University of Jordan - Faculty of Medicine
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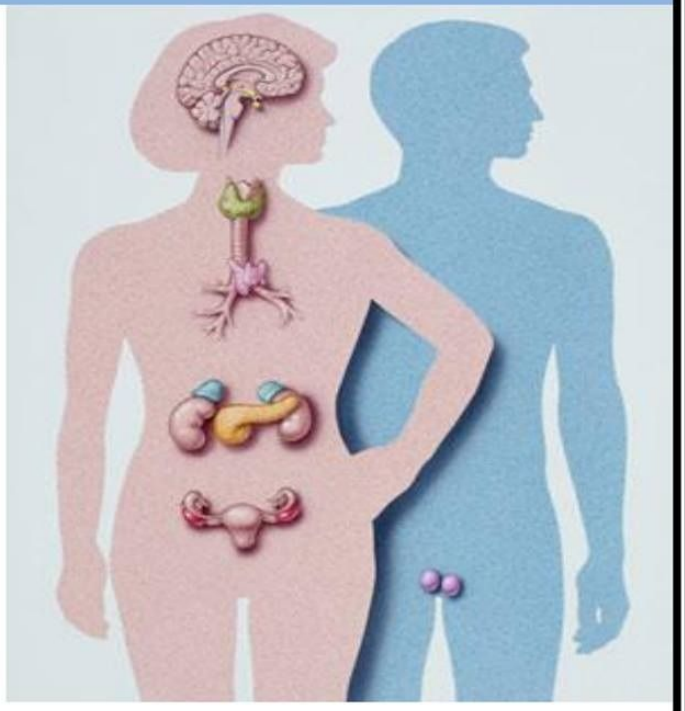
Medical Committee
The University of Jordan

Endocrine System



- ☐ Anatomy/Embryology/Histology
- ☐ Biochemistry
- ■ Physiology
- ☐ Pharmacology
- ☐ Pathology
- ☐ PBL

☐ Slide ■ Sheet ☐ Handout ☐ Other

Lecture #: **5**

Date:

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This sheet includes two topics

1. General notes about thyroid hormones

2. Parathyroid glands and PTH

*Remember that

1- Thyroid hormone along with other hormones (Insulin-like growth factor-I "IGF-I", insulin, cortisol, androgens and estrogens) contribute to the growth process in humans. But GH and IGF-I have been implicated as the major determinants of growth in normal postuterine life (after birth)

2-. Thyroid Hormones are essential in normal amounts for growth, excess doesn't produce overgrowth as with GH, but causes increase catabolism of proteins and other nutrients. But if these thyroid hormones are deficient, many processes in the body will be disturbed.

3- .Normal concentrations of thyroid hormones are very low and the total T4 in adults is approximately (8mcg/dl),while free T4(not bound to protein)is only .03% which is (2ng/dl).Total T3 is (0.12 mcg /dl) and free T3 is .3% that is (0.28 ng/dl) ……pay attention to the units

4.Thyroxine (T4) at normal concentration has**permissive** effect on the action of GH on **protein synthesis**. So, in its absence, amino acids uptake and protein synthesis are not much stimulated.

5-Reduced thyroid activity in childhood produces dwarfs who are mentally retarded, whereas reduced GH in childhood produces dwarfs (short stature) with normal intelligence.

Cretinism(also known as thyroid dwarfism, to differentiate between it and the dwarfism caused by growth hormone deficiency) is a condition arising from the deficiency of thyroid hormone. The fetus fails in developing skeletal, mental and sexual abilities.

Pituitary dwarfism vs cretinism

Pituitary dwarfism is caused by inadequate amounts of growth hormone .Growth hormone deficiency results in abnormally slow growth and short stature with normal proportions. Thyroid dwarfism is when hypothyroidism in an immature animal causes retarded growth and development of bones with disproportionate dwarfism.

*in Fetus, the thyroid gland can produce its hormones, under the effect of the fetus hypothalamus and pituitary hormones (not the mother; maternal TSH can't cross the placenta). The deficiency of thyroid hormones affects skeletal muscle, nervous system and libido

❖ Pathophysiology of thyroid hormones:

❖

- Hyposeceretion:**Hypothyroidism:**(under activity of thyroid**)**

- The most common causes are iodine deficiency, surgical removal of your thyroid, autoimmune diseases, and radiation treatment.

☒ The main symptoms are

1. **Critinism:** - Associated with hyposecretion of thyroid hormone during**childhood**. - It is characterized by: dwarfism; failure of skeletal, sexual and mental growth and development.

2.**Myxedema**: - During**adulthood.**- It's characterized by slowing down of all bodily processes; this is because of thyroid hormone deficiency. –

☒ **The body processes that are slowed down**:

- Tissue oxidation.
- Gut movements.
- Basal Metabolic Rate (BMR).
- Heart and Respiratory Rates.
- Body temperature falls.
- Thought processes.
- Skin.- Thick, leathery
- Blood Cholesterol increases
- Slow husky voice
- Appetite is reduced.
- Hair- Brittle, dry

- Hypersecretion: - (Hyperthyroidism)
- Causes: (Graves' disease) increased production of thyroid stimulating immunoglobulins, secondary to excess hypothalamic and pituitary secretion, hypersecreting thyroid tumor

☒ The main symptoms are

1-Exophthalmos: - The protruding of the eye balls.

Most but not all patients with hyperthyroidism develop some degree of protruding of eye balls. - It usually occurs due to increased production of antibody called **Thyroid Stimulating Immunoglobulin**which acts against a protein of the extraocular muscles and the connective tissue behind the eye which causes these tissues to swell. - It is not due to an excess of the thyroid hormones.

2-Goiter: - The enlargement of the thyroid gland.

- It does occur in both hypothyroidism and hyperthyroidism because of the continuous stimulation of thyroid cells. Sometimes, goiter occurs along with exophthalmos
, but not necessarily in all cases. It may occur alone.
. Having a goiter doesn't necessarily mean that your thyroid gland isn't working normally. Even when it's enlarged, your thyroid may produce normal amounts of hormones. It might also, however, produce too much or too little thyroxine and T3.

Note: Exophthalmos occurs only in case of HYPERTHYROIDISM

- What are the different types of Goiter?

1) **Simple benign (nontoxic)**: in which T3 and T4 levels are **low**
   - A non-cancerous enlargement of the thyroid gland is called a simple goiter and can form as a diffuse or as a nodular goiter
   .
2) **Malignant (toxic):** in which T3 and T4 levels are **high**.
   - Toxic goiters are an enlargement of the thyroid gland resulting from an overproduction of the thyroid hormone, a condition called hyperthyroidism

   - **Graves' disease**, Also known as **toxic diffuse goiter**. It frequently results in hyperthyroidism and an enlarged thyroid.

Note: We can't differentiate from **the appearance**if the goiter is toxic or non-toxic!

❖ Parathyroid glands and PTH

They are small four glands located behind the thyroid gland, each one from (20-50) mg in weight. Almost all of the parathyroid hormone is synthesized and secreted by chief cells; this tells us that there are 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.

✓Regulators of Ca level in the blood:

- **PTH**: functioning 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).

☒ General information about PTH

- ✓ -PTH related protein has similar function to PTH [most probably this protein released from the parathyroid glands].
- ✓ 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 a.a]
- ✓ PTH is free in plasma with a short half-lifeof 25 min.
- ✓ PTH is essential for life, without it Ca++ falls in plasma, neuromuscular excitability increases, tetany& death occurs.
- ✓ The dominant regulator of PTH secretion is the plasma Ca++ level (ionized). Ca++ also regulates the size &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

•**<u>On kidneys</u>**: increase Ca re-absorption, Phosphate Excretion, and the synthesis of VitD (1,25-(OH)2-D)which will function **<u>on the intestines</u>**: increase Ca++ absorption.

•**<u>On bones</u>**: increase resorption of Ca and Phosphate [then phosphate will be excreted through the kidneys]

- So generally, PTH function MAINLY to normalize Ca level due to its functions, such as
  - ✓ Involved in 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.

Pathphysiology of PTH:

☒ **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) mgtetany will occur and if it reaches the respiratory system death occurs

- **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 aTETANIZATION; there is no contraction and relaxation only contraction.

- **The over activity of PTH**: [because of a tumor]

  1. Alot of Ca reabsorption the kidney tubules.
  2. A lot of 1:25 DHCC is produced, so a lot of dietary Ca is absorbed by the intestines.
  3. Alot of Ca isresorbed from the bones. Normal PTH produce calcium from around the bones (from the synovial fluid), but excess PTH would produce it from the structure itself causing softening of the bones and fragility a disease called (**osteitisfibrosacyctica**) not osteoporosis.

  *Plasma Ca may be increased to 16mg/dl

The second major regulator of the Ca level:

- The first regulator is PTH
- Vitamin D is a major regulator of Ca and phosphate [both of them] , sometimes it considered a hormone because it is produced in the body and released into the blood then into the liver and the derivatives are produced. And sometimesit is considered a vitamin taken from the ingested food.
- Vit D has 2 sources firstly through the skin as D3 and from the diet as D2. Vitamins D3 & D2 have a very little difference in their structures, they are

essentially **pro-hormones** that undergo **identical** processing that converts them to Molecules with **identical** qualitative & quantitative Actions. Once vitamin D enters the circulation from the skin or the Gut, it is released in blood and concentrated in the liver. There the liver produces the first derivative 25-0H-D.

- This molecule is transported to the kidneys where it undergoes alternative fates. If the enzyme 24-Hydroxylase is activated, 24,25-(OH)2 will be formed. [in the kidneys the most potent derivative will be formed >>1,25(OH)-D …and another derivative 24,25(OH)-D its potency is 1/20th of the previous one .]

- 24,25(OH)-D mainly serves to dispose of excess vitamin D.[it means that if there is need >>1,25 will be formed ….if there is less need 24,25will be formed) .

- Now we have factors that determine the formation of either 24,25-(OH)2-D or 1,25-(OH)2-D:

  *Excess 1,25-(OH)2-D, Calcium excess, phosphate excess stimulate the synthesis of 24,25-(OH)2-D.
  *Vitamin D deficiency, Calcium deficiency, phosphate deficiency, parathyroid hormone all favor synthesis of 1,25(OH)2-D

- Vitamin D, 25-0H-D & 1,25-(0H)2-D circulate in the plasma bound to specificproteins.V.D3 has many natural sources like codfish, eggs, and 45-milk, in addition To the skin. BUT V.D2 can be obtained only from the diet, mushrooms are rich in it. in addition to vitamin D2and 3 and their derivatives there are other 15 Metabolite without known function

- . **** Conclusion of V.D processing**:

- Vitamin D will be transferred to the liver to become 25(OH)-D. Thiscompound will be transferred to the kidneys, either to become 1,25 OR 24,25 derivatives**. Deficiency of (Ca, phosphate, V.D) and the PTH stimulation leads to formation of the 1, 25(OH)-D by 1-α hydroxylase enzyme.1,25(OH)-D ,,Ca and phosphate excess leads to the formation of 24,25 by 24- hydroxylase enzyme** .

- When calcium in your blood is low, your parathyroid starts secreting PTH. PTH starts pulling calcium from your bones and into your blood. PTH also starts telling your kidneys to start making more $1,25(OH)_2D$. You have vitamin D stores in your body called 25(OH)D that are ready for the kidney to produce $1,25(OH)_2D$ when needed, if you get adequate vitamin D intake.

- When the kidney starts producing $1,25(OH)_2D$, it helps the gut absorb more calcium than usual, to make sure you get enough calcium into your body. When $1,25(OH)_2D$ increases and helps your body get to the right calcium balance, it tells your parathyroid to stop making so much PTH, and stop pulling calcium from your bones.

- On the other hand, when calcium in the blood is high, your parathyroid won't release much PTH at all. The amount of calcium in your blood tells your parathyroid not to release any PTH, and in turn, PTH doesn't tell your kidney to produce more $1,25(OH)_2D$. So you stop absorbing too much calcium and allows your body to lower its blood calcium.

- This interaction between calcium, parathyroid and vitamin D is happening constantly; $1,25(OH)_2D$ and PTH always adjusting to make sure you have the right calcium balance.

- Vitamin D 2and 3 almost identical, with a little bit difference in their structure. V.D2, V.D3 and 25(OH)- D are **prohormones** .

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

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

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