

Title: Thyroid Gland & Hormonal Control of Calcium Metabolism

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I. The Thyroid Gland

- 1. The thyroid gland (follicular cells) produces and secretes *thyroxine* (T_4), *triiodothyronine* (T_3) and reverse *triiodothyronine* (rT_3).**
- 2. Parafollicular (C) cells of the thyroid gland produce and secrete *calcitonin*.** Calcitonin is involved in the regulation of calcium metabolism.
- 3. T_3 is more active than T_4 , while rT_3 is inactive. All these hormones are composed of iodine – containing tyrosine residues.**
- 4. The average diet contains 500 μg of iodine, while 150 μg per day is the minimal iodine intake that is necessary to maintain thyroid function.**
- 5. About 90% of the thyroid hormone secreted by the gland is T_4 while 10% is T_3 . In the target cells, T_4 is converted to either T_3 , or rT_3 .**
- 6. Synthesis of thyroid hormones:**
 - a. Synthesis of thyroglobulin in the follicular cells.
 - b. An active transport of iodides from the extracellular fluid into the follicular cells - “*iodide trapping*” (“*iodide pump*”).
 - c. *Conversion of iodide ions to an oxidized form of iodine.*
 - d. *Binding of iodine with thyroglobulin - formation of *monoiodotyrosine* (MIT) and *diiodotyrosine* (DIT).*
 - e. *Coupling reactions* resulting in the formation of T_4 , T_3 or rT_3 .
 - a. Storage of the thyroid hormones in the follicular colloid.

Iodide oxidation, binding of iodine with thyroglobulin and probably coupling reactions are promoted by the *thyroid peroxidase*.

7. **Secretion of thyroid hormones** requires formation of pinocytic vesicles, and then digestive vesicles. Lysosomal proteases digest the thyroglobulin and liberate the thyroid hormones. About 75% of iodinated (but uncoupled) tyrosine residues is deiodinated by thyroid deiodinase and their iodine is again used to produce thyroid hormones.
8. **Iodide deficiency inhibits the function of the gland, as does high plasma level of iodides.** Since iodides (present in excess) reduce gland's size and blood supply, they are often administered to patients before thyroid surgery.
9. **The synthesis and secretion of thyroid hormones are stimulated by pituitary thyroid stimulating hormone (TSH).**
10. **Most (over 99%) of the circulating hormones is bound to the plasma proteins:** TBG (thyroxine-binding globulin), transthyretin - TBPA (thyroxine-binding prealbumin) and albumin.
11. **T_4 is the principal hormone secreted by the thyroid gland. T_3 is the major hormone that acts on the target cells.**
 - a. The binding affinity of TBG and other plasma proteins is over 6 times greater for T_4 than for T_3 thus *the biologic half-life of T_4 is 6-7 days, while that of T_3 is 1 day.*
 - b. *The latent period of T_4 is 2-3 days, while that of T_3 is 6-12 hours.*
 - c. Triiodothyronine provides 90% of thyroid hormone molecules that bind with the hormone receptor.

12. Thyroid Hormone Effects – Physiology and Thyroid Disorders

- a. **In the cells, thyroid hormone causes nuclear transcription of large numbers of genes and consequently, an increase in the formation of many proteins**, including enzymatic structural, and other proteins. *The major effects of T_3 on target cells are to increase the rate of metabolism, oxygen consumption, and energy (ATP and heat) production in the cell, accounting for the calorogenic effect of the hormone.* This effect is stimulated by cold weather and pregnancy. However, BMR and oxygen consumption in the brain, pituitary, gonads, spleen, and lymph nodes are not affected.
- b. *The thyroid hormone increases body requirement of vitamins.* Therefore, a relative vitamin deficiency may occur in hyperthyroidism.
- c. *The thyroid hormone stimulates almost all aspects of carbohydrate metabolism* and carbohydrate absorption from the gastrointestinal tract. Although thyroid hormone increases insulin secretion, a marked reduction in insulin half-life found in thyrotoxicosis may impair glucose tolerance in some patients.
- d. The thyroid hormone stimulates mobilization, degradation, and synthesis of lipids. *It increases plasma free fatty acids` level and decreases plasma cholesterol*, phospholipids and triglycerides *levels*. Thyroid hormones deficiency that is associated with increased blood cholesterol level promotes severe atherosclerosis development.
- e. *The thyroid hormone increases both protein synthesis and protein break down.* Protein catabolism predominance is partly responsible for muscle weakness (myopathy thyreotoxica) found when thyroid hormone is present in excess. Muscle weakness may be also found in thyroid hormone deficiency; then it is associated with muscle stiffness.
- f. *The thyroid hormone inhibits the synthesis and increases degradation of mucopolisaccharides and fibronectin.* Thyroid hormones deficiency leads to accumulation in the connective tissue of mucopolisaccharides and retention of water. Puffiness of the skin, mainly found on the face, is called myxedema.
- g. The thyroid hormone, which is permissive to action of the growth hormone, *is essential for normal growth and skeletal maturation.* *Thyroid hormone stimulates ossification of cartilage, linear growth of bone, maturation of the epiphyseal bone centers and closure of epiphyses.*
- h. *The thyroid hormone is essential for normal growth and development of brain;* proliferation

of axons, branching of dendrites, synaptogenesis, cell migration, growth of cerebral cortex, and myelin formation. *It's deficiency at birth (congenital hypothyroidism) and/or during infancy or childhood causes mental retardation (cretinism), retarded growth rate, lower body temperature, and thickened facial features.*

- i. ***Under influence of the thyroid hormone, the rate of blood flow in the tissues increases***, that results from both direct and indirect effects of the hormone on the cardiovascular system. Indirect effects include an increase in the number and affinity of beta-adrenergic receptors in the heart. Since the increased heat production and CO₂ level in the tissues cause vasodilatation, a decrease in diastolic blood pressure via a reflex effect contributes to the adrenergic stimulation of the heart.

The thyroid hormone increases cardiac output (heart rate and stroke volume) and the systolic pressure. Tachycardia, arrhythmia, systolic hypertension, and increased pulse pressure may be present in hyperthyroidism. Myocardial failure may be found in severely thyrotoxic patients.

- j. ***The thyroid hormone increases the rate and depth of breathing.***

- k. ***The thyroid hormone increases both the secretion and motility of the gastrointestinal track.*** Thyroid hormones excess may cause increased frequency and softening of the bowel movements, or even diarrhea. Hypothyroidism often causes constipation.

- l. ***Thyroid hormone increases rapidity of cerebation*** and dissociates it. Hyperthyroidic patients have rapid mentation; they may complain of irritability, difficulty sleeping and psychoneurotic tendencies (anxiety, extreme worry, paranoia). Psychosis may be present in either hyperthyroidism, or hypothyroidism, but in the last case mentation is slow, somnolence or even lethargy may be found. Tremor in fingers and hands (10-15 times/second) is one of the most characteristic sign of hyperthyroidism. The speed and amplitude of peripheral nerve reflexes are increased in hyperthyroidism and decreased in hypothyroidism.

- m. ***The thyroid hormone affects the function of other endocrine glands.***

- n. ***Thyroid hormone affects the function of the reproductive system.*** Abnormalities of female menstrual cycle and impotence may be found in either hyperthyroidism, or hypothyroidism.

- o. ***The ophthalmologic manifestations may be found in Graves` disease.*** Infiltrative ophthalmopathy (exophthalmos) is caused by the oedema and infiltration of the extraocular muscles, and connective tissue within the bone walls of the orbits.

13. Thyroid Disorders – Hyperthyroidism

- a. *The major cause of hyperthyroidism is Graves` disease* (toxic goitre).
- b. Other causes of hyperthyroidism include solitary toxic adenoma, toxic multinodular goitre, or TSH – secreting pituitary tumor.

14. Thyroid Disorders - Hypothyroidism

- a. Hypothyroidism may result from autoimmune thyroiditis (Hashimoto disease), head or neck irradiation, or deficiency of TSH.
- b. Congenital hypothyroidism .

15. *Goitre is a pathological enlargement of the thyroid gland.* Endemic goitre is caused by insufficient dietary intake of iodine. Toxic goitre is found in Graves` disease.

II. Hormonal Control of Calcium Metabolism

A. Calcium Homeostasis

1. The majority of the total body calcium is stored in the bones, about 1% - is present in the cells, and 0,1% - in the extracellular fluid.
2. About 41% (1 mmol/L) of plasma calcium is combined with the plasma proteins, 9% (0,2 mmol/L) is bound to the anions (citrate, phosphate), and 50% (1,2 mmol/L) is in the ionized form. *Free, ionized Ca^{2+} is biologically active and its concentration is regulated very precisely.*

B. Parathyroid Hormone (PTH)

1. **PTH is produced and secreted by the parathyroid glands.** It contains 84 amino acids, but a chain of 34 amino acids adjacent to the N terminus of the hormone exhibits the whole PTH activity.
2. *The parathyroids secrete PTH in response to a decrease in calcium ion concentration in the extracellular fluid (hypocalcemia).* Parathyroid glands enlargement occurs under conditions of their prolonged stimulation (rickets, pregnancy, and lactation). Conditions associated with increased calcium ion concentration (enhanced vitamin D and/or calcium intake, bone absorption, which does not result from PTH action) cause decreased activity and reduced size of the glands. Mild decrease in serum Mg^{2+} level stimulates PTH secretion while severe decrease inhibits PTH secretion and produces symptoms of hypoparathyroidism.
3. *PTH causes an increase in calcium ion concentration in the extracellular fluid and a decrease in phosphate level. These effects result from PTH action on three target organs: bone, kidney, and intestine.* The last effect is indirect; PTH increases formation of the active form of vitamin D, which promotes calcium and phosphate absorption by the intestine.

4. PTH effects on bone and kidney:

- a. *The first (rapid) phase results from activation of already existing bone cells (the osteocytic membrane system) and absorption of calcium phosphate salts from amorphous compounds without resorption of the organic matrix (osteolysis).*
- b. *The second phase results from activation of the osteoclastic system. The proteolytic enzymes and acids released from the osteoclasts cause reabsorption of the bone itself, which is reflected by increased hydroxyproline excretion in the urine.*
- c. *Alone, these effects would not increase the ionized calcium in the plasma, because phosphate complexes with calcium ions.*
- d. *In the kidneys, PTH increases the reabsorption of calcium, mainly in the distal tubules, the collecting tubules, the early collecting ducts, and possibly, the ascending loop of Henle. PTH inhibits the reabsorption of phosphate in the early proximal tubules thus increasing phosphate excretion in the urine (a phosphaturic effect).*

C. Vitamin D

1. **Vitamin D is present in the food, of either animal, or plant origin** (called cholecalciferol – D₃, or ergocalciferol – D₂, respectively). **Cholecalciferol is produced in the human body** from a precursor present in the skin (7 – dehydrocholesterol). Ultraviolet rays cause its conversion to vitamin D₃.

2. ***Vitamin D itself is not active and must be converted, via two subsequent hydroxylation, into the active form.***
 - a. First hydroxylation occurs in the liver, where cholecalciferol is converted to 25-hydroxycholecalciferol that, in a feedback effect, inhibits this reaction.
 - b. Second hydroxylation occurs in the kidneys (the proximal tubules). Dependently on body need, 25-hydroxycholecalciferol is converted to either *1,25 - dihydroxycholecalciferol - 1,25(OH)₂D₃*, which is the most active form of vitamin D, or *24,25-dihydroxycholecalciferol - 24,25(OH)₂D₃*, which has almost no vitamin D effect. *PTH activates 1 α -hydroxylase.*

3. Vitamin D action:

- a. *In the intestines, $1,25(\text{OH})_2\text{D}_3$ promotes absorption of calcium (by increasing formation of a calcium binding protein in the intestinal epithelial cells) and phosphate.*
- b. In the kidneys, vitamin D has a very weak effect on the reabsorption of both calcium and phosphate.
- c. In the bone, vitamin D is necessary for either bone deposition, or bone absorption

D. Calcitonin

1. **Calcitonin is a 32-amino acid peptide produced in the parafollicular cells (C cells) of the thyroid.**
2. **Calcitonin has weak effects opposite to those exerted by PTH.**
3. **Calcitonin decreases blood calcium ion concentration;** it decreases the activity and formation of the osteoclasts and, possibly, the effect of the osteocytic membrane system. An increase in plasma calcium ion concentration stimulates the secretion of hormone.

E. Pathophysiology of Parathyroid Hormone and Vitamin D

1. **Primary hyperparathyroidism is most commonly caused by a single adenoma.**
 - a. *In severe hyperparathyroidism bone reabsorption outstrips deposition.*
 - b. *Patients with primary hyperparathyroidism have an extreme tendency to form kidney stones (especially bilateral and/or recurrent).*
 - c. *Calcium deposits found in the renal interstitium (nephrocalcinosis) cause degenerative changes in the renal tubules.*
 - d. Increased level of calcium (especially ionized) in body fluids causes loss of appetite, loss of weight, nausea, and constipation. Hyperparathyroidism may be associated with peptic ulcer and/or pancreatitis.
 - e. *Increased concentration of calcium causes depression of the nervous system, sluggishness of reflex activity, weakness, and asthenia. Drowsiness, lethargy, disorientation, stupor, psychiatric and mental disorders have been described in connection with hypercalcemia.*
 - f. *Hypercalcemia shortens ventricular systole (a shortened QT interval in ECG).*
 - g. Laboratory findings in primary hyperparathyroidism include: \uparrow PTH level, \uparrow $1,25(\text{OH})_2\text{D}_3$ level, \uparrow serum $[\text{Ca}^{2+}]$ -hypercalcemia, \downarrow serum [phosphate] – hypophosphatemia, \uparrow urinary

Ca^{2+} excretion, \uparrow urinary phosphate excretion, \uparrow urinary cAMP, \uparrow urinary excretion of hydroxyproline, \uparrow serum alkaline phosphate (cases of extensive bone involvement).

2. Hypoparathyroidism is most commonly a result of thyroid surgery, or it is congenital. Hypoparathyroidism causes hypocalcemia.

- a. *The classical neuromuscular manifestation of hypocalcemia is tetany* that results from increased excitability of the nervous system. The first sign of tetany is “carpopedal spasm” including tetany of the hand (called “obstetrical hand”). Provocative tests (the presence of Chvostek’s sign and Trousseau’s sign) are used to demonstrate the latent tetany. Tetany occurs when plasma calcium concentration decreases to 6 mg/dl (normal level – 9,4 mg/dl).
- b. Other manifestations of hypocalcemia include prolongation of QT interval in ECG and mental changes.
- c. Laboratory findings include: \downarrow PTH level, \downarrow $1,25(\text{OH})_2\text{D}_3$ level, \downarrow serum $[\text{Ca}^{2+}]$ (hypocalcemia), \uparrow serum [phosphate] (hyperphosphatemia), \downarrow urinary phosphate excretion.