Evidence-Based Management of Hypothyroidism in Primary Care

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Disclosure

- Dr. Cortes disclosed that she has no financial relationships with any ineligible organizations or commercial interests.

Objectives

By completing this educational activity, the participant should be better able to:

1. Identify a diversity of tissue compartments in which hypothyroidism is consequential.
2. Develop a screening protocol to identify patients with risk factors for developing hypothyroidism, order appropriate laboratory tests to diagnose hypothyroidism, and diagnose subclinical hypothyroidism.
3. Prescribe appropriate pharmacotherapy for patients with hypothyroidism and monitor patients accordingly.

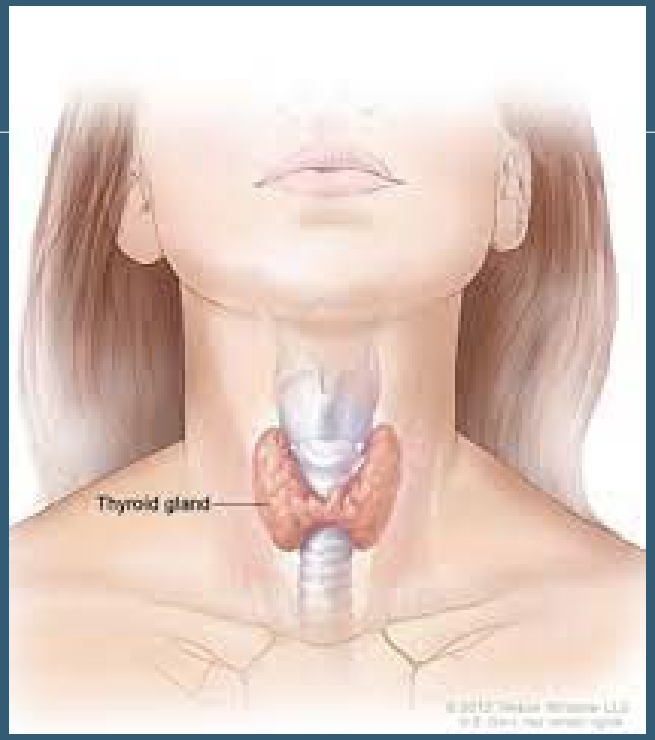
Epidemiology

Prevalence

- 1.9% in women
- 0.1% in men

Annual Incidence

- 0.4% in women
- 0.06% in men



Tunbridge et al *Clin Endocrinol* 1977
Vanderpump et al *Clin Enocrinol* 1995

Top Prescribed Medications in US

1. Atorvastatin
2. Lisinopril
3. Albuterol
4. Levothyroxine

November 2021 GoodRx

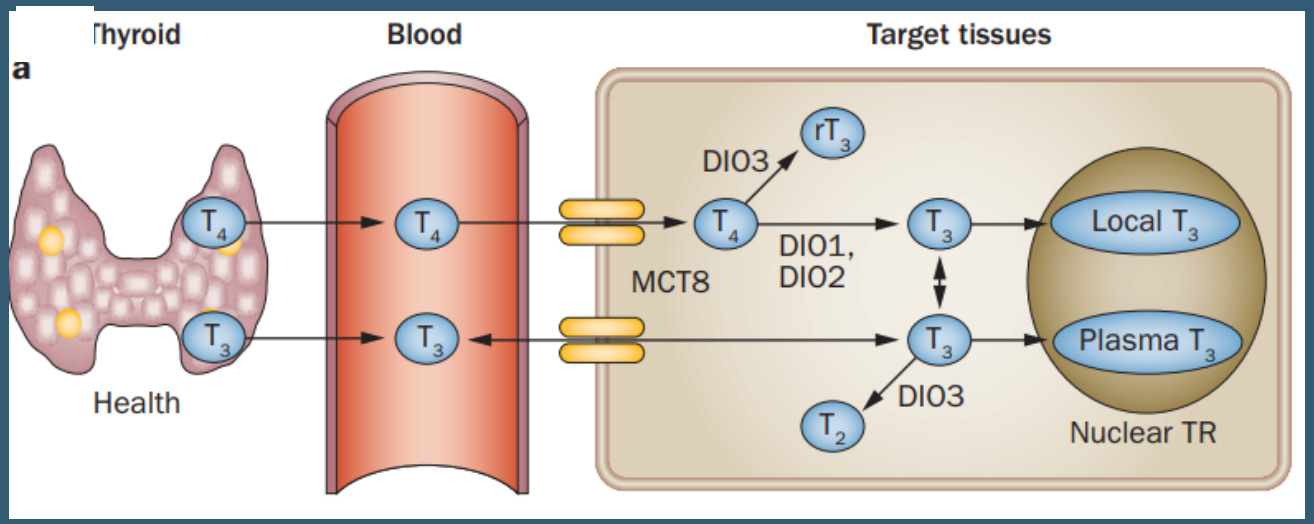
Effects of Hypothyroidism

Audience Polling Question 1

Majority of T3 is produced in the thyroid.

1. True
2. False

Thyroid Hormone Production



All T4 is produced in the thyroid

~80% of T3 is production occurs outside thyroid via T4 deiodination in peripheral tissues

Wiesinga W. *Nat Rev Endocrinol* 2014

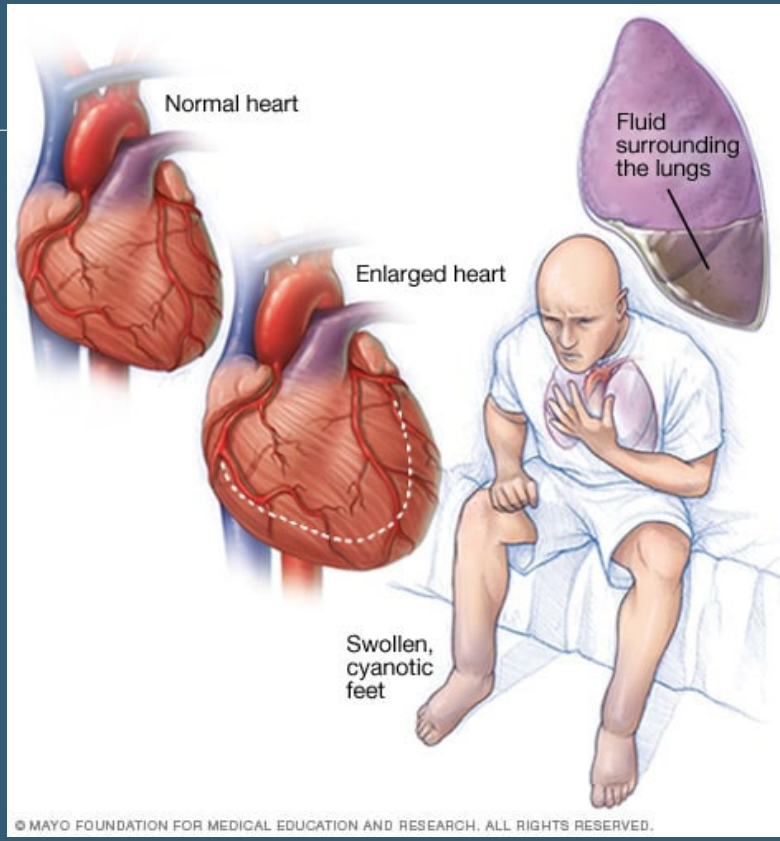
Audience Polling Question 2

Majority of T3 is produced in the thyroid.

1. True
2. False

Cardiovascular

- Impaired left ventricular systolic and diastolic function
- Decline in cardiac output because of decreased stroke volume and heart rate
- Increased systemic vascular resistance



Biondi and Klein. *Endocrine* 2004

Neurology

- Slowed thought and speech
- Decreased attentiveness
- Fatigue
- Reduced efficiency in executive function and poor learning
- Increased susceptibility to depression and reduction in health-related quality of life
- Imaging studies: decreased hippocampal volume, cerebral blood follow, and function globally

Davis and Tremont. *Minerva Endocrinol* 2007
Samuels MH. *Curr Opin Endocrinol Diabetes Obes* 2014

Pulmonary

- Respiratory muscle weakness resulting in hypoventilation
- Reduction of forced vital capacity and forced expiratory flow
- Decreased diffusing capacity of the lunch for carbon monoxide
- Reduced pulmonary responses to hypoxia and hypercapnia

Siafakas et al. *Chest* 1992
Ladenson et al. *Am J Med* 1988
Sadek et al. *Ann Thorac Med* 2017

Reproductive

WOMEN

- Menstrual irregularity
- Reduced fertility

MEN

- Decrease SHBG, total and free testosterone
- Erectile dysfunction
- Abnormalities in sperm morphology

Krassas et al. *Endocrine Reviews* 2010

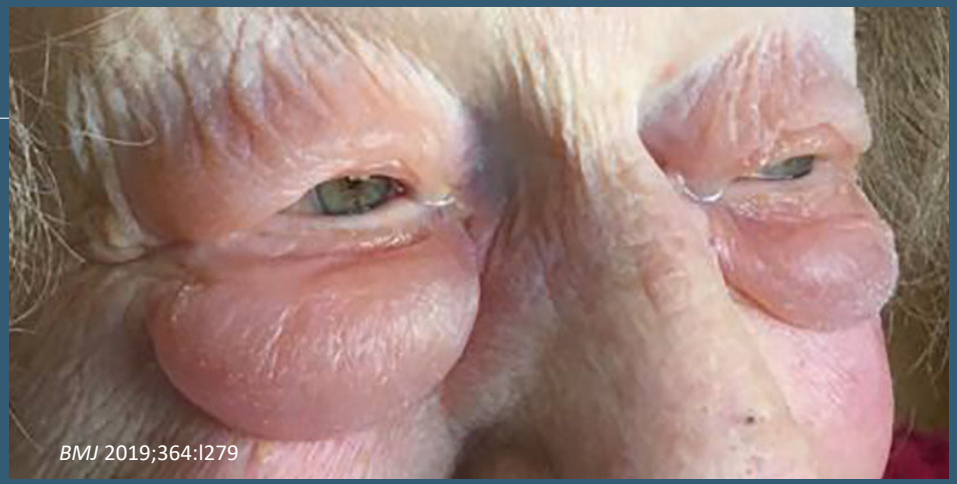
Musculoskeletal

- Weakness
- Myalgias
- Paresthesia
- Numbness
- Carpal tunnel syndrome

Duyuff et al. *J Neurol Neurosur Psychiatry* 2000

Dermatology

- Coarse, rough, dry skin
- Brittle nails
- Hair loss
- Periorbital edema



Biondi et al. *Endocrine Reviews* 2014

Metabolic

- Reduced resting energy expenditure
- Weight gain
- Increased total cholesterol, LDL, HDL and triglyceride

Rizos et al. *Open Cardiovasc Med J* 2011
Kotwal et al. *JCEM* 2020

Older Adults

- Symptoms maybe minimal or asymptomatic
- Especially consider
  - Memory and mental impairment
  - Depression
  - Dementia
  - Anemia
  - Heart Failure

Biondi et al. *Endocrine Reviews* 2014

Effects of Hypothyroidism

- Hypothyroidism can affect a variety of tissue compartments
- Older adults may have more minimal symptoms

Screening

Audience Polling Question 3

Who would you screen for hypothyroidism?

1. 22-year-old female being evaluated for a yearly physical
2. 65-year-old male being evaluated for memory loss
3. 35-year-old female being evaluated for infertility
4. Both 2 and 3

Screening Recommendation for Asymptomatic Adults

- American Thyroid Association
  - Women and men > 35 years, repeat every 5 years
- American Association of Clinical Endocrinologists
  - Older patients, especially women
- US Preventative Task Force
  - No recommendation because of insufficient evidence

Garber et al. ATA/AACE guidelines 2012
US Preventative Task Force 2015

High Risk for Developing Hypothyroidism

- Family history of autoimmune thyroid disorders
- Personal history of autoimmune conditions
- Postpartum women
- Underling thyroid, pituitary, or hypothalamic disorder
- Down's or Turner syndrome
- Previous treatment that can destroy thyroid pituitary or hypothalamic tissue including external radiation therapy, surgery
- Medications: tyrosine kinase inhibitors, immune checkpoint inhibitors, amiodarone, lithium, iodine

Biondi et al. *Endocrine Reviews* 2014

Audience Polling Question 4

Who would you screen for hypothyroidism?

1. 22-year-old female being evaluated for a yearly physical
2. 65-year-old male being evaluated for memory loss
3. 35-year-old female being evaluated for infertility
4. Both 2 and 3

Audience Polling Question 5

Which tests would you order to screen for primary hypothyroidism?

1. TSH
2. Free T4
3. Total T3
4. TPO antibodies

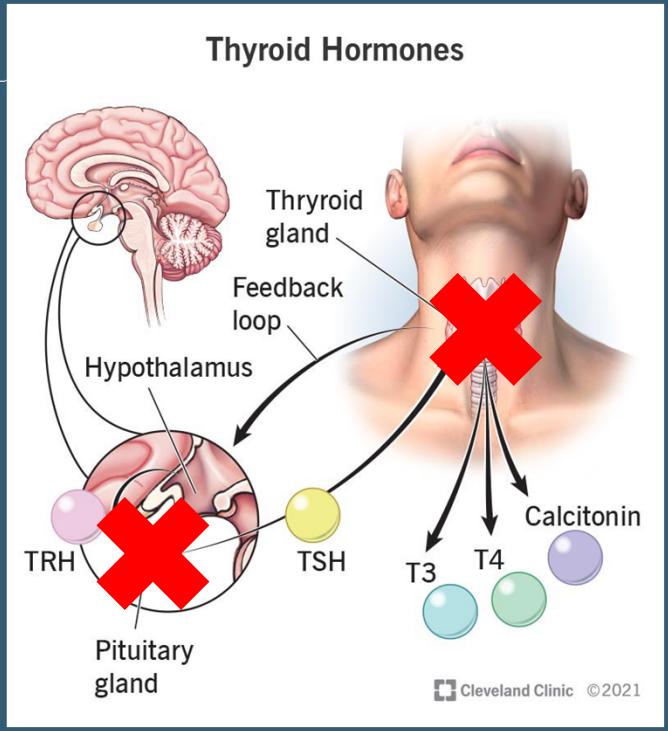
Types of Hypothyroidism

Primary Hypothyroidism

- Overt
  - TSH over 10 mIU/L
  - Low Free T4
- Subclinical
  - TSH above the reference range
  - Normal Free T4

Central Hypothyroidism

- TSH generally not above 7 mIU/L
- Low Free T4



Garber et al. ATA/AACE guidelines 2012

Laboratory Evaluation

TSH is best screening test

- 99% sensitivity and specificity with intact pituitary-hypothalamic axis

If TSH is abnormal, then get free T4

Especially with mild abnormalities, re-evaluation should be done in 3-6 months

Biondi et al, *Endocrine Reviews* 2014

When to Order TPO Antibodies

- Helps to diagnose autoimmune thyroid disease
- Once present the antibodies usually persist
- For those with subclinical hypothyroidism, positive antibodies predict progression to overt hypothyroidism (4.3% vs. 2.6% per year)
- Positive TPO antibodies are seen in 11.3% without hypothyroidism

Garber et al. ATA/AACE guidelines 2012

Audience Polling Question 6

Which tests would you order to screen for primary hypothyroidism?

1. TSH
2. Free T4
3. Total T3
4. TPO antibodies

Screening

- Recommended in those who have symptoms of hypothyroidism
- TSH is the best screening lab
- TPO antibodies to not indicate the need for treatment but can predict those with subclinical hypothyroidism that will convert to overt

Treatment

Audience Polling Question 7

A healthy 25-year-old is diagnosed with overt hypothyroidism. How much L- thyroxine would you start? Weight is 70kg

1. 25 mcg
2. 75 mcg
3. 112 mcg
4. 200 mcg

Overt Hypothyroidism

TSH > 10
Low Free T4

- Young, healthy adults
  - 1.6-1.8 mcg/kg L-thyroxine per day
- >50-60 year without evidence of coronary heart disease on lower dose
  - 50 mcg L-thyroxine per day
  - Incremental dose increase every 3-4 weeks
- Known coronary heart disease or very elderly
  - Start at 12.5-25 mcg L-thyroxine per day
  - Incremental dose increase every 3-4 weeks

Biondi et al. *Endocrine Reviews* 2014
Garber et al. ATA/AACE guidelines 2012

Audience Polling Question 8

A healthy 25-year-old is diagnosed with overt hypothyroidism. How much L- thyroxine would you start? Weight is 70kg

1. 25 mcg
2. 75 mcg
3. 112 mcg
4. 200 mcg

Audience Polling Question 9

A 70-year-old asymptomatic female was found to have a TSH 6.0 and normal FT4. What is the next best step?

1. Start L-thyroxine 1.6 mcg/kg
2. Start L-thyroxine 25 mcg
3. Recheck thyroid function test is 3 months
4. Obtain TPO antibodies

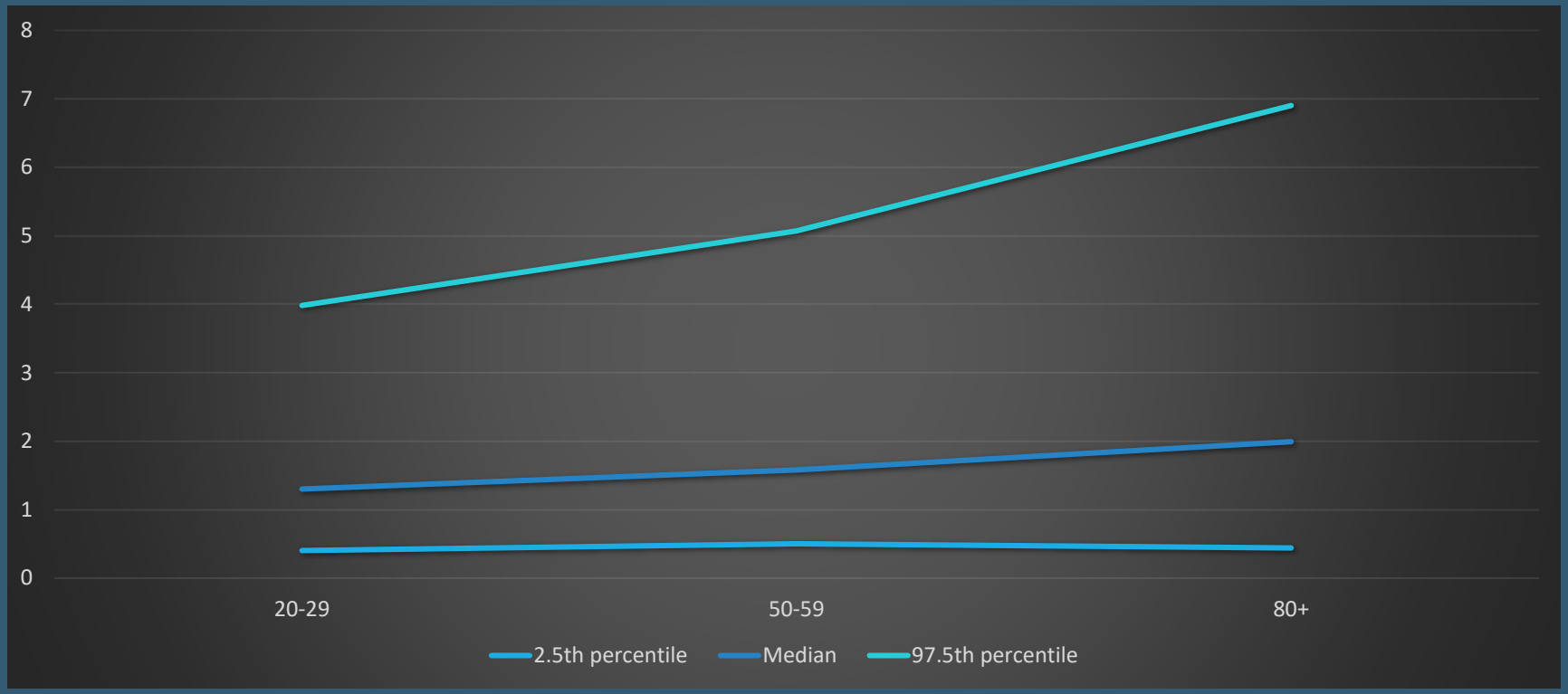
Subclinical Hypothyroidism

TSH elevated
Free T4 normal

- TSH levels > 10mIU/L => Treat
  - Increase risk of heart failure and cardiovascular mortality
- TSH <10mIU/L =>consider
  - Suggestive of hypothyroidism
  - Positive TPO ab
  - Evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these disease
  - Diabetes
  - Hypercholesterolemia
  - Women trying to conceive

Garber et al. ATA/AACE guidelines 2012
Alexander et al. ATA guideline 2017

TSH Ranges Across Ages



Boucai et al *Thyroid* 2011

How Much L-thyroxine for Subclinical Hypothyroidism ?

- 25-75 mcg per day is usually adequate to achieve euthyroidism
- Dosing based on TSH levels
  - 4.0-8.0 mU/L : 25 mcg
  - 8-12 mU/L : 50 mcg
  - >12mU/L : 75 mcg

Bondi et al. *Endocrine Reviews* 2014
Teixeira et al. *Horm Metab Res* 2008

Pharmacology of L-thyroxine

- Bioavailability is 60-80% euthyroid
- Half life is ~ 7 days
- Absorption can be influenced by gastric pH

Colucci et al *Eur Endocrinol* 2013

Audience Polling Question 10

A 70-year-old asymptomatic female was found to have a TSH 6.0 and normal FT4, what is the next best step?

1. Start L-thyroxine 1.6 mcg/kg
2. Start L-thyroxine 25 mcg
3. Recheck thyroid function test is 3 months
4. Obtain TPO antibodies

Optimal Administration of L-thyroxine

- Water 60 minutes before breakfast or at bedtime 4 hours after the last meal on an empty stomach
- Should not be taken with other medications
  - Especially calcium or iron supplements
- If unable to adhere to above, try and emphasize consistency and adjust L-thyroxine dose to obtain euthyroidism

Bondi et al *Endocrine Reviews* 2014

Goals of Treatment

- TSH
  - Most sensitive indicator of adequate treatment
  - Within normal limits of reference range
  - Check every 4-8 weeks to give adequate time to reset the pituitary gland between dosage changes
  - Periodic follow up every 6-12 months on stable doses to ensure at goal
- Free T4
  - Can be considered
  - If checked, should be prior to L-thyroxine dose

Bondi et al *Endocrine Reviews* 2014
Garber et al ATA/AACE guidelines 2012

Biotin

- Some lab assays utilizing streptavidin-biotin separation technique
  - Low TSH
  - Elevated FT4 and FT3
- Not all labs use assays that can be affected by biotin
- Daily amount of 0.03mg do not cause significant interference
- Anything more than the daily recommended amount ask patient to hold for two days

FDA communication 2019
ATA 2016 Hyperthyroidism Guidelines

Different L-thyroxine Formulations

- There are subtle differences between various brand and generic L-thyroxine products
- When preparation is changed, this may result in clinically significant changes in TSH
- If possible, stay with the same formulation
- If product is switched, then repeat thyroid function within 4-8 weeks and adjust as needed

Bondi et al *Endocrine Reviews* 2014

Audience Polling Question 11

What is the physiologic ratio of T4:T3?

1. 1:1
2. 1:4
3. 1:14
4. 1:25

Combination L-thyroxine and Liothyronine

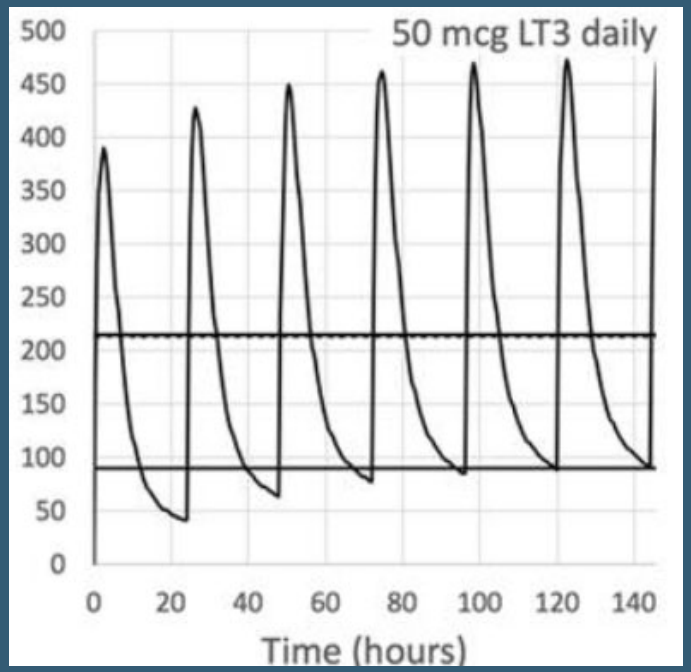
- Controversial, not first line, not to be used in pregnancy
- Some consider in those persistently symptomatic
- Physiologic T4:T3 ratio is 13:1-15:1

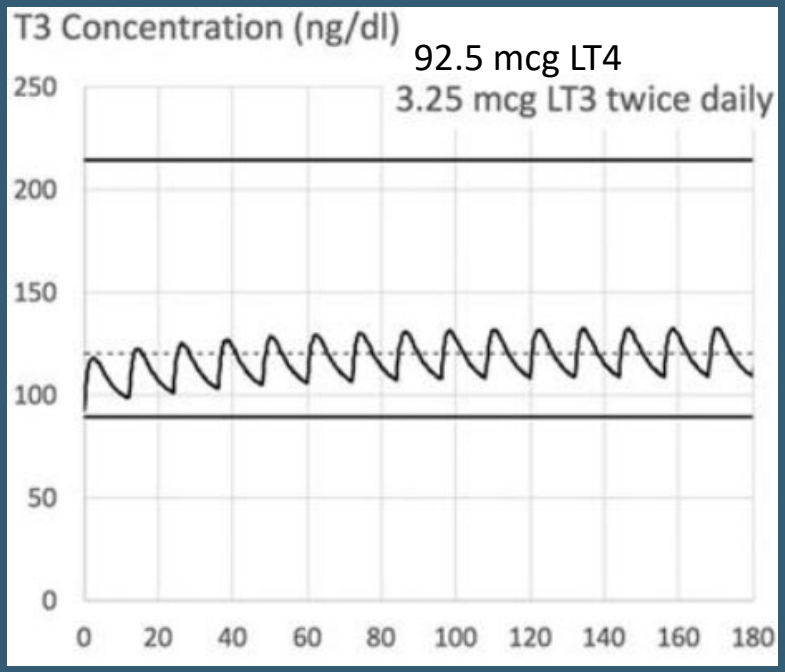
Current T4 therapy	T4 oral dose (mcg/d)	T3 oral dose
75-100 mcg	50-75	2.5 micrograms twice a day
112-137 mcg	88-112	5 micrograms AM , 2.5 mcg PM
150-175 micrograms	112-137	5mcg twice a day
200-250 micrograms	150-200	7.5mcg AM, 5mcg PM

Bondi et al *Endocrine Reviews* 2014
Idrees et al *Thyroid* 2020
Wiersinga et al *Eur Thyroid J* 2012

Split Dosing Liothyronine

Liothyronine has to be administered two to three times a day





Idrees et al *Thyroid* 2020

Desiccated Thyroid Hormone

- Made from dried ground thyroid glands from pigs
- Not recommended because outside formal FDA oversight, consistency is monitored by manufacturers alone, and has supraphysiologic T4:T3 ratio
- T4:T3 ratio is ~4:1

Idress et al *Thyroid* 2020

Audience Polling Question 12

What is the physiologic ratio of T4:T3?

1. 1:1
2. 1:4
3. 1:14
4. 1:25

Treatment

- Overt hypothyroidism, give full replacement dose in young, healthy adults. For older adults or those with cardiovascular disease, start low and titrate up.
- Subclinical hypothyroidism, consider replacement in certain scenarios at lower than weight-based dose
- T4 monotherapy alone is recommended
- If someone is on combination T4 and T3, then T3 needs to be split

Summary

- Hypothyroidism affects multiple organ system
- Screening for hypothyroidism should be completed in those with symptoms
- TSH is best screening method
- L- thyroxine is standard of care for replacement

Questions?

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