Hyperthyroidism (Overactive Thyroid), Graves' Disease (Basedow Disease) and more

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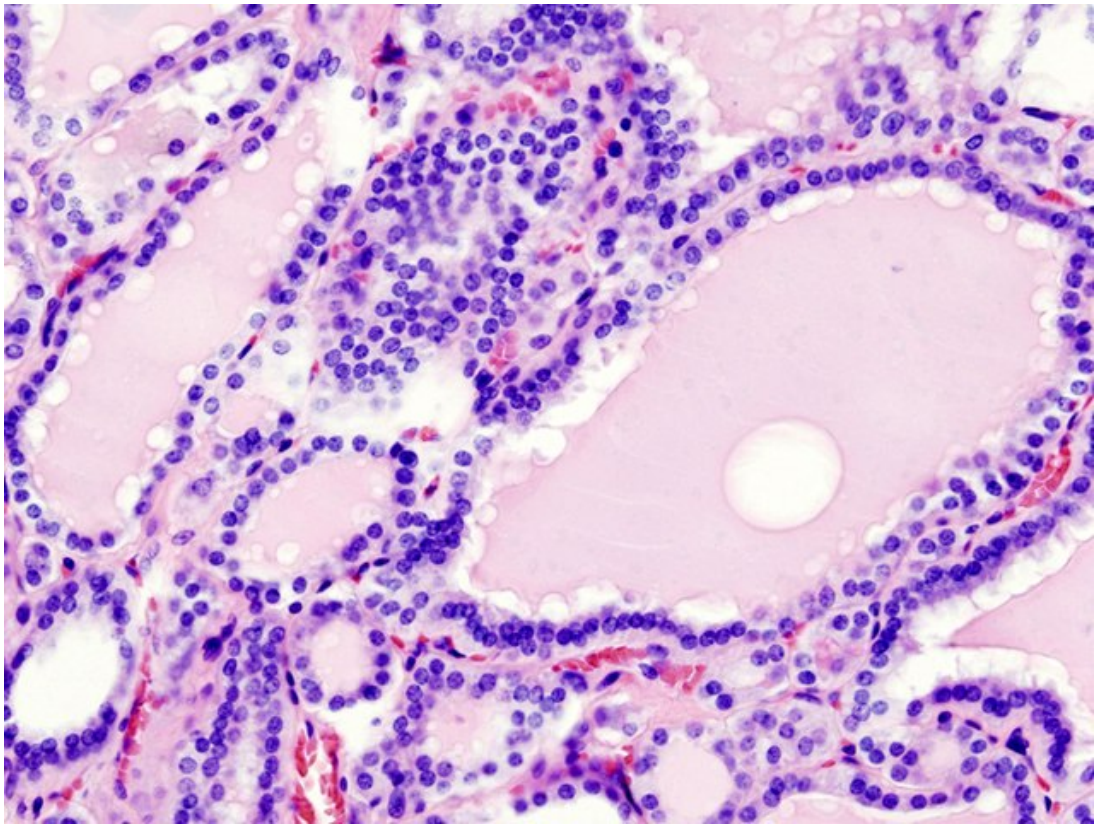
Hyperthyroidism is caused by the excess of thyroid hormones T3 and T4. Graves' disease is the most common cause of hyperthyroidism. Clinical features of hyperthyroidism are mostly due to the increased body's metabolic rate. Hyperthyroidism is diagnosed by estimation of TSH and free T4 and T3. It is treated by pharmacological and surgical means.



Definitions

Hyperthyroidism is a medical condition in which **excess thyroid hormone** is **secreted** by the thyroid gland (hyperfunctioning of the thyroid gland).

Thyrotoxicosis is a more general term defined as the condition of **excess of thyroid hormones** due to **any cause.** It may be due to hyper-functioning of the thyroid gland (hyperthyroidism), or it may be due to other causes such as increased administration of exogenous thyroid hormones or ectopic thyroid hormone production.

Thyroid storm is a rare, acute **life-threatening emergency** with high mortality. It is the **extreme form of thyrotoxicosis** characterized by fever, atrial fibrillation, agitation, confusion, delirium and even coma. It is most commonly precipitated by infection, thyroid surgery or trauma.

Subclinical hyperthyroidism is an asymptomatic condition in which serum TSH is decreased, but serum free-T3 and free-T4 levels are within normal range. Although these patients are clinically asymptomatic, they have an increased risk of developing thyrotoxicosis in subsequent years.

Goiter is simply the abnormal **enlargement of the thyroid gland**. It does not give signs about the thyroid functioning. A goiter can occur in hypothyroidism, hyperthyroidism or euthyroidism.

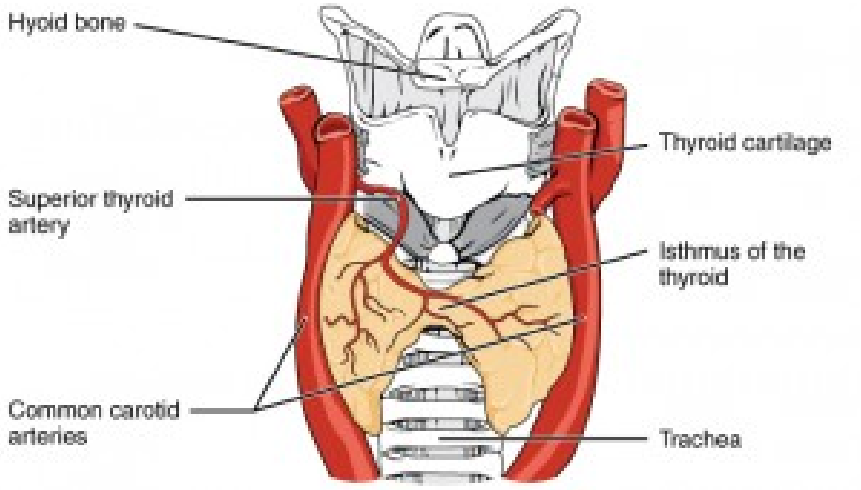


Image: "The human thyroid as viewed from the front, with arteries visible" by CFCF. License: CC BY-SA 3.0

Epidemiology of Hyperthyroidism

All the thyroid disorders are more common in females. Graves' disease is the most common cause of hyperthyroidism, accounting for 60 – 80 % of the cases. It is eight times more common in females than males and often occurs in young females, around 20 – 40 years of age. Its annual incidence is approximately 0.5 cases per 1000 individuals. The toxic multi-nodular goiter comes second with around 15 % of the hyperthyroidism cases.

Etiology and Pathophysiology of Hyperthyroidism

Hyperthyroidism results from the excess production of thyroid hormones. Depending on the site responsible for the excess thyroid hormone production, it can be primary or secondary hyperthyroidism.

- **Primary hyperthyroidism** results when the **primary pathology** lies in the **thyroid gland**. In this condition, the T3 and T4 levels are raised, while TSH is decreased due to negative feedback.
- **Secondary hyperthyroidism** results when the **pathology** lies in the **anterior pituitary gland**. It increases the secretion of TSH, which in turn, stimulates the thyroid gland to increase the synthesis and secretion of thyroid hormones T3 and T4.

Causes of Hyperthyroidism / Thyrotoxicosis

- Graves' disease
- Toxic Multi-nodular goiter
- Solitary thyroid adenoma
- Thyroiditis
    - Subacute (de Quervain's) thyroiditis
    - Post-partum thyroiditis
- Iodide-induced
    - Drugs (such as amiodarone)
    - Radiographic contrast media
    - Iodine prophylaxis program
- Extra-thyroidal source of thyroid hormone
    - Factitious thyrotoxicosis
    - Struma ovarii
- TSH-induced
    - TSH-secreting pituitary adenoma
    - Choriocarcinoma and hydatidiform mole
    - Chorionic gonadotropin-secreting tumors

Clinical Presentation of Hyperthyroidism

The thyroid hormones are physiologically responsible for the body's basal metabolic functioning. Therefore, most of the clinical manifestations of hyperthyroidism are primarily due to the **increased metabolic rate** of the body. The patient loses weight despite enhanced appetite and often complains of heat intolerance, excessive sweating, palpitations, hyperactivity, irritability, anxiety and even insomnia. The hands are warm and moist, and palmar erythema may be present. Hair may be thin with increased hair loss. Deep tendon reflexes may be brisk.

Sinus tachycardia is the most common cardiovascular manifestation, often associated with palpitations. It may cause worsening of angina or heart failure in patients with preexisting heart disease. Atrial fibrillation is more common in older patients (> 50 years).

Gastrointestinal motility is increased, leading to increased stool frequency, often with diarrhea. Women frequently experience menstrual irregularities, especially oligomenorrhea or amenorrhea, with the loss of libido. The thyroid hormones cause bone resorption and in the long run may lead to osteoporosis and increased risk of fractures.

All causes of thyrotoxicosis can cause lid retraction and lid lag, giving a staring look due to sympathetic over-activity. But only Graves' disease causes specific eye signs that constitute **Graves' ophthalmopathy**. These include proptosis (exophthalmos), periorbital edema, conjunctivitis and diplopia. **Pretibial myxedema and the thyroid acropachy are also specific to Graves' disease.**

The common clinical features of thyrotoxicosis are summarized in the following table:

Symptoms	Signs

Hyperactivity, Irritability, Weight loss with increased appetite, Heat intolerance Excessive sweating Palpitations Diarrhea Amenorrhea/Oligomenorrhea Osteoporosis	Sinus tachycardia, Atrial fibrillation in the elderly, Brisk reflexes, Palmar erythema Lid retraction, lid lag Exophthalmos* Pretibial myxedema* Thyroid acropachy*

* Denotes that these signs are specific to Graves' disease

In **mild thyrotoxicosis**, the patient feels warm, is tachycardiac and hyperactive. In **thyroid storm** however, the symptoms of thyrotoxicosis are **severe and exaggerated**. The patient develops fever, arrhythmias, atrial fibrillation, agitation, confusion, delirium and even coma.

Laboratory Evaluation and Diagnosis of Hyperthyroidism

The primary investigation in the evaluation of hyperthyroidism is the measurement of **serum TSH.** The abnormal TSH levels then need to be confirmed by the estimation of **free T3 and T4**. The levels of free (unbound) hormones are important as levels of total hormone may change in response to the binding proteins.

For example, in conditions of estrogen excess such as pregnancy, the serum thyroid-binding globulins are increased, which will lead to increased level of "total" thyroid hormones. However, "free" T3 and T4 levels will be within normal limits, so the patient will be euthyroid.

Similarly, in conditions of androgen excess such as anabolic steroid usage, the serum thyroid-binding globulins are decreased, which will lead to decrease in the level of "total" thyroid hormones. Yet, "free" T3 and T4 levels will be within normal limits, so again, the patient will be euthyroid.

After confirming the diagnosis of thyrotoxicosis, other diagnostic tests should be carried out to identify the underlying cause. Those include the measurement of TSH receptor antibodies, isotope scanning and FNAC, if required.

Radio-iodine uptake tests measure the proportion of isotope that is trapped in the whole gland. It determines the functioning of the thyroid gland.

- In Graves' disease, multi-nodular goiter and thyroid adenoma, the uptake is **increased**.
- In transient thyroiditis and exogenous thyroxine intake, the thyroid hormone production is decreased, and therefore, the uptake is also **decreased**.

Primary hyperthyroidism is diagnosed by the presence of:

- **Decreased TSH**
- Increased free T3
- Increased free T4.

In some patients, free T4 is in the upper part of the reference range, and free T3 is raised. It is called "T3 toxicosis".

Secondary hyperthyroidism is diagnosed by the presence of:

- **Increased TSH**

- Increased free T3
- Increased free T4.

Graves’ disease

Graves’ disease is **the most common cause** of thyrotoxicosis. It is common in females of 20 – 40 years of age. It is an autoimmune disorder with **type-II hypersensitivity**, in which the IgG antibodies are formed that activate the thyroid gland by attaching at TSH-receptors. Hence, they are called **thyroid-stimulating immunoglobulins (TSI)**. This prolonged activation of TSH-receptors by TSI signals the thyroid gland to increase the production and secretion of thyroid hormones.

The clinical manifestations of Graves’ disease are the same as for thyrotoxicosis caused by any etiology, as described before. But there are some findings that are **specific to Graves’ disease** such as **Graves’ ophthalmopathy, pretibial myxedema and thyroid acropachy.**

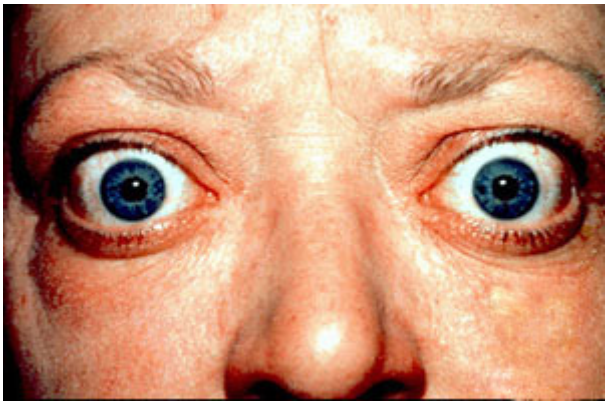


Image: “Graves’ ophthalmopathy” by Jonathan Trobe, M.D..
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Graves’ ophthalmopathy includes proptosis (exophthalmos), periorbital edema, conjunctivitis and diplopia. Proptosis is due to retro-orbital deposition of fat and glycosaminoglycans (GAGs), while the extraocular muscles are infiltrated by the lymphocytes.

Pretibial myxedema is a skin condition in which non-inflamed, indurated, shiny-pink or purple-brown colored lesions are present in the lower anterio-lateral leg, but it may occur anywhere. This term is a double misnomer, as these lesions occur in Graves’ disease (not myxedema) and are not limited to the pretibial area.

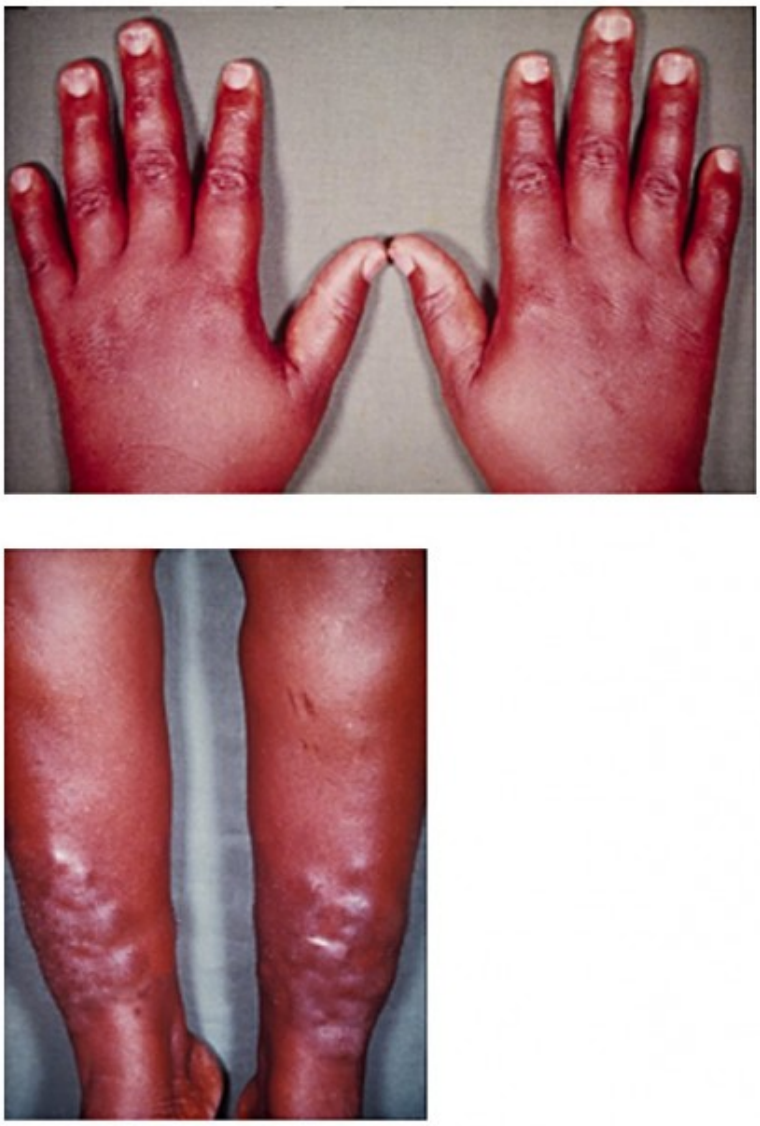

Image: “Pretibial Myxedema” by Herbert L. Fred, MD and Hendrik A. van Dijk. License: CC BY 2.0

Thyroid acropachy is very rare and consists of clubbing, periosteal new bone formation and swollen fingers.

In Graves’ disease, a **non-tender, diffuse, symmetrical goiter** is usually present with **bruit**. These patients are also at increased risk for other autoimmune diseases such as Addison’s disease, type-I DM, pernicious anemia, celiac disease and Sjogren’s syndrome.

The laboratory investigations include elevated serum free-T4 and T3 with decreased, usually undetectable, levels of TSH. The thyroid stimulating antibodies are present in more than two-thirds of thecases and confirm the diagnosis. The radioactive iodine uptake is diffusely and symmetrically increased on the isotope uptake scans. CT and MRI can be used to visualize the Graves’ ophthalmopathy affecting the extraocular muscles.

Toxic Multi-nodular Goiter and Thyroid Adenomas

The autonomous toxic nodule of the thyroid gland may be single (thyroid

adenoma) or may be multiple (toxic multi-nodular goiter). The nodules may be palpated by the expert examiner. They do not need TSH stimulation to produce thyroid hormone, so thyroid-pituitary-hypothalamic axis and negative feedback control is lost.

These can be differentiated from the Graves' disease due to lack of infiltrative ophthalmopathy and dermopathy. Also, there are multiple nodules on palpation in a case of multi-nodular goiter. The radioactive iodine uptake is increased only in the nodular areas (hot nodules) on the isotope uptake scans.

Subacute (de Quervains') Thyroiditis

This condition is also called **viral thyroiditis** or **granulomatous thyroiditis**. Like all thyroid disorders, this is also more common in females. The patient presents with **fever and painful, enlarged and tender thyroid** on palpation. It is thought to be caused by viruses, and symptoms of upper respiratory infection or a sore throat may precede the condition.

In subacute thyroiditis, the **hormones already stored** within the thyroid gland are **released**, causing thyrotoxicosis, and the levels of free-T3 and T4 increase, suppressing TSH. The **new hormone synthesis does not increase**; it even decreases because TSH is low. This is the reason the thyrotoxicosis is transient and usually followed by hypothyroidism, when the thyroid hormone stores are depleted. The radioactive iodine uptake is also decreased on isotope uptake scan for the same reason. The erythrocyte sedimentation rate (ESR) and white blood cell counts are elevated.

The clinical course of subacute thyroiditis is **triphasic** and is usually **self-limited**:

- Initially, **thyrotoxicosis** occurs due to increased secretion of stored thyroid hormones and suppressing TSH.
- As stores are depleted, and TSH is already suppressed, a **hypothyroidism** phase begins.
- TSH will subsequently rise and increase the thyroid hormone production, leading to **normalization** of thyroid function, usually several months after the onset.

The pathophysiology of transient thyroiditis involves characteristic patchy inflammatory infiltration, with disruption of the thyroid follicles. The multinucleated giant cells may be present within some follicles. The follicular changes progress to granulomas accompanied by fibrosis.

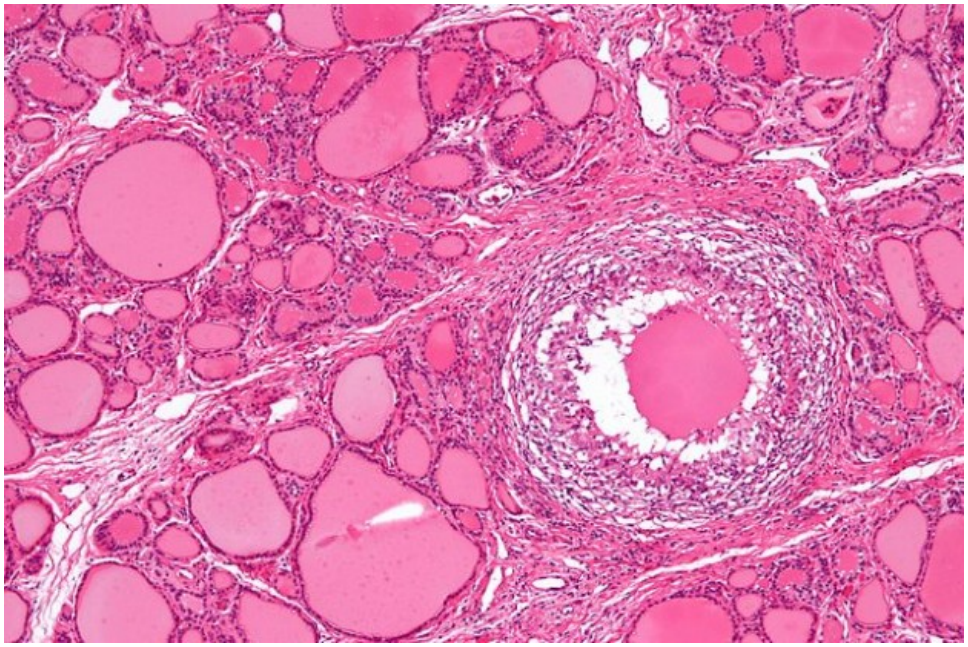

Image: “Granuloma in subacute thyroiditis” by Nephron. License: CC BY-SA 3.0

Goiter	Condition
Diffuse symmetrical goiter with Bruit	Graves’ disease
Tender goiter	Subacute (de Quervains’) thyroiditis
Goiter with multiple nodules	Toxic Multi-nodular Thyrotoxicosis

Other Causes of Thyrotoxicosis

Some of the other causes of thyrotoxicosis are factitious thyrotoxicosis, struma ovarii, pituitary adenomas and chorionic gonadotropin-secreting tumors.

Factitious thyrotoxicosis is due to increased intake of exogenous thyroid hormone, which gives a picture of primary thyrotoxicosis with raised T3 and T4 and suppressed TSH. However, the radioisotope uptake will be **decreased**.

Struma ovarii is a rare condition in which certain ovarian tumors, such as dermoid tumors and teratoma, contain thyroid tissue and autonomously secrete the thyroid hormones.

Pituitary adenomas secreting increased TSH can cause secondary thyrotoxicosis. Blood levels of all TSH, T3 and T4 are increased.

Human chorionic gonadotropin (HCG) has two-subunits. The alpha subunit is similar to TSH, LH, and FSH, while the beta subunit is specific for pregnancy. So, **increased HCG** secretions by chorionic gonadotropin-secreting tumors cause **secondary thyrotoxicosis by acting in a TSH-like manner.**

Condition	TSH	Total T4	Free T4	I^{131} Uptake
Graves’ disease	↓	↑	↑	↑
Excess exogenous thyroxine	↓	↑	↑	↓
Initial phase of Subacute Thyroiditis	↓	↑	↑	↓
Pituitary adenomas	↑	↑	↑	↑
Increased TBG (e.g., estrogen excess, pregnancy)	N	↑	N	N

Decreased TBG (e.g., anabolic steroids)	N	↓	N	N

N denotes “no effect” on the hormone levels

Therapy and Treatment of Hyperthyroidism

The definitive treatment of thyrotoxicosis depends on the underlying cause. There are many treatment options available, both pharmacological and surgical. These include antithyroid drugs, iodide, radioactive iodine or surgery. The beta blockers may be used in short term to control the symptoms; however, they do not affect the thyroid hormone production.

Antithyroid drugs

Propylthiouracil and **methimazole** are the antithyroid agents. They decrease the thyroid hormone production by inhibiting certain keys steps of thyroxine biosynthesis such as iodination of tyrosine residues, the coupling of monoiodothyronine (MIT) and diiodothyronine (DIT). Propylthiouracil also inhibits the peripheral conversion of T4 to T3.

The effects of antithyroid drugs are usually restricted to their use. The discontinuation leads to relapses. The prominent side effects are **agranulocytosis,** dermatitis and hepatic impairment. Frequent complete blood counts are advised in patients taking antithyroid drugs.

The antithyroid drugs should be avoided during pregnancy (cause aplasia cutis) as there are increased risks of teratogenicity. But if used, **propylthiouracil is preferred as it is extensively protein bound.** Propylthiouracil is also preferred during breastfeeding.

Iodide

Iodide blocks the secretion of thyroid hormones by inhibiting the release of T3 and T4 from thyroglobulin. It is used for short term treatment only and usually preoperatively, before thyroid surgery. It decreases gland size and vascularity. It cannot be used for the long term because the thyroid gland escapes from its effects after 2 weeks.

Radioactive Iodine I^{131}

Radioactive Iodine I^{131}actively accumulates within the thyroid gland and causes cell destruction and **permanent cure**. The radioactive iodine is **contraindicated during pregnancy** as radiations are harmful to the fetus.

Beta Blockers

The non-specific beta blockers (propranolol) block the peripheral conversion of T4 to T3. It may be used in the **short term to control the symptoms**, but they do not affect the thyroid hormone production. It relieves tachycardia, palpitations, tremors, sweating and anxiety. It is the **initial treatment of choice for the thyroid storm**.

Surgery

A thyroidectomy is an option when medical treatment fails or cannot be taken because of the side effects or pregnancy. Surgery is also an option when malignancy is suspected as in nodular goiters.

Anti-Thyroid Drugs	Mechanism of Action
Radioactive Iodine I^{131}	Destroys the cells by actively accumulating with the thyroid gland.
Antithyroid drugs (propylthiouracil and methimazole)	Inhibit iodination of tyrosine residues and coupling of MIT and DIT.
Iodide	Blocks thyroid hormone secretion by inhibiting the proteolytic release of T3 and T4 from thyroglobulin,
Propranolol (and propylthiouracil)	Inhibits peripheral conversion of T4 to T3.

Special Points

The **Graves' ophthalmopathy** is treated with **steroids** and **radiations**. In severe cases, the orbital decompression surgery may be required. Graves' dermopathy is also treated with steroids and nocturnal plastic occlusive dressings. **The antithyroid medications are not effective in these conditions.**

Thyroid storm is a medical emergency. Patients should be adequately **rehydrated** and given **beta blockers, iodide, antithyroid drugs and cooling blankets.**

Hyperthyroidism Thyroiditis

Group of diseases characterized by thyroid inflammation.

Types

- Chronic lymphocytic (Hashimoto´s) thyroiditis
- Acute bacterial (suppurative) thyroiditis (rare)
- Subacute thyroiditis (de Quervain´s, granulomatous thyroiditis)
- Silent thyroiditis (painless, postpartum)
- Amiodarone-induced thyroiditis
- Riedel´s thyroiditis (rare)

Painful thyroiditis

Infectious (suppurative) thyroiditis

Acute thyroiditis present with abscess formation caused by gram-positive or -negative organisms gaining access most commonly, and usually in children, via fistual from the piriform sinus adjacent to the larynx, or via a hematogenous spread in an immunocompromised patient.

Chronic thyroiditis usually caused by Aspergillus, Pneumocystitis in immunocompromised patients. A sudden (acute) onset of neck pain, usually unilateral with fever, dysphagia, leukocytosis.

- DDx: Hemorrhage into thyroid nodule and subacute thyroiditis.

Painful thyroiditis

Infectious (suppurative) thyroiditis

Management of thyroiditis DDx:

- Ultrasound
    - Infectious thyroiditis-abscesses
    - Subacute thyroiditis-diffuse heterogeneity and low-intensity vascular flow
- FNA
    - Infectious thyroiditis-fluid collection with microbes on bacteriologic examination and culture
    - Subacute-multinucleated giant cell granulomas
- Treatment: IV antibiotics; drainage if abscess

Subacute (Granulomatous; DeQuervain) Thyroiditis

- Causes by viral infections (mumps; Coxsackie), often preceding URI, strong association with HLA-B35
- Limited, self-resolving course with flu-like symptoms, painful, tender, irregular thyroid
- More common in women
- Typically 3—6 weeks of pain and thyrotoxicosis followed by several months of hypothyroidism, then recovery euthyroidism
- Treated with aspirin or NSAIDs, glucocorticoids if sever; beta blockade for symptomatic thyrotoxicosis
- FNA: Focal destruction of thyroid tissue by granulomatous inflammation

Clinical note: Radiation thyroiditis may manifest 5—10 days post-radioiodine treatment of Grave´s Disease

Painless (silent, lymphocytic) thyroiditis

- 1—5 % of cases of hyperthyroidism
- Any woman (non-post-partum) or man who has had symptoms of mild hyperthyroidism for < 2 months (short duratiomn) and has a small diffuse goiter or no thyroid enlargement
- Autoimmune, considered a variant form of chronic autoimmune thyroiditis (Hashimoto´s)
- Meds: IFN-α, IL-2, lithium
- Phasic course similar to subacute, but 25 % remain hypothyroid
- Post-partum thyroiditis definition: occurs within one year after parturition (or after spontaneous or induced abortion)
- Similar clinically and pathogenetically to painless thyroiditis, however; it differs from painless thyroiditis in that more patients have elevated levels of serum antithyroid antibody (anti-TG, anti-TPO) increasing the likelihood of permanent thyroid disease later

Amiodarone-induces thyroiditis

- Amiodarone structurally resembles thyroid hormone and contains iodine
- Seen in ~ 3 % of patients on amiodarone, usually after 1—3 years of

therapy
- Thyroid is not enlarged or tender
- Can cause both hypo- and hyperthyroidism
- Hypothyroidism by blocking the peripheral conversion of T_4 to T3
- Hyperthyroidism by inducing thyroid inflammation, which results in leakage of thyroid hormone into the circulation
- Low blood flow on color flow doppler thyroid ultrasound

Riedel´s (fibrous) thyroiditis

- Primary fibrosing disorder (mediastinal and retroperitoneal involvement)
- Women > men (50—60 years)
- Dense fibrosis that replaces normal thyroid parenchyma with macrophage and eosinophil infiltration
- Fibrosis invades adjacent structures of the neck and extends beyond the thyroid capsule
- Hard, woody gland, mimicy cancer
- Treated with surgery if compressive symptoms

Review Questions

The correct answers can be found below the references.

1. Which of the following clinical manifestation is specific for Graves' disease?

A. Atrial fibrillation
B. Lid lag
C. Palmar erythema
D. Pretibial myxedema
E. Osteoporosis

2. Which of the following investigation findings will be presented in secondary hyperthyroidism?

A. Undetectable TSH
B. Decreased T3
C. Increased TRH
D. Increased TSH
E. Increased TBG

3. In first-trimester pregnancy, which of the following medications may be given to decrease thyroid hormone production?

A. Propylthiouracil
B. Propranolol
C. Methimazole
D. Radioactive Iodine I^{131}
E. Steroids

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Correct answers: 1D, 2D, 3A

Notes