



Management of Thyroid Disorders: A Case Bases Approach

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Best Practices Pearls



- Have a low threshold to test for thyroid disease
- Treatment of both subclinical and overt disease should be individualized and monitored
- Manage issues around variable therapeutic equivalence of levothyroxine products
- Appropriately counsel, screen, and monitor thyroid function in pregnancy to improve outcomes

Case Study: Grace

- Grace is a 43 year old WF with a swelling in her neck for ~6 weeks. She has noticed a recent onset of myalgias, fatigue, hair loss, weight gain, and dry skin. She also noticed thinning of the lateral third of her eyebrows. Past medical history is remarkable for hyperlipidemia.

Case Study: Grace

- Physical Exam
 - Height: 5'7"
 - Weight: 160 lbs
 - BMI: 25.1
 - BP 132/84 P 76
 - Thyroid smooth, diffusely, enlarged, non-tender
 - TSH 7.45 (0.5-4.5) Free T4: 1.2 (0.8-1.8)

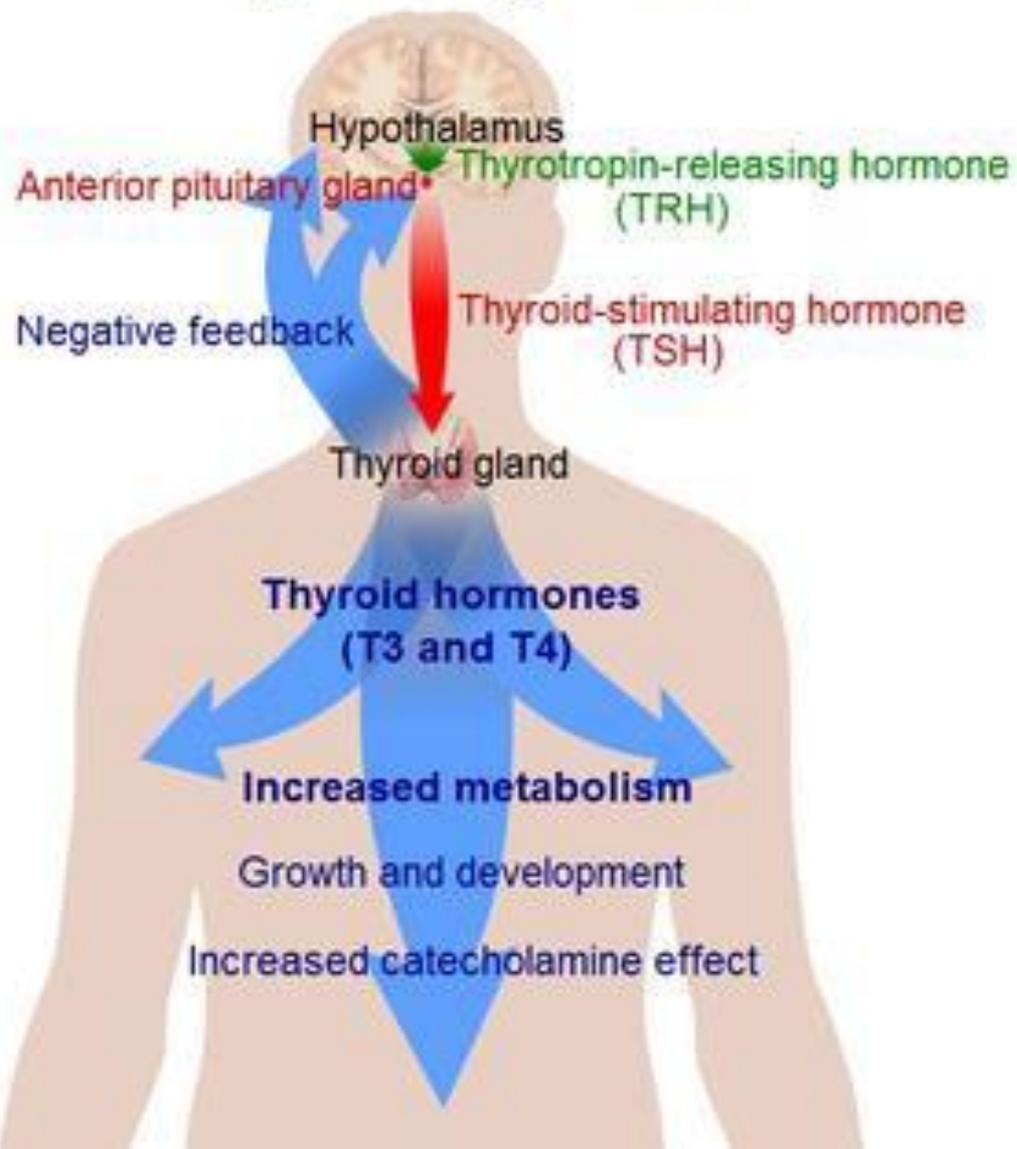
Case Study: Grace

- Is the patient hypothyroid?
- Are additional tests necessary?
- Should she be treated with thyroxine?
- If treatment is initiated, what dose should be initiated?
- What are the potential benefits of treatment?

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Physiology

Thyroid system



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Definitions and Diagnosis

Definitions and Diagnosis Underactive

- Hypothyroidism
 - Primary: high serum thyrotropin (TSH) and a low serum free thyroxine (FT4)
 - Secondary and Tertiary (central): low FT4 and TSH not elevated
- Subclinical Hypothyroidism
 - Only an elevated TSH with a normal FT4 level
- Both overt and subclinical disease can be symptomatic

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Prevalence

Prevalence

NHANES III: 13,344 people (54% female) without known thyroid disease had TSH, T4, thyroglobulin antibodies, and thyroid peroxidase antibodies measured

- Hypothyroidism in 4.6% (0.3% overt and 4.3% subclinical)
- Hyperthyroidism was found in 1.3% (0.5% overt and 0.7% subclinical)
- Serum thyroid peroxidase antibody concentrations elevated in 11%

Higher Prevalence in 70-79 Year-Olds

Hyperthyroidism and Hypothyroidism Study Results

	Hyperthyroidism	Hypothyroidism
Black women	9.7%	6.2%
White women	6.0%	16.5%
Black men	3.2%	1.7%
White men	2.2%	5.6%

- 3 to 8 times more common in women than men
- Mean TSH is lower in blacks than whites or Hispanics
- Mean TSH rises as we age

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Etiology

Etiology of Hypothyroidism

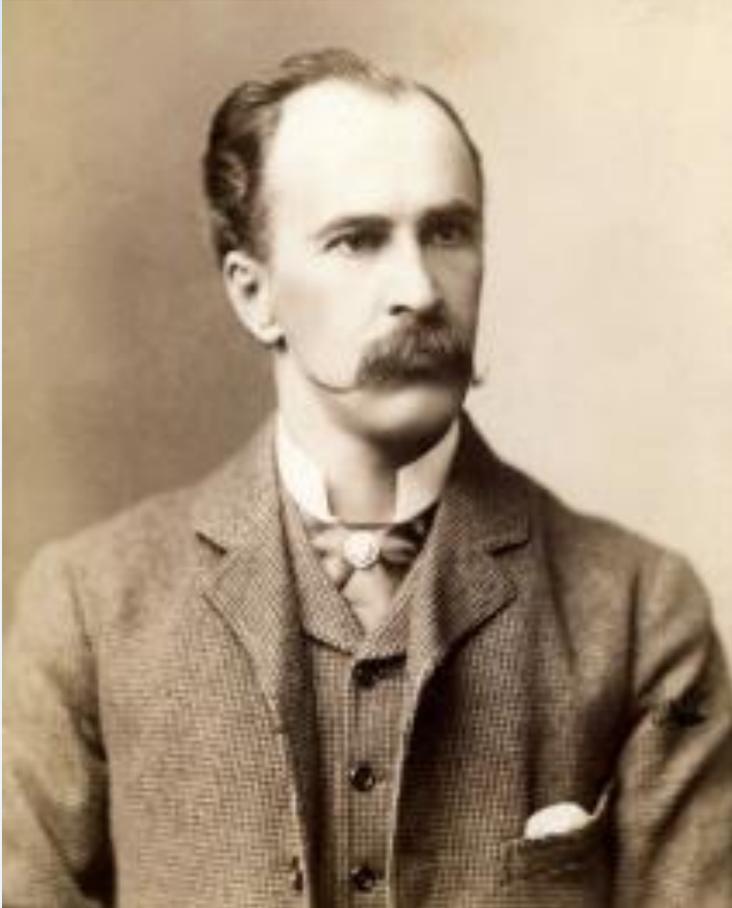
- Hashimoto's Thyroiditis (Chronic Lymphocytic Thyroiditis)
 - Most common in USA
 - Historic Note: 1st discovered Auto-Immune Disorder
 - Diagnosed with antithyroid peroxidase (antiTPO) antibodies or antimicrosomal antibodies (AMA)
- Post Treatment Graves' Disease
 - No function after radiation or surgery
- Iodine Deficiency
 - Most common worldwide associated with a goiter
 - Rare in North America, but (?) re-emergence with "natural" salt
- Hypothalamic-pituitary Disease (secondary or central)

Hypothyroidism Symptoms

Hypothyroidism and Subclinical Hypothyroidism Signs & Symptoms

• Fatigue	• Memory and mental impairment
• Weight gain from fluid retention (but usually not morbid obesity)	• Decreased concentration
• Dry skin and cold intolerance	• Depression
• Yellow skin	• Irregular or heavy menses and infertility
• Coarseness or loss of hair	• Myalgias
• Hoarseness	• Hyperlipidemia
• Goiter	• Macrocytic anemia
• Reflex delay, relaxation phase	• Bradycardia and hypothermia
• Ataxia	• Myxedema fluid infiltration of tissues
• Constipation	• Carpal Tunnel Syndrome

Sir William Osler

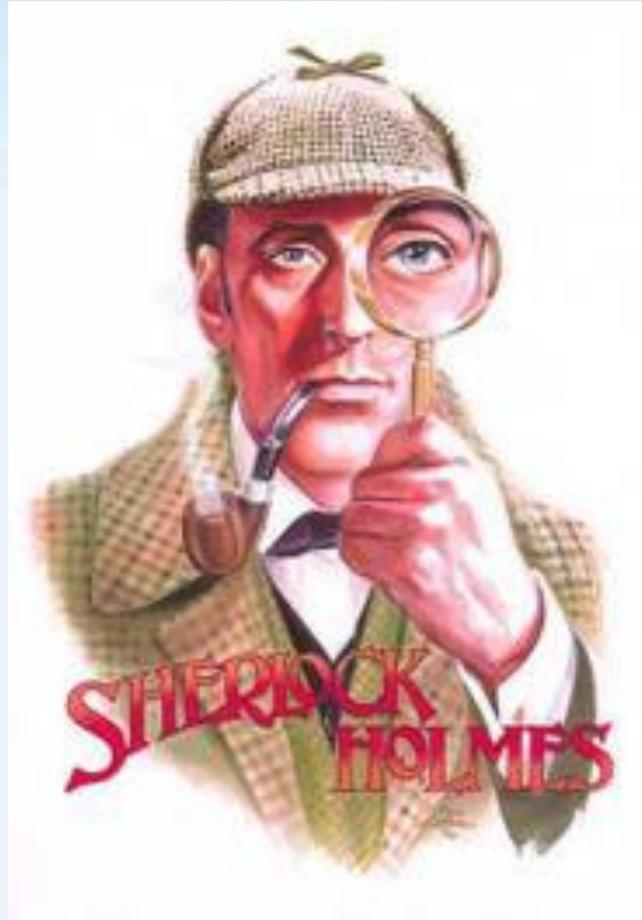


Listen to the patient. They are telling you the diagnosis

- Walked into muggy ward when the yet to be examined new patient was not in her bed
- Asked the students: “Where is the hypothyroid patient?”
- How did he diagnose the unseen, unmet patient?

The Model for Sherlock Holmes?

Sir William Osler



The Model for Sherlock Holmes?

Listen to the patient. They are telling you the diagnosis

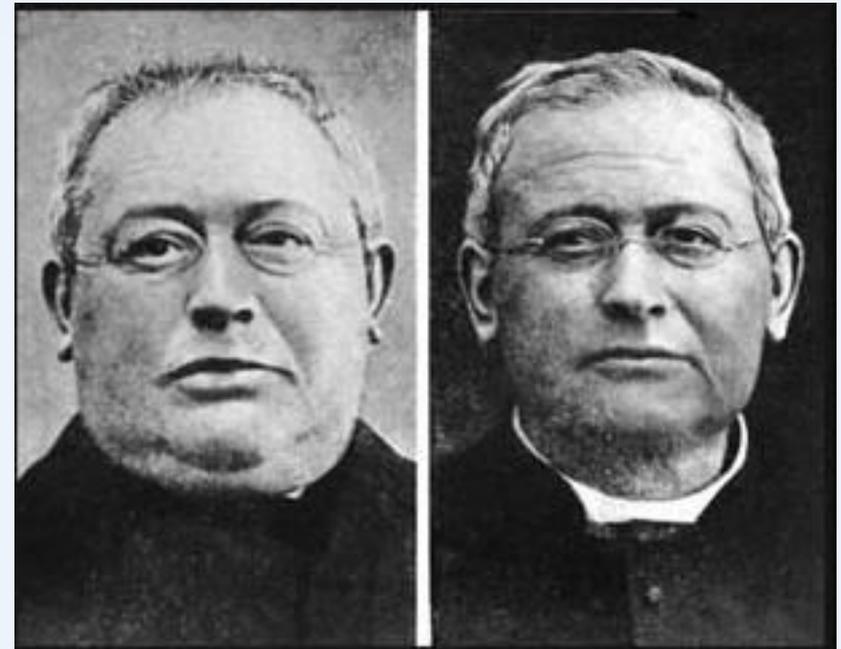
- Walked into muggy ward when the yet to be examined new patient was not in her bed
- Asked the students: "Where is the hypothyroid patient?"
- How did he diagnose the unseen, unmet patient?
 - Extra Blankets
 - Bed undisturbed
 - Hairs and flaked skin on the pillows
 - Clothes suggested obesity

Elementary, my dear Watson...

Hypothyroidism Work-Up

- History
 - Radiation and Surgery
 - Infections
 - TB, Pneumocystis carinii
 - Infiltrative Disease
 - Riedel's, leukemia, scleroderma, hemochromatosis
 - Meds
 - Lithium
 - Prednisone
 - Metformin
 - Androgens and Anabolic Steroids
 - Heparin
 - Tyrosine Kinase Inhibitors
 - Interferon, Interleukin
 - Amiodarone (3mg per 100mg)

Pre and Post Treatment



Hypothyroidism Work-Up

- Physical
 - +/- Goiter
 - Slowed movement and speech
 - Hoarse voice
 - Bradycardia
 - Carotenemia
 - Hung deep tendon reflex
 - Coarse skin
 - Puffy eyes and face
 - Enlarged tongue
 - Galactorrhea
 - Diastolic Hypertension



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Work-Up

Hypothyroidism Work-Up

➤ Lab

➤ TSH, FT4

➤ No need to check thyroid antibodies

➤ CBC, CMP, lipids

➤ Imaging

➤ No need for thyroid imaging unless abnormal palpations or pain

➤ No need of pituitary MRI unless signs of central hypothyroidism (<1%)

Controversy

Hypothyroidism and Subclinical Hypothyroidism

- Decision to treat subclinical disease is controversial and should be individualized
 - Recommended if TSH > 10 or patient is symptomatic
 - Individual decision when no symptoms of TSH only slightly elevated
- Levothyroxine (LT₄) is the recommended replacement
- Average replacement dose is 112 mcg/daily or 1.6 mcg/Kg/day

Special Cases and Considerations

Hypothyroidism and Subclinical Hypothyroidism

- In some older patients and those with CAD start at 25 or 50 mcg as T4 increases myocardial O₂ demands and risk of angina and arrhythmia
- Take on empty stomach (ideally 1 hour before breakfast)
- Coffee, antacids, and calcium interfere with absorption

Hypothyroidism and Subclinical Hypothyroidism

- Patients may feel better as soon as two weeks, but it can take months
- Changes are often incremental, not dramatic
- Takes 6 weeks to see blood levels change
- FT4 rises first, TSH is slower to fall
- Recheck FT4 and TSH at 6 weeks
- If still sub-therapeutic, increase by 12.5 or 25 mcg, and recheck every 6 weeks
- Once stable, check every 6 months for first year, then annually

Controversy T3 and “Natural” Therapy

Arguments **PRO** and **CON** for T3 Supplementation

- The thyroid produces both T3 and T4
- LT4 therapy has no T3
- Patients on T4 alone have higher than normal T4/T3 ratios
- Peripheral conversion of T4 to T3 may be inadequate in some patients → tissues have deficient T3 level
- So is T4 monotherapy = “Tissue hypothyroidism”
- BUT T3 has short half life, may need extended release
- Data doesn't support use of T3 or desiccated thyroid

Controversy

T3 and “Natural” Therapy

- N Eng J Med 1999
 - Mood better with T3: 7 of 8 tests $P < 0.04$
 - No difference in:
 - Neuropsychological tests
 - BP and serum lipids
- Eur J Endocrinol 2009
 - 49% preferred combination of T4 and T3; 15% T3 alone; 36% had no preference

Bunevicius R, et al. *NEJM*. 1999;340:424-429.

Wiersinga WM. *Eur J Endocrinol*. 2009;161:955-959.

Controversy

T3 and “Natural” Therapy

- But no benefit demonstrated in over nine studies¹
- Meta-analysis of >1,200 patients randomized to LT4 monotherapy² or combination therapy with T3 showed no difference in body pain, depression, lipids, anxiety, fatigue, quality of life, body weight

¹Levitt A, et al. *T4 plus T3 treatment for hypothyroidism: a double-blind comparison with usual T4*. 74th Annual Mtg of the American Thyroid Association. Los Angeles, CA, Oct 10, 2002; Walsh JP, et al. *J Clin Endocrinol Metab*. 2003;88:4543-4350; Sawka AM, et al. *J Clin Endo Metab*. 2003; 88:4551-4555; Cassio A, et al. *Pediatrics*. 2003;111:1055-1060; Clyde PW, et al. *JAMA*. 2003; 290:2952-2958; Siegmund W, et al. *Clin Endocrinol (Oxf)*. 2004;60:750-757; Saravanan P, et al. *J Clin Endo Metab*. 2005;90:805-812; Appelhof BC, et al. *J Clin Endo Metab*. 2005;90:2666-2674; Escobar-Morreale HF, et al. *Ann Int Med*. 2005;142:412-424; Ma C, et al. *Nucl Med Commun*. 2009;30:586-593.

²Grozinsky-Glasberg S, et al. *J Clin Endocrinol Metab*. 2006;91:2592-2599.

Controversy

T3 and “Natural” Therapy

- 1891: Dr. George Murray 1st used sheep thyroid extract to successfully treat his patient with myxedema for 28 years
- Same issues with naturally desiccated thyroid or NDT (a mixture of T3 and T4 made from porcine or beef thyroid glands) as with T3
- Must use TSH for monitoring
- NDT contains all thyroid hormones: T4, T3, T2, T1,, and calcitonin which is present in natural thyroid and usually lacking after total thyroidectomy, which removes the parathyroid glands
- Synthetic T4 alone is the recommended therapy by AACE as there is no proven evidence of benefit with NDT
- Daily dose of 100 µg of LT4 = biologic activity to 101 mg of NDT

Protein Binding

- Thyroid hormone is highly protein-bound, so changes in the amount of binding protein and drugs that compete for binding change the amount of active free thyroid hormone
- The thyroid replacement dosage must be changed in response to alterations in binding status
- **HIGHT BINDING:** High estrogen states (pregnancy, oral contraceptive use, or postmenopausal estrogen replacement), so the dose of LT4 must be increased
- **LOW BINDING:** Low androgens, nephrosis, protein-losing enteropathies, cirrhosis, and aging may decrease levels of thyroid binding proteins, and so require a reduced dose

Drug Interactions

Multiple Complex Mechanisms of Actions

- Iodine and iodine-containing drugs such as radiographic contrast (may cause both hypothyroidism and hyperthyroidism weeks later)
- Lithium (therapeutic levels cause thyroid enlargement in half the patients and hypothyroidism in 20%, but may also cause hyperthyroidism)
- Oral tyrosine kinase inhibitors (blocks clearance)
- Proton pump inhibitors
- Concomitant use of calcium, iron, and bile acid sequestrates

Drug Interactions

Multiple Complex Mechanisms of Actions

- Selective estrogen receptor modulators (SERMs), anabolic steroids, and glucocorticoids (decrease protein binding so dose may need to be reduced)
- Amiodarone (multiple causes for both hypothyroidism and hyperthyroidism)
- Phenobarbital, rifampin, phenytoin, and carbamazepine (increase the metabolism of both T4 and T3 so patients on T4 supplementation may need higher dosages)
- Beta adrenergic antagonists including high-dose propranolol (inhibit T3 production)
- NSAIDs including salicylates, heparin, and furosemide (decrease T4 binding)
- Dopamine (suppresses TSH)

Case 1 Answers

- Is the patient Hypothyroid?
 - Elevated TSH and normal T4 is consistent with subclinical hypothyroidism
- Are additional tests necessary?
 - TPO antibodies could be ordered but are not necessary for treatment
- Should she be treated with thyroxine?
 - The patient has symptoms of fatigue, weight gain, hyperlipidemia
- If treatment is initiated, what dose should be started?
 - May start with 5-50 mcg per day, although full dose replacement could be used. TSH should be repeated in 5-6 weeks

Thyroid Preparation

- Levothyroxine-T4 *Preferred Therapy*
- Liothyronine-T3 (Cytomel)
- Liotrix-4:1 mixture T4 and T3 (Thyrolar)
- Thyroid USP-Dessicated thyroid extract (Armor Thyroid)

Case Study: Jonathan

- Jonathan is a 66 year old African-American male with a history of palpitations, fatigue, and tremor. He has a history of coronary artery disease and hyperlipidemia.

Case Study: Jonathan

- Physical Exam and Lab Findings
 - Height: 5'7"
 - Weight: 188 lbs
 - BMI: 29.4
 - BP 142/72 P 112
 - TSH <0.1 Free T4 and T3 wnl
 - Temp 97.8F
 - PE normal except for fine tremor of hands

Case Study: Jonathan

- Is the patient hyperthyroid?
- Are additional tests necessary?
- If indicated, what treatment is necessary?
- What are the potential benefits of treatment?

Definitions and Diagnosis Overactive

- Hyperthyroidism
 - Usually **excess production** of free thyroid hormones (either T3 or T4 or both) in serum with suppressed HS-TSH or highly sensitive (3rd generation) TSH (<0.01mU/L)
- Thyrotoxicosis includes hyperthyroidism but also **excess release** of hormone in thyroiditis or excess exogenous T4
- Subclinical Hyperthyroidism (SH)
 - Low or undetectable (HS-TSH) but normal range for both triiodothyronine (T3) and free thyroxine (FT4)
- Both overt and sub-clinical disease may lead to characteristic signs and symptoms

Etiology of Hyperthyroidism

- Graves' Disease
 - Most common
 - Auto-immune: long acting thyroid stimulating antibodies (LATS)
- Thyroid Nodules
 - "Toxic: nodules (becoming autonomous)
 - Benign or malignant, single or multiple
 - Toxic nodular goiter- most common cause in the elderly

Etiology of Hyperthyroidism

- Excessive Thyroid Supplementation
 - Iatrogenic
 - Exogenous
- Thyroiditis (excessive release, not production)
 - Early Hashimoto's, radiation, palpation, post partum
- Rare Causes: pituitary adenoma, teratomas

Etiology of Subclinical Hyperthyroidism Exogenous

- 10 million Americans and 200 million worldwide take thyroid hormone
- All are at risk for subclinical hyperthyroidism, whether intentional or unintentional
- In patients on LT4 (levothyroxine), up to 25% may have low TSH
 - Associated with lower bone density
 - Associated with atrial fibrillation
- BUT subclinical hyperthyroidism is the goal of thyroid hormone therapy in thyroid cancer, in some thyroid nodules, multinodular or diffuse goiters, or a history of head and neck irradiation

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Symptoms

Hyperthyroid Symptoms

Overt Hyperthyroidism and Subclinical Hyperthyroidism Signs & Symptoms

• Nervousness and irritability	• Exertional intolerance and dyspnea
• Palpitations and tachycardia	• Menstrual disturbance (decreased flow)
• Heat intolerance or increased sweating	• Impaired fertility
• Tremor	• Mental disturbances (anxiety)
• Weight loss	• Sleep disturbances (including insomnia)
• Alterations in appetite	• Changes in vision, photophobia, eye irritation, diplopia, or exophthalmos (with Graves' disease)
• Frequent bowel movements or diarrhea	• Fatigue and muscle weakness
• Dependent lower extremity edema	• Thyroid enlargement (depending on cause)
• Sudden paralysis	• Pretibial myxedema (in patients with Graves' disease)

Hyperthyroidism Work-Up

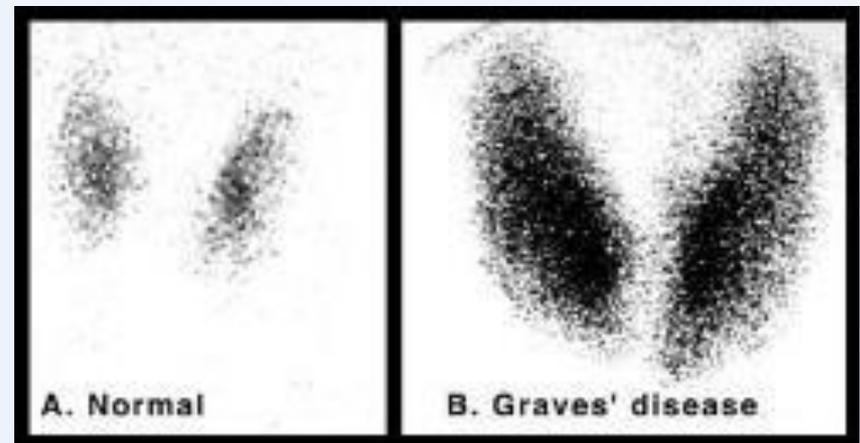
- History
 - Thyroiditis including trauma
 - Meds
 - Amiodarone
 - Iodine
- Physical
 - Hyperactivity and rapid speech
 - Stare (lid retraction) and lid lag
 - Sweaty
 - Fine hair
 - Tachycardia and Atrial Fibrillation
 - Hypertension
 - Hyperreflexia
 - Muscle weakness
 - Tremor
- Thyroid
 - Size, nodularity, tenderness



Hyperthyroidism Work-Up

- Lab
 - 3rd generation TSH (<0.05 mU/L)
 - T4 (RIA), FT4, T3 (RIA), FT3
 - CBC, CMP including alkaline phosphatase
- Imaging
 - Radioiodine uptake and scan
 - If high, increased production such as Graves' or nodule(s)
 - If low, thyroiditis or source is outside of thyroid (struma ovarii or exogenous)

Radioiodine Scan



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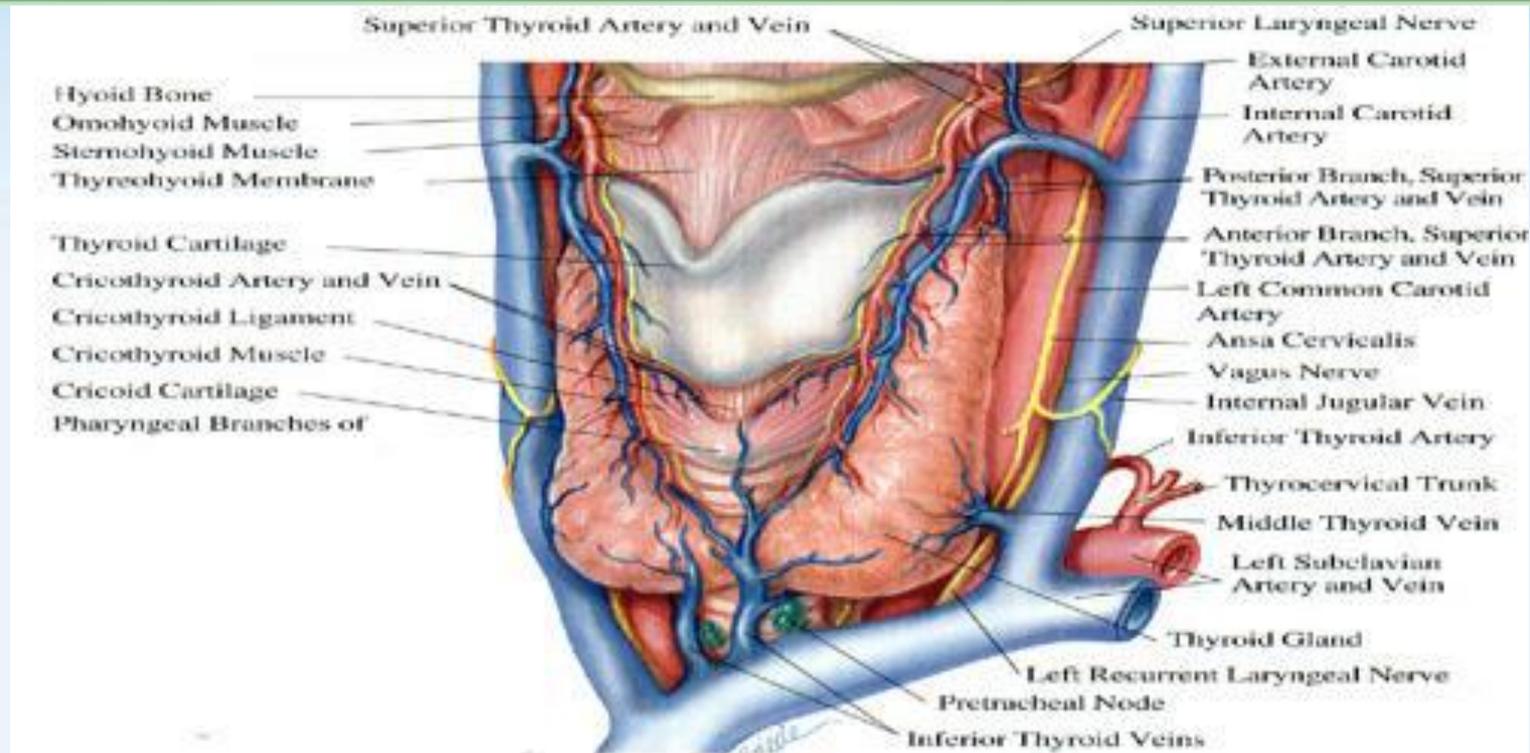
Treatment

Graves' Disease Treatment

Two Step Process

- >95% satisfaction with all three therapy choices, but relapse risk higher with med
- **1st STEP:** Rapid amelioration of symptoms with a beta blocker
 - Palpitations, tachycardia, anxiety, tremor, heat intolerances
- **2nd STEP:** Decreasing thyroid hormone synthesis
 - 1.) Thionamide
 - Methimazole and propylthiouracil (PTU)
 - Inhibit the enzyme thyroid peroxidase
 - 3-8 weeks to work, often a step before permanent ablation, but may be well tolerated long term, 37% relapse
 - 2.) Radioiodine
 - 60% of endocrinologists prefer to treat with a capsule of I131
 - 6-18 weeks to work, worsening of Graves' ophthalmopathy, 21% relapse
 - 3.) Surgery
 - 1% use, lowest relapse (6%), surgical risk (recurrent laryngeal nerve injury)
 - Obstructive goiter or suspicious nodule, ophthalmopathy, contraindications to meds or radioiodine

Anatomy Review



In 1866, Samuel David Gross said, "If a surgeon should be so foolhardy as to undertake it [thyroidectomy] ... every step of the way will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery."

Controversy

Subclinical Hyperthyroidism Treatment

- Treat as high risk patient
 - >65 years old
 - Heart disease
 - Osteoporosis
- Treat as low risk if TSH value is <0.1 mU/mL
- Same treatment options as in Graves'

Faber J, et al. *Eur J Endocrinol.* 2001;145:391-396.

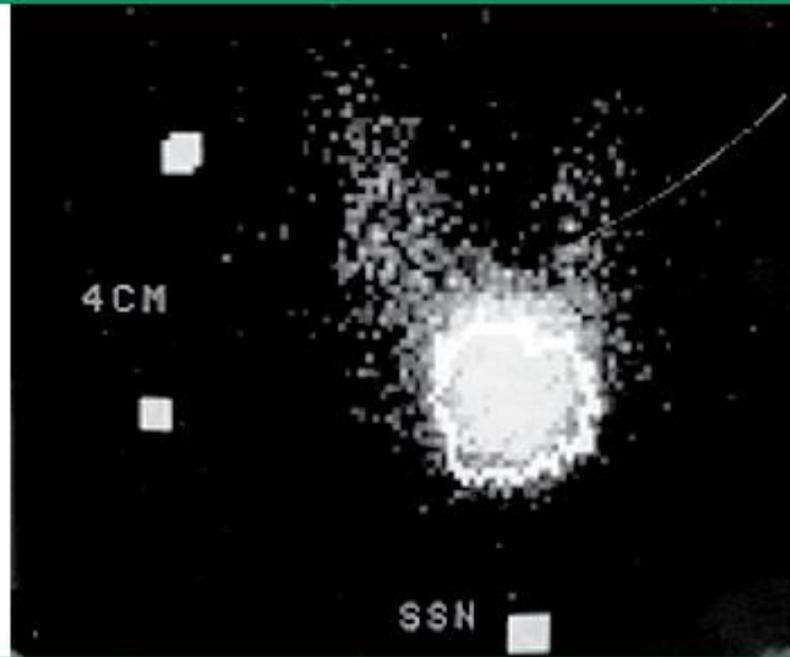
Mudde AH, et al. *Clin Endocrinol. (Oxf)* 1994; 41:421-424.

Faber J, et al. *Clin Endocrinol. (Oxf)* 1998;48:285-290.

Clinical Questions Case 2

- Is the patient hyperthyroid?
 - TSH low with normal T3 and T4 indicating subclinical hyperthyroidism
- Are additional tests necessary?
 - Yes, thyroid uptake scan, CBC, CMP
 - Thyroid scan consistent for autonomous functioning adenoma
- If indicated, what treatment is necessary?
 - Same as for hyperthyroidism

Autonomous thyroid nodule: Appearance on thyroid scintigraphy



¹²³I thyroid scan demonstrating an autonomous ("hot") nodule with suppression of isotope uptake elsewhere. The total 24-hour isotope uptake was normal (12 percent).

SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.

Graphic 79487 Version 3.0

Clinical Questions Case 2

- What are the potential benefits of treatment?
 - Treatment indicated to prevent Atrial fibrillation and osteoporosis

ATA/AACE Guidelines for Treatment of Subclinical Hyperthyroidism (suppressed TSH, normal T4/T3)

Factor	TSH (<0.1 mU/L)	TSH (0.1-0.5 mU/L)
Age >65	Yes	Consider treating
Age <65 with Comorbidities		
Heart Disease	Yes	Consider treating
Osteoporosis	Yes	No
Menopausal	Consider treating	Consider treating
Hyperthyroid Symptoms	Yes	Consider treating
Age <65, Asymptomatic	Consider treating	No

Clinical Considerations: Age adjusted TSH

- Normal TSH (0.4-4)
 - 70yo (5.9-7.5)
 - > 90yo (6.5-7)

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Pregnancy

Pregnancy

- Maternal and fetal hypothyroidism associated with risks to fetal neural development
- Maternal hypothyroidism at increased risk for anemia, myopathy, congestive heart failure, preeclampsia, placental abnormalities, low birth weight, and postpartum hemorrhage
- Maternal thyrotoxicosis is associated with fetal tachycardia, fetal hyperthyroidism, small for gestational-age babies, prematurity, preeclampsia, and stillbirths

Huang SA, et al. *J Clin Endocrinol Metab.* 2003;88:1384-1388.

Kester MH, et al. *J Clin Endocrinol Metab.* 2004;89:3117-3128.

Pregnancy is a “Thyroid Stress Test”

- Thyroid increases 10% to 15% during pregnancy in patients who live in countries with adequate iodine, and by 20% to 40% where there is an iodine deficiency
- T4 and T3 production increases by 50%
- The daily iodine requirement goes up by 50% due > T4 production and > renal clearance
- WHO recommends 250 mcg of iodine daily
- TSH drops the most in the first trimester under the impact of placental human chorionic gonadotropin (hCG), which itself has a weak thyrotropic effect → possible transient hyperthyroidism
- Thyroid Binding Globulin (TBG) increases

Huang SA, et al. *J Clin Endocrinol Metab.* 2003;88:1384-1388.

Kester MH, et al. *J Clin Endocrinol Metab.* 2004;89:3117-3128.

Abalovich M, et al. *J Clin Endocrinol Metab.* 2007;92(8 Suppl);S1-S47.

Controversy Screening

- American Thyroid Association, American College of Obstetricians and Gynecologists, and The Endocrine Society all recommend targeted rather than universal screening
- BUT may miss 1/3 of pregnancies with hypothyroidism

Screening for Thyroid Disease

Suggested indicators for targeted thyroid case finding in pregnancy, where the incidence of clinical hypothyroid disease is high and benefit of therapy is clear, women with:

- | | |
|--|---|
| • A history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy | • Type 1 diabetes |
| • A family history of thyroid disease | • Other autoimmune disorders |
| • A goiter | • Infertility should have screening with TSH as part of their infertility work-up |
| • Thyroid antibodies (when known) | • Prior therapeutic head or neck irradiation |
| • Symptoms or clinical signs suggestive of thyroid under function | • A prior history of preterm delivery |

The following conditions screening may be considered since the incidence might be high enough but no known benefit of treatment has yet been determined:

- | | |
|---|---------------------------------------|
| • Women in whom the last delivery was preterm | • Women with recurrent pregnancy loss |
|---|---------------------------------------|

Lab Findings

- Lab should provide pregnancy and trimester specific ranges of all thyroid tests
- If not provided, then for TSH use:
 - 1.) First trimester 0.1 to 2.5
 - 2.) Second trimester 0.2 to 3.0
 - 3.) Third trimester 0.3 to 3.0
- TBG is higher so total T4 is higher as total T4 reflects the increased protein binding in pregnancy
- FT4 however is more likely to be normal but can be technically difficult to accurately measure

Ain KB, et al. *J Clin Endocrinol Metab.* 1987;65:689-696.

Ballabio M, et al. *J Clin Endocrinol Metab.* 1991;73:824-831.

Glinoev D. *Endocr Rev.* 1997;18:404-433.

Lee RH, et al. *Am J Obstet Gynecol.* 2009;200:260.e1-e6.

Soldin OP, et al. *Thyroid.* 2004;14:1084-1090.

Controversy

Management Consult an Experienced Endocrinologist

- Hyperthyroidism
 - hCG-mediated hyperthyroidism is usually transient and does not require treatment
 - PTU is 1st choice and ATA recommends treatment saying benefits > risks, but is category 4
 - Surgery if PTU is contraindicated

Controversy

Management Consult an Experienced Endocrinologist

- Subclinical Hypothyroidism
 - Lower pregnancy risk than with overt disease
 - RX with LT4 may improve baby's neuro development
 - The Thyroid Dysfunction during Pregnancy and Postpartum Guideline Task Force recommends treatment
- Elevated antithyroid peroxidase antibody (TBO antibodies) in euthyroid pregnant patients
 - Increased risk of fetal loss, perinatal mortality, and large-for-gestational-age
 - High risk to become hypothyroid, so need monitoring
 - LT4 may lower miscarriage rates
 - ATA does not recommend for or against treatment

Best Practices Pearls



- Have a low threshold to test for thyroid disease
- Treatment of both subclinical and overt disease should be individualized and monitored
- Manage issues around variable therapeutic equivalence of levothyroxine products
- Appropriately counsel, screen, and monitor thyroid function in pregnancy to improve outcomes

The End!

