

# Management of hypothyroidism

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## Conflict of Interest Disclosure

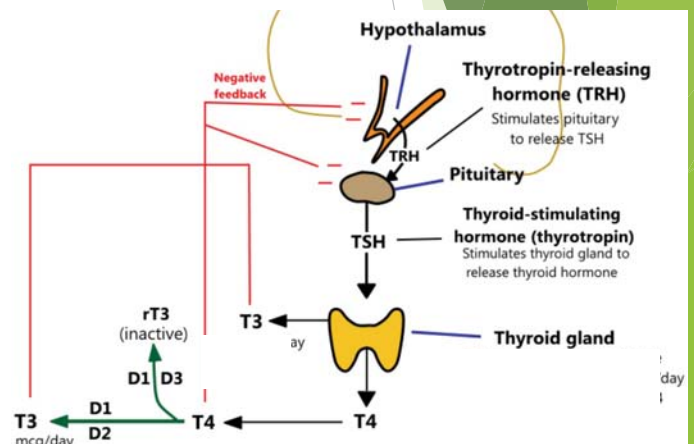
- ▶ No conflicts to declare

# Management of hypothyroidism in family practice

- ▶ Overview of which patients to treat with hypothyroidism
  - ▶ How to start therapy and monitor
- ▶ Special populations to consider
  - ▶ Elderly patients
  - ▶ Cardiovascular disease patient (CVD or CV)
  - ▶ Osteoporotic patient
  - ▶ Pregnancy / conception aged women
  - ▶ Central hypothyroidism
  - ▶ Subclinical hypothyroidism (SCH)
- ▶ Alternatives to Synthroid: why and what

# Hypothyroidism: biochemical diagnosis of reduced / absent thyroid production

- ▶ Distinguish hypothyroidism and subclinical hypothyroidism (SCH)
  - ▶ TSH above normal with **low T4**: overt hypothyroidism
  - ▶ TSH above normal with **normal T4**: subclinical hypothyroidism
- ▶ Primary hypothyroidism: etiology within thyroid gland (often +TPO or thyroidectomy or radioactive iodine)
- ▶ Secondary hypothyroidism: pituitary issue (absence of TSH) >>> hypothalamic



## Overt hypothyroidism (low T4) or TSH >10 generally warrants therapy

- ▶ Recommendation to treat patients with TSH > 10 (can repeat to confirm especially if asymptomatic) or patients with low T4 (ie overt hypothyroidism)
  - ▶ No imaging required for diagnosis/treatment
  - ▶ Anti TPO ab can be drawn once to confirm auto-immune nature but have little role to play otherwise (more on this later)
- ▶ Symptoms of hypothyroidism lack specificity -> TSH used for diagnosis

Walsh et al. 2006 *J Clin Endocrinol Metab* 91:2624-2630  
Zulewski et al 1997 *JCEM* 82:771-776

## Levothyroxine (T4) is first line therapy to target normal range TSH

- ▶ Levothyroxine best absorbed on empty stomach but ultimately **consistency** is key
  - ▶ 30-60 min prior to breakfast / 3 hours post meal (bedtime)
  - ▶ Avoid calcium/fiber/soy rich foods
  - ▶ Avoid iron, phosphate binder, aluminum based antacid, bile acid sequestrants and calcium supplements (4 hours)
- ▶ There is no evidence to support difference between brand and generic T4 replacement therapy in adults
  - ▶ Would repeat TSH 6 weeks later if change made
  - ▶ No reason to change if TSH in target

Lomenick et al 2013 *J Clin Endocrinol Metab* 98:653-658  
Hennessey et al 2003 *Thyroid* 13:279-282  
Hennessey JV et al 2013 *J Clin Endocrinol Metab* 98:511-514

# Initiate 1.6mcg/kg/day Levothyroxine or treat low and titrate: little gain in overtreating fast



- ▶ Many factors influence absorption of Levothyroxine: ideal body weight, age, etiology of hypothyroidism, lean body weight
  - ▶ Patients with CV disease/tachy-arrhythmia or >65, start low (0.025-0.05mg)
  - ▶ TSH <10 or SC hypothyroidism: start 0.05mg and titrate up (likely need lower doses)
  - ▶ Patients with thyroidectomy or young/healthy: weighted dose can be used but no harm in 0.05mg initiation
- ▶ There is no urgency to normalize TSH other than pregnancy or metastatic thyroid cancer / high risk thyroid cancer
  - ▶ If in doubt, start low and go slow: no difference in time to symptom resolution

Pecina et al 2014 Am J Med 127:240-245  
Roos A et al 2005 Arch Int Med 2005;165(15):1714

# Repeat TSH 6 weeks after dose change and aim for normal TSH

- ▶ TSH as best marker of adequate thyroid function rather than symptoms
  - ▶ Very little role for T3 and T4 in follow up
  - ▶ Symptom assessment not well correlated with adequacy of dosing (little perceived difference in symptoms and strong expectation of benefit)
- ▶ Repeat TSH every 6-12 months or sooner if modifying condition/drug:
  - ▶ Menopause (estrogen)
  - ▶ New drug that interfere with absorption
  - ▶ GI conditions
  - ▶ Symptoms of hypo/hyperthyroidism
  - ▶ Change in weight

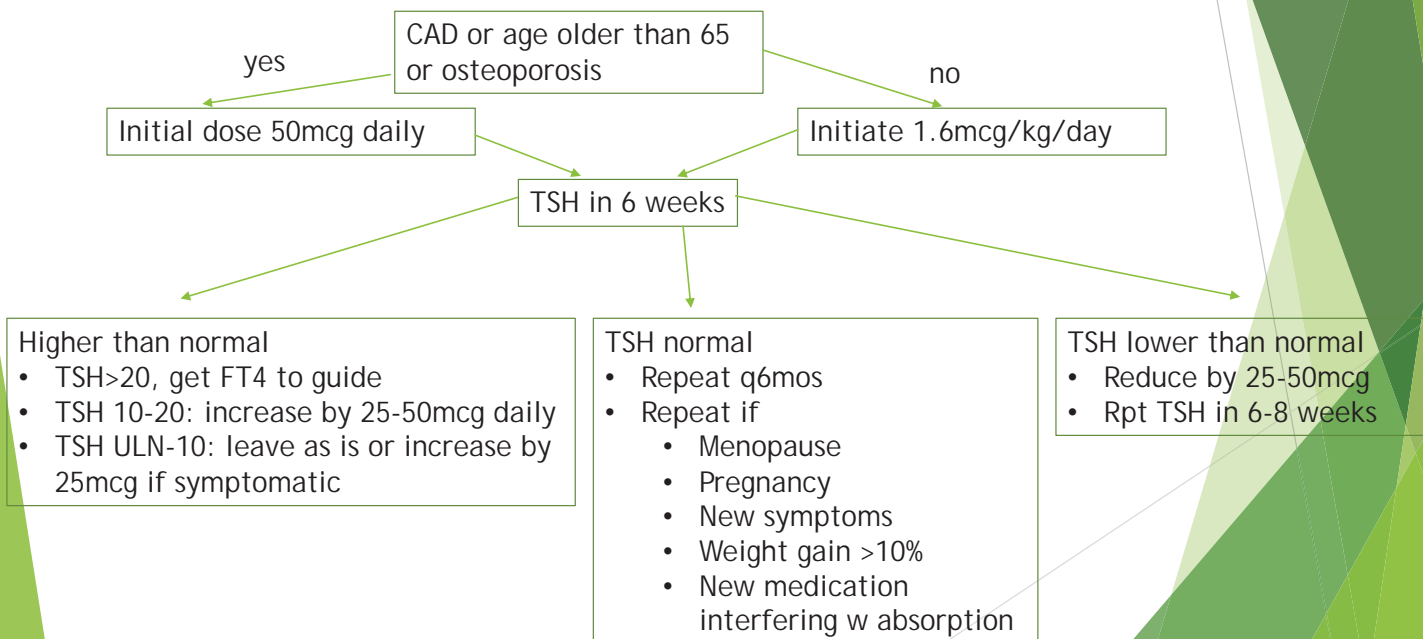
Perez et al 2013 Thyroid 23:779-784  
Walsh et al 2006 JCEM: 91(7):2624  
Samuels et al 2018 JCEM;103(5):1997

# Goals of treatment are normalization of TSH and avoid over-treatment

- ▶ Target normal range TSH: use range liberally (use full range especially if patient feels better)
- ▶ Avoid iatrogenic overtreatment: risk of osteoporosis and atrial fibrillation
  - ▶ Thyroid cancer: ask endocrinologists as only select cases warrant TSH below range (do not assume)
- ▶ Delta in TSH from baseline important: depending on baseline TSH might take time to normalize, wait until plateau to increase

Jonklaas *et al.*, *Thyroid* 24(12): 1670-1751, 2014

# Rule of thumb for titration of Levothyroxine based on TSH (non pregnant)



## Specific populations with caveats on therapy and therapeutic goals

- ▶ Patients over 65 yrs of age : more likely to have either of the two above conditions
- ▶ Patients with arrhythmia
- ▶ Patients with osteoporosis

Groups of patients in whom there is harm in over-treatment

- ▶ Pregnant women or women seeking pregnancy
- ▶ Central hypothyroidism (pituitary problem)

Groups of patients in whom different targets must be considered

- ▶ Subclinical hypothyroidism: little benefit in older patients and potential hazard

Groups of patients in whom benefit debatable

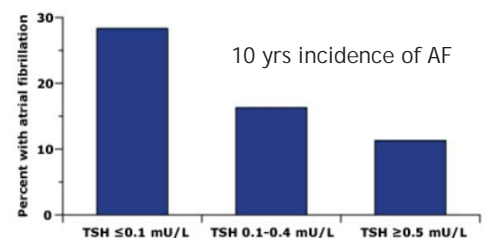
## Groups of patients in whom there is harm in over treatment

## In patients over 65 years of age: caution with dosing and likely age-matched TSH more accurate

- ▶ More likely to have osteoporosis / arrhythmia / susceptible to iatrogenic overtreatment
- ▶ Age-specific TSH: normal range might be closer to 6-7 in patients >70-80
  - ▶ Patients over 65 yrs of age have lower thyroid dose requirements

## Patients with CV disease or arrhythmia: start low, go slow and only if warranted

- ▶ Levothyroxine as inotrope /chronotrope : slow dosing in setting of (recent) CVD
  - ▶ Start low and go slow: 25-50mcg daily
  - ▶ Would ensure that proper Beta-blockade in setting of AF
  - ▶ TSH <0.1 3x higher risk of AF over 10 yr period



## Iatrogenic hyperthyroidism / overreplacement associated with fracture risk

- ▶ In population with osteoporosis, keep TSH well within normal range or higher than range
  - ▶ Discussion with patients about risk benefit
- ▶ Higher risk of fracture with subclinical hyperthyroidism
- ▶ Dose of T4 correlated with fracture risk in patients over 65 and in thyroid cancer cohorts
  - ▶ Based on T4 dose not TSH

Turner et al. 2011 BMJ 342:d2238  
Bauer et al. 2001 Ann Inter Med 134:561-568  
Flynn et al. 2010 J Clin Endocrinol Metab 95:186-193  
Shin et al 2018 JBMR;33(6);1037-43

## Groups of patients in whom different targets need to be considered



## In women with pre-existent hypothyroidism, plan for pregnancy and different TSH targets

- ▶ In **known hypothyroid** women of child bearing age: aim TSH 0.5-2.5 pre-conception (reduced risk of miscarriage)
  - ▶ Majority will require increase of 30% when pregnant, can be achieved by doubling dose (2x tablet) twice weekly as soon as positive test
- ▶ During pregnancy: TSH q4 weeks until 22-26 weeks then stabilization
  - ▶ Target 0.1-2.5 T1 and 0.3-3.0 T2-T3
- ▶ Post partum, back to pre-conception dosing and check TSH 3mos postpartum

Stagnaro-Green 2005 Thyroid;15(4):351  
Mannisto T et al 2013 JCEM;98(7):2725-33

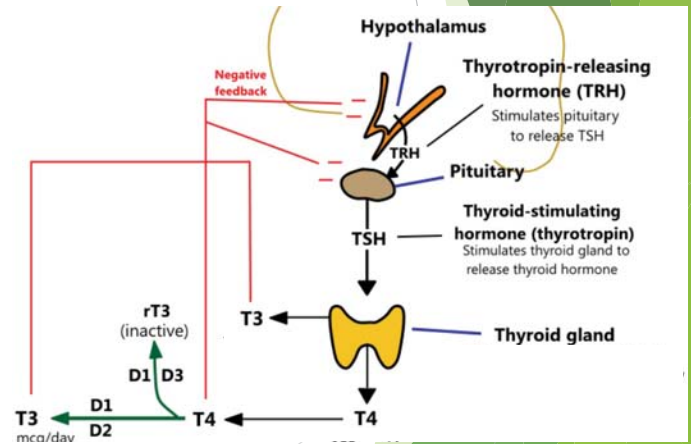
## In patients with SCH prior to pregnancy: debatable whether to initiate therapy

- ▶ In setting of Assisted Reproduction / IVF there is data on improved pregnancy outcomes in context of TSH >2.5 or +TPO ab status
  - ▶ Prior to pregnancy or with first TSH in pregnancy, treat
- ▶ Higher risk of pregnancy complications with SCH, especially with TPO+ and TSH >2.5 or TPO- and TSH >4
  - ▶ Unclear if T4 helps outcome
  - ▶ Would treat TSH >2.5 TPO+ or TSH >4 TPO- (no universal consensus)
- ▶ At CHUM: universal screening and treatment if TSH >2.5
  - ▶ TSH 2.5-10:0.025-0.75mcg PO daily with discontinuation postpartum
  - ▶ TSH >10: starting dose 2mcg/kg/day and cut 50% post partum, with follow up TSH 3mos post partum

Toulis et al 2010 Eur J Endocrinol;162(4):643  
Baker 2006 Am J Obstet Gynecol;194(6):1668  
Akhtar MA Cochrane Database Syst Rev 2019;6:CD011009  
Horacek J Eur J Endo 2010;163(4):645  
Negro JCEM 2010;95(4):1699

## Patients with central/secondary hypothyroidism: follow the T4 values to titrate

- ▶ TSH not reliable in this population (low or normal with low T4)
  - ▶ Pituitary surgery or radiation
  - ▶ Usually in association with other pituitary deficits
- ▶ Use T4 in normal range as marker of treatment (dose q6 weeks as you would with TSH)
  - ▶ TSH will always be normal or low in these patients, unreliable
- ▶ Isolated central hypothyroidism very rare: check rest of pituitary function



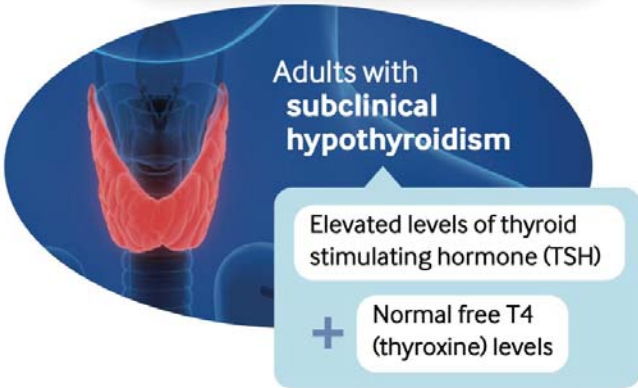
## Groups of patients in whom treatment benefit debatable

## Patients with SC hypothyroidism: high TSH normal T4, generally treat with TSH >10

- ▶ Patients with TSH >10 tend to progress to overt hypothyroidism
- ▶ Most clinical effects of SCH are seen in patients with TSH >10 (excluding pregnancy / fertility context)
  - ▶ Greater CVD/CHF/CHF seen in patients with TSH >10 (not all studies show this)
  - ▶ Modest impact on LDL (0.2mmol/L difference in total cholesterol)
  - ▶ Heterogeneous effects on cardiovascular inflammatory makers
  - ▶ Conflicting results on CV mortality (no effect on all-cause mortality)
- ▶ Very limited benefit has been shown in SC hypothyroidism in patients over 70 when TSH <10

Lindeman et al 2003 Thyroid;13:595  
Walsh JP et al 2005 Intern Med 165:2467  
Razvi et al 2010 JCEM 95:1734  
Hyland et al 2013 JCEM;98:533  
Sato Y et al Can J cardiol 2018;34:80  
Inoue et al 2020; JAMA Netw Open 2020;3:e1920745  
Grossman et al 2016 Am J Med 2016;23:279

Most endocrine societies will recommend holding off therapy when TSH < 10 especially in individuals over 70 years of age



**Adults with subclinical hypothyroidism**

Elevated levels of thyroid stimulating hormone (TSH)

+ Normal free T4 (thyroxine) levels

**Including:**

- ✓ Patients with no symptoms (diagnosed after screening)
- ✓ Patients with non-specific symptoms

**May not apply to:**

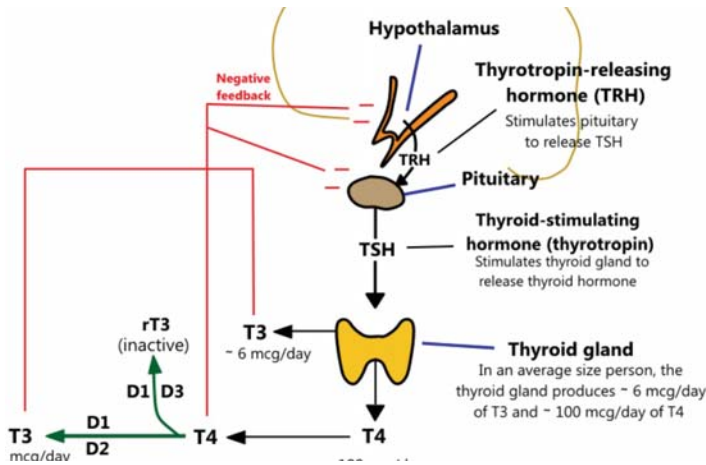
- ? Patients with severe symptoms
- ? Young adults (such as <30 years)

**Does not apply to:**

- ✗ Women who are or trying to become pregnant
- ✗ Patients with TSH above 20 mIU/L

# Is T3 or combination therapy the optimal thyroid replacement therapy?

- T3 = Cytomel
- Combination T4:T3 = Desiccated Thyroid / Thyroid /AOR



90% of T3 is produced in periphery, by conversion (deiodination of T4)



# Does addition of T3 to T4 produce better results?

- ▶ Most guidelines do not recommend use of T3 or combination therapy
- ▶ T3 lower on replacement than in euthyroid patients and cannot be normalized on therapy with T4 (15%)
  - ▶ Small, non controlled, non randomized trials: heterogeneous results but sometimes better mood / cognitive function
- ▶ Randomized trials of T4 vs T4+T3 have not produced any difference in health-related parameters during combination therapy
- ▶ Unlikely that T3 harmful: monitor for hyperthyroidism
  - ▶ T3 10x more potent than T4 and increases cardiac oxygen consumption significantly

Gullo D et al 2011 PloS One; 6(8):e22552  
 Panicker et al. JCEM 2009; 94(5):1623-9.  
 Carle et al Eur Thyroid J. 2017; 6(3):143-51  
 Biondi et al Endocrine 2019 Oct; 66(1):18-26  
 Appelhof BC et al 2005 JCEM; 90(5):2666

## T3 is available as Cytomel in Canada: BID dosing and cut back T4 dose

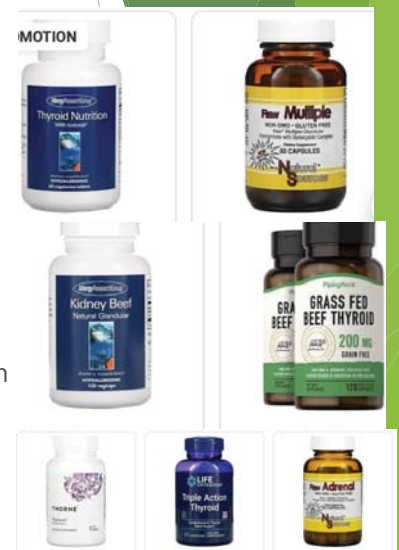
- Monitor TSH 6 weeks post dose change
- TSH 5-10 can increase T4 by 12.5-25mcg
- TSH >10 can increase both T4 and T3, keep ratio 13:1-16:1
- TSH detectable but low: lower T3, aim for ratio closer to 16:1
- TSH undetectable, lower both T4 and T3 to keep ratio 13-16:1
- Unclear if T3 measurement of benefit

T4 current dose	Combined T4 and T3 therapy that reflect physiologic ratio	
	T4 dose	T3 dose
75-100mcg	50-75mcg	2.5mcg BID
112-137mcg	88-112mcg	2.5mcg TID or: 5mcg qAM-2.5mcg qPM
150-175mcg	112-137mcg	5mcg BID
200-250mcg	150-200mcg	7.5mcg qAM - 5mcg qPM

Wiersinga et al 2012 Thyroid 1:55

## Combination therapies (Armour and Thyroid) contain much higher ratio T4:T3

- ▶ Formulation available in Canada = Dessicated thyroid (thyroid)
  - ▶ 1 grain = 60mg = approximately 100mcg T4
  - ▶ 4.2:1 ratio of T4:T3
- ▶ T4 and TSH can be misleading as generally patients received T3 at much higher ratio than physiologic -> iatrogenic hyperthyroidism via T3
  - ▶ Goal of maintaining normal T4 and TSH much more difficult as high T3 will often suppress TSH
- ▶ Very little change in health parameters except weight loss (2.8 lbs) and patient preference for desiccated therapy



Hoang 2013 JCEM 98(5):1982  
 Escobar M et al Ann Int Med 2005;142(6):412-24

## Generally consider addition of T3 or combination in specific populations

- ▶ Can do trial in patients where no obvious harm: monitor for hyperthyroidism usually related to T3
- ▶ Not tested in pregnancy and would not use
- ▶ Not tested in thyroid cancer and would not use
- ▶ Would be very cautious in anyone with prior CV disease or arrhythmia given T3 potency and high T3 ratio

## Conclusions

- ▶ T4 as mainstay of therapy, wait at least 6 weeks for repeat TSH
- ▶ Limited role for treatment of SCH when TSH <10 except in certain populations such as women of reproductive age
  - ▶ Trial of T4 therapy reasonable
- ▶ Cautious therapy in patients with CVD, osteoporosis or arrhythmia: do not overtreat and strongly reconsider SCH therapy in patients above 70
  - ▶ Repeat TSH in circumstances that would change T4 dosing requirements
- ▶ Very limited (if any) data to support T3/ combination therapy even though subset of patients do not iodinate in periphery / feel unwell with T4
  - ▶ can do trial of T3 with goal to keep TSH normal

# Thank you

- ▶ Excellent website for patient information : [mythyroid.com](http://mythyroid.com) (curated by Dr. Daniel Drucker, University of Toronto)