AUTOIMMUNE THYROIDITIS

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Regulation of thyroid hormone production

Thyrotropin-releasing hormone (TRH) increases the secretion of thyrotropin (TSH), which stimulates the synthesis and secretion of triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. T3 and T4 inhibit the secretion of TSH, both directly and indirectly by suppressing the release of TRH. T4 is converted to T3 in the liver and many other tissues by the action of T4 monodeiodinases. Some T4 and T3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine. Some T4 and T3 formed in the intestine may be reabsorbed. Drug interactions may occur at any of these sites.
THYROID FOLLICLES

GA Tanner, Medical Physiology 2nd Ed
Thyroid hormone biosynthesis includes the following steps: (1) iodide (I⁻) trapping by the thyroid follicular cells; (2) diffusion of iodide to the apex of the cells; (3) transport of iodide into the colloid; (4) oxidation of inorganic iodide to iodine and incorporation of iodine into tyrosine residues within thyroglobulin molecules in the colloid; (5) combination of two diiodotyrosine (DIT) molecules to form tetraiodothyronine (thyroxine, T₄) or of monoiodotyrosine (MIT) with DIT to form triiodothyronine (T₃); (6) uptake of thyroglobulin from the colloid into the follicular cell by endocytosis, fusion of the thyroglobulin with a lysosome, and proteolysis and release of T₄, T₃, DIT, and MIT; (7) release of T₄ and T₃ into the circulation; and (8) deiodination of DIT and MIT to yield tyrosine. T₃ is also formed from monodeiodination of T₄ in the thyroid and in peripheral tissues.

Structures of the thyroid hormones

Thyroxine (T₄)

3,5,3'-Triiodothyronine (T₃)

3,3,5'-Triiodothyronine (rT₃)
Autoimmune thyroid disease (AITD) is a common organ specific autoimmune disorder seen mostly in women between 30-50 yrs of age.

**Autoimmune thyroiditis**, or Chronic Autoimmune thyroiditis, is a disease in which the body interprets the thyroid glands and its hormone products T3, T4 and TSH as threats, therefore producing special antibodies that target the thyroid’s cells, thereby destroying it.

It presents with hypothyroidism or hyperthyroidism and the presence or absence of goiters.
Autoimmune Disorders-
  - disease present, chronic

Autoimmunity-
  - no disease but self-antigen specific antibodies and t-cells present, can be transient
THYROID ANTIGENS

- The major antigens are:
  - Thyroglobulin (Tg)
  - Thyroid peroxidase (TPO, formerly known as the microsomal antigen)
  - The TSH receptor – blocking or stimulating ab
MECHANISMS

A. Thyroid autoimmunity:

- Thyroid antibodies are directed against thyroid peroxidase, TSH receptor and against thyroglobulin.

- Both cellular and humoral immunity.
B. Genetic susceptibility:

- Association with HLA-DR3,4&5 has been reported in patients with HT & PPT.

- CTLA-4 may be associated with familial HT.

- Subacute thyroiditis had higher incidence in those with HLA-bw35.
C. Environmental factors:

- Hypothyroidism in patients with HT develop more in smokers. Also, PPH happens more with smokers.

- Iodine insufficiency in diet may be protective against autoimmune thyroiditis.
# Mechanisms of thyroid autoimmunity with an emphasis on Hashimoto's thyroiditis

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<td>Pregnancy and fetal microchimerism</td>
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<td>Iodine</td>
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</table>
Molecular mimicry — According to this proposal, Hashimoto's disease is caused by the immune response to a foreign antigen that is structurally similar to an endogenous substance.
Examples;

- Rheumatic fever, in which antibodies to the M protein of streptococci cross-react with myosin, laminin, and other matrix proteins. Deposition of these autoantibodies in the heart initiates an inflammatory response.

- Molecular mimicry between microbial proteins and host tissues has been reported in type 1 diabetes mellitus (insulin), rheumatoid arthritis (synovium), and multiple sclerosis (myelin sheet).
**Bystander activation**

- The arrival of a thyroid-cell virus or activated non-specific lymphocytes within the thyroid may cause the local release of cytokines, which in themselves may activate resident local thyroid-specific T cells.

- This bystander effect hypothesis has support from studies in an animal model of insulitis & a model of experimental autoimmune thyroiditis.
THYROID-CELL EXPRESSION OF HLA ANTIGENS

MHC class II molecules are present on thyroid follicular cells from patients with Hashimoto's thyroiditis, but not normal subjects.

MHC Class II expressed by Antigen Presenting Cells (macrophages/t-cells/B-cells)

Follicular cells function as APCs and present self antigens to activate T-cells in genetically susceptible hosts.

T-cells mediate antibody and cellular immune reaction and inflammatory attack on thyroid tissues.

Thyroid glands have abundance of thyroid specific antibodies, t-cells and plasma cells.
Autoimmunity represents the end result of the breakdown of one or more of the basic mechanisms regulating immune tolerance or identifying **Self vs non-self antigens**.
Forms of autoimmune thyroid diseases

- Hyperthyroid Graves' disease (GD)
- Hashimoto's (goitrous) thyroiditis
- Atrophic autoimmune hypothyroidism
- Postpartum thyroiditis (PPT)
- Thyroid associated orbitopathy (TAO)
<table>
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<tr>
<th>Type</th>
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<td>Hashimoto’s thyroiditis</td>
<td>Chronic lymphocytic thyroiditis</td>
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<tr>
<td></td>
<td>Chronic autoimmune thyroiditis</td>
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<tr>
<td></td>
<td>Lymphadenoid goiter</td>
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<tr>
<td>Painless postpartum thyroiditis</td>
<td>Postpartum thyroiditis</td>
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<tr>
<td></td>
<td>Subacute lymphocytic thyroiditis</td>
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<tr>
<td>Painless sporadic thyroiditis</td>
<td>Silent sporadic thyroiditis</td>
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<tr>
<td></td>
<td>Subacute lymphocytic thyroiditis</td>
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<tr>
<td>Painful subacute thyroiditis</td>
<td>Subacute thyroiditis de Quervain’s thyroiditis</td>
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<td></td>
<td>Giant-cell thyroiditis</td>
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<td></td>
<td>Subacute granulomatous thyroiditis</td>
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<td></td>
<td>Pseudogranulomatous thyroiditis</td>
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<td>Suppurative thyroiditis</td>
<td>Infectious thyroiditis</td>
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<td></td>
<td>Acute suppurative thyroiditis</td>
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<td></td>
<td>Pyrogenic thyroiditis</td>
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<td></td>
<td>Bacterial thyroiditis</td>
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<tr>
<td>Drug-induced thyroiditis</td>
<td></td>
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<tr>
<td>(amiodarone, lithium, interferon alfa, interleukin-2)</td>
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<tr>
<td>Riedel’s thyroiditis</td>
<td>Fibrous thyroiditis</td>
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</table>
Specialists clinically separate autoimmune thyroiditis into two categories.

- If goiters are present, it is understood as Hashimoto’s Thyroiditis.

- On the other hand, if the thyroid is atrophic, but does not present goiters, it is denominated Atrophic Thyroiditis
If the symptoms of thyroiditis appear in women after giving birth, it is attributed to such and therefore called **Postpartum Thyroiditis**.

The effects of this disease are not permanent but **transient**.
SYMPTOMS

The symptoms for autoimmune thyroiditis may vary depending on whether it causes hyperthyroidism or hypothyroidism.

- **Hyperthyroidism**
  - Hyperthyroidism can cause sweating, rapid heart rate, anxiety, tremors, fatigue, difficulty sleeping, sudden weight loss, and protruding eyes.

- **Hypothyroidism**
  - Hypothyroidism can cause weight gain, fatigue, dry skin, hair loss, intolerance to cold, and constipation.
Tests for antibodies against:
  Thyroid peroxidase (TPOAb),
  Thyroglobulin (TgAb) and
  TSH receptors (TRAb)
are used in the diagnosis of autoimmune thyroid disorders.
A. Thyrotoxicosis:

In painless ST, PPH, SAT; Inflammatory destruction of the thyroid may lead to transient thyrotoxicosis as preformed thyroid hormones are released from the damaged gland.

As the stored are depleted, there is often a progression through a period of euthyroidism to hypothyroidism.

Tg will increase first, TSH will be suppressed, T3, T4 will be elevated.

Symptoms are usually not severe.
B. Hypothyroidism:

- Gradual depletion of stored thyroid hormones.
- HT most common, but all other causes may progress to permanent hypothyroidism.
- TSH will rise, t3, t4 will be low. If they are normal with high TSH, this is called 'subclinical hypothyroidism'.
Hashimoto’s Thyroiditis

- Most common cause.

- Most have goiter. Firm, bumpy, symmetric painless. 10% have atrophic thyroid gland.

- Hypothyroidism is the commonest presentation.

- TPO are present in 90%, ATG in 20-50%.

- 24 hr RAI uptake is not helpful in dx.

- Levothyroxine is the treatment of choice.

- Lymphoma is a very rare complication.
Antibodies attacking bacteria.

Normal body tissue.

Autoimmune diseases like Hashimoto's thyroiditis.

Tissue affected by the immune system.
Hashimoto's thyroiditis  Fine needle aspirate of the thyroid in Hashimoto's thyroiditis. Lymphocytes are predominant, sometimes surrounding rare follicular cells. No formed follicles are seen. Some colloid is present in the background.
Hashimoto's thyroiditis  Fine needle aspirate of the thyroid in Hashimoto's thyroiditis. Tearing of tissue lymphocytes is seen with scant follicular cells and colloid.
Hashimoto’s thyroiditis  Surgical specimen from a patient with Hashimoto’s thyroiditis. Some areas show normal appearing follicles with minimal lymphocytic infiltrates, while other areas have complete destruction of follicles with a dense lymphocytic infiltrate, in which the lymphocytes form germinal centers.
THYROID CELL APOPTOSIS

— Thyroid-cell death in Hashimoto's disease is the central pathological phenomenon.

Normal thyroid epithelial cells express a variety of death receptors, including Fas.

Activation of the Fas-ligand-Fas signaling system could contribute to the follicular cell destruction characteristic of Hashimoto's thyroiditis.

In autoimmune thyroiditis, thyroid follicular cells are induced to express functional Fas and also Fas ligand by cytokine stimulation from antigen-presenting cells and Th1 cells (eg, IL-1). This may cause self-apoptosis.
FAS - FAS LIGAND INTERACTION
HYPERTHYROIDISM

- Graves’ disease is the most common cause of hyperthyroidism.

- Hyperthyroidism versus thyrotoxicosis.

ANTI-HYROID RECEPTOR ANTIBODIES

Hypothetical structure of the TSH receptor. Stimulating (in Graves' disease) and blocking (in Hashimoto's thyroiditis) anti-TSH receptor antibodies may bind to different regions of the extracellular
Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety.

- Normal thyroid
- Enlarged thyroid
- Diffuse goiter

Exophthalmos (bulging eyes)
HYPERTHYROIDISM

- Skin manifestation:
  - Warm, moist and velvety hands. Hot sweaty hands, Onycholysis. Pretibial myxedema.
  - Thyroid acropachy.

- Test
  - TSH.
  - Free t3, free t4.
  - TSI, antibodies.
  - Thyroid uptake of RA iodine.
  - Thyroid scan role.
PAINLESS POSTPARTUM THYROIDITIS

- 10% of women in USA may develop it within first few months after delivery.

- Most common in women with high TPO levels during 1st trimester, immediately after therapy, have other autoimmune diseases like IDDM (type 1).

- 30% will have the classic triphasic hormone pattern.
The initial thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles. The result is **unregulated** release of large amounts of thyroxine (T4) and triiodothyronine (T3) into the circulation and therefore hyperthyroidism. This state lasts only until the stores of thyroglobulin are exhausted, because new hormone synthesis ceases. As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume. There may be a transient period of hypothyroidism and increased TSH secretion before thyroid secretion becomes normal again. However, some patients have only a hyperthyroid or hypothyroid phase.
POSTPARTUM THYROIDITIS

- 70% chance of recurrence with subsequent pregnancies.

- Hypothyroidism may be treated if symptoms are present for a period of time.

- Antithyroid medications are contraindicated.

- Beta blockers can be used if symptoms are severe.
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<tr>
<th></th>
<th>Post Partum Thyroiditis</th>
<th>Graves Disease</th>
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<tbody>
<tr>
<td>Thyrotoxicosis</td>
<td>Transient</td>
<td>Persistent</td>
</tr>
<tr>
<td>TSH Receptor Antibodies</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Radioactive Iodine Uptake</td>
<td>Normal/low</td>
<td>High</td>
</tr>
<tr>
<td>Symptom Duration</td>
<td>&lt;3 Months</td>
<td>&gt; 3 Months</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>No</td>
<td>30% Yes</td>
</tr>
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</table>
PAINLESS SPORADIC THYROIDITIS

- Indistinguishable from PPT except by the relation of the later to pregnancy.

- Account for 1% of cases with thyrotoxicosis.

- Small, non-tender, very firm, diffuse goiter is present in 50% of patients.

- Low or undetectable concentration of I123 at 24 hrs.

- Treatment, same as PPT.
PAINFUL SUBACUTE THYROIDITIS

- Most common cause of thyroid pain.
- Self-limited inflammatory disorder.
- Follows URTI, high incidence in summer, with the peak of Enterovirus.

Clinical scenario: Generalized myalgias, pharyngitis, low grade fever and severe neck pain, swelling or both.
PAINFUL SUBACUTE THYROIDITIS

- Other names:
  - Subacute nonsuppurative thyroiditis,
  - de Quervain's thyroiditis, or
  - subacute granulomatous thyroiditis.

- Viral as cause

- Many have Hx of URTI preceding

- Associated with epidemics of Coxsackievirus or other viral infections.

- There is a strong association with HLA-B35.
PAINFUL SUBACUTE THYROIDITIS

- 50% have symptoms of thyrotoxicosis.
- State of biochemical euthyroidism.
- Hypothyroidism will last for 4-6 months.
- 5% will have residual hypothyroidism.
- Hallmark is ELEVATED ESR.
- Leukocyte count is normal or slightly elevated.
- High T4, T3. (T4 ratio to T3 < 20). Undetectable TSH.
PAINFUL SUBACUTE THYROIDITIS

- 24-hour I(123) is low in the toxic phase.
- Treatment: symptomatic relief.
- NSAIDS, ASA.
- Glucocorticoids in more severe cases.
- Beta-blockers.
Suppurative Thyroiditis

- Bacterial infection, fungal, mycobacterial or parasitic infection.

- Thyroid is resistant to infection (encapsulated, high iodide content, rich blood supply and extensive lymphatic drainage).

- People at risk:
  1. Preexisting thyroid disease.
  2. Congenital anomalies (*pyriform sinus fistula* most common source of infection in children).
  3. Immuno-suppressed, elderly.
  4. AIDS (*pneumocystis carinii* and others).
**Suppurative Thyroiditis**

- Presentation: ill with fever, dysphagia, dysphonia, anterior neck pain and erythema and a tender thyroid mass.

- Normal thyroid function test.

- High ESR, WBC.

- FNA with gram’s staining and culture is the diagnostic test of choice.

- Therapy: appropriate antibiotics and drainage of any abscess.
Riedel’s Thyroiditis

- Progressive fibrosis.
- Rare disease.
- High serum thyroid antibody in 67% of patients.
- Rock-hard, fixed & painless goiter.
- Tracheal, esophageal compression or hypoparathyroidism.
- Open biopsy is needed.
- Glucocorticoids, methotrexate and tamoxifen can be used.
- Surgery is the treatment of choice.
Thyroid follicles trapped within Fibroblasts
Drug-induced thyroiditis

- Amiodarone (hypo/hyperthyroid)
- Lithium. (hypothyroid)
- Interferon alpha.
- Interleukin 2.
## Other autoimmune disorders

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<td>Hashimoto's thyroiditis</td>
<td>Autoimmune hemolytic anemia</td>
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<tr>
<td><strong>Autoimmune</strong> polyglandular syndrome</td>
<td><strong>Autoimmune</strong> thrombocytopenic purpura</td>
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<td>Type 1 diabetes mellitus</td>
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<td>Dermatitis herpetiformis</td>
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<td><strong>Autoimmune</strong> alopecia</td>
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<td><strong>Organ Nonspecific (Systemic)</strong></td>
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<td>Rheumatoid arthritis</td>
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<td>Systemic necrotizing vasculitis</td>
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- www.uptodate.com