King Saud University
College of Medicine
Second year – Endocrine Block

Hypo, Hyperthyroidism and Hashimoto's Thyroiditis

Lecture - 1

430 Pathology Team

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Red: Doctors' and important notes.
Green: Team notes.

Thyroid Gland:

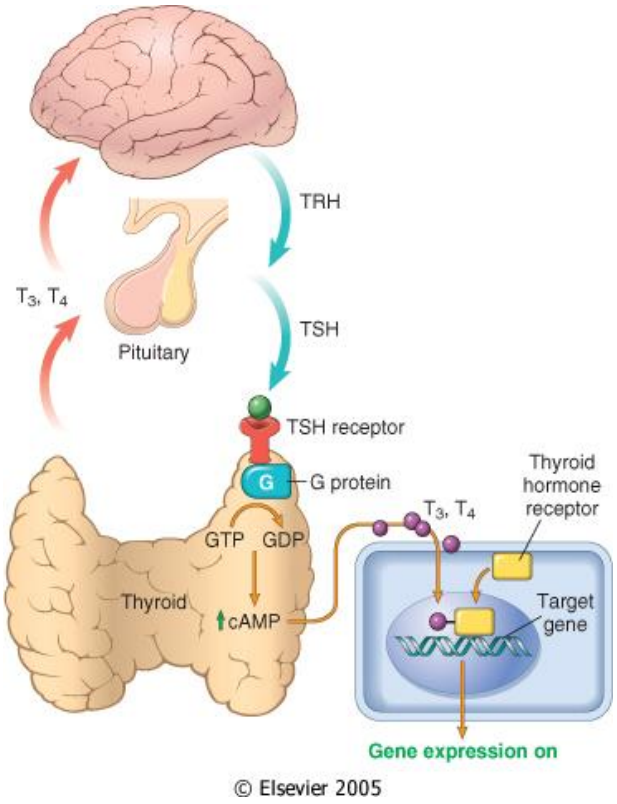
Anatomy:

- The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx.
- The thyroid gland is one of the most responsive organs in the body and contains the largest store of hormones of any endocrine gland.

Physiology:

Secretion of thyroid hormones (T_3 and T_4) is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary.

Decreased levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary, causing T_3 and T_4 levels to rise. Elevated T_3 and T_4 levels, in turn, suppress the secretion of both TRH and TSH. This relationship is termed a negative-feedback loop. TSH binds to the TSH receptor on the thyroid follicular epithelium, which causes activation of G proteins, and cyclic AMP (cAMP)-mediated synthesis and release of thyroid hormones (T3 and T4). In the periphery, T_3 and T_4 interact with the thyroid hormone receptor (TR) to form a hormone-receptor complex that translocates to the nucleus and binds to so-called thyroid response elements (TREs) on target genes initiating transcription.



Diseses of the thyroid gland:

1. Hypothyrodism
2. Hyperthyrodism
3. thyroditis

1- Hypothyroidism:

Definition: any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone

Epidemiology:

- Overt hypothyroidism (clinically obvious) is 0.3%
- Subclinical hypothyroidism (not sever enough to present symptoms) can be found in greater than 4%.
- Prevalence increases with age
- it is ten times more common in women than in men

Causes:

It can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis.

Classification:

1. Primary (Problems in the Thyroid gland itself)
Developmental (thyroid dysgenesis: PAX8, FOXE1, TSH receptor mutations).
Postablative (after it has been destroyed by surgery, radioiodine therapy, or external irradiation).
Iodine deficiency.
Autoimmune hypothyroidism (can be duo to antibodies or T cell mediated injury).
Hashimoto thyroiditis*
Congenital biosynthetic defect (dyshormonogenetic goiter)*
2. secondary (central) (duo to):
Pituitary failure
Hypothalamic failure (rare)

Signs and symptoms:

Thyroid hormones are required for normal Nervous development. Because thyroid hormones can cross the placenta, maternal thyroid hormone levels are an important factor that greatly contributes to the severity of the disease. If there is maternal thyroid deficiency before the development of the fetal thyroid gland, mental retardation is severe. In contrast, reduction in maternal thyroid hormones later in pregnancy, after the fetal thyroid has developed, allows normal brain development

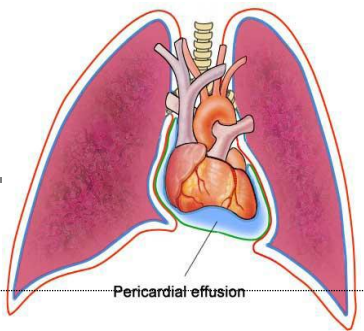
- Cretinism: refers to hypothyroidism developing in infancy or early childhood.
  This condition includes:
  - Severe mental retardation
  - Short stature
  - Coarse facial features
  - Protruding tongue
  - Umbilical hernia.


Patient showing Myxedema

- Myxedema: refers to hypothyroidism developed in late childhood or adulthood and its clinical manifestations include:
  - Slowing of physical and mental activity
  - Mental sluggishness
  - Weight gain - overweight

Note: Mental sluggishness and apathy can mimic depression and may cause misdiagnosis.

- Glycosaminoglycans and hyaluronic acid in: skin, subcutaneous tissue and visceral sites which might cause:
  - Pericardial effusion
  - Non-pitting edema



- Broadening coarsening of facial features
- Enlargement of the tongue
- Deepening of the voice.

2- Hyperthyroidism:

Thyrotoxicosis doesn't always equal hyperthyroidism, but what is the difference between the two terms?

Thyrotoxicosis is a hypermetabolic state of the body caused by elevated free circulating levels T3 and T4 that can be caused by hyperfunction of the thyroid gland (also known as hyperthyroidism). However, it can also be caused by oversupply of thyroid hormones that can be related either to excessive release of preformed thyroid hormone (e.g., in thyroiditis) or to an extra-thyroidal source e.g. ectopic thyroid tissue (lingual thyroid)

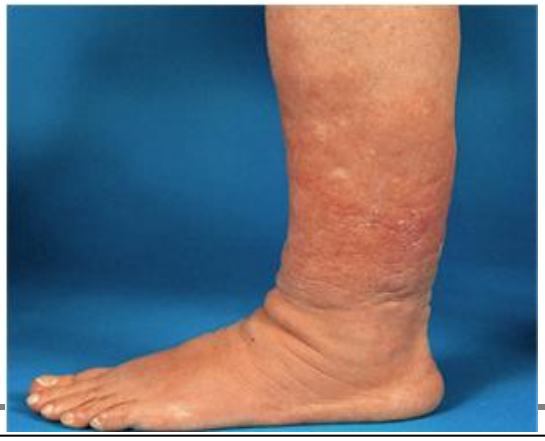
Thyrotoxicosis can be attributed to a number of etiologies, but the most common cause of these etiologies is graves disease. Other causes are :

Associated With Hyperthyroidism:	May Not Be Associated With Hyperthyroidisim:
Primary: 1- Diffuse hyperplasia of the thyroid associated with Graves disease (accounts for 85% of cases) 2- Hyperfunctional multinodular goiter 3- Hyperfunctional adenoma of the thyroid	1. Granulomatous (de Quervain) thyroiditis (painful) 2. Subacute lymphocytic thyroiditis (painless) 3. Struma ovarii (ovarian teratoma with ectopic thyroid) 4. Factitious thyrotoxicosis (exogenous thyroxine intake
Secondary: TSH-secreting pituitary adenoma (rare)	

Graves Disease:

- In 1835, Robert Graves reported on his observations of a disease characterized by "violent and long continued palpitations in females" associated with enlargement of the thyroid gland.
- Graves disease is the most common cause of endogenous hyperthyroidism.
- It is characterized by a tirade of features (not all have to be present for diagnosis):
  1. Thyrotoxicosis due to a diffusely bilaterally enlarged, hyperfunctional thyroid gland. (seen in all patients)
  2. Infiltrative ophthalmopathy (exophthalmos) (seen in almost half of patients)
  3. Localized, infiltrative dermopathy (pretibial myxedema) (seen in a minority of patients)

Patient has exophthalmos and a diffuse enlargement of the thyroid gland (goiter)



Pretibial myxedema in Graves' disease with area of erythema involving the pretibial area and dorsum of the foot.

Pathophysiology:

Graves disease is an autoimmune disorder in which a variety of antibodies that act on the thyroid gland may be present in the serum, and include:

1. TSH receptor antibody (most important)

LATS IgG antibody (long acting thyroid stimulating immunoglobulin) anti-TSH receptor:

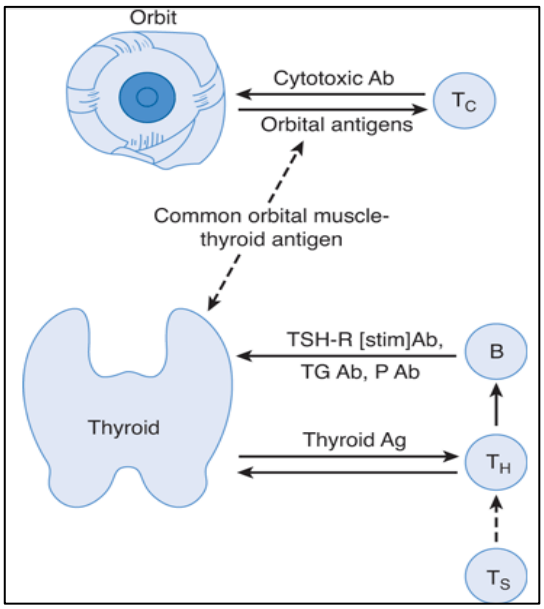
- Mimics action of TSH
- More specific to graves than the other antibodies
- The antibody has a trophic effect

2. Thyroid peroxisomes antibody
3. Thyroglobulin antibody

Coexistence of stimulating and inhibiting immunoglobulins in the serum of the same patient is the finding that could explain why some patients with Graves disease spontaneously develop episodes of hypothyroidism.

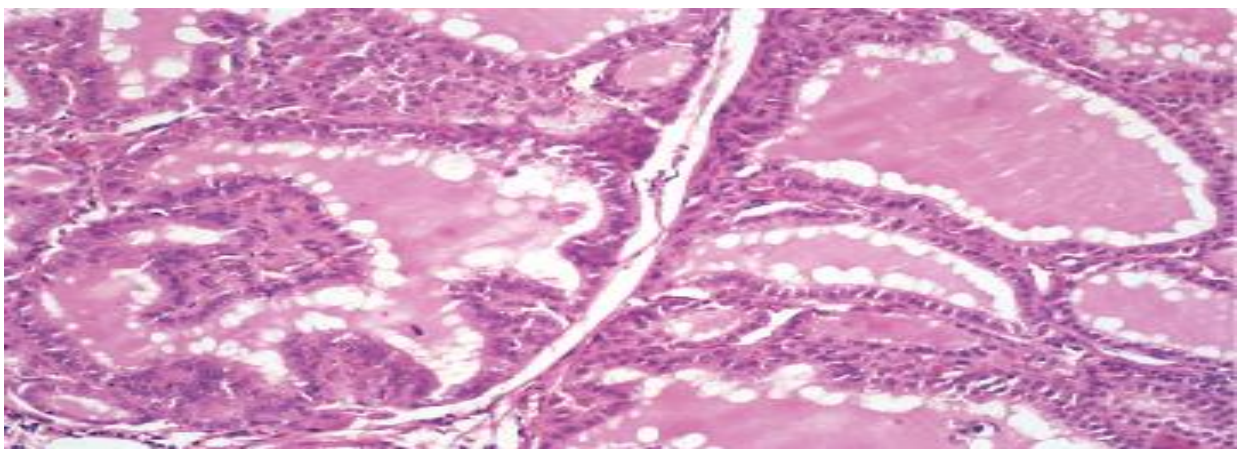
Note: TSH-binding inhibitor immunoglobulins (TBII) is an antibody seen in some cases of graves where it prevents TSH from binding normally to its receptor on thyroid epithelial cells and may cause hypothyroidism.

Pathophysiology explanation: A defect in suppressor T lymphocytes (Ts) allows helper T lymphocytes (TH) to stimulate B lymphocytes (B) to synthesize thyroid autoantibodies. The thyroid receptor-stimulating antibody (TSH-R [stim] Ab) is the driving force for thyrotoxicosis. Inflammation of the orbital muscles may be due to sensitization of cytotoxic T lymphocytes (Tc), or killer cells, to orbital antigens linked to an antigen in the thyroid. What triggers this immunologic cascade is not known. Ag, antigen; P Ab, peroxidase antibody; Tg Ab, thyroglobulin antibody



Histopathology:

1. Thin colloids
2. Vacuolization
3. Slight enlargement of the follicles



Diffusely hyperplastic thyroid in a case of Graves disease. The follicles are lined by tall, columnar epithelium. The crowded, enlarged epithelial cells project into the lumens of the follicles. These cells actively resorb the colloid in the centers of the follicles, resulting in the "scalloped "appearance of the edges of the colloid

3- Thyroiditis:

Definition: is inflammation of the thyroid gland, regardless of the etiology and can be caused by a diverse group of diseases

It includes:

- Acute illness with severe thyroid pain (e.g., infectious thyroiditis, subacute granulomatous thyroiditis) (presents with edema, pain, hotness, redness)
- Disorders: little inflammation,thyroid dysfunction (subacute lymphocytic thyroiditis and fibrous [Reidel] thyroiditis (chronic)).

Most common diseases:

1. Hashimoto thyroditid (chronic lymphocytic thyroditis)
2. Subacute granulomatous thyroditis
3. Subacute lymphocytic thyroiditis

Hashimoto's Thyroiditis:

Definition: Hashimoto's thyroiditis is an autoimmune disease in which the immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase) resulting in gradual thyroid failure by autoimmune destruction of the thyroid gland.

Hashimoto thyroiditis and Graves's disease are the two most common immunologically mediated disorders of the thyroid.

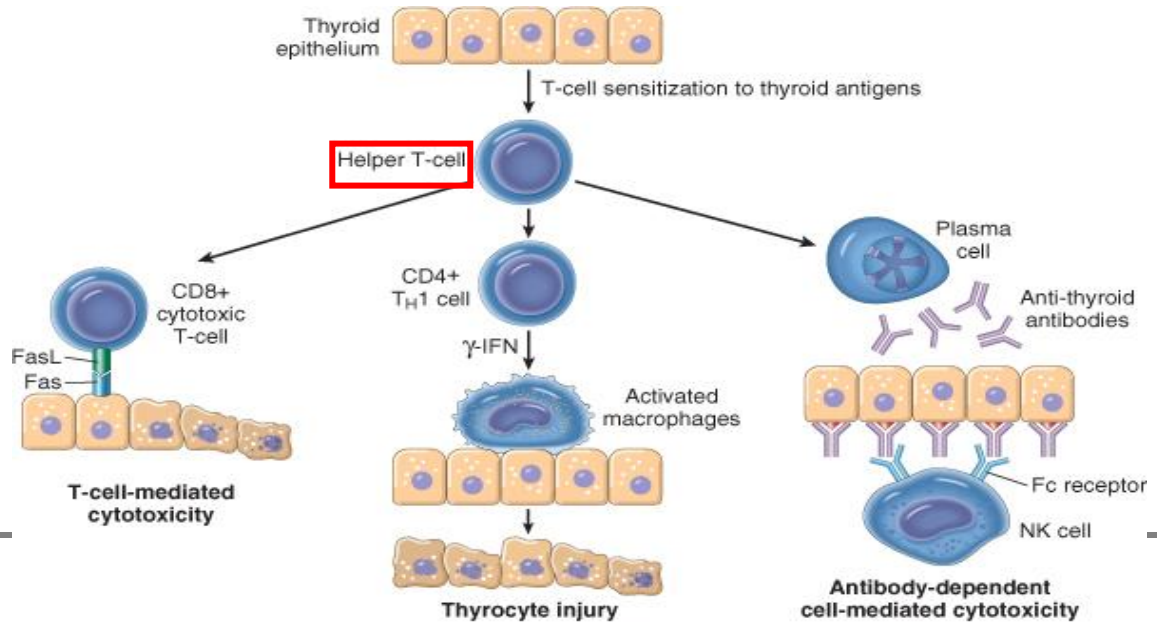
Hashimoto thyroiditis is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.

The name Hashimoto thyroiditis is derived from 1912 report by Hashimoto describing patients with goiter and intense lymphocytic infiltration of the thyroid (struma lymphomatosa).

Pathophysiology:

The feature of Hashimoto's thyroiditis is progressive depletion of thyroid epithelial cells (thyrocytes), replaced by mononuclear cell infiltration and fibrosis.

The cellular mechanisms in Hashimoto's thyroiditis are shown in this graph:



Epidemiology:

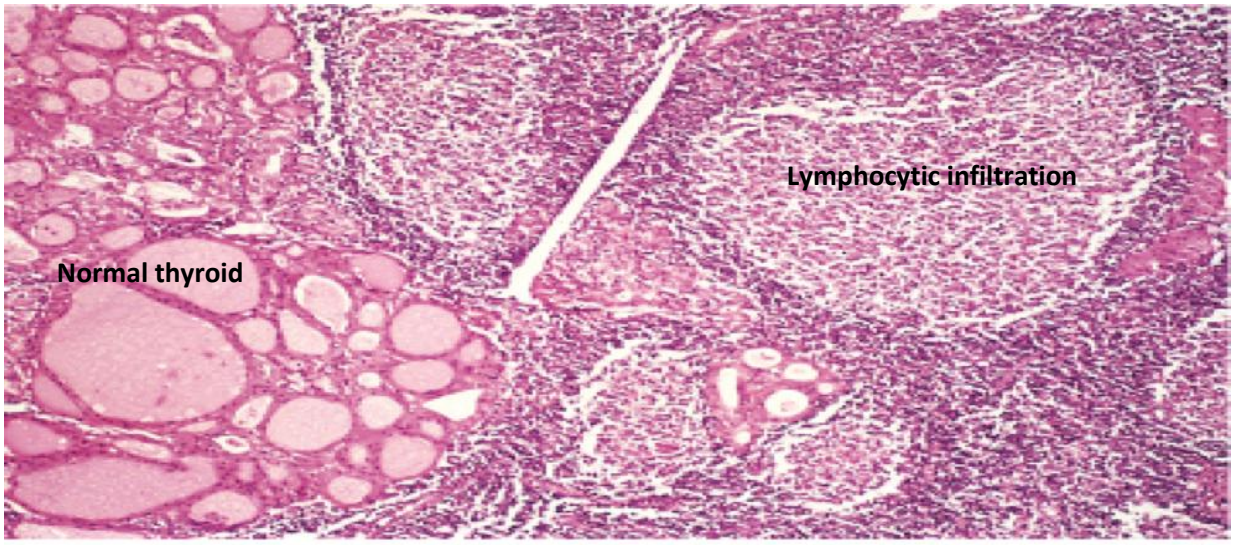
- Female predominance of 10: 1 to 20: 1.
- Although it is primarily a disease of older women, it can occur in children and is a major cause of nonendemic goiter in the pediatric population.
- The disorder is most prevalent with ages of 45-65 .
- Strong genetic component, 40% of monozygotic twins, as well as the presence of circulating antithyroid antibodies in approximately 50% of asymptomatic siblings

Diagnosis:

- Auto antibody in the blood
- Surgically
- Fine needle biopsy (Hürthle cells transformation, plasma cells, lymphocytes infiltration)

What are Hürthle cells?

It occurs when the thyroid follicles are atrophic and are lined in many areas by epithelial cells distinguished by the presence of abundant eosinophilic, granular cytoplasm(it is also known as oxyphil). Moreover, it is a metaplastic response of the normal cuboidal epithelium to ongoing injury.



Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells are also seen.

Prognosis:

Increases risk of developing papillary thyroid carcinoma.

Summary

- Abnormalities of the thyroid are hyperthyroidism, hypothyroidism, and mass nodules.
- Thyroid diseases are generally more common in women than in men.
- Hypothyroidism: is any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone.
- Hypothyroidism's Prevalence increases with age and is ten times more common in women than in men.
- It can be Primary hypothyroidism (great majority), where the problem in the thyroid itself or secondary (rare) where the problem is in the hypothalamus (defective TRH formation or secretion) or the anterior pituitary (defective TSH formation or secretion).
- Hashimoto thyroiditis, Surgery, radioiodine therapy, or external irradiation are the most common causes of hypothyroidism.
- Aside from the physiological symptoms of hypothyroidism certain conditions may develop and include:
    A. Cretinism: refers to hypothyroidism developing in infancy or early childhood that mainly shows severe mental retardation and a short stature.
    B. Myxedema: refers to hypothyroidism developed in late childhood or adulthood and its clinical manifestations include: depressed mental and physical activity (may mimic depression), non-pitting edema, coarsening of facial expressions, skin and visceral deposition, and pericardial effusion.
- Thyrotoxicosis is a hypermetabolic state of the body caused by elevated free circulating levels of free T3 and T4, while Hyperthyroidism is only hyperfunction of the thyroid gland, but because it is caused most commonly by hyperfunction of the thyroid gland, hyperthyroidism and thyrotoxicosis are almost always used interchangeably.
- Thyrotoxicosisis is caused by a number of conditions, but graves is the most common cause. Another important cause is hyperfunctioning multiple goiter.
- Graves disease is characterized by a tirade of features (not all have to be present for diagnosis):
    1. Thyrotoxicosis due to a bilaterally, diffusely enlarged, hyperfunctional thyroid gland.
    2. Infiltrative ophthalmopathy (exophthalmos)
    3. Localized, infiltrative dermopathy (pretibial myxedema)
- Graves disease is an autoimmune disorder in which a variety of antibodies that act on the thyroid gland may be present in the serum, and include: 1) TSH receptor antibody, an IgG antibody and is most important because intensly mimics TSH function. 2) Thyroid peroxisomes antibody and 3) Thyroglobulin antibody.
- Microscopic features of graves disease are: 1) A Diffusely hyperplastic thyroid 2) follicles are lined by tall, columnar epithelium. 3) "Scalloped "appearing cells at the edges of the colloid
- Thyroiditis: is inflammation of the thyroid gland, regardless of the etiology and can be caused by a diverse group of diseases
- Hashimoto's thyroiditis is an autoimmune disease in which the immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase) resulting in gradual thyroid failure by autoimmune destruction of the thyroid gland.
- Hashimoto thyroiditis is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.
- Hashimoto thyroiditis and Graves's disease are the two most common immunologically mediated disorders of the thyroid.
- Hashimoto disease has great female predominance (20:1) and is most prevalent in ages 45 – 65, especially those with genetic alterations.
- Microscopically, the thyroid parenchyma contains a 1) dense lymphocytic infiltrate with germinal centers. 2) Residual thyroid follicles lined by deeply eosinophilic Hürthle cells.