Thyroid Physiology, Pharmacology, & Pharmacotherapy

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Thyrotoxicosis / "Thyroid Storm" Therapy

[Diagnosis: Burch & Wartofsky Endocrinol Metab Clin North Amer 1993;22:263.]. Below adapted from S Med J 2002;95:493-505, Endocrinol Metab Clin N Am 2006;35:663-686 and Chiha M, J Intensive Care Med 2013;1-10.

1. **Control acute symptoms**: Propranolol 60-1200 mg PO/NG q4-6h or IV 1mg/min, or Esmolol 250-500 µg load + 50-100 µg/kg/min infusion. Target: HR<100 bpm.
2. **Inhibit further T4 production**: Begin PTU 500-1000mg PO/NG load + 250mg q4h; May be preferred (vs MMI) d/t blocade of T4->T3 conversion. Methimizole 60-120mg daily is alternative.
3. **Prevent release of existing T4**: Start K-iodide 130mg cap PO/NG/PR 1 hour after thionamide (giving I⁻ before thionamide could cause further T4 production/release); OR 15 drops of saturated solution of potassium iodide (SSKI), then 5 drops PO q6h; OR 1mL (4-8 drops) Lugol's solution (KI, N/A in Canada) PO TID. Use x 3-7 days or until resolution.
4. **Dexamethasone** 0.5-2mg PO/NG q6h; or Hydrocortisone 100 mg IV q8-12h. (blocks T4->T3 and may inhibit T4 release)
5. Vigorous correction of **fluid** deficits and electrolyte imbalances.
6. **Hyperthermia** management with acetaminophen & cooling blankets.
7. Treatment of **infection** or other precipitating causes.

Types of Hyperthyroidism & Management: [ATA-AACE Guidelines: Endocr Pract. 2011;17(3):456-520]

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

High I131 uptake (oversynthesis):

Graves' Disease: thyroid-stimulating immunoglobulins which act like TSH. Accompanied by goiter + orbitopathy (proptosis). Most common cause of hyperthyroidism. A.K.A. Basedow's, Begbie's, Flajani's, Flajani-Basedow, Marsh'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 relapse with thionamides, more orbitopathy with I-131.** (J Clin Endocrinol Metab 1996;81:2986-93)

Hashitoxicosis: 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: hydatiform mole or choriocarcinoma and Germ cell tumors: testicular. **Therapy**: Thionamides + surgery.

TSH-mediated: rare. Pituitary adenoma. **Therapy**: Surgery, octreotide 50-750mcg SC bid-tid supresses 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/silent/painless, postpartum, amiodarone-induced, radiation, interferon alpha-induced, palpation (parathyroid surgery)-induced. **Therapy**: NSAIDs, B-blockers, steroids (if painful), iopanoic acid (see box). Thionamides useless.

Exogenous/Ectopic: overdose (use B-blocker), "Struma ovarii" (surgery), follicular thyroid cancer metastases (surgery).

Subclinical Hyperthyroidism

Definition: TSH <0.1 + Normal T3 & T4 + no symptoms of hyperthyroidism

~1% prevalence in community, 14-21% in L-thyroxine-treated patients

Issues: Increased total (HR 1.24) & CHD mortality (HR 1.29), sudden cardiac death [Circulation 2016;6SEP], atrial fibrillation (HR 1.7) [Arch Intern Med. 2012;172(10):799-809], fractures (HR 1.38 hip, 1.20 non-spine) [Ann Intern Med 2014;161:189-99], possibly more risk in men [ArchIntern Med 2010;170:1876-83], progression to hyperthyroidism.

Management: in absence of underlying hyperthyroid diagnosis (eg, Graves), no evidence that treatment alters any of these outcomes. Consider thionamides in pts with AF, elderly, cardiac risk. [[ATA-AACE Guidelines: Endocr Pract. 2011;17(3):456-520]. 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-deficient areas & in patients with underlying multinodular goitre

-treat with thionamides (MMI 40-60 mg/d)+K-perchlorate (KClO4) 0.5-1g/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)

-prefered 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 opthalmopathy - NEJM 1998;338:73-8)

-dose based on thyroid gland mass + Iodine uptake %.

-stop MMI 3-7 days before dose to prevent failure of I-131 uptake. Do not use PTU prior to I-131 (reduces efficacy of I-131, while MMI does not - Thyroid 2004;14:525-30, J Int Med Res 2009;37:576-82)

-usually start MMI 3-7 days after I-131 dose to prevent early temporary thyrotoxicosis [resumption or not has no effect on 12month outcome - Eur J Endocrin 2003;149:485-92]

-some use Li for 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: Methimizole (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) supressive therapy. 20-30% have prolonged remission after 1-2y of thionamide therapy (probably spontaneous, similar with propranolol).

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;65:719-23), once-daily dosing (vs. q8h 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). Initial dose to achieve euthyroidism: 10-20mg daily. Once euthyroid taper to lowest effective dose (2.5-10mg) 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;83:814-8), so combination therapy not recommended at present. Avoid in pregnancy due to aplasia cutis.

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;60:676-81, 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)]. Cholestatis with MMI. Liver failure (sometimes fatal) with PTU [FDA Alert April 2010]. Up to 38% ANCA positivity with PTU (vs. 0% with MMI) but vasculitis is rare.

Goal: Acheive euthyroidism (normal T4 & T3) within 3-8 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 CBC's, 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.

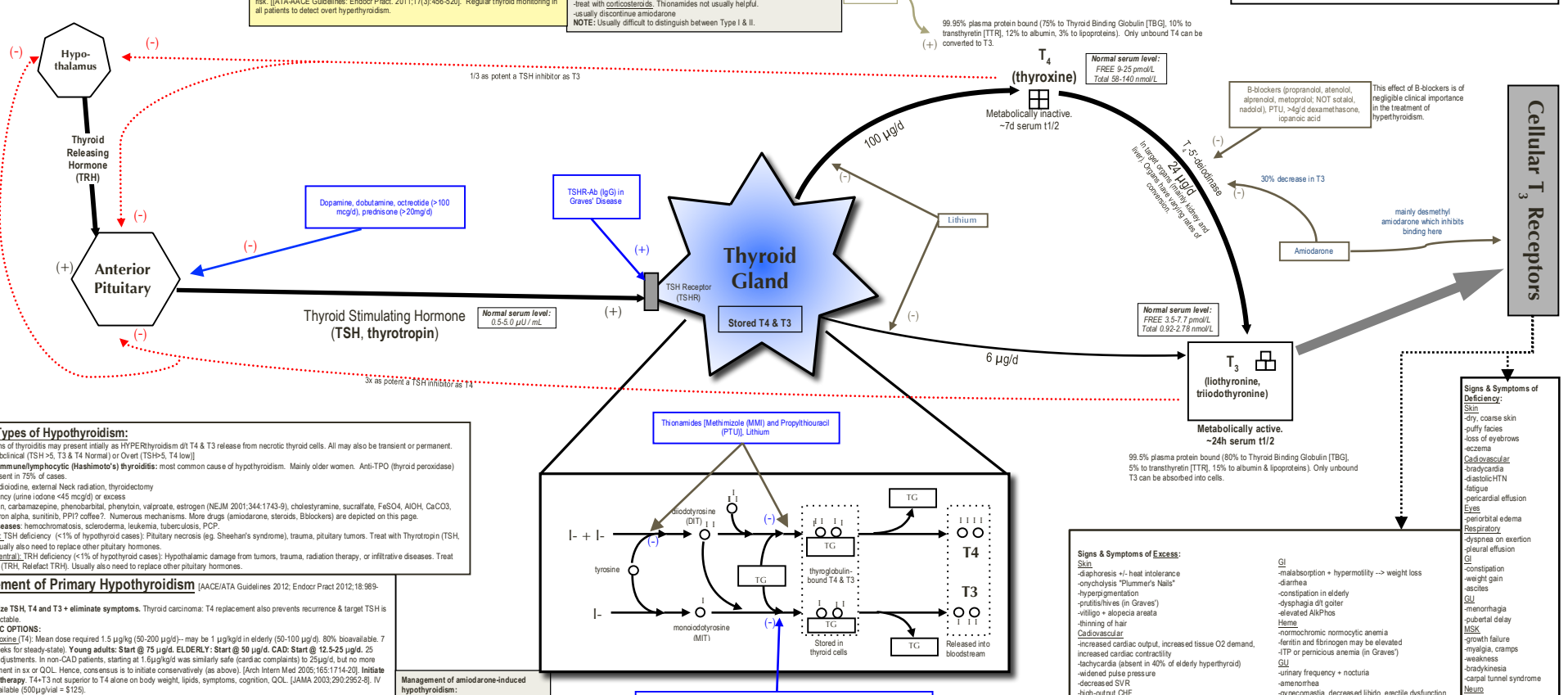
Iopanoic acid (Telepaque) - not available in Canada

-oral radiocontrast agent for cholecystography

-less effective than thionamides as monotherapy, may exacerbate hyperthyroidism d/t iodine content (67%)

-1g/d reduces T3 and heart rate more rapidly than MMI or PTU alone in acute thyrotoxicosis (Clin Endocrinol 1988;28:305-14)

-use short term only (< 10 days). Use with Bblocker + steroid in thyroiditis (where thionamide is useless) and if thionamide allergy.



Causes/Types of Hypothyroidism:

NOTE: All forms of thyroiditis may present intially 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) or Overt (TSH>5, T4 low)]

Chronic autoimmune/lymphocytic (Hashimoto's) thyroiditis: most common cause of hypothyroidism. Mainly older women. Anti-TPO (thyroid peroxidase) antibodies present in 75% of cases.

Iatrogenic: radioiodine, external Neck radiation, thyroidectomy

Iodine: deficiency (urine iodine <45 mcg/d) or excess

Drugs: rifampin, carbamazepine, phenobarbital, phenytoin, valproate, estrogen (NEJM 2001;344:1743-9), cholestyramine, sucralfate, FeSO4, AlOH, CaCO3, lithium, interferon alpha, sunitinib, PPI? coffee?. Numerous mechanisms. More drugs (amiodarone, steroids, Bblockers) 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, Relefact TRH). Usually also need to replace other pituitary hormones.

Management of Primary Hypothyroidism

[AACE/ATA Guidelines 2012; Endocr Pract 2012;18:989-1027.]

Goal: Normalize TSH, T4 and T3 + eliminate 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 1.6µg/kg/d was similarly safe (cardiac complaints) to 25µg/d, but no more rapid improvement in sx 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]. IV formulation available (500µg/vial = $125).

TIMING: Lower TSH and higher T3 & fT4 with BEDTIME dosing vs. AM. [Arch Intern Med. 2010;170(22):1996-2003]

PREGNANCY: In hypothyroid woman (TSH>2.5), increase T4 dose by 25-30% immediately to prevent fetal cognitive impairment & mortality. Mean 47% dose ↑ required, usually at ~8 weeks. [NEJM 2004;351:292-4, 241-9]. Target TSH <2.5 mIU/L + normal T4 in trimester1, 3.0-3.5 thereafter. TSH, T4, T3 q4 weeks (AACE/ATA guideline).

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.**

T4/T3 combinations (none in Canada, Thyrolar, Liotrix): 3-4:1 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, Curr Opin Endocrinol Diabetes Obes 2013;20:460–6.). However, probably use ~10:1 ratio of T4:T3.

MONITORING: Measure TSH & T3 3-6 weeks after initiation or dosage adjustments. TSH annually once stable. Avoid chronically low TSH even if asymptomatic due to **OSTEOPOROSIS** risk (TSH <0.1 → 3.6 x ↑ in hip fracture risk & 4.5 x ↑ in vertebral fracture risk vs. normal TSH in women >65 y/o. [Ann Intern Med 2001;134:561-568, BMJ 2011;342:d2238]. **Pregnancy**: see above.

Targeting lower half of TSH range no better than upper half w.r.t. Sx, QOL, cognition. [JCEM 2006:91: 2624 –2630]

Factors possibly requiring UPWARD dosage adjustment: worsened thyroid function, pregnancy (see above), hi-fiber diet, concurrent rifampin, carbamazepine, phenobarbital, phenytoin, **estrogen** (NEJM 2001;344:1743-9), cholestyramine, sucralfate, FeSO4, AlOH, **CaCO3** (JAMA 2000;283:2822), lithium, nephrotic syndrome [Eur Thyroid J 2015;4(2):138-142].

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

Management of amiodarone-induced hypothyroidism:

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

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

1. Measure T4, TSH, cortisol.
2. 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)] then 50-100 µg PO daily.
3. Give 50-100mg IV hydrocortisone q6-12h if cortisol low (some recommending giving to all patients until adrenal function confirmed).
4. Thereafter, T4 50-100 µg IV daily (until taking PO T4) [+/- T3 2.5-10 µg IV/PO q8h] 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; JAGS 2015;63:1663-73]

Definition: TSH 4.5-10 + no symptoms of hypothyroidism. (If TSH>10 treat regardless of sx.)

~10% prevalence, 16-25% in >65 y/. 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 4.5-9.9; 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 CD003419). Consider L-thyroxine if pregnant (borderline hypothyroidism may --> fetal neuropsych problems, tx may reduce preterm delivery [Cochrane Database Syst Rev 2010 Jul 7;(7):CD007752]). In elderly: possibly improved BMI, BP [Arch Gerontol Geriatr 2007;44:13-19], but no benefit on cognition [J Clin Endocrinol Metab 2006;91:145–53, 2010;95:3623-32]. Regular thyroid monitoring in all patients to detect overt hypothyroidism.

Signs & Symptoms of Excess:

Skin
-diaphoresis +/- heat intolerance
-onycholysis "Plummer's Nails"
-hyperpigmentation
-pruritis/hives (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 seum 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
-tachypnea→respiratory muscle weakness
-dyspnea (hypoxemia + hypercapnia)
-obstruction d/t goiter
-asthma exacerbation
GI
-malabsorption + hypermotility --> weight loss
-diarrhea
-constipation in elderly
-dysphagia d/t goiter
-elevated AlkPhos
Heme
-normochromic normocytic anemia
-ferritin and fibrinogen may be elevated
-ITP or pernicious anemia (in Graves')
GU
-urinary frequency + nocturia
-amenorrhea
-gynecomastia, decreased libido, erectile dysfunction
MSK
-increased bone resorption --> osteomalacia (more in cortical than trabecular bone) --> hypercalcemia --> parathyroid H inhibition --> decreased Ca absorption + decreased calcidol conversion to calcitriol --> osteoporosis
-"thyroid acropathy" (Graves'): clubbing periosteal bone formation in phalanges & metacarpals
-proximal muscle weakeness
-myasthenia gravis (in Graves')
Neuro
-temor (hands, tongue)
-hyperactive deep tendon reflexes
-emotional lability, anxiety, hyperactivity, insomnia, inability to concentrate

Signs & Symptoms of Deficiency:

Skin
-dry, coarse skin
-puffy facies
-loss of eyebrows
-eczema
Cardiovascular
-bradycardia
-diastolicHTN
-fatigue
-pericardial effusion
Eyes
-periorbital edema
Respiratory
-dyspnea on exertion
-pleural effusion
GI
-constipation
-weight gain
-ascites
GU
-menorrhagia
-pubertal delay
MSK
-growth failure
-myalgia, cramps
-weakness
-bradykinesia
-carpal tunnel syndrome
Neuro
-paresthesia
-depression
-cognitive dysfunction
-decreased hearing
-slow speech
-sleep apnea
Other
-cold sensitivity
-hoarseness
-galactorrhea
-hyperprolactinemai
-tongue enlargement
-increased LDL & TChol
-hyponatremia? (Rare, only in severe hypothyroidism. BMJ 2006;332:854)