Hyperthyroidism (Graves' Disease)

Index Terms

- Graves' disease
- Thyrotoxicosis

Basics

Definition

- Thyrotoxicosis: state of thyroid hormone excess of any etiology
- Hyperthyroidism: state of thyroid hormone excess due specifically to excessive thyroid gland function
    - Primary hyperthyroidism: result of a disorder originating in the thyroid gland
        - Graves' disease
        - Toxic multinodular goiter (Plummer's disease)
        - Toxic adenoma
    - Secondary hyperthyroidism: result of stimulation of the thyroid gland by either:
        - Excess thyroid-stimulating hormone (TSH) (usually a TSH-secreting pituitary adenoma)
        - Human chorionic gonadotropin (hCG) (gestational or hCG-secreting tumors)
        - Rarely, patients with thyroid resistance syndrome may have evidence of thyrotoxicosis.
- Graves' disease: an autoimmune disorder that is the most common cause of hyperthyroidism (60-80% of cases of thyrotoxicosis)
- Thyrotoxic crisis/thyroid storm: life-threatening exacerbation of hyperthyroidism

Epidemiology

- Graves' disease
    - Prevalence
        - In the U.S.: about 400 per 100,000 persons, with a lifetime risk of 1% (up to 2%

in women).

        - High iodine intake is associated with increased prevalence.

    - Sex

        - Female-to-male ratio is 7-10:1.

    - Age

        - Rare before adolescence

        - Typical age range: 20-50 years

        - May occur in elderly persons and can cause "apathetic hyperthyroidism"

- Thyrotoxicosis

    - 60-80% of cases are due to Graves' disease.

Risk Factors

- Susceptibility to Graves' disease is determined by a combination of genetic, environmental, and endogenous factors.

    - Genetic

        - Polymorphisms in HLA-DR, cytotoxic T lymphocyte-associated antigen (CTLA) 4 variants, CD25, TSH receptor, and protein tyrosine phosphatase-22 (PTPN22*:* a T cell regulatory gene)

        - Monozygotic twin concordance: 20-30%

        - Dizygotic twin concordance: < 5%

    - Environmental

        - Psychological and other forms of stress (presumably via neuroendocrine effects on the immune system)

        - Smoking

            - Minor risk factor for Graves' disease

            - Major risk factor for ophthalmopathy

    - Exposure to iodine

        - Sudden increases in dietary iodine intake

        - Radiocontrast materials containing high iodine content
        - Medications (amiodarone)
    - Postpartum period
        - 3-fold increase in Graves' disease
    - Following highly active antiretroviral therapy (HAART) or alemtuzumab treatment
        - May occur during the immune reconstitution phase

Etiology

- Graves' disease
    - Caused by thyroid-stimulating immunoglobulins (TSI) directed against the thyrotropin (TSH) receptor
    - These antibodies bind to and activate the receptor, causing autonomous production of thyroid hormones and thyroid growth.
- Thyroid-associated ophthalmopathy
    - Cytokines appear to play a major role initiate a process of inflammation and eventual fibrosis in the muscles.
    - May result from immunoglobulins directed to specific antigens (i.e., the TSH receptor) expressed by the preadipocyte subpopulation of orbital fibroblasts.
    - Precise pathogenesis still unclear
- Dermopathy (also known as *pretibial myxedema*)
    - Characterized by lymphocytic infiltration of the dermis, accumulation of glycosaminoglycans, and nonpitting edema

Associated Conditions

- Conditions associated with Graves' disease include other autoimmune disorders such as:
    - Type 1 diabetes mellitus
    - Addison's disease
    - Vitiligo
    - Pernicious anemia

- Alopecia areata
- Myasthenia gravis
- Celiac disease

- Thyrotoxic periodic paralysis
  - An unusual disorder associated with hyperthyroidism characterized by sporadic episodes of acute muscle weakness and hypokalemia
  - Incidence is highest among Asian men.
  - Prodromal symptoms include muscle aches and stiffness, followed by lower-extremity proximal muscle weakness, progressing to flaccid quadriplegia.
  - Serum potassium concentration decreases during an attack but is not always below the normal range.
  - Typical clinical symptoms of hyperthyroidism may be subtle.
  - Emergency treatment involves potassium supplementation.
  - Treatment of the underlying cause of hyperthyroidism will usually eradicate attacks of thyrotoxic periodic paralysis.

Diagnosis

Symptoms & Signs

Thyrotoxicosis

Classic symptoms

- Unintentional weight loss despite increased caloric intake, with ravenous appetite
- Heat intolerance and excessive sweating
- Palpitations
- Hyperactivity
- Anxiety
- Tremulousness
- Fatigue and weakness

- Insomnia
- Irritability, dysphoria
- Impaired concentration
- Increased stool frequency, with occasional diarrhea and mild steatorrhea
- Pruritus
- Oligomenorrhea or amenorrhea
- Erectile dysfunction
- Polyuria

Unusual symptoms

- Weight gain
    - Occurs in 5% due to disproportionate increase in caloric intake that exceeds the elevation in metabolic rate
- Gynecomastia
- Urticaria

Signs

- Thyroid examination
    - Variable findings, depending on the etiology of thyrotoxicosis
        - Diffusely enlarged goiter (2-3 times): Graves' disease
        - Nodular: toxic multinodular goiter or toxic adenoma
- Cardiovascular
    - Sinus tachycardia
    - Bounding pulse/widened pulse pressure
    - Aortic systolic murmur
    - Atrial fibrillation, more common in patients > 50 years of age
- Neurologic/musculoskeletal
    - Hyperreflexia

    - Muscle wasting
    - Proximal myopathy without fasciculation
    - Tremor
    - Rarely: chorea, hypokalemic periodic paralysis (See Associated Conditions.)
- Dermatologic
    - Warm, moist skin
    - Palmar erythema
    - Onycholysis
    - Fine hair texture
        - Diffuse alopecia (up to 40% of patients)
- Ophthalmologic
    - Lid retraction or lag
    - Stare
    - Rarified blinking

Apathetic hyperthyroidism

- A presentation of Graves' disease often observed in elderly persons
- Characterized by a paucity of classic symptoms of thyrotoxicosis
- Fatigue and weight loss are the predominant symptoms.
- Often accompanied by atrial fibrillation, which may be sole clinical manifestation
- May be mistaken for depression

Thyrotoxic crisis or thyroid storm

- Rare but life-threatening exacerbation of hyperthyroidism, usually precipitated by acute illness or surgery
- Signs and symptoms
    - Fever

    - Delirium
    - Seizures
    - Coma
    - Vomiting
    - Diarrhea
    - Jaundice

Specific to Graves' disease

- Graves' ophthalmopathy (or orbitopathy)
    - Also called *thyroid-associated ophthalmopathy*, as it occurs in the absence of Graves' disease (such as in autoimmune hypothyroidism) in 10% of patients
    - Symptoms
        - Earliest symptoms include sensation of grittiness, eye discomfort, and excessive tearing.
        - Later symptom: diplopia (in 5-10% of patients, due to eye muscle dysfunction, swelling, and fibrosis)
    - Signs
        - Proptosis in about one-third of patients (often asymmetrical)
        - Periorbital edema
        - Conjunctival injection
        - Chemosis
        - Papilledema due to optic nerve compression
        - Peripheral field defects due to optic nerve compression
        - If optic nerve compression is left untreated, it can lead to permanent loss of vision.
        - Unilateral in up to 10%
    - NO SPECS: acronym of eye changes
        - 0 = No signs or symptoms

        - 1 = Only signs (lid retraction or lag), no symptoms
        - 2 = Soft-tissue involvement (periorbital edema)
        - 3 = Proptosis (>22 mm)
        - 4 = Extraocular muscle involvement (diplopia)
        - 5 = Corneal involvement
        - 6 = Sight loss
        - Patients do not necessarily progress from one class to another.
- Thyromegaly
    - Degree of thyroid enlargement varies from minimal to substantial.
    - Enlargement is bilateral and usually symmetric.
    - Consistency is moderately firm, with increased turgor.
    - May be accompanied by a thrill or bruit in more severe cases, due to the increased vascularity of the gland and the hyperdynamic circulation
- Thyroid dermopathy (< 5%)
    - Noninflamed, indurated plaque with a deep pink or purple color; may have an "orange-skin" appearance
    - Most frequently observed over anterior and lateral aspects of the lower leg (pretibial myxedema), but may occur at other sites, particularly after trauma
    - Nodular involvement can occur, and the condition can rarely extend over the whole lower leg and foot, mimicking elephantiasis.
    - Almost always accompanied by moderate or severe ophthalmopathy
    - May improve spontaneously
- Thyroid acropachy (< 1%)
    - Form of clubbing
    - Strongly associated with presence of thyroid dermopathy

Differential Diagnosis

- Differential diagnosis for thyrotoxicosis

- Primary hyperthyroidism
  - Graves' disease
  - Toxic multinodular goiter
  - Toxic adenoma
  - Activating mutation of the TSH receptor
    - Somatic: Toxic adenoma
    - Germ line: Familial or sporadic non-autoimmune hyperthyroidism (rare)
  - Activating mutation of Gs_{α} (McCune-Albright syndrome)
  - Rare
    - Functioning follicular thyroid carcinoma metastases
    - Struma ovarii
  - Drugs: iodine excess (Jod-Basedow phenomenon)
- Thyrotoxicosis without hyperthyroidism
  - Subacute thyroiditis, early stage
  - Silent thyroiditis
  - Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
  - Surreptitious ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue
- Secondary hyperthyroidism (rare except for gestational form)
  - TSH-secreting pituitary adenoma
  - Thyroid hormone-resistance syndrome (occasional patients may have features of thyrotoxicosis)
  - An hCG-secreting (germ-cell) tumor
  - Gestational thyrotoxicosis (hCG-mediated)
    - Human chorionic gonadotropin in high concentrations can activate the TSH receptor (structural similarity between hCG and TSH).

- Disorders that can mimic features of thyrotoxicosis
    - Panic attacks
    - Mania
    - Pheochromocytoma
    - Weight loss due to cancer
- Differential diagnosis of unilateral exophthalmos
    - Retrobulbar tumor
    - Arteriovenous malformation

Diagnostic Approach

Diagnostic approach to suspected thyrotoxicosis

- Measurement of serum TSH with a third- or fourth-generation immunoassay is recommended to reliably distinguish euthyroidism from mild hyperthyroidism.
- Measurement of both TSH and free thyroxine (T_4) is appropriate when thyrotoxicosis is suspected on clinical grounds.
- After analysis of these values, measurement of free triiodothyronine (T_3) is recommended when the serum TSH level is low and the free T_4 level is within the normal range.
- Accurate diagnosis of hyperthyroidism during pregnancy can be difficult because total thyroid hormone levels increase, reflecting an increased thyroid-binding globulin level and the action of hCG.

Establishing the etiology of thyrotoxicosis

- Determination of the underlying cause of thyrotoxicosis is essential after its biochemical diagnosis (see Laboratory Tests).
- Supportive information that may be useful in identifying an underlying cause of thyrotoxicosis
    - Previous thyroid function test results
    - History of recent upper respiratory illness
    - Use of amiodarone
    - Pregnancy

- Features supporting a diagnosis of Graves' disease
    - Diffuse goiter on palpation
    - Ophthalmopathy
    - Positive thyroid peroxidase (TPO) antibodies
    - Personal/family history of autoimmune disorders
- Features necessary and sufficient to confirm a diagnosis of Graves' disease in a patient with biochemical hyperthyroidism without need for further testing
    - Diffuse goiter
    - Signs of ophthalmopathy or dermopathy
- Thyroid radionuclide studies are useful to distinguish among the other causes of thyrotoxicosis in patients with biochemical thyrotoxicosis lacking the above features.
    - Radionuclide scan of the thyroid (^{99m}technetium, ^{123}iodine, or ^{125}iodine).
    - Radionuclide thyroid uptake (^{123}iodine or ^{125}iodine).
- Measurement of serum TSH receptor antibodies may be useful to establish a diagnosis of Graves' disease in select cases.
- A diagnosis of secondary hyperthyroidism should be followed by further investigation into its underlying cause and usually requires endocrinologic consultation.

Laboratory Tests

Tests for thyrotoxicosis

- Normal TSH and free T_4 levels exclude a diagnosis of thyrotoxicosis.
- Primary thyrotoxicosis is indicated by any of the following 3 testing patterns:
    - Low TSH level, high free T_4 level
    - Low TSH level, high free T_4 level, high free T_3 level
    - Low TSH level, normal free T_4 level, high free T_3 level (T_3 toxicosis)
- Subclinical thyrotoxicosis
    - Low TSH level, normal free T_4 and T_3 levels (See Subclinical Hyperthyroidism.)

- Secondary thyrotoxicosis
    - Normal or increased TSH level, high free T_4 level in TSH-secreting pituitary adenoma or thyroid-hormone resistance
    - Low TSH level, high free T4 in gestational thyrotoxicosis or germ-line tumor
- Other laboratory abnormalities associated with thyrotoxicosis
    - Elevated bilirubin and liver aminotransferase levels
    - Elevated ferritin level
    - Microcytic anemia
- Long-standing thyrotoxicosis
    - Mild hypercalcemia (20%)
    - Hypercalciuria
    - Thrombocytopenia

Tests for Graves' disease

- TSH receptor antibodies
    - Knowledge of the assay methodology is important for interpretation.
    - Second-generation assays using human recombinant TSH receptor have a high sensitivity and specificity for Graves' disease.
    - Measurement may be useful to establish the diagnosis when nuclear imaging studies cannot be performed (i.e., during pregnancy or after recent iodine load).
    - Measurement is recommended in pregnant women in the third trimester to assess the likelihood of neonatal hyperthyroidism.
    - TSH receptor antibody level may predict likelihood of remission in patients who have been treated with thionamides (see Prognosis).
- TSH-binding inhibiting immunoglobulins or thyroid-stimulating immunoglobulins
    - 80% sensitivity for Graves' disease
    - Not needed routinely
- TPO antibodies are often positive in Graves' disease (up to 80%), but are nonspecific; therefore, measurement is not recommended.

Imaging

- Radionuclide scanning
    - For imaging/scans (non- or semiquantitative uptake) technetium is the radionuclide of choice.
    - For quantitative thyroid uptake studies, radioiodine must be used.
- Radioiodine uptake by the thyroid will help to distinguish hyperthyroidism from other causes of thyrotoxicosis (technetium is not suitable for thyroid uptake studies).
    - High radioiodine uptake
        - Graves' disease
        - Toxic multinodular goiter
        - Toxic adenoma (overall thyroid uptake may be normal depending on size of tumor)
        - Trophoblastic disease and germ-cell tumors that produce hCG
    - Low radioiodine uptake
        - Any form of thyroiditis (usually < 1%)
        - Ectopic thyroid tissue (struma ovarii)
        - Functioning metastatic follicular thyroid carcinoma (rare)
        - Factitious thyrotoxicosis
- Radionuclide scan (technetium or iodine) of the thyroid will also help to distinguish among the causes of high radionuclide uptake hyperthyroidism.
    - Graves' disease: enlarged gland, homogeneously increased uptake
    - Nodular thyroid disease
        - Toxic adenoma: focal area of increased uptake with suppressed uptake in remainder of gland
        - Toxic multinodular goiter: enlarged gland with multiple areas of increased and decreased uptake
- Orbital imaging for Graves' ophthalmopathy is indicated if there is uncertainty about the cause of ophthalmopathy.

- Ultrasonography or CT of the orbits detects enlarged extraocular muscles.
- Ultrasonography or CT is much more sensitive for detecting ophthalmopathy than is clinical examination.

- Pituitary MRI is indicated for the further evaluation of secondary hyperthyroidism to search for a TSH-secreting pituitary adenoma (rare).
- Ultrasonography of the thyroid demonstrating increased color Doppler flow is helpful in conditions where radionuclide scanning is contraindicated or ineffective: [1]
  - Pregnancy
  - Breast-feeding
  - Following recent iodine exposure

Diagnostic Procedures

- Not indicated

Treatment

Treatment Approach

- Thyrotoxicosis
  - Treatment depends on its etiology. (See additional specific thyroid topics: Multinodular Goiter, Subclinical Hyperthyroidism.)
  - Regardless of etiology, therapy with β-adrenergic blockers may be started as soon as biochemical confirmation of thyrotoxicosis is made, to ameliorate adrenergic symptoms.
    - All β-adrenergic blockers are effective in ameliorating symptoms.
    - Typical doses: atenolol, 25-50 mg/d; propranolol, 20-40 mg 4 times daily
- Graves' disease
  - Goals of treatment are to alleviate clinical symptoms and reduce thyroid hormone synthesis.
  - 3 forms of therapy
    - Administration of thionamides (antithyroid medications)
    - Radioiodine (^{131}iodine) treatment

        - Subtotal thyroidectomy
    - Factors that are important to consider in the choice of treatment
        - Pregnancy, breast-feeding, or planning pregnancy
        - Presence of ophthalmopathy
        - Patient age
- Risks and benefits of each form of therapy should be weighed in selecting a treatment plan.
- No single approach is optimal, and multiple treatments may be necessary to achieve control.

Specific Treatments

Antithyroid drugs

- Thionamides
    - In Graves' disease, thionamide therapy is frequently used as the first choice of therapy since spontaneous remissions of the disease occur in some patients.
    - Thionamides are also used as initial therapy to attain euthyroidism before radioiodine therapy or surgery.
- Mechanism of action
    - Inhibit TPO, thereby blocking oxidation and organification of iodide and inhibiting thyroid hormone synthesis.
    - Possible immunomodulatory role to attenuate the autoimmune process
- Dosing considerations
    - Lower doses may suffice in areas of low iodine intake.
    - Starting doses can be gradually reduced after 3-4 weeks (titration regimen) as thyrotoxicosis improves.
- Initial dosing
    - Methimazole
        - 10-20 mg every 8-12 hours
        - Once-daily dosing is possible after euthyroidism is restored.
        - Drug of choice except in first trimester pregnancy, treatment of thyroid storm, or

in patients with methimazole drug reaction

        - Concerns about possible teratogenicity (aplasia cutis, choanal atresia, etc.)
        - Methimazole lacks the inhibitory effect on peripheral T_4 to T_3 conversion inherent in propylthiouracil.
    - Propylthiouracil
        - 100-200 mg every 6-8 hours
        - Divided doses are usually given throughout the course.
        - Associated with significant hepatotoxicity, especially in children but also in adults
            - Therefore, no longer recommended as the first choice of treatment
    - Carbimazole (not available in the U.S.)
        - 10-20 mg every 8-12 hours
        - Once-daily dosing is possible after euthyroidism is restored.
        - Contraindications are the same as those for methimazole.
- Alternative regimen (block-replace regimen)
    - High doses of thionamides may be given combined with levothyroxine supplementation.
    - Benefit: avoids possibility of inadvertent drug-induced hypothyroidism
    - Disadvantages: does not provide an index of treatment response and exposes patients to higher doses
    - Not commonly used
- Maintenance dosing
    - Titration regimen
        - Methimazole or carbimazole, 2.5-10 mg/d
        - Propylthiouracil, 50-100 mg/d
    - Block-replace regimen
        - Initial dose of antithyroid drug held constant
        - Dose of levothyroxine adjusted to maintain normal free T_4 level

- Effects
    - Euthyroidism can usually be achieved within 4-6 weeks.
    - Treatment is recommended to be continued for 12-18 months.
        - Associated with a lower relapse rate
    - Long-term remission after cessation of thionamides occurs in ~20% and can be up to 30-50% in some populations.
- Risks/adverse effects
    - Rare but serious adverse effects that require discontinuation of antithyroid drugs
        - Agranulocytosis (< 1%)
            - Written instructions should be provided regarding symptoms (e.g., sore throat, fever, mouth ulcers) and need to stop treatment pending evaluation.
            - A complete blood count should be obtained in patients who develop these symptoms while taking a thionamide.
        - Hepatitis
        - Systemic lupus erythematosus-like syndrome
    - Common adverse effects that may resolve spontaneously or after substituting an alternative antithyroid drug
        - Rash
        - Urticaria
        - Fever
        - Mild leukopenia
        - Arthralgia (1-5% of patients)
- Important drug interactions
    - Warfarin
        - Thionamides potentiate the action of warfarin because of accelerated plasma clearance of vitamin K-dependent clotting factors.
        - Higher warfarin doses are usually required as hyperthyroidism subsides.

- Digoxin
    - Increased doses are often needed in the thyrotoxic state because of increased clearance.
    - Digoxin doses are reduced as hyperthyroidism subsides.

- Pregnancy
    - Titration regimen of antithyroid drugs should be used to manage Graves' disease rather than the block-replace regimen, which often results in fetal hypothyroidism.
    - Propylthiouracil
        - Preferred thionamide because of its greater safety profile
        - Should be considered as the first-line agent in the treatment of Graves' disease during pregnancy
        - Lowest effective dose should be given, with frequent monitoring of thyroid hormone levels and dosing adjustments to ensure maternal euthyroidism.
        - Spontaneous remission of hyperthyroidism may occur in the third trimester, permitting discontinuation of thionamides at that time.
        - Breast-feeding is safe with low doses of antithyroid drugs (≤450 mg propylthiouracil/day).
    - Methimazole and carbimazole
        - Use of these drugs during pregnancy is discouraged owing to a weak association with aplasia cutis and other defects (e.g., choanal atresia).
        - Methimazole may be considered if the patient is intolerant of or has an allergic reaction to propylthiouracil.
            - However, methimazole may have a greater association with certain birth defects such as choanal atresia or aplasia cutis.

Radioiodine therapy (^{131}iodine)

- May be used as initial treatment or for relapses after failed medical or surgical therapy
- Mechanism of action: specifically transported into thyroid cells and causes progressive destruction of thyroid cells
- Dose (range, 5-15 mCi) is based on thyroid gland size, radioiodine uptake, and severity of thyrotoxicosis.

- Risks
    - A small risk of thyrotoxic crisis immediately after radioiodine therapy is minimized by pretreatment with a thionamide for at least 1 month before treatment.
    - Pretreatment with a thionamide is highly recommended for elderly patients or patients with cardiovascular disease.
        - Discontinue 3-5 days before treatment, restart 3-7 days after treatment, and taper over 4-6 weeks as thyroid function normalizes. [1]
    - Overall risk of cancer after treatment in adults is not increased.
- Effects
    - Efficacy depends on several factors (see Prognosis).
    - High doses are associated with high rate of cure but cause hypothyroidism in most patients.
    - Full effects of therapy require 2-3 months.
    - Persistent hyperthyroidism can be treated with a second dose of radioiodine 6 months after the first dose.
- Adverse effects
    - Mild pain may rarely occur 1-2 weeks after treatment, due to radiation thyroiditis.
    - Possible worsening of Graves ophthalmopathy [2]
    - Hypothyroidism: Most patients who are effectively treated end up with hypothyroidism.
- Concurrent use of antithyroid drugs
    - Methimazole or carbimazole must be stopped at least 3 days before radioiodine administration to achieve optimum iodine uptake.
    - Propylthiouracil has a prolonged radioprotective effect and should be stopped several weeks before radioiodine is given, or a larger dose of radioiodine will be necessary.
    - Antithyroid drugs and β-adrenergic blockers may be resumed after administration of radioiodine until full effects of radioiodine are achieved.
- Precautions
    - Patients should be advised to avoid close, prolonged contact with children and pregnant women the first few days after treatment due to possible transmission of residual isotope

and radiation emanating from the gland.

- Radioiodine should be used cautiously in the following patients:
  - Children and adolescents (theoretical risk of cancer)
    - Emerging evidence suggests that radioiodine can be used safely in older children.
  - Patients with iodine allergy
    - This is more of a theoretical than an actual concern as the amount of iodine administered with ^{131}iodine therapy is very small (typically < 100 ng) and at least a 1000-fold less than the daily dietary iodine intake.
  - Concurrent severe ophthalmopathy, especially in smokers
    - Glucocorticoid therapy (prednisone, 40 mg/d at time of radioiodine treatment, tapered over 3 months) is recommended in these patients to prevent exacerbation of ophthalmopathy.
- Absolute contraindications
  - Patients who are pregnant or breast-feeding
    - Patients can conceive safely 6 months after treatment.
    - Coexisting thyroid cancer or suspicion of thyroid cancer [1]

Subtotal or near-total thyroidectomy

- Usually reserved for the following situations:
  - Pregnant women whose thyrotoxicosis is not controlled by thionamides
  - Patients who have relapse after antithyroid drugs and decline treatment with radioiodine
  - Patients with very large goiters in whom the probability of effective treatment with radioiodine or thionamides is judged to be low
  - Patients for whom there is a risk of thyroid cancer
- Control of thyrotoxicosis with antithyroid drugs, followed by potassium iodide (3 drops of saturated solution PO tid), is necessary before surgery to avoid thyrotoxic crisis and reduce vascularity of the gland.
- Possible surgical complications
  - Bleeding

- Laryngeal edema
- Hypoparathyroidism
- Damage to recurrent laryngeal nerves

Treatment of thyroid storm (thyrotoxic crisis)

- Management requires intensive monitoring/supportive care, identification and treatment of precipitating cause, and urgent reduction of thyroid hormone synthesis.
  - Large doses of propylthiouracil (600-mg loading dose and 200-300 mg every 6 hours), orally, by nasogastric tube, or by rectum
    - One hour after the first dose, iodide is given to block thyroid hormone synthesis.
  - Saturated solution of potassium iodide (5 drops every 6 hours) or, if available, ipodate or iopanoic acid (0.5 mg every 12 hours PO)
    - Sodium iodide (0.25 g IV every 6 hours) is an alternative but is not generally available.
  - Propranolol should be given to reduce tachycardia and other adrenergic manifestations (40-60 mg PO every 4 hours, or 2 mg IV every 4 hours).
    - High-dose propranolol also inhibits T_4-to-T_3 conversion.
  - Glucocorticoids (dexamethasone, 2 mg every 6 hours) inhibit peripheral T_4-to-T_3 conversion.
  - Other supportive measures
    - Antibiotics (if infection is present)
    - Cooling
    - Oxygen
    - Intravenous fluids

Treatment of ophthalmopathy and dermopathy

- Mild/moderate ophthalmopathy
  - General measures
    - Meticulous control of thyroid hormone levels

        - Counseling for smoking cessation
        - Explanation of natural history of ophthalmopathy
    - Ocular discomfort can be relieved with artificial tears (e.g., 1% methylcellulose) and use of dark glasses with side frames.
    - Periorbital edema may respond to a more upright sleeping position or a diuretic.
    - Corneal exposure during sleep can be avoided by using patches or taping the eyelids shut.
    - Minor degrees of diplopia improve with prisms fitted to spectacles.
- Severe ophthalmopathy (with optic nerve involvement or chemosis resulting in corneal damage) is an urgent condition requiring co-management with an ophthalmologist.
    - High-dose glucocorticoids (e.g., prednisone, 40-80 mg/d) improve symptoms in two-thirds of patients.
        - Sometimes combined with cyclosporine
        - Intravenous therapy may be more effective than oral, but requires monitoring of liver function.
        - Taper by 5 mg every 1-2 weeks over 3 months.
        - Pulse therapy with intravenous methylprednisolone (500-1000 mg of methylprednisolone in 250 mL of saline infused over 2 hours daily for 1 week) may be given before the above regimen.
    - Orbital decompression surgery may be indicated for optic neuropathy and improvement of appearance.
    - External-beam radiotherapy of the orbits has been used for many years, although objective evidence that this therapy is beneficial remains equivocal.
        - Best reserved for those who have failed or are not candidates for glucocorticoid therapy
    - Selenium may prove to be an effective agent
        - May reduce ocular involvement and slow progression in patients with mild Graves' ophthalmopathy.
- Thyroid dermopathy
    - Treatment usually not required

- If necessary, topical high-potency glucocorticoid ointment may be applied under occlusive dressing.
- Octreotide may be tried, although the evidence for efficacy is equivocal.

Ongoing Care

Monitoring

- Primary hyperthyroidism
  - Antithyroid drug therapy
    - Thyroid function tests and clinical manifestations are reviewed 3-4 weeks after starting treatment, and the dose is titrated based on T_4 levels.
    - Follow free T_4 levels until TSH normalizes, then use both TSH and free T_4 levels.
    - Titrate antithyroid medication dose on the basis of free T_4 levels (until TSH normalizes).
    - Monitor closely for adverse effects.
    - Follow all patients closely for relapse during the first year after discontinuing antithyroid drug therapy, then at least annually thereafter for life.
  - Radioiodine therapy
    - Patients treated with radioiodine are at high risk for hypothyroidism.
    - Close follow-up is required for the first 1 year after therapy, followed by at least annual thyroid function testing thereafter for life.
    - Free T_4 levels, rather than TSH levels, should be monitored for the first several months following therapy until a euthyroid state is reached.
- Pregnancy
  - Frequent monitoring of thyroid hormone levels throughout pregnancy is mandatory to make adjustments in antithyroid medications to ensure maternal euthyroidism.
  - Monitor thyroid function closely in the postpartum period.
  - Measurement of TSH receptor antibodies in the third trimester may be useful to assess the risk of neonatal hyperthyroidism.
  - Fetal hyperthyroidism may develop even if the mother has been rendered euthyroid

because TSH receptor antibodies can persist.

Complications

- Spontaneous autoimmune hypothyroidism may develop in up to 15% of patients with Graves' disease.
- Radioiodine-induced hypothyroidism develops in ~80% of patients treated with this method.
- Thyrotoxic crisis or thyroid storm is an uncommon complication of thyrotoxicosis, but may be precipitated by:
    - Acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis)
    - Surgery (especially on the thyroid)
    - Radioiodine treatment for partially treated or untreated hyperthyroidism
- Long-standing thyrotoxicosis leads to osteopenia.
    - Small increase in fracture rate
- Pregnancy complicated by uncontrolled hyperthyroidism is associated with increased risks of:
    - Spontaneous abortion
    - Premature labor
    - Preeclampsia
    - Stillbirth

Prognosis

- Natural history of Graves' disease
    - Symptoms generally worsen without treatment.
    - Some patients with mild Graves' disease may experience spontaneous relapses and remissions.
    - Rarely, a patient with Graves' disease will fluctuate between hypo- and hyperthyroidism due to changes in the functional activity of TSH receptor antibodies.
- Prognosis with treatment
    - Radioiodine ablation
        - Incomplete treatment or early relapse is more common in men < 40 years of age.

        - Predictors of persistent hyperthyroidism: younger age, larger thyroid gland, higher serum T_4 concentrations at diagnosis, higher 24-hour ^{123}iodine thyroid uptake value
        - Pretreatment with a thionamide before radioiodine is associated with a lower rate of successful treatment.
        - Risk of hypothyroidism after radioiodine treatment depends in part on dosage: at least 10-20% in the first year, 5% per year thereafter.
        - Most patients progress to hypothyroidism over 5-10 years.
    - Antithyroid medication therapy
        - Maximum remission rates (up to 30-50% in some populations) are achieved by 18-24 months for titration regimen and by 6 months for block-replace regimen.
        - Remission rates appear to vary in different geographic regions.
        - Predictors of remission: disappearance of TSH receptor antibodies, smaller goiters, mild hyperthyroidism, age > 40 years, female sex
        - Approximately 15% of patients who achieve remission after use of antithyroid drugs develop hypothyroidism 10-15 years later.
    - Subtotal thyroidectomy
        - Recurrence rates in the most successful series are < 2%.
        - Rate of hypothyroidism is only slightly less than with radioiodine treatment.
- Ophthalmopathy
    - Clinical course does not parallel that of thyroid disease.
    - Typically worsens over the initial 3-6 months, plateaus over the next 12-18 months, then gradually improves, particularly in the soft-tissue changes
    - Course is more fulminant in 5% of patients, requiring intervention in the acute phase (for optic nerve compression or corneal ulceration).
    - Radioiodine treatment may worsen eye disease (especially in smokers).
- Thyroid dermopathy
    - Appears 1-2 years after development of Graves' hyperthyroidism
    - May improve spontaneously

- Postpartum period: risk for relapse of Graves' disease that has been mitigated during pregnancy.
- Thyrotoxic crisis or thyroid storm
    - The rate of death due to cardiac failure, arrhythmia, or hyperthermia is as high as 30%, even with treatment.

Prevention

- No known preventive measures

Resources

See Also

- Amiodarone Effects on Thyroid Function
- Multinodular Goiter
- Myasthenia Gravis
- Polyglandular Failure Syndromes
- Solitary Thyroid Nodule
- Subclinical Hyperthyroidism
- Thyroid Disease and Pregnancy
- Thyroid Function Tests
- Type 1 Diabetes Mellitus
- Weight Loss, Unintentional

Internet Sites

- Professionals
    - Graves Disease PubMed Health
    - Management of Thyroid Dysfunction during Pregnancy and Postpartum The Endocrine Society
- Patients
    - Hyperthyroidism MedlinePlus

- Graves disease MedlinePlus

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- This topic is based on *Harrison's Principles of Internal Medicine, 18th edition*, chapter 341, Disorders of the Thyroid Gland by JL Jameson and AP Weetman.

Pearls

- The presence of ophthalmopathy and a diffusely enlarged thyroid gland suggest Graves' disease as the cause of thyrotoxicosis.
- TSH levels may be suppressed for several months after restoration of euthyroidism for Graves' disease.
- Antithyroid drugs are most effective in patients with small goiters and mild thyrotoxicosis who have the greatest chance for a permanent remission.
- Because maternal TSH receptor antibodies persist, fetal hyperthyroidism may occur in women with a history of Graves' disease.
- In pregnant patients with hyperthyroidism, maternal thyroid function should be kept on the high side of normal (low thionamide doses) to minimize the possibility of fetal hypothyroidism.
- Amiodarone-induced thyrotoxicosis may be caused by 3 mechanisms.
    - A Jod-Basedow effect from the iodine load in the setting of multinodular goiter
    - Thyroiditis-like condition
    - Induction of autoimmune Graves' disease
- Eye signs in hyperthyroidism are of 2 varieties:
    - Thyrotoxic eye signs are a result of increased sympathetic activity: lid lag, stare, rarified blinking.
        - They are seen in any type of thyrotoxicosis.
    - Proptosis due to Graves' ophthalmopathy: also results in lid lag due to anatomical change of eye protrusion
        - Other signs of orbitopathy are present, and exophthalmus can be documented by measurement.

ICD9 Code

- 242.0 Toxic diffuse goiter with mention of thyrotoxic crisis or storm
- 648.1_ Thyroid dysfunction (as a complication of pregnancy, childbirth & puerperium)
- 775.30 Neonatal thyrotoxicosis

Topics

- Hyperthyroidism
- Thyroid hormone

Specialties

- Endocrinology