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Outpatient Management of Thyroid Dysfunction: Diagnosis and Monitoring

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Disclosures

- None

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Thyrotoxicosis/Hyperthyroidism

- Thyrotoxicosis-clinical state that results from inappropriately high thyroid hormone action in tissues due to high thyroid hormone levels

- Hyperthyroidism - form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone by the thyroid

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

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Etiologies

- Hyperthyroidism-excess thyroid hormone production from the thyroid
  - Graves' disease - most common, 50-60%
  - Toxic adenoma (3-5%) and toxic multinodular goiter (15-20%)
  - Iodine-induced hyperthyroidism
  - hCG-mediated- Trophoblastic disease and germ cell tumors, hyperemesis gravidarum
  - Central hyperthyroidism/TSH-mediated hyperthyroidism
    - TSH –secreting pituitary adenoma
- Release of preformed hormone
  - Thyroiditis
    - subacute granulomatous thyroiditis (de Quervain's thyroiditis)
    - painless thyroiditis
    - Other- radiation, iodine, medications (check-point inhibitors, amiodarone)
- Extrathyroidal
  - Ectopic hyperthyroidism - struma ovarii
  - Exogenous

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Clinical features/symptoms

- Variable clinical presentation- depending on age, severity, duration

- Younger patients: increased sympathetic activity
- Older patients-
  - cardiac manifestations (**Atrial fibrillation**, tachycardia, DOE, edema);
  - weight loss, less increase in appetite (may have decrease in appetite);
  - "**apathetic thyrotoxicosis"**
- Graves' disease: may have more pronounced symptoms

- **Weight loss**
  - Despite increased or normal appetite (some may gain weight)
- **Heat intolerance**, excess sweating
- **Palpitations**
  - **Cardiac manifestations: tachycardia, atrial fibrillation, DOE, edema**
- **Tremor**
- **Fatigue**
- Anxiety, nervousness
- Hyperactivity
- Weakness
- Hyperdefecation
- Women- Oligomenorrhea/amenorrhea
- Men- Gynecomastia/ED
- Neck fullness
- Eye symptoms (Graves')- swelling, pain, redness, double vision)

Boelaert, et al, J Clin Endocrinol Metab. 2010 Jun;95(6):2715-26
Smith, et al, N Engl J Med. 2016 Oct 20;375(16):1552-1565

Hyperthyroidism- Physical exam

- Hyperactivity, hyperkinesis, rapid speech
- Stare/lid retraction and lid lag (sympathetic hyperactivity)
- Goiter- depending on etiology
  - A single, palpable nodule raises the possibility of an autonomously functioning thyroid adenoma
  - Thyroid is painful and tender in subacute (granulomatous) thyroiditis
  - Diffuse symmetric enlargement in Graves' disease
- Tachycardia, afib; systolic HTN; hyperdynamic precordium
- Tremor
- Proximal muscle weakness
- Hyperreflexia
- Skin- warm, moist
- Hair thin and fine
- Graves' disease- exophthalmos, periorbital and conjunctival edema, scleral injection, EOM dysfunction; infiltrative dermopathy (pretibial myxedema)

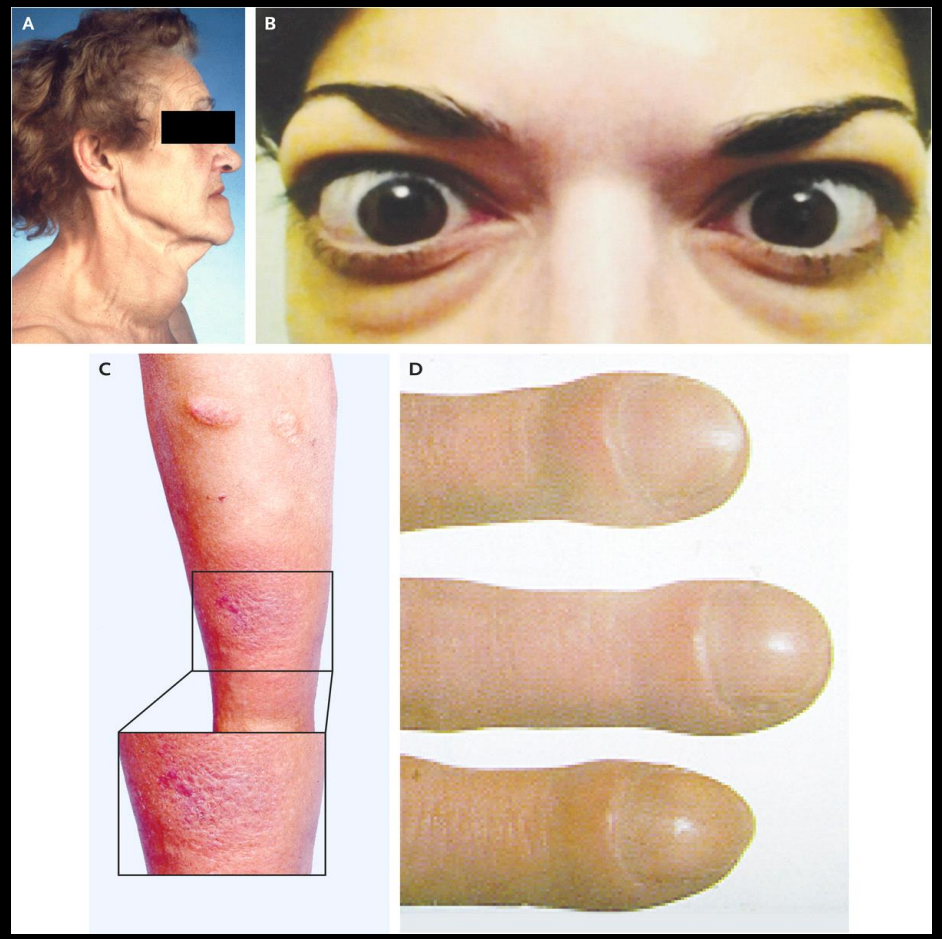
Boelaert, et al, J Clin Endocrinol Metab. 2010 Jun;95(6):2715-26
Smith, et al, N Engl J Med. 2016 Oct 20;375(16):1552-1565

Consider evaluation for hyperthyroidism in the following:

- Weight loss
- New onset atrial fibrillation
- Myopathy
- Menstrual disorders
- Gynecomastia
- Osteoporosis
- Hypercalcemia
- Heart failure
- Deterioration in glycemic control in diabetes

Boelaert, et al, J Clin Endocrinol Metab. 2010 Jun;95(6):2715-26
Smith, et al, N Engl J Med. 2016 Oct 20;375(16):1552-1565
Williams, et al, J Endocrinol Invest. 2018 Jan;41(1):99-109.

Clinical Manifestations of Graves' Disease.



Smith TJ, Hegedüs L. N Engl J Med 2016;375:1552-1565.

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Manifestations of Graves' Disease.

Panel A shows a diffuse, moderately enlarged goiter in a woman with Graves' hyperthyroidism. Panel B shows moderate-to-severe, thyroid-associated ophthalmopathy characterized by bilateral proptosis, periorbital edema, scleral injection, and lid retraction. Panel C shows the plaque form of pretibial dermopathy. Panel D shows acropachy with clubbing of the fingers.

Diagnosis- biochemical evaluation

- The diagnosis of thyrotoxicosis is based upon thyroid function tests
- Clinical suspicion → the most reliable single initial test is serum TSH
  - TSH assays more sensitive and specific than T4/T3 measurements
  - Reasonable to obtain TSH, free T4, and total T3 if strong suspicion
  - If hyperthyroidism is strongly suspected despite a normal or elevated TSH→ obtain free T4 and total T3
- Free T4 and total T3

Surks et al, JAMA. 1990 Mar 16;263(11):1529-32
Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Laboratory findings

- Primary hyperthyroidism, overt
  - Low TSH- TSH usually suppressed <0.01 mU/L
  - High free T4 and T3
  - In some patients, only the serum T3 or serum T4 is elevated
  - T3 toxicosis- Graves', toxic nodular goiter
  - T4 toxicosis- thyroiditis, hyperthyroidism plus concurrent NTI, amiodarone

*(TSH-mediated hyperthyroidism/Central hyperthyroidism- i.e. TSH-secreting adenoma (very rare) will have normal or high TSH)

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Subclinical hyperthyroidism

- TSH low (<0.4 mU/L, but often in detectable range), free T4, T3 are normal
- No manifestations or mild and nonspecific symptoms
- Osteoporosis/fractures, cardiovascular manifestations, dementia
- Many patients have a multinodular goiter with autonomy (toxic nodular goiter) or mild Graves' disease
- Treat in >65, postmenopausal women, especially if TSH <0.1 mU/L

Biondi, et al, N Engl J Med. 2018 Jun 21;378(25):2411-2419..

Differential diagnosis for lab findings:

- Assay interference – biotin; heparin
- Euthyroid hyperthyroxinemia — abnormalities in serum thyroid hormone-binding proteins (TBG, transthyretin, albumin) that result in high total T4, T3 concentrations
  - normal TSH
  - Eg, Hereditary X linked trait, pregnancy/high estrogen state
- Central HYPOthyroidism
- Nonthyroidal illness ("euthyroid sick syndrome") → may have low TSH but low or low-normal free T4 and T3 concentrations
    - Recheck TFTs 4-8 weeks as outpatient
- High-dose glucocorticoids

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

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Assay interference- Biotin

- Ingestion of high doses of biotin (5-10mg/day) can lead to spurious results in assays based on streptavidin–biotin interaction
  - Falsely low values in immunometric assays (i.e., used to measure TSH)- excess biotin displaced biotinylated antibodies
  - Falsely high values in competitive binding assays (i.e., used to measure free T4, T3, TBII/TBI)- excess biotin competes with biotinylated analogue
- Hold biotin for at least two days prior to assessing thyroid function

Barbesino, et al, Thyroid. 2016 Jun;26(6):860-3.
Li, et al, JAMA. 2017 Sep 26;318(12):1150-1160

Etiologies

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  - Graves' disease - most common, 50-60%
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Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Thyrotoxicosis- diagnostic approach

- The diagnosis/etiology may be obvious on presentation; moderate to severe hyperthyroidism, symmetrically enlarged non-nodular thyroid, new-onset ophthalmopathy → Graves' disease
- If the diagnosis is not apparent based on the clinical presentation:
  - Measurement of thyrotropin receptor antibodies (TRAb)
    - TBII/TBI (TSH binding inhibition immunoglobulin) – competition assays; cannot distinguish TSH-R antibody types
    - TSI (thyroid stimulating immunoglobulin)- measure ability of TSI to increase the intracellular level of cAMP
  - Radioactive iodine uptake
  - Measurement of thyroidal blood flow on US
- Approaches w/ or w/o nodular disease

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.
Barbesino, et al, J Clin Endocrinol Metab. 2013 Jun;98(6):2247-55.

Determining etiology

- Without nodular disease
  - Measure TRAb first- if pos→ Graves' disease (GD)
    - Sensitivity and specificity high 90% in new overt hyperthyroidism
  - If TRAb neg→ does not r/o GD especially if mild/subclinical disease-→ RAIU
  - US to assess thyroidal blood flow if RAIU contraindicated
  - Use of TRAb measurements to diagnose GD compared to RAIU measurements can reduce costs and lead to quicker diagnosis
- With nodular disease
  - RAIU to distinguish toxic nodular goiter from GD, and/or assess functionality of nodules that may coexist w/ Graves' disease
  - TRAb
  - US to assess thyroidal blood flow if RAIU contraindicated

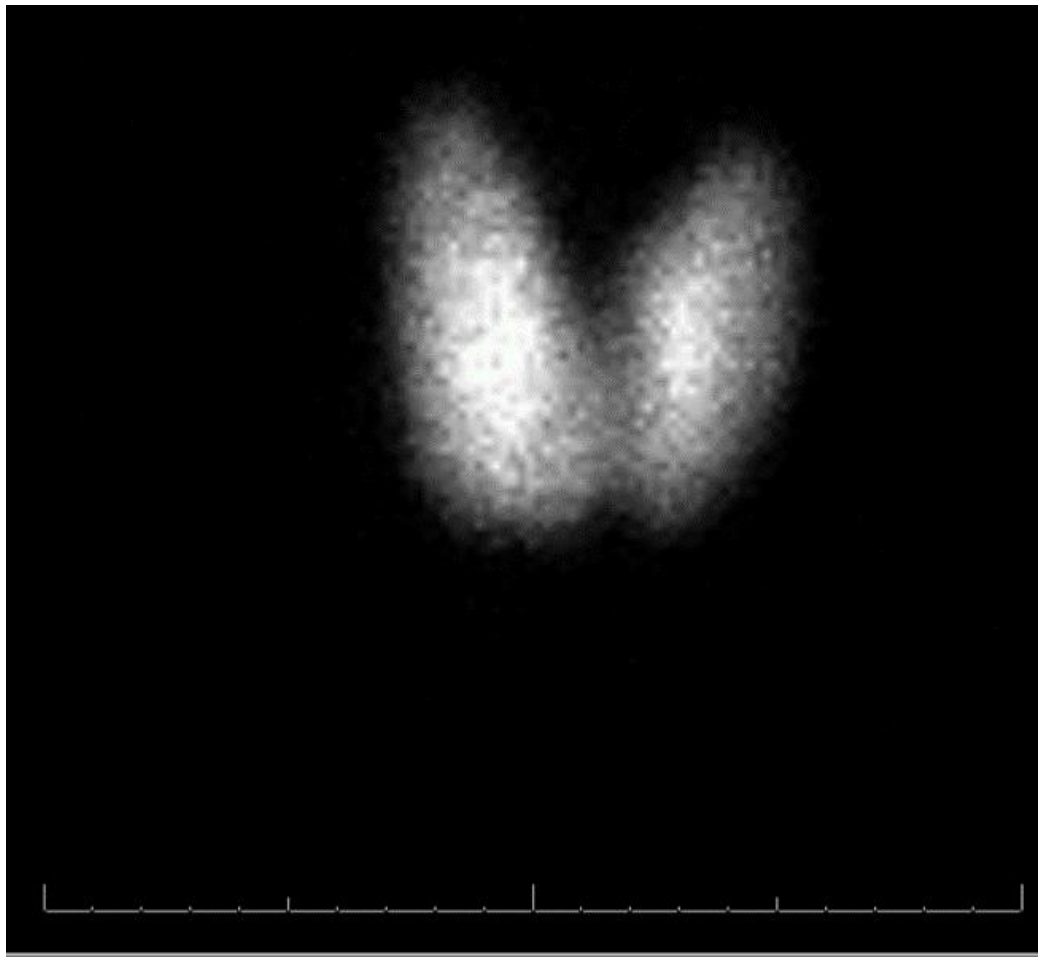
Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.
McKee et al, Am J Manag Care 2012 18:e1–14.
Barbesino, et al, J Clin Endocrinol Metab. 2013 Jun;98(6):2247-55
Kurita, et al, Thyroid. 2005 Nov;15(11):1249-52.

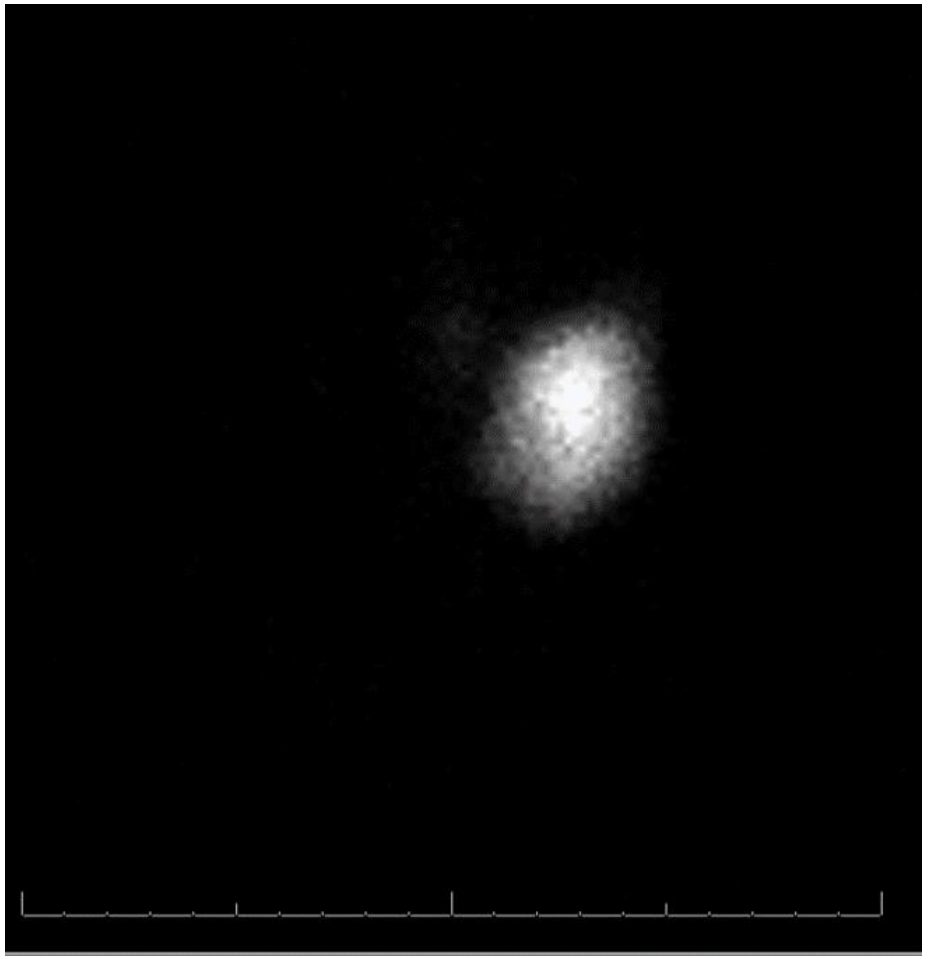
Diagnostic I-123 RAIU

- RAIU measures the % of administered RAI that is concentrated in thyroid tissue after fixed interval
- Nodular thyroid disease or if negative TSI
- Contraindicated in pregnant and breastfeeding women
- High (or normal) radioiodine uptake indicates de novo synthesis of hormone
  - Graves' disease
  - Toxic adenoma/toxic MNG (autonomous thyroid tissue)
  - TSH mediated hyperthyroidism (i.e. TSH-oma)
  - Hcg mediated hyperthyroidism (hyperemesis gravidarum, trophoblastic disease)
- Low, nearly absent, radioiodine uptake indicates either inflammation and destruction of thyroid tissue with release of pre-formed hormone into the circulation or an extrathyroidal source of thyroid hormone
  - Thyroiditis
  - Exogenous thyroid hormone intake (over-replacement, factitious hyperthyroidism)
  - Ectopic hyperthyroidism (i.e. struma ovarii)
  - **patients who received iodine may have a misleading low radioiodine uptake**
  - **If suspect excess iodine exposure (i.e. iodinated contrast within 1-2 months, or high dietary intake), can check spot or 24hr urine iodine**

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Diagnostic I-123 RAIU





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Evaluation

- Ratio of T3 to T4
  - hyperactive gland will have higher T3 to T4 ratio;
  - T4 more elevated in thyroiditis, factitious thyrotoxicosis

- Thyroiditis
  - Subacute- painful; elevated ESR
  - Painless thyroiditis- FH history of autoimmune thyroid disease: + anti-TPO abs
    - within 1st year of pregnancy (post partum thyroiditis)

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Hyperthyroidism- treatment

- Symptom control – beta blockade
  - Symptomatic thyrotoxicosis, patients >65, cardiovascular disease
  - Goal HR <90
- Antithyroid drugs- methimazole (or PTU)
  - At the start of MMI therapy, initial doses of 10– 30mg daily are used to restore euthyroidism, and the dose can then be titrated down to a maintenance level (generally 5– 10mg daily)
- Radioactive iodine
- Thyroidectomy

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

Treatment

- Choice of treatment depends on etiology
- GD: patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ATD, RAI, surgery
  - No difference in QOL
- Toxic nodular goiter/TA
  - RAI or surgery
  - On occasion long-term low dose ATD may be appropriate

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

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Monitoring of patients taking ATDs for GD

- Obtain Free T4 and total T3 ~2–6 weeks after initiation of therapy, depending on the severity of the thyrotoxicosis
- T3 should be monitored as well- free T4 levels may normalize despite persistent elevation of total T3
- TSH may remain suppressed for several months after starting therapy- thus not reliable parameter for monitoring early in the course
- Once FT4/T3 normalized, the dose of MMI can be decreased by 30%–50%, and biochemical testing repeated in 4–6 weeks
- Once euthyroid levels are achieved with the minimal dose of medication, evaluated at intervals of 2–3 months.
- If long-term MMI (>18 months), this interval can be increased to 6 months
- TRAb to help predict likelihood of remission

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

- Monitoring of patient treated with RAI for GD, TMNG, or TA
  - Follow-up within the first 1–2 months after RAI therapy -- free T4, total T3, and TSH
  - Biochemical monitoring should be continued at 4- to 6-week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement

- Surgery
  - Total thyroidectomy- check TSH 4-8 weeks after starting weight-based dose of levothyroxine
  - Lobectomy (i.e. for TA)- check TSH 4-8 weeks after surgery to assess residual thyroid function

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421.

ATD Adverse effects: Monitoring for agranulocytosis and hepatotoxicity

- Agranulocytosis (absolute neutrophil count <500)- 0.1-0.5% with ATDs; if occurs with on ATD, cannot use the other due to crossreactivity
- Hepatocellular injury - 2.7% of patients taking PTU and 0.4% of patients taking MMI
- Obtain baseline WBC and hepatic function panel- low WBC not uncommon in GD, elevated LFTs in thyrotoxicosis
- WBC count w/ differential should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication
- There is insufficient evidence to recommend for or against routine monitoring of WBC counts in patients taking ATDs.
  - Frequency of this condition is low and usually sudden in onset
  - If monitoring is employed, the maximum benefit would be for the first 90 days of therapy, when the vast majority of agranulocytosis occurs
- Liver function should be assessed in patients taking MMI or PTU who experience pruritic rash, jaundice, light-colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue
- There is insufficient information to recommend for or against routine monitoring of liver function tests in patients taking ATDs
- While there is no evidence that neutropenia or liver disease increases the risk of complications from ATDs, ATAG recommend that a baseline ANC <1000/mm3 or LFTs elevated more than 5-fold above the upper limit of normal should prompt serious reconsideration of initiating ATD therapy

Ross, et al, Thyroid. 2016 Oct;26(10):1343-1421
Sundaresh et al, J Clin Endocrinol Metab 98:3671–3677.
Otsuka et al, Clin Endocrinol (Oxf) 77:310–315.

Hypothyroidism

Hypothyroidism- symptoms

- Highly variable; depends on age at onset and duration and severity of thyroid hormone deficiency
- Fatigue
- DOE
- Cold intolerance
- Weight gain (not morbid obesity)
- Constipation
- Dry skin,
- Hoarseness,
- Edema
- Myalgia
- Menstrual irregularities /menorrhagia

- Generalized slowing of metabolic processes
- Accumulation of matrix glycosaminoglycans in interstitial tissues

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751.
Endocr Rev. 1989 Aug;10(3):366-91.

Hypothyroidism – physical exam

- Hypokinesis, slowed speech
- Puffy facies
- Loss of eyebrows
- Periorbital edema
- Goiter (patients with iodine deficiency or goitrous chronic autoimmune thyroiditis)
- Bradycardia
- Diastolic hypertension
- Delayed relaxation phase of the deep tendon reflexes
- Nonpitting edema
- Coarse skin

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751.
Smith, et al, Endocr Rev. 1989 Aug;10(3):366-91.

Hypothyroidism- etiology

- Primary hypothyroidism (95%)
  - **Chronic autoimmune hypothyroidism (Hashimoto's)-most common in iodine sufficient areas**
  - Thyroidectomy
  - RAI
  - Drugs- thionamides, lithium, amiodarone, TKIs, checkpoint inhibitor immunotherapy, interferon alpha, IL-2
  - Infiltrative diseases- hemochromatosis, sarcoidosis, fibrous thyroiditis
  - Transient hypothyroidism (thyroiditis, subacute granulomatous or painless/lymphocytic
  - Congenital thyroid agenesis, dysgenesis, or defects in hormone synthesis)
  - Iodine deficiency or excess
- Central hypothyroidism
  - TSH or TRH deficiency

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751

Hypothyroidism- screening

- Symptoms of hypothyroidism
- Asymptomatic patients at increased risk for:
  - Goiter
  - History of T1D and other autoimmune disease
  - Previous radioactive iodine therapy, and/or head and neck irradiation,
  - Family history of thyroid disease
  - Use of medications that may impair thyroid function (amiodarone)
  - Pituitary or hypothalamic disorders
  - Consideration for patients >60
- Also in evaluating: severe hyperlipidemia, hyponatremia, elevated muscle enzymes, macrocytic anemia
- Screening test: TSH
  - (plus Free T4 if suspect central)

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Garber, et al, Thyroid. 2012 Dec;22(12):1200-35.

Hypothyroidism- diagnosis

- The diagnosis of hypothyroidism relies heavily upon laboratory tests because of the lack of specificity of the typical clinical manifestations
- TSH should be the initial test
- If TSH is elevated- repeat TSH with a free T4 to make the diagnosis of hypothyroidism
  - ULN ~ 4 to 5 mU/L
- If the repeat TSH value is still high and free T4 is low, consistent with primary hypothyroidism→replacement therapy with T4 should be initiated
- If the TSH is normal but the patient has convincing symptoms of hypothyroidism→measure a repeat TSH and a free T4 to assess for central hypothyroidism. Suspect if:
  - Known hypothalamic or pituitary disease
  - Mass lesion in the pituitary
  - Other hormonal deficiencies

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751

Hypothyroidism – diagnosis

- Primary hypothyroidism, overt – high TSH, low free T4
- Subclinical hypothyroidism – high TSH, normal free T4
- Secondary (central) hypothyroidism - low free T4, TSH not appropriately elevated
- Thyroid peroxidase (TPO) antibodies are elevated in chronic autoimmune thyroiditis (Hashimotos')
  - Elevated in >90%
  - Do not need to check in overt primary hypothyroidism as most cases are Hashimoto's, but consider in subclinical hypothyroidism

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751
Marliotti, etal, J Clin Endocrinol Metab. 1990 Sep;71(3):661-9.

Differential diagnosis for lab findings

- Nonthyroidal illness (recovery phase)
- Hypothyroid phase of thyroiditis
- Assay interference (heterophilic antibodies)
- Medications- amiodarone and lithium
- Resistance to TSH or thyroid hormone- very rare
- Thyrotropin-secreting pituitary adenomas - very rare
- Physiologic - aging

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751

Subclinical hypothyroidism

- TSH elevated but free T4 normal
- Chronic mild thyroid failure
- TSH <10- mild subclinical hypothyroidism
- TSH >10- severe subclinical hypothyroidism

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751
Peeters, et al, N Engl J Med. 2017 Jun 29;376(26):2556-2565

Subclinical hypothyroidism

- Rule out transient increase in TSH by repeating in 2-3 months - TSH, free T4, anti-TPO antibodies
- Among persons who have a single elevated TSH <7 mIU/L, up to 46% have normalization within 2 years
- Risk of progression to overt hypothyroidism is 2-6% per year
- Higher risk in women, higher TSH levels, low normal FT4, higher levels of anti-TPO antibodies
  - + anti-TPO abs supports autoimmune cause and doubles the risk of progression to overt hypothyroidism

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751
Peeters, et al, N Engl J Med. 2017 Jun 29;376(26):2556-2565

Subclinical hypothyroidism

- Decision about T4 replacement is made on a case-by-case basis and depends partly upon the degree of TSH elevation
- Many are asymptomatic
- Symptoms of overt hypothyroidism- fatigue, weakness, weight gain, constipation
- Depressive symptoms, reduced quality of life, cognitive function, memory
- Treatment can improve symptoms – TSH >10-12
- Elderly persons have fewer symptoms
- Linked with increased risk of cardiovascular disease (though effect of treatment on cardiovascular outcomes is unclear)

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751
Peeters, et al, N Engl J Med. 2017 Jun 29;376(26):2556-2565

Hypothyroidism- treatment/monitoring

- Full dose replacement 1.6 mcg/kg, or partial replacement with gradual increments in dose titrated upward using TSH
  - Lower doses in older persons, cardiac disease; consider 25-50mcg
  - Subclinical hypothyroidism- start 25-75mcg daily
  - More dependent on lean body mass than total BW (elderly often require lower doses)
  - doses >2 mcg/kg/day suggest T4 malabsorption or poor adherence
- LT4 dose adjustments of 12.5–25 mcg/d are made; the serum TSH is then repeated in 4–6 weeks, until the TSH target has been reached
- Thereafter, serum TSH should be measured in 4–6 months and then yearly to assure stability
- Significance of T3 variability within or mildly below normal range is not known; typically not monitored
- If no treatment is started (subclinical hypothyroidism)- recheck every 6-12 months

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751
Peeters, et al, N Engl J Med. 2017 Jun 29;376(26):2556-2565

Treatment: TSH targets

- 0.5 to 3.5 or 4 mIU/L- 2014 ATA Guidelines
- 0.5-2.5/lower half of normal range – 2013 ETA guidelines
- 2014 ATA guidelines: Reasonable to raise the target TSH to 4–6 mIU/L in persons greater than age 70–80 years
- Avoid thyroid hormone excess and subnormal TSH values, <0.1 mIU/L, especially in older persons and postmenopausal women
  - Risk of osteoporosis, atrial fibrillation

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751
Pearce et al, Eur J Thyroid. 2013;2:215-28
Baloch et al, Thyroid. 2003 Jan;13(1):3-126.

Monitoring - Changes in LT4 requirements occur with:

- Progression of thyroid failure
- Aging
- Weight loss
- Pregnancy
- Medications- may alter T4 metabolism, changing concentration of TBG
  - Increase in hepatic metabolism: phenobarbital, phenytoin, carbamazepine, rifampin
  - Increase deiodination: tyrosine kinase inhibitors
  - Changes in TBG concentrations- estrogens/androgens
- Switching levothyroxine products- differences in biologic availability

Jonklaas, et al, Thyroid. 2014 Dec;24(12):1670-751

Thank you

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