

# Thyroid Physiology, Pharmacology, & Pharmacotherapy

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## Thyrotoxicosis / "Thyroid Storm" Therapy

- [Diagnostic criteria: Burch & Wartofsky Endocrinol Metab Clin North Amer 1993;22:263]. Below adapted from Fisher, JN. S Med J 2002;95:493-505 and Nayak & Burman Endocrinol Metab Clin N Am 2006;35:663-686.
- Control acute symptoms:** Propranolol 40-80 mg PO q 6h or IV 1mg/min, or Esmolol 250-500 µg load + 50-100 µg/min infusion. Target: HR<100 bpm.
  - Inhibit further T4 synthesis:** Begin PTU 200-400mg POING q6h. May be preferred (vs MMI) d/t blockade of T4-T3 conversion. Methimazole 25-50mg q6h is alternative.
  - Prevent release of existing T4:** Start KI-iodide 130mg cap POING/PR 1 hour after thionamide giving. Iodine/amide could cause further T4 production/release. OR Na iodide (NA in Canada) 0.5 g slow IV drip over 24 hours. OR 15 drops of saturated solution of potassium iodide (SSKI), twice 5 drops PO q6h. OR 1mL (4-5 drops) Lugol's solution (KI, NA in Canada) PO TID. Use x 3-7 days or until resolution.
  - Dexamethasone 0.5-2mg POING q6h** or Hydrocortisone 100 mg IV q12h. (Blocks T4-T3 and may inhibit T4 release)
  - Vigorous correction of fluid deficits and electrolyte imbalances.
  - Hyperthermia** management with acetylaminophen.
  - Treatment of infection or other precipitating causes.

## Types of Hyperthyroidism & Symptom:

B-blockers (eg. atenolol 25-200mg QD) useful for symptom reduction (palpitations, tachycardia, tremulousness, anxiety, heat intolerance) regardless of cause/etiology.

**High T3 uptake (oversensitivity):**  
Graves' Disease: thyroid-stimulating immunoglobulins which act like TSH. Accompanied by goiter + ophthalmopathy (proptosis). Most common cause of hyperthyroidism. A.K.A. Basedow's, Bégbie's, Plaján's, Faján-Baseow, Marini's, Parry's disease. **Therapy:** (1) I-131 (2) Subtotal thyroidectomy (3) Thionamides (see box). **All 3 options equal biochemical outcomes at 6 weeks and 2y satisfaction & sick leave outcomes. Most relate with thionamides, more ophthalmopathy with I-131.** (J Clin Endocrinol Metab 1996;81:2886-83)  
**Hasthloxicosis:** Early stages of Hashimoto's thyroiditis may exhibit hyperthyroidism (later hypothyroidism). **Therapy:** Hyperthyroidism is transient, so use B-blockers. ASA/steroids only if tender.

**Toxic Adenoma + Multinodular goiter:** TSH-independent thyroid adenomas due to TSH receptor mutations. **Therapy:** I-131. Surgery is less preferable.  
**Iodine-induced:** rare. **Therapy:** decrease iodine intake. Radioiodine if underlying adenoma.  
**Trophoblastic diseases:** hydatidiform mole or choriocarcinoma and Germ cell tumors: testicular. **Therapy:** Thionamides + surgery.  
**TSH-mediated:** rare. Pituitary adenoma. **Therapy:** Surgery, octreotide 50-75mg SC bid 6-8 weeks TSH, dopamine agonists (bromocriptine 10-20mg/d, cabergoline 0.25-0.5mg 1-2x/wk).

**Low (<1%) I131 uptake (thyroiditis, overstimulation, extrathyroid source):**  
**Thyroiditis:** post-viral (de Quervain's, granulomatous, giant-cell, creeping), lymphocytic/alein/painless, postpartum, amiodarone-induced, radiation, interferon alpha-induced, papillon (parathyroid surgery)-induced. **Therapy:** NSAIDs, B-blockers, steroids (if painful), iopanoic acid (see box). Thionamides useless.  
**Exogenous/Endo:** overdose (use B-blocker), "Struma ovarii" (surgery), follicular thyroid cancer metastases (surgery).

## Subclinical Hyperthyroidism [JAMA 2004;291:228-38, JAMA 2006;296:1033-1041, J Clin Endocrinol Metab 2007;92:3-8]

**Definition:** TSH <0.1 + Normal T3 & T4 + no symptoms of hyperthyroidism  
~1% prevalence in community, 14-21% in L-thyroxine-treated patients  
**Issues:** atrial fibrillation (RR 2.0), osteoporosis (inconsistent evidence, possibly more risk in men [Arch Intern Med 2010;170:1876-83], progression to hyperthyroidism. No in cardiac death [Arch Intern Med 2007;167(14):1526-1532].  
**Management:** In absence of underlying hyperthyroid diagnosis (eg. Graves), no evidence that treatment alters any of these outcomes. Consider thionamides in pts with AF + >60yo. Regular thyroid monitoring in all patients to detect overt hyperthyroidism.

## Management of amiodarone-induced hyperthyroidism (3%) [J Clin Endocrinol Metab, June 2010, 95(6):2529-2535]

**Type I (increased T3 & T4 synthesis "Jod Basedow")**  
-mainly in I-iodine deficient areas & in patients with underlying multinodular goiter  
-treat with thionamides (MMI 40-60 mg/d or PTU 400-600 mg/d) for first 2-6 weeks. Several weeks required to achieve euthyroidism. If refractory, thyroidectomy.  
-may continue amiodarone  
-response slow regardless of discontinuation of amiodarone d/t its long t1/2  
**Type II (thyroiditis) - most common form**  
-treat with corticosteroids. Thionamides not usually helpful.  
-usually discontinue amiodarone  
**NOTE:** Usually difficult to distinguish between Type I & II.

## Radioiodine (I-131)

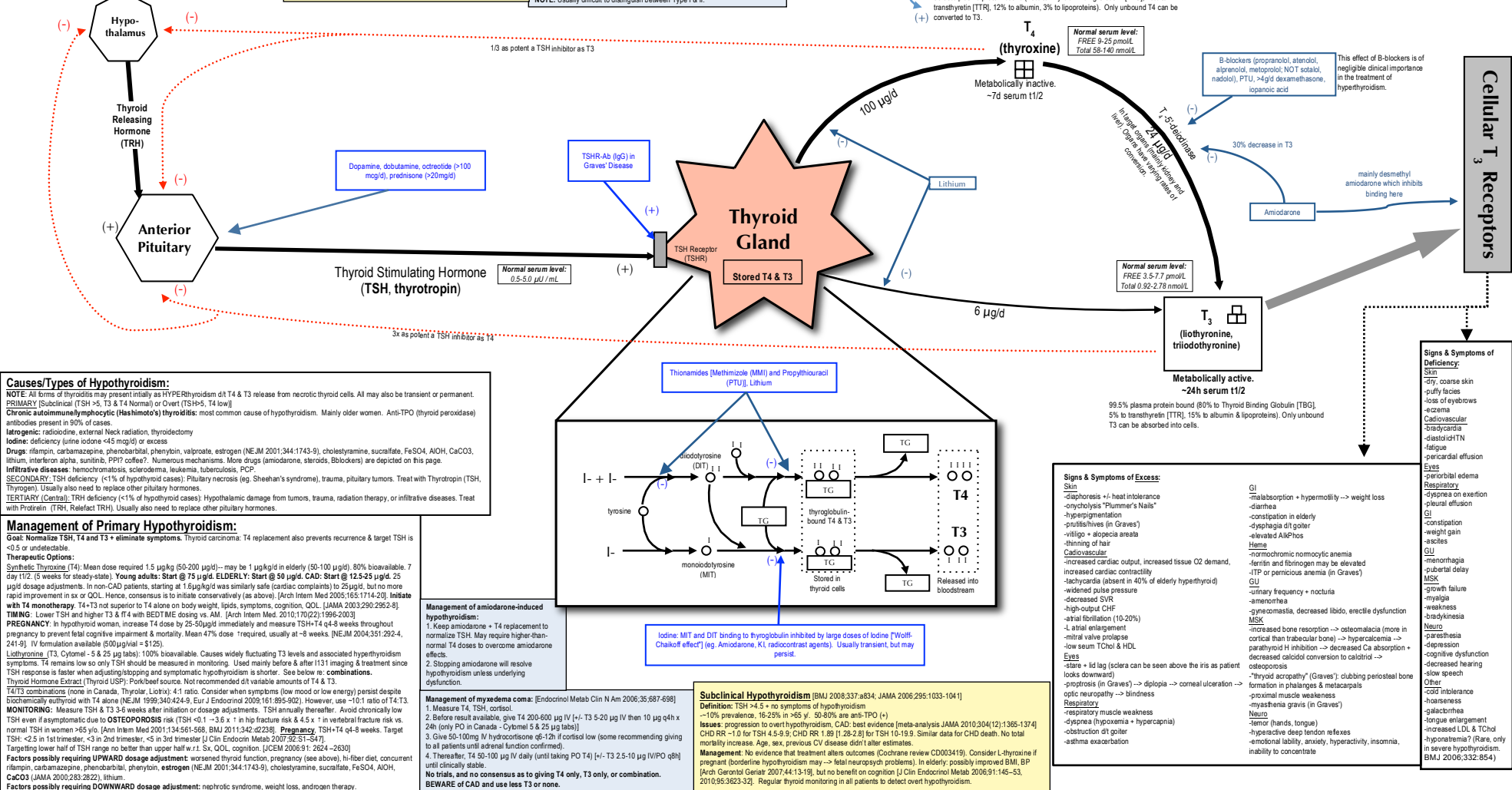
- preferred treatment for Graves' by ~70% of endocrinologists in NA.
- given PO as solution or capsule
- high dose (128 to 155 µCi/g [4.7 to 5.7 MBq/g]) cures hyperthyroidism in 90% of patients @6-18 weeks, but eventually causes hypothyroidism in ~80%
- lower doses cause less hypothyroidism, but <33% are euthyroid @ 10 years.
- may cure or worsen proptosis in Graves' (give prednisone 20-40 mg/d x 2-3 months starting 5-7 days after I131 in patients with severe ophthalmopathy - NEJM 1986;336:73-8)
- dose based on thyroid gland mass + iodine uptake %
- usually start 3-7 days after I-131 dose to prevent early temporary hypothyroidism (assumption or not has no effect on 12month outcome - Eur J Endocrin 2003;149:485-82)
- some use I-131 several weeks after I-131 to enhance its efficacy, but conflicting data
- 20% require second dose 6-12 months after initial dose
- only toxicity is radiation thyroiditis (1% - treat with NSAIDs.
- instruct patients to avoid sharing cups or utensils; sexual contact and close contact with children and pregnant women for one week
- delay pregnancy for 6-12 months after therapy
- monitor via serum T4, implement T4 replacement when indicated

## Thionamides: Methimazole (MMI, Tapazole) & Propylthiouracil (PTU, Propyl-Thyracil) in Graves' Disease

- Used to attain euthyroid state, either in prep for I-131 or thyroidectomy or for long-term (usually 1-2y) suppressive therapy. 20-30% have prolonged remission after 1-2y of thionamide therapy (probably spontaneous, similar with propylthiouracil).
- MMI:** Generally preferred. More rapid onset (~80% euthyroid @ 10 weeks, 5-8 weeks to normalization vs. ~50% with PTU. 16.8 weeks to normalization - J Clin Endocrinol Metab 1987;65:1719-23). once-daily dosing (vs. q6h with PTU), fewer serious adverse effects. 10 or 15mg PO daily (similar response as 30 or 40mg/d) (Clin Endocrinol 1995;43:257-63, J Clin Endocrinol Metab 2007;92: 2157-62). Use 20 or 30mg/d if large goiter or "severe" hyperthyroidism (FT<sub>4</sub> >90 pmol/L). Divide into TID if GI side effects. If using long-term therapy, taper to lowest effective dose based on T4 & T3. One study showed higher remission rates with MMI-T4 than MMI alone ("block-replace regimen"), but subsequent studies have not confirmed (J Clin Endocrinol Metab 1998;83:14-8), so combination therapy not recommended at present. Avoid in pregnancy due to rarely reported aplasia clefts.
- PTU:** Preferred in pregnancy (less placental transfer). 100mg PO tid or 150 tid if large goiter or "severe" hyperthyroidism. Relevance of inhibition of peripheral T4->T3 conversion questionable. Single-daily-dose trials (150mg QD) show inferior efficacy to MMI 15mg QD (Clin Endocrinol 2004;60:616-9, 2001;54:385-90)
- Toxicity:** Common (~13%): pruritus, rash, urticaria, arthralgias, arthritis, fever, abnormal taste sensation, nausea/vomiting. 33% have transient liver enzyme elevation with PTU. Excessive initial doses cause HYPOTHYROIDISM. **Rare/Serious:** agranulocytosis (0.2-0.5, rapid recovery on discontinuation) Dose-dependent with MMI (4%vs.0.3% over 10 years with 30mg vs. 15 mg/d [Endo J 2007;54:39-43]). Check status with MMI. Liver failure (sometimes fatal) with PTU (FDA Alert April 2010). Up to 38% ANCA positive with PTU (vs. 0% with MMI) but vasculitis is rare.
- Goat:** Achieve euthyroidism (normal T4 & T3) within 3-4 weeks.
- Monitoring:** q4-6 weekly T4 & T3 (TSH may take several months to recover). After TSH normalizes, no need to continue T3 monitoring. Most do not recommend regular CBCs, but advise pts to seek attention at first sign of fever or pharyngitis.
- Duration:** taper/withdraw after 12-24 months of therapy to assess for remission. Relapse rates not well defined (30-50% @ 1-2y). If relapse (50%), consider I131 therapy.

## Iopanoic acid (Telepaque) - not available in Canada

- oral radiocontrast agent for cholecystography
- less effective than thionamides as monotherapy, may exacerbate hyperthyroidism d/t iodine content (67%)
- I<sup>131</sup> reduces T3 and T4 release more rapidly than MMI or PTU alone in acute thyrotoxicosis (Clin Endocrinol 1988;28:305-14)
- use short term only (< 10 days). Use with Blocker + steroid in thyroiditis (where thionamide is useless) and if thionamide allergy.



## Causes/Types of Hypothyroidism:

**NOTE:** All forms of hypothyroidism may present initially as HYPERTHYROIDISM d/t T4 & T3 release from necrotic thyroid cells. All may also be transient or permanent.

**PRIMARY:** (Subclinical [TSH <5, T3 & T4 normal])

- Chronic autoimmune/lymphocytic (Hashimoto's) thyroiditis:** most common cause of hypothyroidism. Mainly older women. Anti-TPO (thyroid peroxidase) antibodies present in 90% of cases.
- Iatrogenic:** radioiodine, external neck radiation, thyroidectomy
- Iodine:** deficiency (yine iodone <45 mg/d) or excess
- Drugs:** rilpampin, carbamazepine, phenobarbital, phenytoin, valproate, estrogen (NEJM 2001;344:1743-9), cholestyramine, succralfate, FeSO4, AIOH, CaCO3, lithium, interferon alpha, sunitinib, PPI? coffee??. Numerous mechanisms. More drugs (amiodarone, B-blockers) are depicted on this page.
- Infiltrative diseases:** hemochromatosis, scleroderma, leukemia, tuberculosis, PCP
- SECONDARY:** TSH deficiency (<1% of hypothyroid cases). Pituitary necrosis (eg. Sheehan's syndrome), trauma, pituitary tumors. Treat with Thyrotropin (TSH, Thyrogen). Usually also need to replace other pituitary hormones.
- TERTIARY (Central):** TRH deficiency (<1% of hypothyroid cases). Hypothalamic damage from tumors, trauma, radiation therapy, or infiltrative diseases. Treat with Protirelin (TRH, Relactin TRH). Usually also need to replace other pituitary hormones.

## Management of Primary Hypothyroidism:

**Goal:** Normalize TSH, T4 and T3 + alleviate symptoms. Thyroid carcinoma: T4 replacement also prevents recurrence & target TSH is <0.5 or undetectable.

**Therapeutic Options:**

**Synthetic Thyroxine (T4):** Mean dose required 1.5 µg/kg (50-200 µg/d) - may be 1 µg/kg/d in elderly (50-100 µg/d), 80% bioavailable. 7 day t1/2. (5 weeks for steady-state). **Young adults:** Start @ 75 µg/d. **ELDERLY:** Start @ 50 µg/d. **CAD:** Start @ 12.5-25 µg/d. 25 µg/d dosage adjustments. In non-CAD patients, starting at 1 µg/kg/d was similarly safe (cardiac complaints) to 25µg/d, but no more rapid improvement in sex or QOL. Hence, consensus is to initiate conservatively (as above). [Arch Intern Med 2005;165:1714-20]. **Initiate with T4 monotherapy.** T4+T3 not superior to T4 alone on body weight, lipids, symptoms, cognition. QOL [JAMA 2003;290:2952-8]

**TMNG:** Lower TSH and higher T4 with BEDT/ME dosing vs. AM. [Arch Intern Med 2010;170:1922-1996-2003]

**PREGNANCY:** In hypothyroid woman, increase T4 dose by 25-50µg/d immediately and measure TSH-T4 q4-8 weeks throughout pregnancy to prevent fetal cognitive impairment & mortality. Mean 47% dose required, usually at ~8 weeks. [NEJM 2004;351:2924, 241-9]. IV formulation available (500µg/ml = 5125).

**Liothyronine (T3, Cytomel - 5 & 25 µg tabs):** 100% bioavailable. Causes widely fluctuating T3 levels and associated hyperthyroidism symptoms. T4 remains low so only TSH should be measured in monitoring. Used mainly before & after I131 imaging & treatment since TSH response is faster when adjusting/stopping and symptomatic hypothyroidism is shorter. See below re combinations.

**Thyroid Hormone Extract (Thyro-T USP):** Pork/beef source. Not recommended d/t variable amounts of T4 & T3.

**T4/T3 combinations (none in Canada, Thyrolar, Liotrix):** 4:1 ratio. Consider when symptoms (low mood or low energy) persist despite biochemically euthyroid with T4 alone [NEJM 1999;340:424-9, Eur J Endocrinol 2009;161:895-902]. However, use ~1:1 ratio of T4:T3.

**MONITORING:** Measure TSH & T3 3-6 weeks after initiation or dosage adjustments. TSH annually thereafter. Avoid chronic low TSH even if asymptomatic due to **OSTEOPOROSIS** risk (TSH <0.1 -3.6 x 1 m in hip fracture risk & 4.5 x 1 m in vertebral fracture risk vs normal TSH in women >65 yo. [Ann Intern Med 2001;134:561-568, BMJ 2011;342:42238]. **Pregnancy:** TSH-T4 q4-8 weeks. Target TSH <2.5 in 1st trimester, <3 in 2nd trimester, <5 in 3rd trimester [J Clin Endocrinol Metab 2007;92:521-S4-7]. Targeting lower half of TSH range no better than upper half w/ 1x. QOL, cognition. [JCEM 2006;91:2624 -2630]

**Factors possibly requiring UPWARD dosage adjustment:** worsened thyroid function, pregnancy (see above), hi-fiber diet, concurrent rilpampin, carbamazepine, phenobarbital, phenytoin, estrogen (NEJM 2001;344:1743-9), cholestyramine, succralfate, FeSO4, AIOH, CaCO3 (JAMA 2000;283:2822), lithium.

**Factors possibly requiring DOWNWARD dosage adjustment:** nephrotic syndrome, weight loss, androgen therapy.

## Management of amiodarone-induced hyperthyroidism:

- Keep amiodarone + T4 replacement to normalize TSH. May require higher-than-normal T4 doses to overcome amiodarone effects.
- Stopping amiodarone will resolve hypothyroidism unless underlying dysfunction.

## Management of myxedema coma: [Endocrinol Metab Clin N Am 2006;35:687-698]

- Measure T4, TSH, cortisol.
  - Before result available, give T4 200-600 µg IV (-/- T3 5-20 µg IV then 10 µg q4h x 24h (only PO in Canada - Cytomel 5 & 25 µg tabs))
  - Give 50-100mg IV hydrocortisone q6-12h in cortisol low (some recommending giving to all patients until adrenal function confirmed).
  - Thereafter, T4 50-100 µg IV daily (until taking PO T4) (-/- T3 2.5-10 µg IV/PO q6h until clinically stable.
- No trials, and no consensus as to giving T4 only, T3 only, or combination.**
- BEWARE of CAD and use less T3 or none.**

## Subclinical Hypothyroidism [BMJ 2008;337:a834, JAMA 2006;295:1033-1041]

**Definition:** TSH >4.5 + no symptoms of hypothyroidism  
~10% prevalence, 16-25% in >65 yo, 50-80% are anti-TPO (+)  
**Issues:** progression to overt hypothyroidism. CAD: best evidence [meta-analysis JAMA 2010;304(12):1365-1374] CHD RR ~1.0 for TSH 4.5-9, CHD RR 1.89 [1.28-2.8] for TSH 10-19.9. Similar data for CHD death. No total mortality increase. Age, sex, previous CV disease didn't alter estimates.  
**Management:** No evidence that treatment alters outcomes (Cochrane review DC003419). Consider L-thyroxine if pregnant (borderline hypothyroidism may -> fetal neuro-psych problems). In elderly, possibly improved BMJ, BP [Arch Genet Geniv 2007;44:13-19], but no benefit on cognition [J Clin Endocrinol Metab 2006;91:146-53, 2010;95:3623-32]. Regular thyroid monitoring in all patients to detect overt hypothyroidism.

## Cellular T3 Receptors

## Signs & Symptoms of Deficiency:

- Skin**
  - dry, coarse skin
  - puffy face
  - loss of eyebrows
  - eczema
  - Cardiovascular**
    - bradycardia
    - diastolic HTN
    - pericardial effusion
  - Eyes**
    - periorbital edema
  - Respiratory**
    - dyspnea on exertion
    - nasal effusion
    - constipation
    - weight gain
    - asthma
  - GI**
    - constipation
    - weight gain
    - asthenia
    - malabsorption
    - anorexia
    - hypochromic normocytic anemia
    - ferritin and ferritinogen may be elevated
    - TTP or pernicious anemia (in Graves)
  - GU**
    - oliguria
    - proteinuria + nocturia
    - anemia
    - gynecomastia, decreased libido, erectile dysfunction
    - MSK**
      - myalgia
      - arthralgia
      - muscle fatigue
      - MSK
      - growth failure
      - myalgia
      - weakness
      - bradychinesia
      - parasthesia
      - depression
      - cognitive dysfunction
      - decreased hearing
      - slow speech
      - HSD intolerance
      - hirsuteness
      - galactorrhea
      - growth enlargement
      - increased LDL & Chd
      - hypoparathyria? (Rare, only in severe hypothyroidism)
      - BMJ 2006;332:854)

## Signs & Symptoms of Excess:

- Skin**
  - diaphoresis +/- heat intolerance
  - onychia "Plummer's Nails"
  - hyperpigmentation
  - pruritus/rhives (in Graves)
  - vitiligo + alopecia areata
  - thinning of hair
  - Cardiovascular**
    - increased cardiac output, increased tissue O2 demand,
    - increased cardiac contractility
    - tachycardia (absent in 40% of elderly hyperthyroid)
    - widened pulse pressure
    - decreased SVR
    - high-output CHF
    - atrial fibrillation (10-20%)
    - l. atrial enlargement
    - mitral valve prolapse
    - low serum TChol & HDL
  - Eyes**
    - stare + lid lag (sclera can be seen above the iris as patient looks downward)
    - proptosis (in Graves) -> diplopia -> corneal ulceration
    - optic neuropathy -> blindness
    - Respiratory**
      - respiratory muscle weakness
      - dyspnea (hypoxemia + hypercapnia)
      - obstruction d/t goiter
      - asthma exacerbation
    - GI**
      - malabsorption + hypermotility -> weight loss
      - diarrhea
      - constipation in elderly
      - dyslipid d/t goiter
      - elevated ALT/Phos
    - Heme**
      - normochromic normocytic anemia
      - ferritin and ferritinogen may be elevated
      - TTP or pernicious anemia (in Graves)
    - GU**
      - oliguria
      - proteinuria + nocturia
      - anemia
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