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Management of Common Thyroid Issues

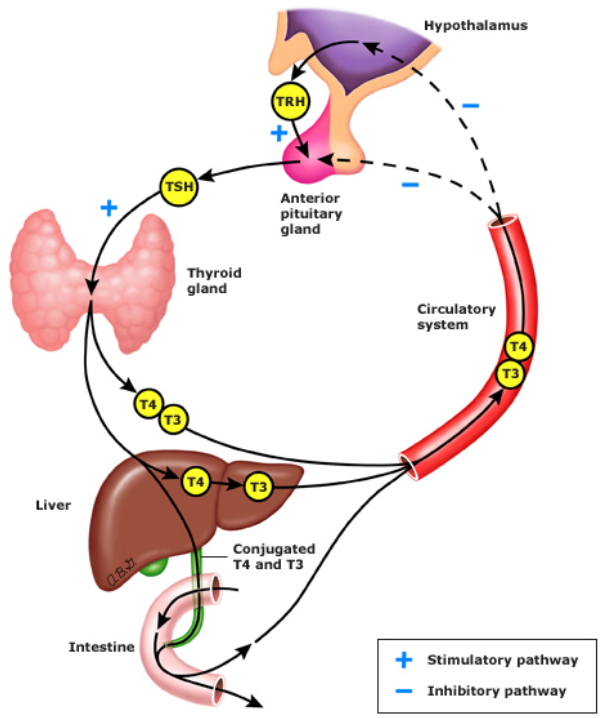
Disclosures

- I have no financial disclosures

Objectives

- Hypothyroidism
- Hyperthyroidism
- Thyroiditis
- Thyroid nodules

Regulation of thyroid hormone production



Thyrotropin-releasing hormone (TRH) increases the secretion of thyrotropin (TSH), which stimulates the synthesis and secretion of trioiodothyronine (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.

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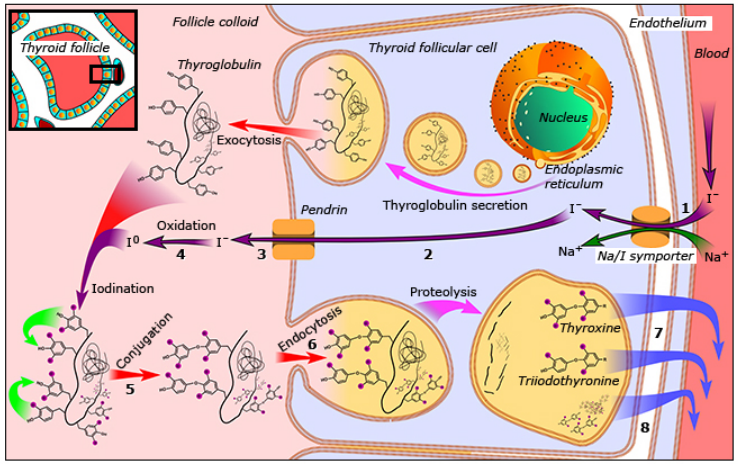
Case #1

- 16 yo F, no PMH, presents with 4-6 months of:
  - Irregular periods
  - 14 lb weight gain
  - Puffy face
  - Fatigue
  - Tongue swelling
  - Decreased concentration, falling asleep in class
  - Unable to keep up with water polo practices
  - Family history: mother and aunt with thyroid disease
- Physical exam
  - BMI 28
  - Periorbital edema
  - Delayed relaxation phase achilles tendon reflex
- Labs
  - TSH 288
  - FT4 0.4
  - TPO Ab >1000
  - Tg Ab >20

Hypothyroidism

Thyroid hormone biosynthesis

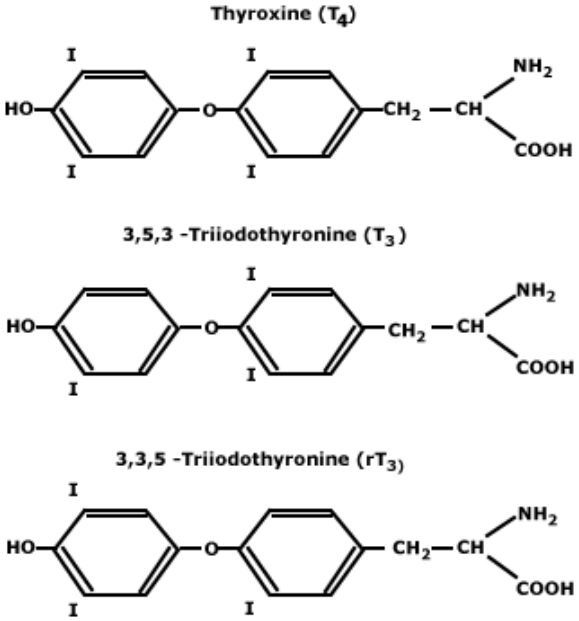


Thyroid hormone synthesis includes the following steps, marked by numbers in the diagram above:

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
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



Hypothyroidism

- Prevalence: 0.3% for TSH>5
  - Over age 60: 6-9% women, 1-2% men for TSH>10
- Positive TPO Ab prevalence: 11%
- 5-8X more common in women
- Etiology
  - Iodine deficiency (most common worldwide)
  - US: 95% primary, autoimmune (Hashimoto's thyroiditis=chronic lymphocytic thyroiditis)
  - Drugs
  - Subacute thyroiditis recovery phase
  - Central: pituitary or hypothalamic dysfunction
  - Congenital
  - Consumptive (rare): paraneoplastic

Presentation of Hypothyroidism

- Hypercholesterolemia (especially LDL)
- Macrocytic anemia
- Hyponatremia
- Hyperuricemia
- Elevated CK
- Bleeding risk: acquired vWB syndrome
- Hypogonadism
- Carpal tunnel syndrome
- Peripheral neuropathy
- Hypothermia

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Mental retardation (infantile onset) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

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Risk Factors for Hypothyroidism

- Goiter
- Iodine deficiency *or* excess
- History of postpartum or deQuervain's thyroiditis
- History of thyroidectomy, radioactive iodine, head/neck radiation
- Family or personal history of autoimmune disease
- Radiation, surgery, trauma, or infiltrative diseases to pituitary or hypothalamus
- Drugs
- Increased TBG clearance: nephrotic syndrome, liver disease

Screening for Hypothyroidism

Table 8
Recommendations of Six Organizations Regarding Screening of Asymptomatic Adults for Thyroid Dysfunction

Organization	Screening recommendations
American Thyroid Association	Women and men >35 years of age should be screened every 5 years.
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened.
American Academy of Family Physicians	Patients ≥60 years of age should be screened.
American College of Physicians	Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated.
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified

Diagnosis of Hypothyroidism

- TSH is the most sensitive screening test
- What is the normal TSH range?
  - 95% of young adults have TSH 0.4-2.5 mU/L
  - Adults over 65:
    - higher TSH correlated with *lower* CV and all-cause mortality
    - No correlation between higher TSH (4-10) and symptoms, ADLs
- TSH>10 associated with increased CVD mortality and CHF

Diagnosis of Hypothyroidism

Table 7
Thyrotropin Upper Normal

Group, study, society	TSH upper normal	Comments
NACB	2.5	When there is no evidence of thyroid disease
NHANES III, disease free	4.5	No self-reported thyroid disease Not on thyroid medications
NHANES III, reference population	4.12	No self-reported thyroid disease Not on thyroid medications Negative anti-thyroid antibodies Not pregnant Not on estrogens, androgens, lithium
Hanford Thyroid Disease Study	4.10	No evidence of thyroid disease Negative anti-thyroid antibodies Not on thyroid medications Normal ultrasound (no nodules or thyroiditis)
Pregnancy, first trimester	2.0-2.5	See sections *L-thyroxine treatment of hypothyroidism* and *Hypothyroidism during pregnancy*
Pregnancy, second trimester	3.0	See sections *L-thyroxine treatment of hypothyroidism* and *Hypothyroidism during pregnancy*
Pregnancy, third trimester	3.5	See sections *L-thyroxine treatment of hypothyroidism* and *Hypothyroidism during pregnancy*

Sources: Stagnaro-Green et al., 2011 (10); Hollowell et al., 2002 (11); Hamilton et al., 2008 (81); Baloch et al., 2003 (85).
NACB, National Academy of Clinical Biochemists; NHANES, National Health and Nutrition Examination Survey

Diagnosis of Hypothyroidism

- TPO Ab 90% sensitive for autoimmune thyroiditis
- DDx of discordant thyroid function tests: thyroid hormone resistance, HAMA Ab, recovery from non-thyroidal illness, non-functioning pituitary adenoma, recovery from subacute thyroiditis, TSH-secreting adenoma

Subclinical Hypothyroidism

- Elevated TSH, normal FT4
- Prevalence: 4.3%
- Progression to overt hypothyroidism 5% per year
- TSH 2.5-4.5: treatment improves lipids, intima media thickness, endothelial dysfunction, but *no* data on outcomes

Treatment of Hypothyroidism

- Take on empty stomach 30 min before breakfast or 4 hours after dinner
- May be subtle differences in bioavailability between brands and generics, best to stick with the same formulation
- Full replacement dose: 1.6mcg/kg; more correlated to lean mass than total body weight
- Start with 25-50mcg in elderly or CVD patients
- 16% Hashimoto's patients have type 2 deiodinase deficiency, may benefit from T4/T3 combination
- May need dose adjustments with OCP, pregnancy, menopause

Drugs Affecting Thyroid Function

Drugs that cause hypothyroidism, hyperthyroidism, or changes changes in thyroid function tests

Drugs causing hypothyroidism
Inhibition of thyroid hormone synthesis and/or release - thionamides, lithium, perchlorate, aminoglutethimide, thalidomide, and iodine and iodine-containing drugs including amiodarone, radiographic agents, expectorants (Organidin, Combid), kelp tablets, potassium iodine solutions (SSKI), Betadine douches, topical antiseptics
Decreased absorption of T4 - cholestyramine, colestipol, colesevelam, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole, and possibly other medications that impair acid secretion, sevelemer, lanthanum carbonate, and chromium; malabsorption syndromes can also diminish T4 absorption
Immunedysregulation - interferon-alfa, interleukin-2, alemtuzumab
Suppression of TSH - dopamine
Possible destructive thyroiditis - sunitinib
Increased type 3 deiodination - sorafenib
Increased T4 clearance and suppression of TSH - bexarotene
Drugs causing hyperthyroidism
Stimulation of thyroid hormone synthesis and/or release - iodine, amiodarone
Immunedysregulation - interferon-alfa, interleukin-2, ipilimumab, alemtuzumab
Drugs causing abnormal thyroid function tests without thyroid dysfunction
Low serum TBG - androgens, danazol, glucocorticoids, slow-release niacin (nicotinic acid), l-asparaginase
High serum TBG - estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane
Decreased T4 binding to TBG - salicylates, salsalate, furosemide, heparin (via free fatty acids), certain NSAIDs
Increased T4 clearance - phenytoin, carbamazepine, rifampin, phenobarbital
Suppression of TSH secretion - dobutamine, glucocorticoids, octreotide
Impaired conversion of T4 to T3 - amiodarone, glucocorticoids, contrast agents for oral cholecystography (eg, iopanoic acid), propylthiouracil, propanolol, nadolol

T4: thyroxine; TSH: thyroid-stimulating hormone; TBG: thyroxine-binding globulin; NSAIDs: nonsteroidal anti-inflammatory drugs; T3: triiodothyronine.

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Bioidential Thyroid Hormones

- Dessicated thyroid hormone: naturethroid, armour thyroid
  - Porcine extracts cleaned of connective tissue
  - Supraphysiologic ratio of T4/T3
    - Humans: 14:1
    - Pigs: 4:1
- Crossover study of dessicated thyroid vs. LT4
  - No difference in physiologic or psychologic parameters
  - Significant difference in weight loss (mean 3 lbs)

Iodine Supplements

- RDA 150mcg/day, 250mcg/day pregnancy
- Kelp-containing supplements: up to 9x RDA
- Na/I symporter highly regulated based on dietary supply
- Wolff-Chiakoff effect
- Jod-Basedow effect
- AACE guidelines: “No data support the role of iodine in enhancing thyroid function”

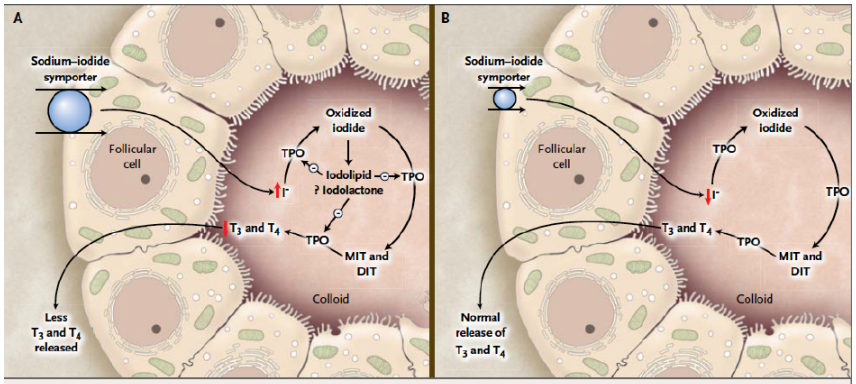
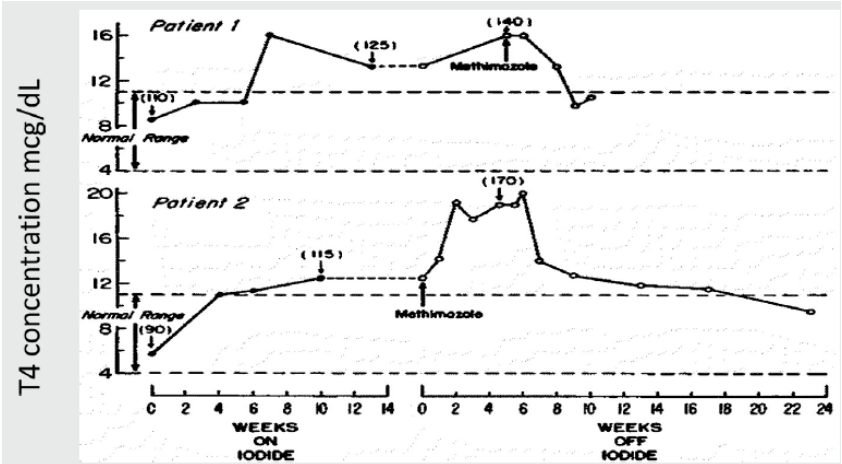


Figure 1. The Wolff–Chaikoff Effect.
Panel A shows a proposed mechanism of the acute Wolff–Chaikoff effect. During the first day of iodine exposure, the sodium–iodide symporter transports the excess iodine into the thyroid, resulting in transient inhibition of thyroid peroxidase (TPO) and a decrease in thyroid hormone synthesis. Panel B shows the mechanism that turns off the acute Wolff–Chaikoff effect: a dramatic decrease in sodium–iodide symporter expression results in decreased iodine transport and the subsequent resumption of thyroid hormone synthesis. DIT denotes diiodotyrosine, I^- iodide, MIT monoiodotyrosine, T_3 triiodothyronine, and T_4 thyroxine.



Potassium iodide (5 drops SSKI) administration to patients with nontoxic goiter

Other Thyroid Supplements

- Phytoestrogens
  - Subclinical hypothyroidism-no difference at 8 wks
- Soy
  - No difference in TFTs at 2 years
- Selenium
  - May decrease anti-TPO Ab
  - No difference on thyroid hormone synthesis in normal population
  - Pregnant patients: decrease in postpartum thyroid dysfunction and incidence of hypothyroidism with selenium supplementation during and after pregnancy

Thyroid Hormone in OTC Supplements

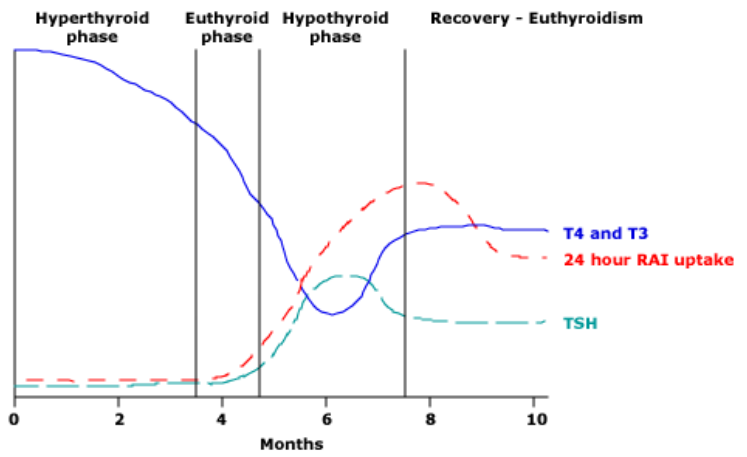
- Porcine or bovine thyroid extracts
- 9/10 supplements have T3 content >10mcg=50% T3 produced/day
- 4/10 supplements have T4 content 8.5-91.6mcg/day
- TRIAC(3,5,3'-triiodothyroacetic acid): metabolite of T4 with metabolic action
  - Binds to T3 receptor, decreases TSH
  - Increased hepatic and skeletal effects compared to T4
  - Banned by FDA but still available online

Case #1 Revisited

- 16 yo F, no PMH, presents with 4-6 months of:
  - Irregular periods
  - 14 lb weight gain
  - Puffy face
  - Fatigue
  - Tongue swelling
  - Decreased concentration, falling asleep in class
  - Unable to keep up with water polo practices
  - Family history: mother and aunt with thyroid disease
- Physical exam
  - BMI 28, 70 kg
  - Periorbital edema
  - Delayed relaxation phase achilles tendon reflex
- Labs
  - TSH 288
  - FT4 0.4
  - TPO Ab >1000
  - Tg Ab >20
- Treatment
  - Levothyroxine 175mcg daily, recheck TSH, FT4 6 weeks
  - Levothyroxine tapered down to 125mcg over the next 12 weeks
  - Lost 12 lbs, menstruation normalized, symptoms improved

Thyroiditis

Characteristic course of thyroiditis (painless, postpartum or subacute)



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.

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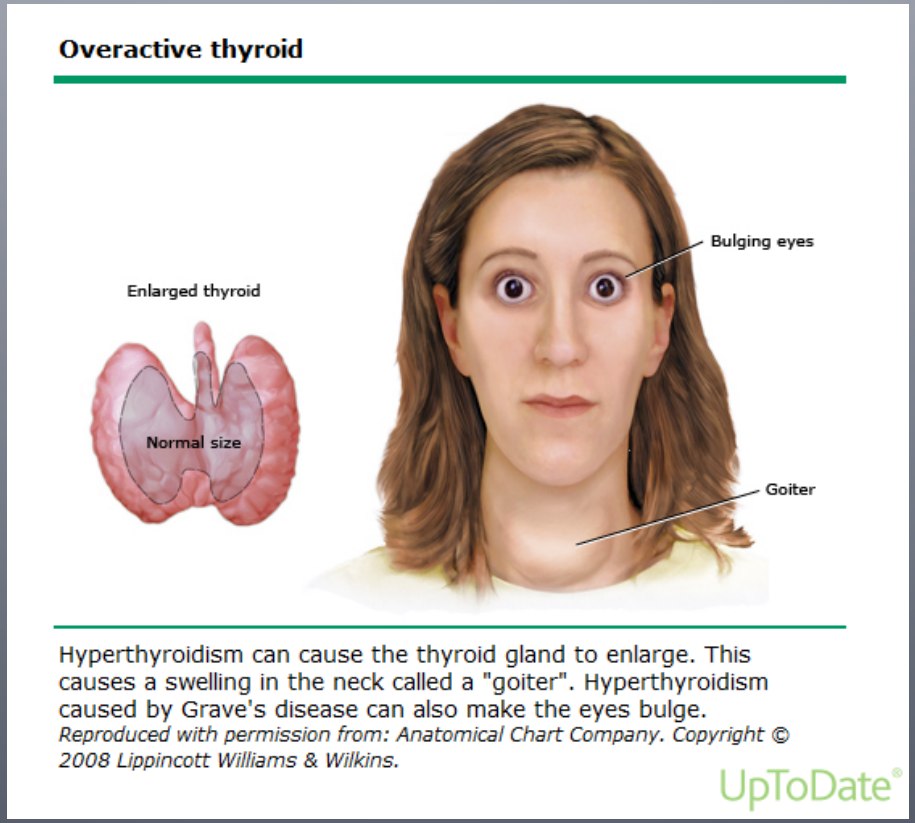
- Thyrotoxicosis: TT3: TT4 >20
- Thyroiditis or iodine excess TT3: TT4<20

Case #2

- 42 yo F, no PMH, presents with:
  - Insomnia
  - Palpitations
  - Excessive sweating
  - Fatigue
  - Dry eyes
  - Mood swings
  - 8 months postpartum, lactating
- Physical exam
  - HR 108
  - Mild proptosis
  - Non-tender, symmetric, firm goiter
  - Fine tremor
- Labs
  - TSH <0.01
  - FT4 5.8
  - TT3 217
  - TPO Ab 270
  - Tg Ab neg
  - TSI 313

Hyperthyroidism



Hyperthyroidism

- Prevalence in US: 1.2%
- Etiology
  - **Graves or Hashitoxicosis (autoimmune)**
  - **Toxic nodular goiter**
  - Subacute or acute thyroiditis
  - Iodine excess
  - Exogenous thryoid hormone
  - Struma ovarii
  - Hyperemesis gravidarum or trophoblastic disease
  - Metastases from follicular thyroid Ca

Presentation of Hyperthyroidism

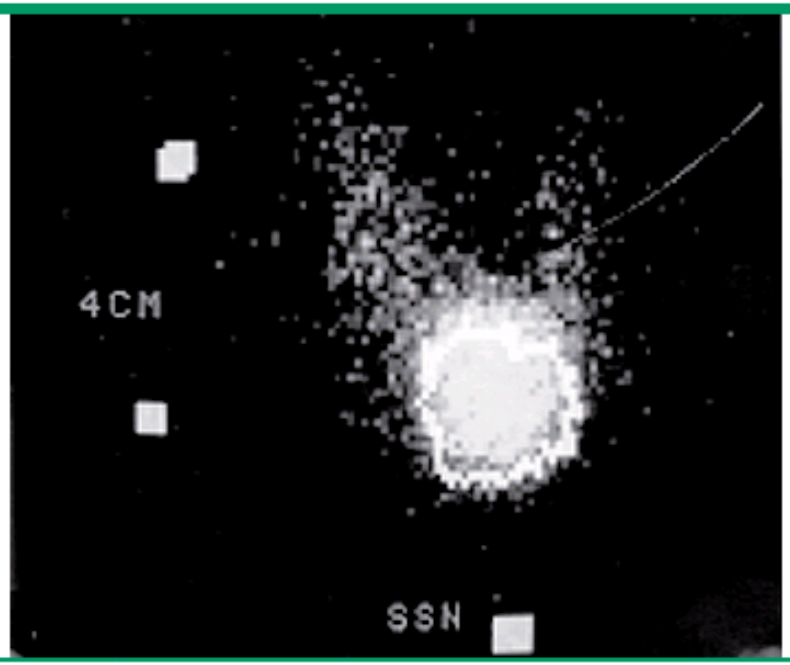
- Symptoms: anxiety, weakness, tremors, **palpitations**, heat intolerance, excessive sweating, **menstrual problems**, hyperdefecation, urinary frequency, insomnia, weight loss, increased appetite, dyspnea, depression, psychosis, **apathy (older patients)**, hair loss
- Signs: **atrial fibrillation**, **osteoporosis**, CHF, hyperglycemia, **lid lag, stare, proptosis**, thyroid bruit, **hyperthermia**, systolic HTN, hyperreflexia, periorbital edema, pretibial myxedema, goiter, elevated AP, onycholysis, normochromic normocytic anemia, gynecomastia

Diagnosis of Hyperthyroidism

- Suppressed TSH (usually undetectable), elevated FT4 and/or TT3
- Thyrotoxicosis: TT3: TT4 >20
- Thyroiditis or iodine excess TT3: TT4<20
- Elevated TSI, elevated TPO or Tg Ab
- Increased radioactive iodine uptake
- DDx for discordant TFTs: thyroid hormone resistance, TSHoma, TBG abnormality, androgens or estrogens, antiepileptics, Ab to T3 or T4, paraneoplastic, non-thyroidal illness

Toxic Nodular Thyroid

Autonomous thyroid nodule: Appearance on thyroid scintigraphy



123-I thyroid scan demonstrating an autonomous ("hot") nodule with suppression of isotope uptake elsewhere. The total 24-hour isotope uptake was normal (12 percent).
SSN: suprastenal notch.
Courtesy of Douglas Ross, MD.

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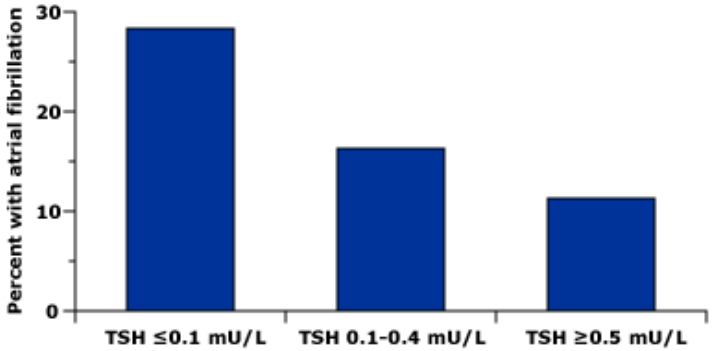
Subclinical Hyperthyroidism

- Prevalence 0.7% (TSH<0.1)
- Most common cause toxic nodular disease
- Progression to overt hyperthyroidism: 6% year 1, 1-25% at 5 years
- Increased risk of cardiac events (HR 1.21), CVD (HR 1.39), CHF (2-3x)
- 20-30% increased RR CV and all-cause mortality
- Treat if TSH <0.1, consider if TSH 0.1-0.5

Increased incidence of atrial fibrillation in subclinical hyperthyroidism



Cumulative incidence of atrial fibrillation in subjects over age 60 according to the serum concentration of thyrotropin (TSH). The risk of atrial fibrillation was increased almost threefold in the subjects with marked suppression of TSH (left panel) as compared with those who had normal serum TSH concentrations and were presumably euthyroid (right panel); patients with slightly low serum TSH concentrations (middle panel) had a lesser increase in risk.
Data from: Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331:1249.

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Treatment of Hyperthyroidism

- **Beta-blockers**
- Thionamides
  - Methimazole
  - Propylthiouracil
  - Remission in 30-50% after 18 months
- Radioactive iodine ablation
- Thyroidectomy
- Refractory disease: iodinated contrast, glucocorticoids, lithium, cholestyramine rituximab

Case #2 Revisited

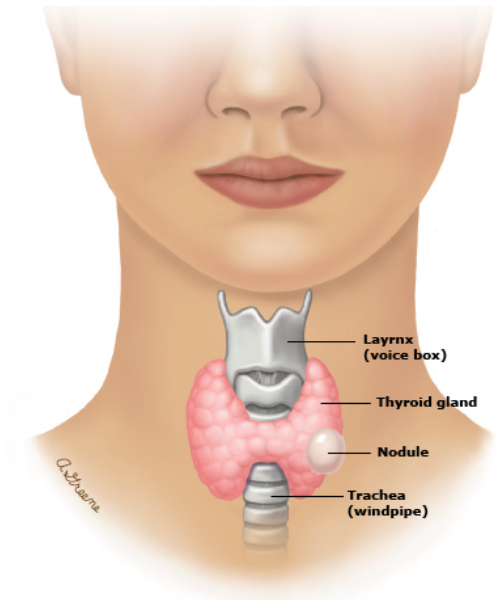
- 42 yo F, no PMH, presents with:
  - Insomnia
  - Palpitations
  - Excessive sweating
  - Fatigue
  - Dry eyes
  - Mood swings
  - 8 months postpartum, lactating
- Physical exam
  - HR 108
  - Mild proptosis
  - Non-tender, symmetric, firm goiter
  - Fine tremor
- Labs
  - TSH <0.01
  - FT4 5.8
  - TT3 217
  - TPO Ab 270
  - Tg Ab neg
  - TSI 313
- Treatment
  - Methimazole 10 BID→20 daily, propranolol 10-20mg TID PRN
  - Methimazole tapered down to 5 daily over the next 3 months, propranolol stopped
  - Goiter shrunk, lost 5 lbs, improvement in symptoms

Case #3

- 72 yo F, h/o HTN, osteoporosis, osteoarthritis, p/w 2-3 months right neck lump, discomfort with swallowing
  - 3cm right-sided thyroid nodule on exam
- Workup
  - TSH 2.46
  - Thyroid US: 3.6cm mixed solid/cystic nodule taking up most of the right thyroid lobe, no LN
  - US-guided FNA: benign
  - Right hemithyroidectomy-follicular thyroid cancer, 3.9cm tumor, no invasion, no LN
  - Left completion thyroidectomy-normal thyroid

Thyroid Nodules

Thyroid nodule



This figure shows a thyroid nodule on the left side of the thyroid. Thyroid nodules feel round or oval-shaped, and differ from the surrounding normal thyroid tissue. A person may have one or more thyroid nodules.

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Thyroid Nodules

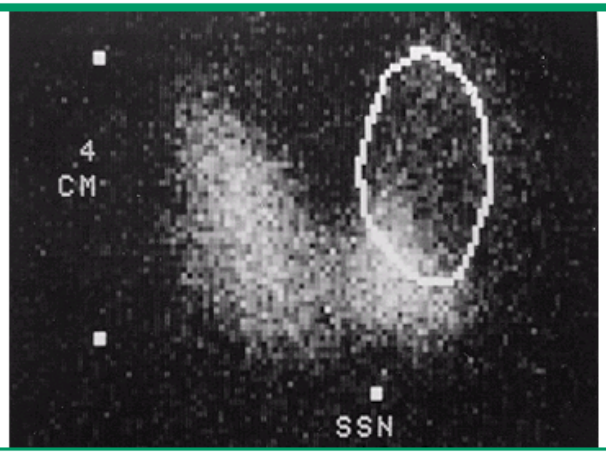
- US: annual incidence 0.1%
- Risk increases 2-3x every half decade above age 25
- Risk of malignancy 5-10%
- Higher risk of nodules in women, but higher risk of malignancy in men
- Risk factors for thyroid cancer: 1st degree FHx, head/neck radiation, compressive symptoms, high TSH, familial syndrome, rate of nodule growth

Indications for biopsy

- Suspicious US features: hypoechoic, increased vascularity, irregular margins, microacalcifications, absent/irregular halo, taller than deeper, cervical lymph nodes, invasion of muscle
- Mixed cystic/solid nodule
  - <1cm with risk factors, suspicious features
  - 1.5-2cm with suspicious features
  - >2cm
- Rapid growth, compressive symptoms
- Purely cystic-almost always benign, no need to biopsy
- Cold nodule on thyroid scan

Suspicous Nodules

Nonfunctioning thyroid nodule: Appearance on thyroid scintigraphy



123-I thyroid scan demonstrating typical appearance of a large, 3.5 cm hypofunctioning ("cold") nodule in the left upper lobe of the thyroid. The position of the nodule is outlined in white.
SSN: suprasternal notch.
Courtesy of Douglas Ross, MD.

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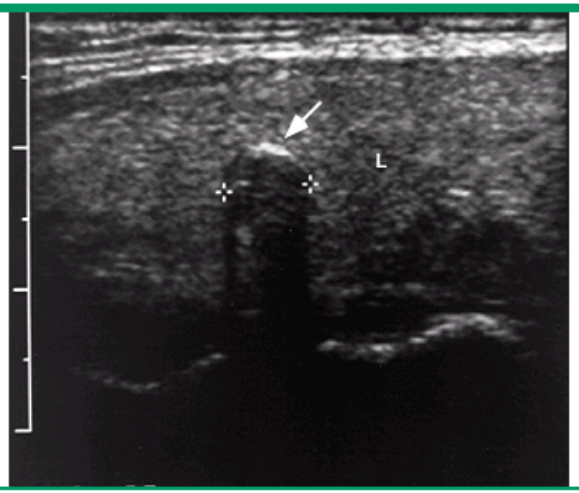
Thyroid calcification



Sonogram of the right lobe of the thyroid gland in the longitudinal plane that shows a dense bright arc (arrow), which is a coarse calcification. Blockade of the ultrasound signal distally produces shadowing.
L: thyroid lobe.
Courtesy of Manfred Blum, MD.

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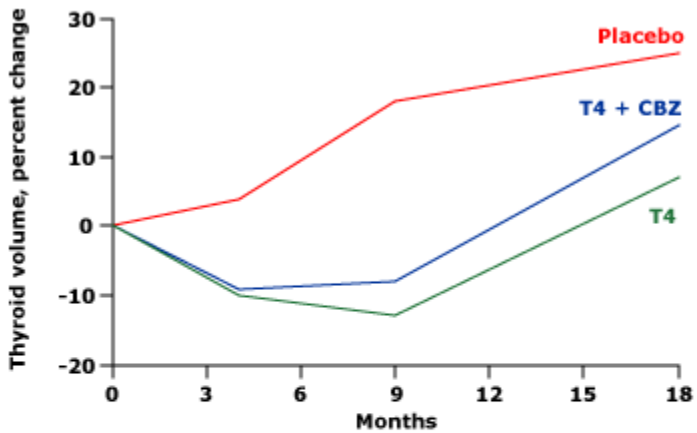
Suppressive Therapy for Nodules

Thyroxine suppresses goiter growth



Relative changes in thyroid volume in patients with nontoxic goiter treated with placebo, thyroxine (T4) plus carbamizole (CBZ), or thyroxine alone for nine months and then followed for an additional nine months. Thyroxine suppressed thyroid volume, an effect that persisted only during the phase of active treatment. Carbimazole was of no added benefit.

Data from: Berghout A, Wiersinga WM, Drexhage HA, et al. Comparison of placebo with L-thyroxine alone or with carbimazole for treatment of sporadic non-toxic goitre. Lancet 1990; 336:193.

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Summary

- Functional thyroid disease is common
  - Screen with TSH
  - When to refer to endocrinology
    - Severe symptoms
    - Unable to achieve euthyroidism with standard treatment
    - Discordant thyroid function tests
    - Consideration for radioactive iodine treatment
- Thyroid nodules risk increases with age
  - Most are benign
  - When to refer to endocrinology
    - Suspicious findings on ultrasound
    - Compressive symptoms

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