Managing/Diagnosing Hypo/Hyperthyroidism and Interpreting Thyroid Function Tests

Part 2: Hyperthyroidism

Faculty

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Definitions

Hyperthyroidism: an increase in thyroid hormone synthesis/secretion from the thyroid gland.

Thyrotoxicosis: clinical manifestations that stem from effect of excess thyroid hormone levels on various tissues, regardless if thyroid hormone excess is secondary to hyperthyroidism (e.g. Graves' disease) or other causes (e.g. a supraphysiologic dose of levothyroxine).

Definitions

Examples of thyrotoxicosis:

- Constitutional: weight loss, hyperphagia
- Skin: onycholysis, increased perspiration
- Cardiovascular: atrial fibrillation, congestive heart failure
- Abdominal: hyperdefecation, cholestasis
- Gynecological: irregular menstrual cycles
- Neuro/Psych: anxiety, agitation, psychosis, tremor
- Metabolic: hypercalcemia, hyperglycemia/insulin resistance, increased bone resorption

Interpreting Thyroid Function Tests

	TSH	Free/Total T4	Free/Total T3
Hyperthyroidism (overt hyperthyroidism)	↓	↑	↑
T3-toxicosis	↓	↔	↑
Subclinical hyperthyroidism	↓	↔	↔
TSH-secreting pituitary adenoma (TSHoma)	↔ **or** ↑	↑	↑

Key: ↑ above the reference range, ↓ below the reference range, ↔ within the reference range

Types/Causes of Hyperthyroidism

Endogenous hyperthyroidism: Graves' disease, toxic multinodular goiter, toxic adenoma

Pregnancy-related thyroid disease: gestational transient thyrotoxicosis, hyperemesis gravidarum, trophoblastic hyperthyroidism, postpartum thyroiditis

Iodine-induced hyperthyroidism: iodinated CT contrast, amiodarone-induced thyrotoxicosis

Types/Causes of Hyperthyroidism

Exogenous causes: accidental/surreptitious thyroid hormone ingestion, “hamburger hyperthyroidism”

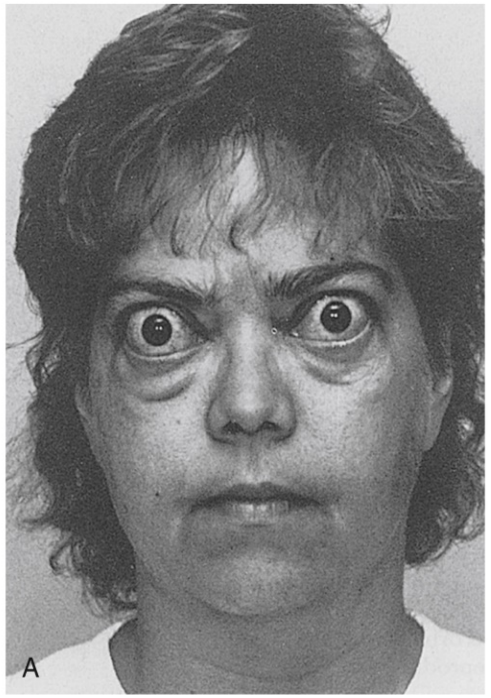
Subacute thyroiditis: viral/bacterial infections, radiation thyroiditis

Rare causes: struma ovarii, TSHoma

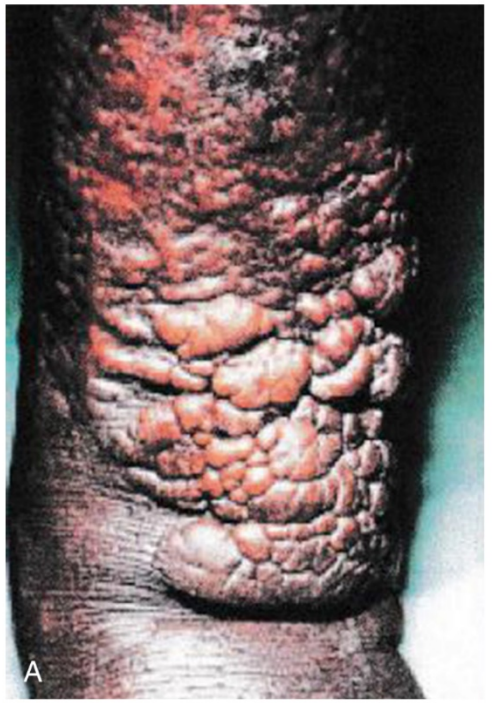
Graves' Disease

Clinical features:

- Diffuse goiter: a bruit may be auscultated
- Graves' ophthalmopathy: proptosis, periorbital oedema, conjunctival erythema, chemosis.



Graves' orbitopathy: bilateral periorbital edema, stare, and exophthalmos



Pretibial myxoedema secondary to Graves' disease

Graves' Disease

Work-up:

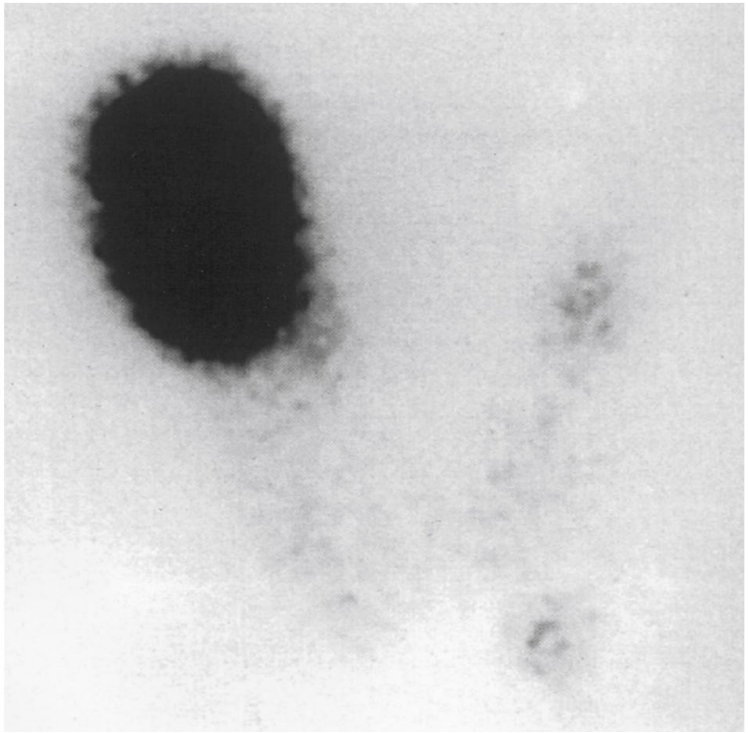
- Positive thyrotropin receptor antibody (TSHR-Ab) and/or thyroid-stimulating immunoglobulin (TSI)
- Diffusely increased uptake on radionuclide uptake and scan
- Hyperthyroidism or subclinical hyperthyroidism
- Normal thyroid function test results in the absence of thionamides indicate disease remission

Toxic Adenoma or Toxic Multinodular Goiter (MNG)

Labs: hyperthyroidism or subclinical hyperthyroidism.

Radionuclide imaging:

- Toxic adenoma: focally increased radiotracer uptake, with reduced or no uptake in the remainder of the gland
- Toxic MNG: heterogeneous/patchy uptake with areas of increased uptake corresponding to "hot" nodules.



Radioiodine (^{123}I) thyroid scan depicting a toxic adenoma with a faint outline of the remaining suppressed thyroid gland.

Melmed, S., Auchus, R.J., Goldfine, A.B., Koenig, R.J., & Rosen, C. J. (2020). *Williams Textbook of Endocrinology 14th edition E-Book*. Elsevier Health Sciences.

- Thionamides: methimazole or propylthiouracil
- Surgery:
  - Compressive symptoms (e.g. dysphagia or dyspnea) are a compelling indication
  - Ipsilateral lobectomy is performed for toxic adenoma
  - Near-total thyroidectomy may be considered for toxic MNG
- Radioactive iodine ablation:
  - Toxic adenoma/MNG: it often reduces the size of the nodule(s).
  - Graves' disease: proceed with caution if Graves' ophthalmopathy is present

Radioactive iodine ablation or total thyroidectomy may be considered for hyperthyroidism that persists beyond 18 months after the initiation of thionamides.

Nevertheless, low-dose methimazole is a safe and acceptable alternative for long-term treatment of Graves' disease.

Functional thyrotropin receptor antibody assays (TSH-R-Ab) serve as a predictor of Graves' disease recurrence. TSH-R-Ab is also predictive for extrathyroidal manifestations (orbitopathy).

Teprotumumab is FDA approved for the treatment of adults with severe and active thyroid eye disease

Treatment of Endogenous Subclinical Hyperthyroidism

The presence of any of these factors may influence decision to start treatment:

- Symptomatic
- Age ≥65 years
- TSH ‹ 0.1 mIU/L
- Cardiovascular disease e.g. atrial fibrillation, coronary artery disease
- Osteoporosis

hCG-mediated Hyperthyroidism during Pregnancy

Beta-subunit of serum human chorionic gonadotropin (hCG) is homologous to TSH. hCG therefore exerts mild thyroid-stimulating activity by direct activation of TSH receptor. This results in hCG-induced hyperthyroidism, particularly when serum hCG concentrations peak during pregnancy (weeks 10 to 12 of gestation).

hCG-mediated Hyperthyroidism during Pregnancy

- **Gestational transient thyrotoxicosis:** physiologic subclinical or overt hyperthyroidism occurs towards end of first trimester. No treatment required.
- **Hyperemesis gravidarum:** associated with higher serum hCG concentrations, which may induce overt hyperthyroidism. No treatment required.
- **Trophoblastic hyperthyroidism:** hydatidiform mole and choriocarcinoma associated with higher serum hCG concentrations. Treatment against tumor itself.
- **Note:** testicular germ cell tumors in men can also result in hCG-mediated hyperthyroidism.

	hCG-mediated Hyperthyroidism*	Graves' disease	Toxic Nodular Goiter
Onset	Late first/early second trimester	Anytime	Anytime
Thyroid gland	No goiter	Goiter may be present	Goiter
Ophthalmopathy	Absent	May be present	Absent

*hCG-mediated hyperthyroidism: hyperemesis gravidarum or gestational transient thyrotoxicosis.

Thyrotropin receptor stimulatory antibody (TSH-R-Ab) can be used to predict fetal or neonatal risk of thyroid dysfunction.

TSH-R-Ab should, therefore, be measured in all patients with Graves' disease during early pregnancy, including those who already underwent radioactive iodine ablation or total thyroidectomy. If not elevated, no further TSH-R-Ab testing is required. If elevated during early pregnancy, repeat testing at 18-22 weeks gestation.

Fetal ultrasound: indicated for uncontrolled maternal hyperthyroidism during the second half of pregnancy, or high TSH-R-Ab levels (› 3 times the upper limit of normal) at any time during pregnancy. If a fetal goiter is identified, cordocentesis could then be considered to assess fetal thyroid function.

- Compared to methimazole (MMI), propylthiouracil (PTU) demonstrates lower placental transfer and less severe thionamide-induced embryopathy. PTU is, therefore, first-line therapy during the first trimester of pregnancy.
- Thyroid function tests are monitored every four weeks during pregnancy. The lowest effective dose of MMI or PTU is used.
- Treatment target: maternal serum free T4 at the upper limit of (or moderately above) the reference range.

- Block-replace therapy for Graves' disease: for mothers with Graves' disease and post-surgical or post-ablative hypothyroidism, a combination regimen of levothyroxine and thionamide is rarely considered to treat isolated fetal hyperthyroidism.
- Thyroidectomy during pregnancy is considered for exceptional circumstances e.g. thionamide allergy. Optimally timed during the second trimester.

Postpartum Thyroiditis

Autoimmune-mediated destructive thyroiditis that occurs within a year of giving birth. Characterized by transient hyperthyroidism, potentially followed by hypothyroidism, which is either transient or permanent.

- Clinical features: mild or absent signs and symptoms of hyperthyroidism
- Hypothyroid phase: levothyroxine for symptomatic hypothyroidism. Withdraw thyroid hormone replacement if hypothyroidism remits.

Postpartum Thyroiditis

Work-up:

- Hyperthyroid phase: overt or subclinical hyperthyroidism.
- Hypothyroid phase: overt or subclinical hypothyroidism.
- Serum anti-thyroid peroxidase (TPO) antibody often elevated.
- Low radioiodine uptake during the hyperthyroid phase. Note that radionuclide imaging is contraindicated during lactation.

Postpartum Thyroiditis

Treatment:

- Hyperthyroid phase: beta blocker if symptomatic. Thionamides are NOT indicated.
- Hypothyroid phase: levothyroxine for symptomatic hypothyroidism. Withdraw thyroid hormone replacement if hypothyroidism remits.

Exogenous Hyperthyroidism

- Jod-Basedow phenomenon: hyperthyroidism that is induced by the administration of iodine or iodide (e.g. iodinated contrast for a CT scan).
- Examples of exogenous thyroid hormone replacement:
  - Thyroid hormone extract e.g. contaminated weight loss supplements
  - "Hamburger hyperthyroidism:" inadvertently ingesting thyroid tissue from livestock
- Work-up for exogenous hyperthyroidism:
  - Low serum thyroglobulin concentration (provided residual/metastatic thyroid cancer is absent)
  - Reduced radioiodine uptake in the thyroid gland.

Exogenous Hyperthyroidism

Deliberate TSH suppression with Levothyroxine: certain individuals with differentiated thyroid cancer (e.g. papillary or follicular thyroid cancer) are prescribed higher than conventional doses of levothyroxine to preempt tumor growth/recurrence. This is standard practice.

Type 1 AIT:

- Hyperthyroidism due to pre-existing Graves' disease or toxic multinodular goiter.
- Clinical features may therefore include a diffuse or asymmetric goiter.

Type 2 AIT:

- Destructive thyroiditis resulting from a direct toxic effect of hyperthyroidism.
- First manifests with transient hyperthyroid phase (weeks-months), followed by hypothyroid phase, which eventually remits (normal thyroid function) or persists (chronic hypothyroidism).

Note: both types of AIT can present concurrently (mixed AIT). Thus initial treatment for AIT may entail both thionamide and glucocorticoid therapy, pending further investigation and/or response to treatment.

	AIT Type 1	AIT Type 2
Onset of disease relative to starting amiodarone	Shorter (months)	Longer (often years)
24-hour radioiodine uptake	Detectable or low	Low
Color flow Doppler sonography	Increased vascularity	Absent vascularity
Technetium-99m (99mTc)-sestamibi thyroid uptake and scintigraphy	Normal or increased	Low
Treatment	Methimazole	Prednisone

Note: Both types of AIT can present concurrently (mixed AIT). Thus initial treatment for AIT may entail both thionamide and glucocorticoid therapy, pending further investigation and treatment response.

Subacute Thyroiditis

- Also known as subacute granulomatous thyroiditis, de Quervain's thyroiditis, subacute granulomatous thyroiditis, subacute non-suppurative thyroiditis.

- Transient inflammatory process that follows a viral infection e.g. upper respiratory infection, COVID-19.

- Clinical features: thyroid tenderness, asymmetrically or diffusely enlarged thyroid gland.

Subacute Thyroiditis

Work-up:

- Elevated serum thyroglobulin concentration, erythrocyte sedimentation rate and C-reactive protein
- Early stage: hyperthyroidism often present for 2-8 weeks
- Subclinical hypothyroidism may follow transient hyperthyroidism
- Low radioiodine uptake

Treatment: short-term NSAID or glucocorticoid

Other Forms of Thyroiditis

Acute infectious thyroiditis / Suppurative thyroiditis:

- Associated with bacterial, fungal or parasitic infections; abscess may be present
- Thyroid function tests are often normal; hyperthyroidism is rare
- Confirmed with fine-needle biopsy: neutrophils on cytology. Obtain stains and cultures.

Radiation thyroiditis:

- Radiation-induced inflammation of thyroid follicular cells
- Anterior neck pain (potentially radiating to the jaw) within 5-10 days of treatment
- Spontaneously resolves or treated with brief course of glucocorticoid therapy

Other Forms of Thyroiditis

Painless thyroiditis / Silent Thyroiditis / Subacute Lymphocytic Thyroiditis:

- Transient thyroid inflammation that mimics the pathogenesis of autoimmune thyroiditis.
- Non-tender thyroid gland, often accompanied by mild diffuse enlargement.
- Transient hyperthyroidism, potentially followed by hypothyroidism and then spontaneous remission.
- Treatment often not required during the hyper- or hypothyroid phases.

Thyroid Storm

Clinical features: hyperpyrexia, tachycardia, altered mentation, nausea, vomiting, diarrhea or abdominal pain. Organ dysfunction may also be present e.g. jaundice with liver failure, decompensated heart failure.

Labs:

- Degree of hyperthyroidism is similar to uncomplicated thyrotoxicosis
- Abnormal liver panel , hyperglycemia, leukocytosis/leukopenia

Thyroid Storm

Treatment:

- Beta blocker
- Propylthiouracil (PTU) is preferred over methimazole since PTU additionally inhibits peripheral deiodination of T4 to T3
- Glucocorticoids also inhibit T4 to T3 conversion
- Iodine solution inhibits release of thyroid hormone; only administer **after** thionamide has been started
- Bile acid sequestrants disrupt enterohepatic circulation of thyroid hormone

Clinical features: thyrotoxicosis, diffuse goiter, headache, visual field deficits.

TSH-secreting Pituitary Adenoma

Work-up:

- High serum free T4 / T3 with unsuppressed (inappropriately normal or high) TSH
- Elevated alpha subunit, high serum sex hormone-binding globulin (SHBG)
- TRH stimulation: serum TSH rises in response to thyrotropin-releasing hormone
- Pituitary tumor on MRI

Differential diagnosis: TSH assay interference, syndrome of resistance to thyroid hormone.

Treatment: somatostatin analog (to restore biochemically euthyroid status) followed by neurosurgical intervention.

Struma Ovarii

Benign or malignant ovarian teratoma; mature thyroid tissue comprises at least 50% of mass.

Potentially asymptomatic: pelvic and hyperthyroid signs/symptoms often absent.

Graves' disease or toxic nodular goiter may co-exist.

Work-up:

- Thyroid function tests are often normal
- Radioactive iodine uptake: present in pelvis but low or absent in thyroid gland
- Pelvic ultrasound: ovarian mass, otherwise no hallmark sonographic features

Treatment: unilateral oophorectomy; bilateral oophorectomy, hysterectomy and/or radioiodine may be considered for malignant struma ovarii.

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