MANAGEMENT OF THYROID DISEASE

Eva M. Vivian, PharmD, MS, PhD

Professor (CHS)

UW School of Pharmacy

Thyroid disease: Objectives

- List four signs and symptoms of hypothyroidism and state two laboratory tests useful in its management
- Describe a drug treatment plan for a patient with a new diagnosis of hypothyroidism
- List four signs and symptoms of hyperthyroidism and state two laboratory tests useful in its management
- Describe a treatment plan for a patient with a new diagnosis of hyperthyroidism

Thyroid Hormone Functions

- Plays essential role in neural and skeletal development in the fetus

- Stimulates oxygen consumption
- Increases bone turnover

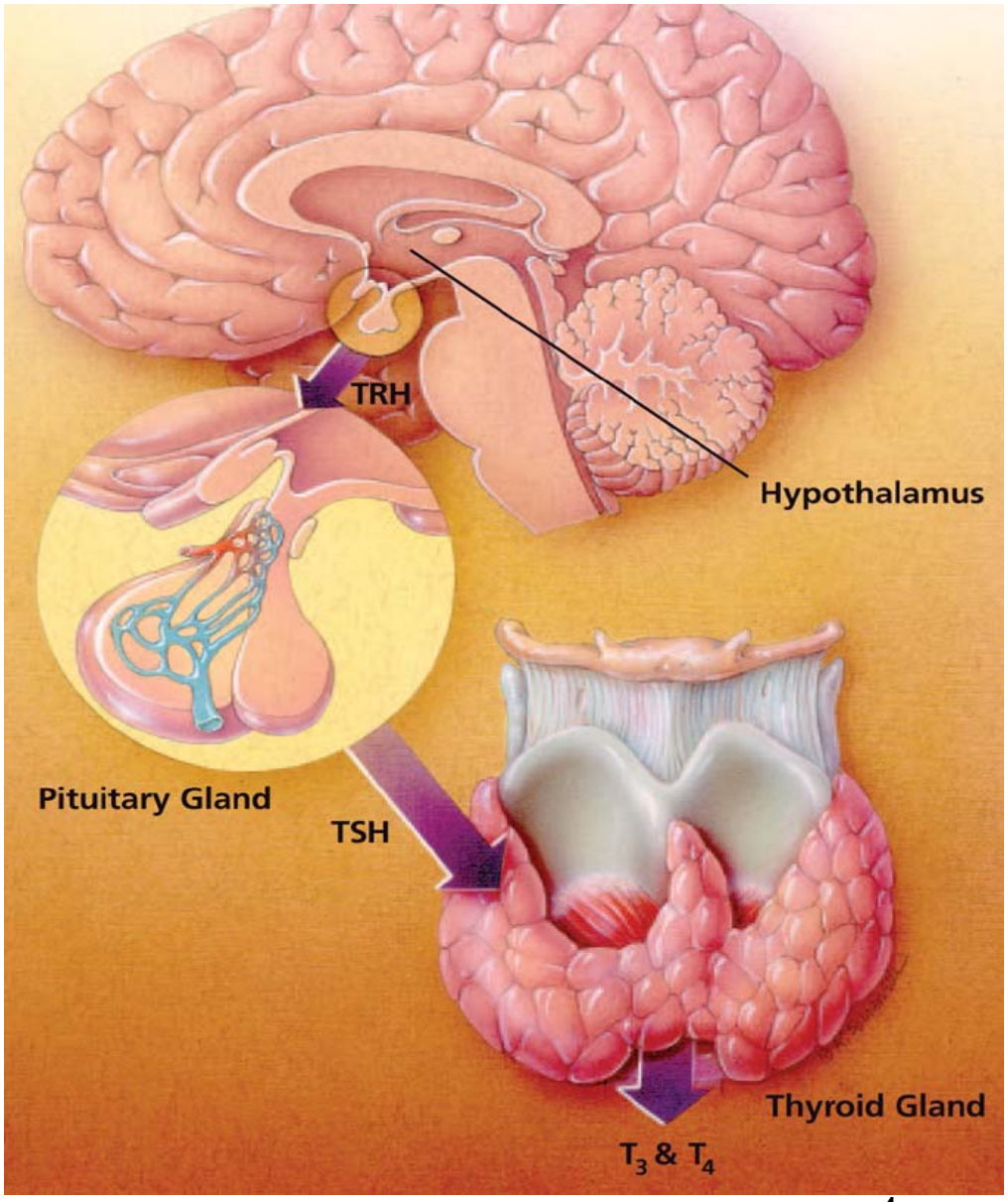
- Promotes chronotropic and inotropic effects on heart.

- Increases production of red blood cells.

- Helps regulate metabolism of carbohydrates, fats, and protein

The players

- Hypothalamus
  - Releases TRH
- Pituitary
  - Releases TSH
- Thyroid gland
  - Releases thyroid hormone



Hypothyroidism

- Overall prevalence 0.1 to 2 percent
  - Much more common in women
  - Increased risk with age

- Screening recommendations vary greatly

  see next slides

- Screening for congenital hypothyroidism in newborns: recommended and routinely done
  - Early treatment crucial

- Screening of pregnant women or those intending pregnancy who do not have risk factors is standard of care in some settings but not others

Garber JR.. Endocr Pract. 2012 Sep 11:1-207.

De Groot L. *J Clin Endocrinol Metab*. 2012;97:2543-2565

To Screen or Not?

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.
College of American Pathologists	Women ≥50 years of age should be screened "if they seek medical care"; all geriatric patients should be screened on admission to the hospital and at least every 5 years.
American Academy of Family Physicians	Patients ≥60 years of age should be screened.

Garber JR.. Endocr Pract. 2012 Sep 11:1-207.

To Screen or Not?

American College of Obstetrics and Gynecology	Women in "high-risk groups" (those with autoimmune disease or a strong family history of thyroid disease) should be screened starting at 19 years of age.
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

Garber JR.. Endocr Pract. 2012 Sep 11:1-207.

TABLE 1. Recommended patient profiles for targeted thyroid disease case finding in women seeking pregnancy or newly pregnant

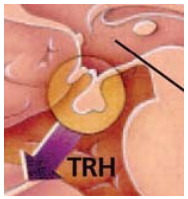
Women over age 30 yr
Women with a family history or autoimmune thyroid disease or hypothyroidism
Women with a goiter
Women with thyroid antibodies, primarily thyroid peroxidase antibodies
Women with symptoms or clinical signs suggestive of thyroid hypofunction
Women with type 1 DM or other autoimmune disorders
Women with infertility
Women with a prior history of miscarriage or preterm delivery
Women with prior therapeutic head or neck irradiation or prior thyroid surgery
Women currently receiving levothyroxine replacement
Women living in a region with presumed iodine deficiency

De Groot L. *J Clin Endocrinol Metab*. 2012;97:2543-2565

Hypothyroidism

- Primary:
  - Failure of thyroid to secrete hormone (95% of cases)

- Secondary:
  - Failure of hypothalamus



or anterior pituitary

- Cause: most commonly autoimmune
  - Autoantibodies decrease production of thyroid hormone (Hashimoto's disease)
- Iatrogenic
  - Radioiodine or surgery for hyperthyroidism
  - External radiation
  - Drugs (antithyroid drugs, iodine, lithium, amiodarone)

Signs and Symptoms of Hypothyroidism

- Dry skin
- Cold intolerance
- Wt gain
- Constipation
- Weakness
- Lethargy, fatigue, loss of energy
- Muscle cramps
- Coarse skin and hair
- Cold skin
- Puffy face
- Periorbital puffiness
- Bradycardia
- Reversible neurologic syndromes (i.e. CTS)

Thyroid Function Tests

- TSH is the best initial measure for assessing thyroid status
- Do NOT measure thyroid function in patient in hospital unless a specific reason to do so
- If TSH is elevated, measure free T_4**
- If TSH elevated and free T_4 suppressed
  - Indicates PRIMARY hypothyroidism, need to TREAT
  - (If thyroid underperforming, pituitary tries to compensate by making more TSH)
- **The Endocrine Society (DeGroote) and the Amer Assoc Clin Endoc and Amer Thyroid Assoc (Garber) recommend each lab establish trimester-specific reference ranges for free T_4. Total T_4 may be a better measure if such reference ranges are not available.

Garber JR.. Endocr Pract. 2012 Sep 11:1-207.

**De Groot L. *J Clin Endocrinol Metab*. 2012;97:2543-2565

If TSH elevated and free T_4 normal

- Considered subclinical hypothyroidism in the person who has no symptoms
- Do not usually treat unless Sx, goiter, or hx of thyroid disease
- Continuing debate among experts re treating subclinical hypothyroidism.
- NO debate in pregnancy. Treat the pregnant woman to avoid possible irreparable damage to fetus**
- Recent: high TSH in combination with thyroid autoimmunity in early pregnancy was linked to a fourfold increased risk for gestational diabetes (RR=4.3; 95% CI, 2.1-8.9) and a threefold increased risk for low-birth-weight neonates (RR=3.1; 95% CI, 1.2-8).

**De Groot L. *J Clin Endocrinol Metab*. 2012;97:2543-2565

What about secondary hypothyroidism

- Rarely occurs (<5% of cases of hypothyroidism)

- Caused by hypothalamic or pituitary dysfunction
  - For these persons, will not catch by screening for high TSH
  - Usually noticed because the patient has signs and symptoms strongly suggestive of hypothyroidism
  - Treat with levothyroxine and monitor treatment with free T_4 measurement
  - Aim for the UPPER HALF of the reference range for T_4

Treatment of Clinical Hypothyroidism

- Replacement therapy: levothyroxine (L-thyroxine; T_4)
  - Little activity compared to T_3, T_4 is converted to T_3 in the body which is more active. BOTH highly protein bound
- Desiccated porcine thyroid; other drugs: Not recommend although on market still
- No compelling evidence for T_3 or T_3/T_4 combo for routine care; still being investigated: possible genetic reasons T_3 could be useful
- T_4 has narrow Therapeutic Window
- Generic issue
  - FDA approved generic substitution in 2004
  - But, the American Thyroid Association, Endocrine Society, and American Association of Clinical recommend that patients remain on the same brand that was initially prescribed

Garber JR.. Endocr Pract. 2012 Sep 11:1-207.

Treatment of Clinical Hypothyroidism

- Mean replacement dose of T4 in adults ~ 1.6 mcg/kg body weight/day
- Young healthy adults sometimes started at expected full replacement dose
- Wide range of final required dose: ~50 to 200 mcg/day.
- Start low and go slow in the elderly
  - If healthy elderly, can start at 50mcg/day.
- In those with cardiac risk, start with 12.5-25 mcg levothyroxine daily
  - If cardiac sx appear, maintenance dose may have to be less than full replacement dose

Treatment of Clinical Hypothyroidism

Titrate to obtain normal TSH, increase at 25-50mcg increments
Retest TSH, Free T4 in 4-8 weeks, retest periodically until TSH normal

- Then six months after that, then annually
- Be sure to take blood BEFORE dose taken that day
- If age based upper limit not available in a given lab, use 4.12mIU/L for TSH
- Upper limit for TSH is set specifically for each trimester for pregnant women

Increase in increments of 25-50 mcg, or less if extra caution required

Administration of levothyroxine

- L-thyroxine should be taken with water consistently 30–60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption.
- Consistency is the key
- Be sure to take at least 4 hours apart from drugs that interfere with absorption
  - If taking levothyroxine in morning; wait at least 4 hrs before taking calcium
- See page 13 from the Garber Clinical Practice Guidelines…

Garber JR.. Endocr Pract. 2012 Sep 11:1-207.

Factors that affect the requirement for T_4

- Pregnancy
- Weight gain
- Malabsorption or increased excretion of T_4
  - Gastrointestinal disorders (eg, celiac disease)
  - Impaired acid secretion
- Nephrotic syndrome
- Progressive thyroid dysfunction
  - Autoimmune thyroiditis
  - Previous thyroid irradiation

UpTo Date Inc

Adverse effects of thyroid replacement

Usually not seen when person is on correct dose to achieve euthyroid status

- Palpitations
- Anxiety
- Angina, usually in those with known cardiac disease
- Weight Loss
- Tachycardia
- Diarrhea
- Atrial Fibrillation
- Bone Loss

Hyperthyroidism

Hyperthyroidism

- Overall prevalence approximately 1.3%
- Prevalence in women ~5x higher than in men
- Causes
  - Graves' disease
  - Toxic multinodular goiter
  - Solitary thyroid adenoma
  - Other
- Primary hyperthyroidism: low TSH, high free T_4
- Less common: Secondary hyperthyroidism : high TSH, high free T_4
  - Pituitary (very rarely hypothalamic) cause

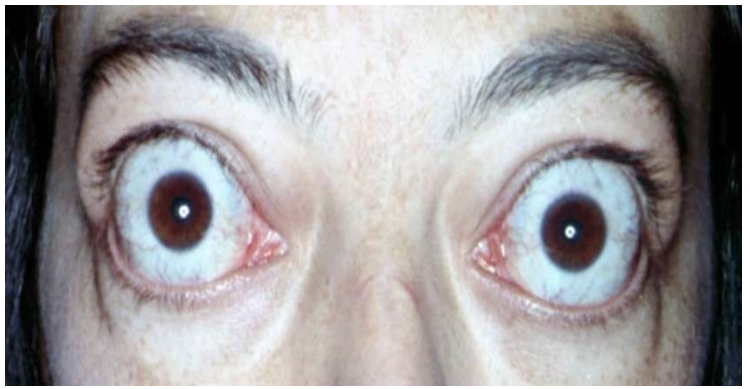
ATA/AACE Endocr Pract. 2011;17(No. 3)

Hyperthyroidism

- Graves' disease is the most common cause of hyperthyroidism, accounting for 60 to 80 percent of all cases.
- It is an autoimmune disease caused by an antibody, active against the thyroid-stimulating hormone (TSH) receptor, which stimulates the gland to synthesize and secrete excess thyroid hormone.
- It can be familial and associated with other autoimmune diseases. Pernicious anemia, adrenal insufficiency, type 1 diabetes, myasthenia gravis

Hyperthyroidism

- Graves' Disease
  - Iodine-123 scan: diffuse increased uptake by thyroid
  - May resolve spontaneously or after treatment
  - Ophthalmopathy in 30% of cases



Hyperthyroidism

- Toxic adenoma
  - Single benign mass in the thyroid
  - Produces thyroid hormone autonomously
  - Takes up Iodine 123 on scan ("hot" spot)

Causes of Hyperthyroidism

- Toxic multinodular goiter
  - Thyroid nodules making thyroid hormone autonomously
  - I-123 scan: numerous "hot" spots
  - Other thyroid follicles suppressed (lower than normal uptake)
- Subacute thyroiditis (usually viral, short term)
- Tumors or malignancies
- Drugs: amiodarone, iodine (pharmacologic amounts as in contrast dye), lithium

Hyperthyroidism: Clinical Manifestations

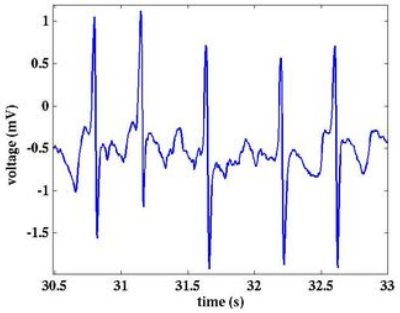
- Weight loss with preserved appetite

- Heat intolerance and diaphoresis
- Nervousness
- Anxiety
- Fatigue
- Tremor
- Hyperreflexia

- Proximal muscle weakness
- Increased frequency of bowel movements

- Palpitations

- Atrial fibrillation



- Hypertension

Hyperthyroidism often looks different in the elderly

- May include
  - Worsening left ventricular function
  - Atrial fibrillation
  - Depression
  - Fatigue
  - Hypokinesia (pt is slow-moving)
  - Weight loss
  - Poor appetite
  - Constipation

Drugs for Hyperthyroidism: Methimazole

- Blocks synthesis of thyroid hormones by interfering with thyroid peroxidase enzyme
- Is THE recommended drug now, except for first trimester of pregnancy

- Baseline complete blood count, including white count with differential, and a liver profile including bilirubin and transaminases

- Methimazole initial dose 10-20 mg daily
  - Maintenance dose usually 5-10 mg daily

- Once daily dosing

ATA/AACE Endocr Pract. 2011;17(No. 3)

Drugs for Hyperthyroidism: Propylthiouracil

- Blocks synthesis of thyroid hormones by interfering with thyroid peroxidase enzyme
- Recommended for first trimester of pregnancy
- Baseline complete blood count, including white count with differential, and a liver profile including bilirubin and transaminases
- Propylthiouracil initial dose 50-150 mg given three times a daily
  - Maintenance dose usually 50mg two or three times daily

ATA/AACE Endocr Pract. 2011;17(No. 3)

Efficacy Monitoring for Drugs for Hyperthyroidism

- Measure free T_4 at about 4 weeks, adjust dose prn.
  - Serum T_3 is sometimes also monitored.
  - Serum TSH will not respond quickly so free T_4 measured early on in therapy
- Monitor every 4–8 weeks until patient is euthyroid with the minimal dose of medication.
- Once euthyroid, evaluate every 2–3 months, depends on situation
- An assessment of serum free T_4 and TSH are required before treatment and at intervals after starting the treatment.

ATA/AACE Endocr Pract. 2011;17(No. 3)

Drugs for Hyperthyroidism

- Side effects of each
  - Overall incidence 5-16%
  - Pruritic rash
  - Liver dysfunction, **see next slide**
  - Arthalgias
  - Benign transient leukopenia common
  - Agranulocytosis
    - 0.5%
    - Usually reversible with discontinuation
- Problem is relapse of hyperthyroidism after discontinuation of drug
  - Sometimes does NOT recur

ATA/AACE Endocr Pract. 2011;17(No. 3)

Propylthiouracil liver toxicity

- FDA safety alert, June 2009: risk for liver failure or death with propylthiouracil (PTU) compared with methimazole.
- 22 adult cases of serious liver injury were linked to PTU use; 17 died or liver Tx.
- 10 pediatric cases. 7 died or required liver Tx
- Methimazole: only five cases of serious liver injury reported, all in adults, three died.
- FDA advises close monitoring for symptoms and signs of liver injury, especially during 1st 6 months.
- Stop drug right away if liver toxicity suspected, the patient should be evaluated, supportive care as needed.

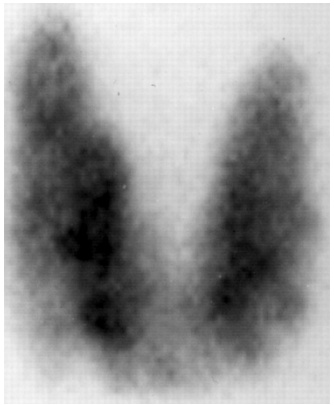
http://www.medscape.com/viewarticle/703851

Treatment of Hyperthyroidism (Grave's disease)

New guidelines 2011: Radioactive iodine, drugs, surgery (thyroidectomy) all reasonable options, depending on patient situation/preference (I-131 preferred before)

Radioactive iodine uptake

- Thyroid gland takes up I-131 and is destroyed



- Can have transient worsening of thyrotoxicosis
  - Pre-treatment with antithyroid drugs prudent
- Hypothyroidism usually occurs later
  - Treatment with thyroid replacement
- Drugs: Methimazole now preferred, (PTU: liver toxicity)
- Surgery another option

ATA/AACE Endocr Pract. 2011;17(No. 3)

Hyperthyroidism in pregnancy

- The two most common types of biochemical hyperthyroidism that occur during pregnancy are gestational hyperthyroidism (e.g., hCG-mediated transient TSH suppression) and GD.
- There is no evidence that treatment of gestational hyperthyroidism with antithyroid drugs (ATDs) is beneficial and use of ATD in early pregnancy has been associated with an increase in risk of birth defects. In these patients, physical examination and repeat thyroid function tests at intervals of 3–4 weeks is recommended. In the case of very symptomatic disease, a trial of beta-blocker therapy (propranolol or metroprolol, but not atenolol for this transient disorder may be considered.

Hyperthyroidism in pregnancy

- ATD therapy should be used for overt hyperthyroidism due to GD during pregnancy. PTU should be used when ATD therapy is given during the first trimester. MMI should be used when ATD therapy is started after the first trimester. **Strong recommendation, low-quality evidence.**
- Switching from MMI to PTU before conception would eliminate the risk from early pregnancy exposure to MMI in women where pregnancy is not recognized within the first few weeks after conception.

Hyperthyroidism in pregnancy

Women with hyperthyroidism caused by GD who are well controlled on MMI and desire pregnancy have several options:

a) Patients could consider definitive therapy before they become pregnant.

b) Patients could switch to PTU before trying to conceive.

c) Patients could switch to PTU as soon as pregnancy is diagnosed.

d) Appropriately selected patients could withdraw from ATD therapy as soon as pregnancy is diagnosed. If ATD therapy is withdrawn, thyroid function should be assessed weekly throughout the first trimester, then monthly. **Weak recommendation, low-quality evidence.**

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis. Thyroid. 2016 Aug 12. [Epub ahead of print]

Hyperthyroidism in pregnancy

- MMI associated birth defects occur in 2-4 % of children exposed in early pregnancy, and abnormalities may be severe. PTU associated birth defects are less well documented. They may occur in 2-3 % of children but they seem to be mostly less severe. PTU is associated with liver failure with an estimated 1:10,000 risk of severe liver failure in adult patients (136).
- Thus, mothers must balance the risk of PTU to themselves vs. the risk to the child. Switching to PTU before conception may be preferred in younger women with regular menses who are expected to be able to conceive within 1 to 3 months. *In a German prospective study of 340 such women, 68 % became pregnant within 3 months*

Drug-associated thyrotoxicosis and its management

Drug	*Mechanism(s)*	*Timing of onset following initiation of the drug*	*Therapy*
Amiodarone	Iodine induced (type 1)	Months to Years	Supportive care[a] Antithyroid drugs; perchlorate[b] Surgery
	Thyroiditis (type 2)	Often >1 year	Supportive care[a] Corticosteroids Surgery
Lithium	Painless thyroiditis	Often >1 year	Supportive care[a] Antithyroid drugs
Interferon α	Painless thyroiditis; GD	Months	Supportive care[a] Antithyroid drugs and/or radioactive iodine (GD only)
Interleukin-2	Painless thyroiditis; GD	Months	Supportive care[a] Antithyroid drugs and/or radioactive iodine (GD only)
Iodinated contrast	Underlying thyroid autonomy	Weeks to months	Antithyroid drugs
Radioactive iodine, early	Destruction	1–4 weeks	Observation; if severe, administer corticosteroids
Radioactive iodine for TMNG, late	GD	3–6 months	Antithyroid drugs Repeat radioactive iodine Surgery

[a]Supportive care may include beta-adrenergic blockers during the thyrotoxic stage and levothyroxine if hypothyroidism develops.
[b]Not available in the United States.

ATA/AACE Endocr Pract. 2011;17(No. 3)

Thyrotoxicosis

Beta blockers offer prompt relief of the adrenergic symptoms of hyperthyroidism such as tremor, palpitations, heat intolerance, and nervousness. Propranolol (Inderal) has been used most widely, but other beta blockers can be used. Nonselective beta blockers such as propranolol, are preferred because they have a more direct effect on hypermetabolism.

Therapy with propranolol should be initiated at 10 to 20 mg every six hours.

- Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 bpm or coexistent cardiovascular disease. **Strong recommendation, moderate-quality evidence.**

Conclusions

- For hypothyroidism, universal screening not yet recommended, risk factors matter
- Have a high index of suspicion for hypothyroidism in the elderly, especially those with specific risk factors
- Presentation of hypothyroidism can be insidious and subtle
  - Get a TSH
- Start low and go slow with levothyroxine replacement therapy
  - Overmedication unwise especially for those with cardiovascular disease
- Pregnant women require specialized care!

Conclusions

- For hyperthyroidism, universal screening not yet recommended
- Do suspect in elderly with weight loss, fatigue, anorexia, new onset atrial fibrillation, or other S/Sx as listed
- Low TSH, high free T_4 most commonly seen
  - Overproduction by the thyroid gland
- Treatment with drugs, surgery, or I-131 all good options, but will depend on the patient situation
- Pregnant women require specialized care!

AMY T., a 28-YEAR-OLD FEMALE, visited her physician with complaints of weakness, fatigue, weight gain, hoarseness, cold intolerance, and unusually heavy periods worsening over the past 2–3 months. Her pulse was 50, and her blood pressure (BP) was 110/70. Her physical exam was normal, except for a mildly enlarged thyroid gland, pallor, and diminished tendon reflexes. She denied taking any medications or changing her diet.

The patient's chemistry results were sodium 130 mEq/L (136–145 mEq/L), potassium 3.8 mEq/L (3.5–5.0 mEq/L), carbon dioxide 28 mEq/L (24–30 mEq/L), calcium 9.5 mg/dL (8.5–10.8 mg/dL), magnesium 2 mEq/L (1.5–2.2 mEq/L), glucose 80 mg/dL (70–110 mg/dL), blood urea nitrogen (BUN) 20 mg/dL (8–20 mg/dL), serum creatinine 1.1 mg/dL (0.7–1.5 mg/dL), and cholesterol 235 mg/dL (<200 mg/dL). The cholesterol concentration was elevated since a screening 6 months ago. A test for mononucleosis was negative. Hematocrit was low at 35% (37% to 47%)—close to her usual. Her total serum T4 was 8 mcg/dL (4–12.5 mcg/dL), her T3 resin uptake was 15% (25% to 34%), and her free T4 index was 1.2 (1.0–4.0).

Question: How should these results be interpreted? Are confirmatory tests needed?

Recommended Reading

- Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al.; American Association of **Clinical** Endocrinologists and American Thyroid Association Taskforce on **Hypothyroidism** in Adults. **Clinical** practice **guidelines** for **hypothyroidism** in adults: cosponsored by the American Association of **Clinical** Endocrinologists and the American Thyroid Association. Endocr Pract. 2012 Nov-Dec;18(6):988-1028. Erratum in: Endocr Pract. 2013 Jan-Feb;19(1):175.
- Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, et al.2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis. Thyroid. 2016 Aug 12. [Epub ahead of print]