over-secretion occurs after being adult, after the fusion of the long bones, the person cannot grow taller (bones cannot grow), but the soft tissues can continue growing and the bones can grow in thickness leading to Osteopetrosis.

- These individuals will suffer from enlargement of the small bones of hands, feet, cranium, nose, forehead, supraorbital ridges, the lower jaw bone and portions of the vertebrae.
- Many soft tissues or organs such as: liver, tongue, kidneys are enlarged. "Also the heart but it's a little bit enlargement."
- There's NO appropriate proportion in the development.

Parathyroid hormone

●**Parathyroid glands** are small four glands located behind the thyroid gland, each one weights from (20-50) mg.

- These glands have two types of cells:

1. *Chief cells* that produce most of the PTH.
2. *Oxyphil cells*: The function is uncertain until now, but probably they are modified or depleted chief cells that no longer secrete PTH, but they play a role in PTH metabolism. Oxyphil cells are not present in young people, even in some animals, but in the human being it might develop later as modified chief cells.

- Almost all of the parathyroid hormone is synthesized and secreted by chief cells.

●The general functions of PTH is to regulate Ca++ levels in the blood.

- PTH functions on kidney tubules, bones and intestines so as to normalize the Calcium level which is 11mg/100ml of plasma (*Ca level must be maintained within a narrow range the same as PH*)
- PTH has two types of receptors (sometimes three), and it uses as a second messenger either cyclic AMP or (DAG and IP3).
- PTH related protein has similar function to PTH *(most probably this protein released from the parathyroid glands)*.

●General information about PTH:

- The parathyroid glands develop at 5-14 weeks of gestation.
- PTH is a single chain protein that contains 84 amino Acids. The biologic activity of the hormone resides within amino acids from one to thirty four (Within the first 34 amino acid).
- PTH is free in plasma with a short half-life of 25 min.

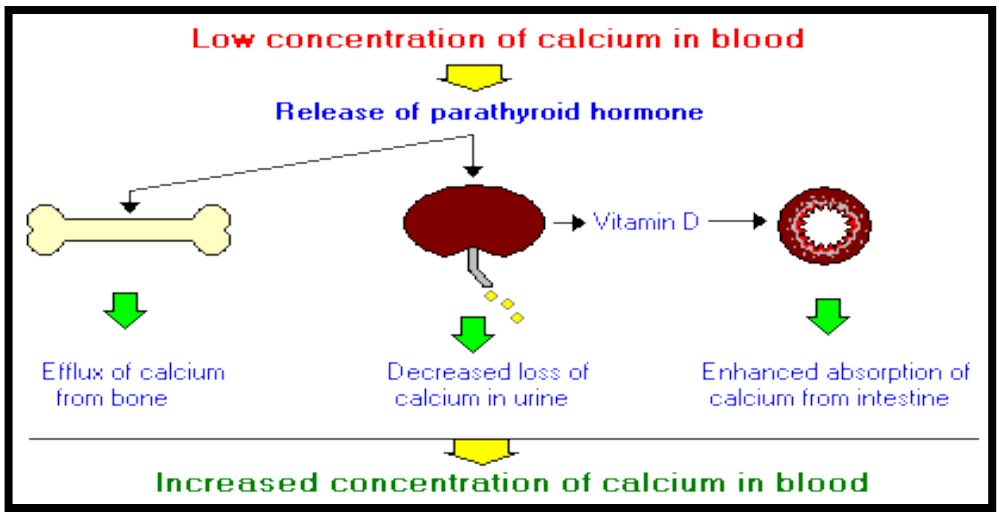
- PTH is essential for life, without it Ca++ falls in plasma, neuromuscular excitability increases, tetany and death occurs.
- The dominant regulator of PTH secretion is the plasma Ca++ level (ionized). Ca++ also regulates the size and the number of Parathyroid cell.

Regulators of parathyroid hormone

●PTH secretion and synthesis are primarily regulated by serum calcium level, although other factors such as Vitamin D, Mg, phosphate and neurotransmitters play a role.

- Hypomagnesaemia stimulates PTH secretion, same as Ca++ but less potent.
- Arise in plasma phosphate conc. indirectly causes transient increase in PTH secretion.
- *1,25-$(OH)_2$ D* directly reduces PTH Secretion.

The effects of parathyroid hormone



●As we said, PTH works on kidneys, intestines as well as bones in order to elevate Ca++ levels in the plasma:

- In kidneys: increase Ca re-absorption, Phosphate Excretion, and the synthesis of active form of VitD (1,25-$(OH)_2$ D) which will function on the intestines to increase Ca++ absorption.
- In bones: increase resorption of Ca and Phosphate *(and therefore, increasing renal excretion of phosphate, so it may be just an artificial effect of high phosphate levels in the blood)*.

●So, as you see, **PTH function mainly to normalize Ca level**, ***but why?*** Actually because Ca++ conc. In the blood affects many physiological functions, such as:

- Triggering the release of Acetylcholine from nerve endings at the neuromuscular junction (either the release will be deficient or absent depending on the degree of Ca deficiency).
- Involved in excitation-contraction coupling In muscle cells.
- Serves as an intracellular signal for some Hormones and enzymes (especially hormones that use DAG and IP3).
- Required by some enzymes for normal Activity.
- Required for blood clotting to occur normally.
- Required for proteins secretion (Such as insulin).
- Constituent of the bones.

Clinical applications

●**The under activity of the PTH** because of atrophy or removal of the parathyroid during thyroidectomy.

- When PTH decreases the bone resorption of ca++ decreases, kidney reabsorption of calcium also decreases, and calcium absorption from intestine is decreased.
- The result will be decrease in the Ca plasma level (normal limit is 10-11 mg/dl), if it is reduced to (5-6) mg.
- Tetany will occur and if it reaches the respiratory system death occurs.

●**Note#1** How does the tetanization occur?

Ca regulates the function of Na channels, In the case of Hypo-parathyroidism the Ca plasma level is low, leading to continuous opening of sodium channels and continuous entry of Na, continuous

depolarization that results in a tetanization; there is no contraction and relaxation only contraction.

●**The over activity of PTH** because of a tumor:

- A lot of Ca reabsorption the kidney tubules.
- A lot of 1:25 DHCC is produced, so a lot of dietary Ca is absorbed by the intestines.
- A lot of Ca is resorbed from the bones.
- Normal PTH produce calcium from around the bones (from the synovial fluid), but in the case of excess PTH would produce it from the structure itself causing softening of the bones and fragility a disease called **Osteitis fibrosa cyctica** (not osteoporosis).
- Plasma Ca may be increased to 16mg/dl.

Vitamin D and its role in Ca homeostasis

●It is the second major regulator of Ca^{+2} and phosphate metabolism.

- The role of vitamin D is to promote mineralization of new bone, and its actions are coordinated to increase both $Ca^{2}+$ and phosphate concentrations in plasma (by increasing the absorption of Ca and Phosphate from the GI tract mainly, same effect on the Kidney and on the bones it activates the osteoclast to work on them) so that these elements can be deposited in new bone mineral.

Synthesis and Metabolism of vitamin D

●Vitamin D can be obtained either from UV light/skin and here it is called D3 (*Cholecalciferol*), or from dietary sources and here it is called D2 (*Ergocalciferol*).

-- Due to the fact that it can be synthesized in the body and also obtained from the diet it is can be called vitamin D or Hormone D. --

- Both of these prohormones are the same with only slight differences in their structure, still they undergo identical processing that converts them into the active form.

●D2 and D3 get concentrated in the liver where they are converted into 25-(OH)-D (*vitamin D that is hydroxylated on carbon number 25*)

● This molecule is then transported to the kidney where it is converted to either 24,25-$(OH)_2$-D by 24- hydroxylase or 1,25-$(OH)_2$-D by 1α-hydroxylase.

●**Note#2** How does the kidney know what it should convert 25-(OH)-D into?

- If we have Vitamin D deficiency, Ca^{+2} deficiency, phosphate deficiency, or PTH stimulation, then the enzyme 1α-hydroxylase is activated and 1,25-$(OH)_2$-D is formed. ***Why***?
  Because this molecule can Increase Ca2+ and phosphate absorption from the intestines, Increase their reabsorption from the kidneys and decrease their excretion as well as Promoting PTH action.

- So Overall result of 1,25-$(OH)_2$-D formation is increase in blood Ca^{+2} levels

- And when we have excess Ca2+ , excess phosphate, or excess 1,25-$(OH)_2$-D, the enzyme 24-hydroxylase is activated and 24,25-$(OH)_2$-D is formed. ***Why?*** Because this molecule can serve to dispose of excess vitamin D, as it is 1/20 of the strength of 1,25-$(OH)_2$ D.

●**Note #3** All these three vit. D prohormones are found in the plasma bounded to proteins, all of them can function bet 1,25-$(OH)_2$ D is the strongest.

●**Note #4** The are more than 20 derivatives of vit. D found in the plasma but there functions are not known yet.

●**Note #5** Vitamin D is important for new bone mineralization. PTH produces calcium for the many functions in the body. They work synergistically.

●**Note #6** Vitamin D is stored in adipose tissue, so obese individuals especially those who have lot of fat in their abdomen (men) have their vitamin D retained by this fat so vit. D is not released. They are exposed to many problems even heart problems.

●**Note #7** Vitamin D deficiency causes rickets in children and osteomalacia in adults.

●The end – wa 25eran ☹-

●Please refer to the slides

●Good luck