Hypothyroidism for Primary Care - A Case-based Review

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Disclosure

Consultant: AstraZeneca; Bayer; Corcept Therapeutics; Diasome; Eli Lilly; Novo Nordisk; Merck; Sanofi

Research Support: Bayer; Novo Nordisk; Merck; Twinhealth

Speaker Bureau: AstraZeneca; Corcept Therapeutics; Merck; Novo Nordisk

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Objectives

- Review thyroid gland physiology, regulation, and hormone production
- Review diagnosis and treatment of hypothyroidism
- Recognize conditions/disorders other than primary hypothyroidism which can rarely present with the finding of an elevated TSH
- Review rationale and potential role for T3 therapy in the management of hypothyroidism
- Review diagnosis and management of euthyroid sick syndrome/non-thyroidal illness

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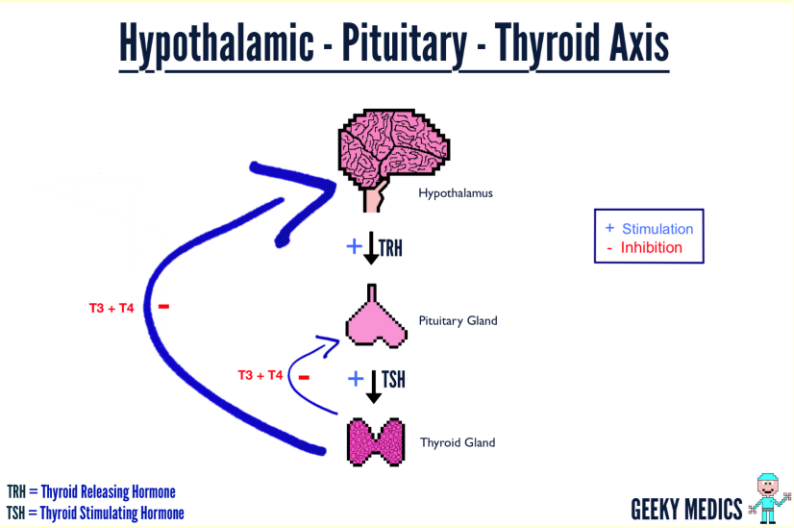
Thyroid Hormone Production



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Case 1

- A 52-year-old women presents to her PCP for routine physical
  - Only complaint is fatigue and 10 lbs. of weight gain since menopause at the age of 51
- A TSH is obtained and found to be TSH: 22.4 uU/mL (0.4-5.5 uU/mL)
- Levothyroxine 50 mcg is started
  - Repeat TSH 6 weeks later is 28.6
- Levothyroxine is increased to 75 mcg, TSH 24.8
  - She reports taking the medication as prescribed, on empty stomach, upon awakening, and waiting 1 hour to eat breakfast
- She takes no other supplements, vitamins, or medications
- Patient notes starting to feel “jittery” and “anxious”
- A free-T4 is obtained and found to be 2.6 (0.7-1.8 ng/dL)

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Diagnosis

- TSH appears to be inaccurate and not responding appropriately
  - If compliance or malabsorption are not concerns, then lab interfering antibodies should be considered
  - TSH was checked after HAMA (heterophile mouse antibody) was excluded by lab technique,
    - Repeat TSH: 0.005 uU/mL (0.4-5.5 uU/mL)
- Levothyroxine was stopped
  - TSH 6 weeks later 1.8 uU/mL (0.4-5.5 uU/mL)
  - Patient’s symptoms resolved

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HAMA

- The most common encountered heterophile antibody may be present in the serum of up to 10% of patients
- The incidence increases in people who have received or have been treated with radiolabeled mouse monoclonal antibodies
- It is now believed, on circumstantial evidence, that these heterophile antibodies are natural antibodies in normal people, although they could also represent autoantibodies

Krishnan SGS et al. Postgrad Med J. 2006 Nov; 82(973): e27.

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Primary Hypothyroidism Elevated TSH

- Hashimoto's Disease (Autoimmune)
- Post-surgical Hypothyroidism
- Post-RAI treatment (Graves, Toxic MNG)

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Primary Hypothyroidism Diagnosis

- Elevated serum TSH in routine clinical practice
- Very few other disorders than can cause an elevated TSH
  - Lab interference (HAMA)
  - TSH secreting pituitary adenoma (rare)
  - Recovery from Euthyroid Sick Syndrome
  - Adrenal Insufficiency

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Diagnosis

Per the "Experts"

- In most patients with symptoms or signs suggestive of hypothyroidism the serum TSH should be the initial test
  - ↑TSH, repeat the TSH with a serum free T4 to make the dx
    - Repeat ↑TSH and ↓FT4
      - Consistent with primary hypothyroidism, replacement therapy with T4 should be initiated
  - Repeat ↑TSH but normal range FT4
    - May indicate subclinical hypothyroidism
      - The decision about T4 replacement is made on a case by case basis and depends partly upon the degree of TSH elevation and symptoms reported by the patient

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Diagnosis

- If TSH is within the normal reference range, but the patient has convincing symptoms of hypothyroidism
  - Repeat serum TSH and obtain free T4 to assess for central hypothyroidism (hypothalamic/pituitary disorder)
- Do not always assume that because the TSH is normal they do not have a thyroid problem (see later case)

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Signs & Symptoms of Hypothyroidism

Symptoms

- Weight gain
- Cold intolerance
- Fatigue
- Hair loss
- Constipation
- Depression

Signs

- Delayed DTR
- Amenorrhea
- Nail pitting
- Dry skin
- Periorbital puffiness
- Slowed speech/movement
- Hair loss
- Unusual loss of hair in the outer edge of the eyebrow

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Case 2:

- A 38-year-old woman, diagnosed with hypothyroidism a year ago
- Takes 112 mcg of levothyroxine. Most recent set of TFTs:

  TSH – 2.197 uU/mL (0.5-5.5)
  Free T4 – 1.2 ng/dL (0.9-1.8)
  Free T3 – 2.9 pg/mL (2.6-4.6)

- Energy is not good, + fatigue; wants to try T3 therapy…..

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Some Patients Have Persistent Symptoms Despite Adequate T4 Therapy

- Some patients have symptoms consistent with hypothyroidism despite adequate TSH and T4 levels

Saravanan P. Clin Endocrinol 2002; 57:577-85.
Walsh JP. Curr Opin Pharmacol 2002; 2:717-22.
Wekking EM. Eur J Endocrinol 2005; 153:747-53.

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Some Patients Have Persistent Symptoms Despite Adequate T4 Therapy

- Some of these patients ask for addition of T3 to the treatment regimen
  - Many of them have found claims of need for T3 on the internet
  - Some have friends whose doctors claim that only combination therapy works

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It Is Not Your Thyroid (Usually)!!!

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A Significant Number of These Patients Will Have Other Conditions Responsible for These Residual Symptoms

- Sleep disorders (Untreated OSA)
- Depression
- Medications causing fatigue
- Obesity
- Anemia
- Vitamin D deficiency
- Lack of EXERCISE!!!!
- Adrenal Insufficiency (rare)
  - Note, I did not mention Adrenal Fatigue!

- Treatment of these may lead to clinical improvement

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But Is There More to This Story?

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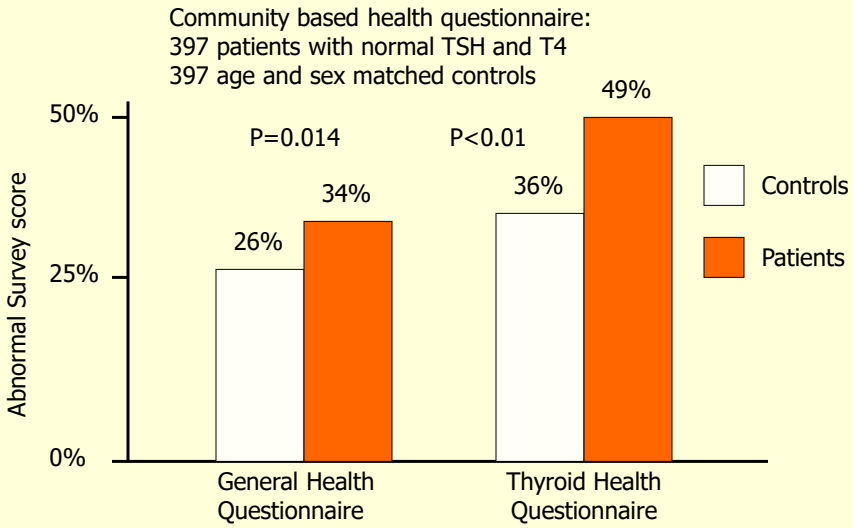
How Many with Persistent Symptoms?



Saravanan P. Clin Endo. 2002:57:577-85.

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To T3 or Not to T3, That Is the Question?

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Do Patients Really Need T3 Therapy?

- Most patients do well with just T4/Levothyroxine
  - Some of the oral T4 is converted to T3
- Symptoms of hypothyroidism are vague and non-specific
  - Often, residual symptoms, despite appropriate treatment, are unrelated to the thyroid condition
- A minority of patients may feel better with T3 therapy

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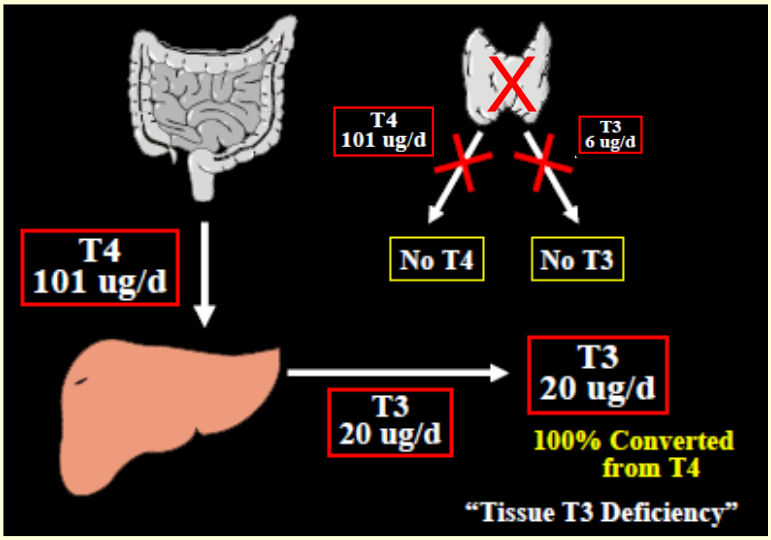
T3 Therapy Needed Theory:



Pilo A et al. Am J Physiol 1990; 258:E715-26.

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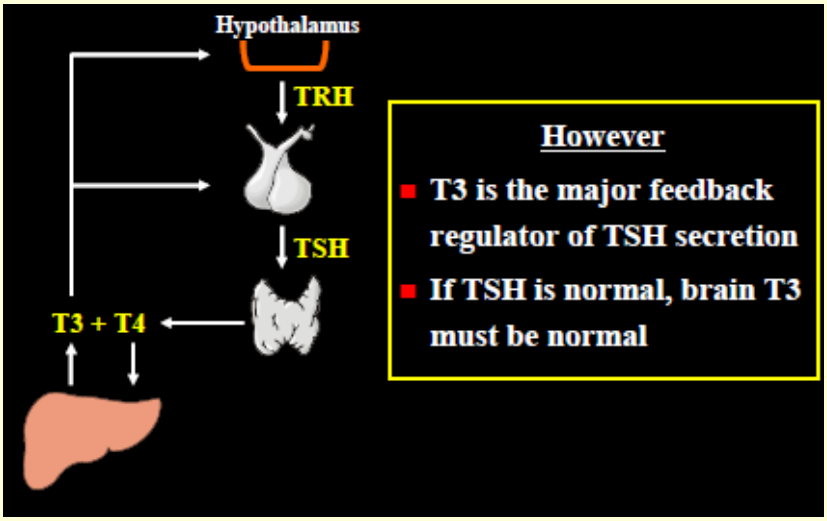
No T3 Therapy Needed Theory:



Pilo A et al. Am J Physiol 1990; 258:E715-26.

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Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study

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Objective: Our objective was to investigate the effectiveness of DTE compared with L-T_4 in hypothyroid patients.

Design and Setting: We conducted a randomized, double-blind, crossover study at a tertiary care center.

Patients: Patients (n = 70, age 18–65 years) diagnosed with primary hypothyroidism on a stable dose of L-T_4 for 6 months were included in the study.

Intervention: Patients were randomized to either DTE or L-T_4 for 16 weeks and then crossed over for the same duration.

Outcome Measures: Biochemical and neurocognitive tests at baseline and at the end of each treatment period were evaluated.

Results: There were no differences in symptoms and neurocognitive measurements between the 2 therapies. Patients lost 3 lb on DTE treatment (172.9 ± 36.4 lb vs 175.7 ± 37.7 lb, $P < .001$). At the end of the study, 34 patients (48.6%) preferred DTE, 13 (18.6%) preferred L-T_4, and 23 (32.9%) had no preference. In the subgroup analyses, those patients who preferred DTE lost 4 lb during the DTE treatment, and their subjective symptoms were significantly better while taking DTE as measured by the general health questionnaire-12 and thyroid symptom questionnaire ($P < .001$ for both). Five variables were predictors of preference for DTE.

Conclusion: DTE therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over L-T_4. DTE therapy may be relevant for some hypothyroid patients. (*J Clin Endocrinol Metab* 98: 1982–1990, 2013)

Hoang TD et al. J Clin Endocrinol Metab. 2013 May;98(5):1982-90.

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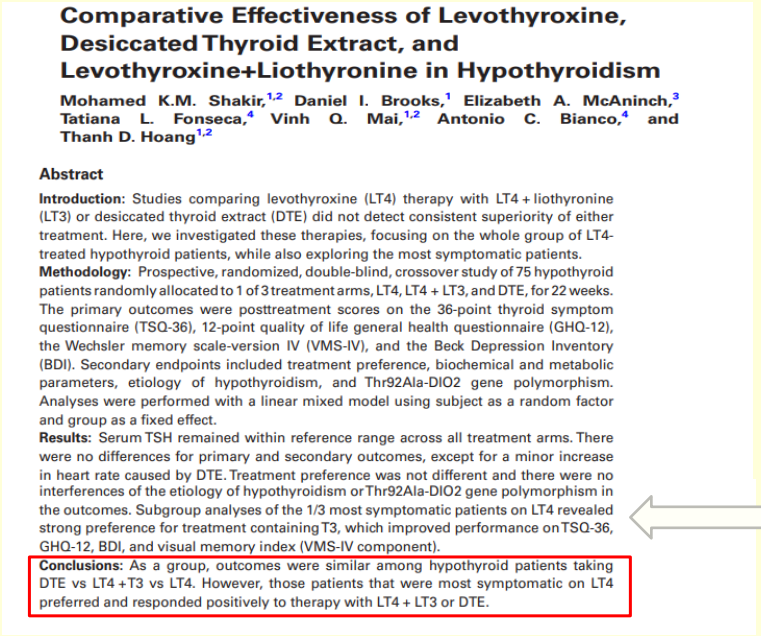

Comparative Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine+Liothyronine in Hypothyroidism

Mohamed K.M. Shakir,[1,2] Daniel I. Brooks,[1] Elizabeth A. McAninch,[3] Tatiana L. Fonseca,[4] Vinh Q. Mai,[1,2] Antonio C. Bianco,[4] and Thanh D. Hoang[1,2]

Abstract

Introduction: Studies comparing levothyroxine (LT4) therapy with LT4 + liothyronine (LT3) or desiccated thyroid extract (DTE) did not detect consistent superiority of either treatment. Here, we investigated these therapies, focusing on the whole group of LT4-treated hypothyroid patients, while also exploring the most symptomatic patients.

Methodology: Prospective, randomized, double-blind, crossover study of 75 hypothyroid patients randomly allocated to 1 of 3 treatment arms, LT4, LT4 + LT3, and DTE, for 22 weeks. The primary outcomes were posttreatment scores on the 36-point thyroid symptom questionnaire (TSQ-36), 12-point quality of life general health questionnaire (GHQ-12), the Wechsler memory scale-version IV (VMS-IV), and the Beck Depression Inventory (BDI). Secondary endpoints included treatment preference, biochemical and metabolic parameters, etiology of hypothyroidism, and Thr92Ala-DIO2 gene polymorphism. Analyses were performed with a linear mixed model using subject as a random factor and group as a fixed effect.

Results: Serum TSH remained within reference range across all treatment arms. There were no differences for primary and secondary outcomes, except for a minor increase in heart rate caused by DTE. Treatment preference was not different and there were no interferences of the etiology of hypothyroidism or Thr92Ala-DIO2 gene polymorphism in the outcomes. Subgroup analyses of the 1/3 most symptomatic patients on LT4 revealed strong preference for treatment containing T3, which improved performance on TSQ-36, GHQ-12, BDI, and visual memory index (VMS-IV component).

Conclusions: As a group, outcomes were similar among hypothyroid patients taking DTE vs LT4 + T3 vs LT4. However, those patients that were most symptomatic on LT4 preferred and responded positively to therapy with LT4 + LT3 or DTE.

Shakir MKM et al. JCEM 2021;106(11):e4400-e4413.

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Treatment of Primary Hypothyroidism

- Levothyroxine, LT4 (generic, name brand, etc.)
  - Remind them how to take it correctly!
- T3 therapy (Liothyronine, Cytomel®)
  - Not generally recommended for monotherapy
    - T3 ~ 4X potency of T4
  - 5 mcg of T3 ~ 20-25 mcg LT4
- Desiccated Thyroid Extracts, DTE
  - Pig thyroid (T4 and T3)
  - Armour® Thyroid and other variants
  - 1 grain DTE=60 mg of DTE ~ 75 mcg of LT4 (38 mcg LT4, 9 mcg of T3)

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Who Is a Good Candidate for Combined T4 and T3 Therapy?

Ideal	The patient has not felt well since her thyroidectomy
	The patient has not felt well since radioiodine
Poor	The patient felt well on levothyroxine monotherapy in the past
	The patient no longer feels well
Contraindicated	Elderly
	Cardiovascular disease
	Pregnancy

Ross DS. J Intern Med.2022;291:128–140.

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Case 3

- 74-year-old woman was seen by her PCP for her annual physical
- She reported feeling fine, with only occasional fatigue
- HTN-controlled
  - lisinopril 10 mg/hydrochlorothiazide 25 mg
- HPL-LDL 78 mg/dL
  - atorvastatin 20 mg daily
- Physical exam was unremarkable
- Laboratory testing, including CMP, CBC, and HbA1c were normal, but TSH was found to be 6.5 mIU/L (0.5-5.5)

What to Do Next?

A. Check FT4
B. Start 25 mcg levothyroxine
C. Check microsomal Ab
D. Repeat TSH and check FT4

Diagnosis

Per the "Experts"

- In most patients with symptoms or signs suggestive of hypothyroidism the serum TSH should be the initial test
  - ↑TSH, repeat the TSH with a serum free T4 to make the dx
    - Repeat ↑TSH and ↓FT4
      - Consistent with primary hypothyroidism, replacement therapy with T4 should be initiated
  - Repeat ↑TSH but normal range FT4
    - May indicate subclinical hypothyroidism
      - The decision about T4 replacement is made on a case by case basis and depends partly upon the degree of TSH elevation and symptoms reported by the patient

Case 3

Repeat testing was conducted in 6 weeks

TSH – 7.2 uU/mL (0.5-5.5)

Free T4 – 1.2 ng/dL (0.9-1.8)

What Do You Do Now?

A. Start levothyroxine
B. Monitor TSH

Subclinical Hypothyroidism vs. Physiological Age-related TSH Elevation

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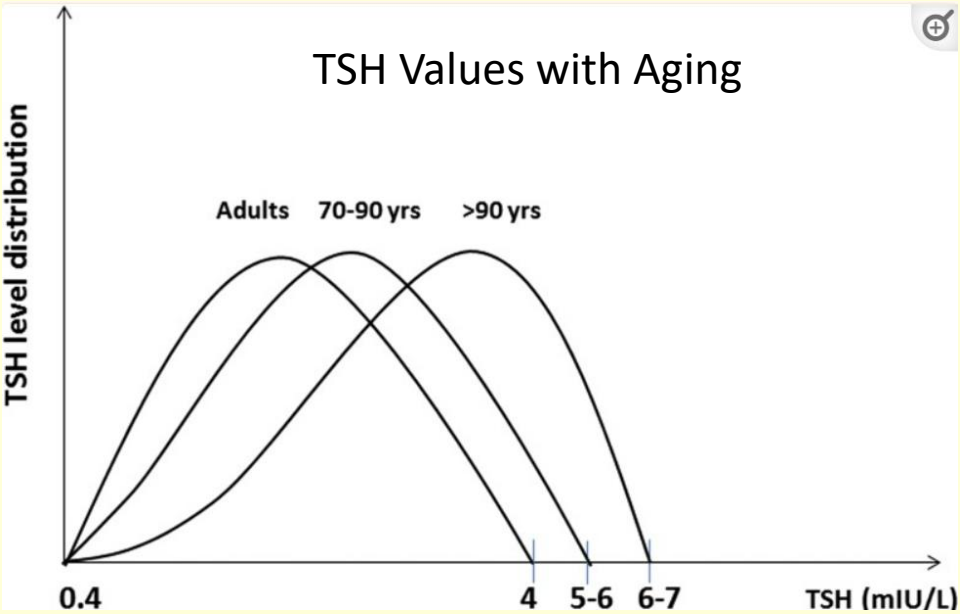

Calsolaro V et al. J Endocr Soc. 2019 Jan 1; 3(1): 146–158.

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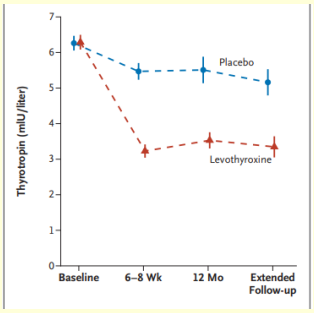
Subclinical Hypothyroidism TRUST RCT



- N=737, ≥65 years of age
- TSH: 4.60 to 19.99 mIU/L
- FT4 within the reference range
- LT4 vs. placebo
- Median age 74.4 years
- Mean baseline TSH 6.40±2.01 mIU/L
- After 1 year of treatment, there was no significant difference in the coprimary outcomes of hypothyroid symptoms or fatigue scores
- Flip-side: 1/3 of patients ≥65 years receiving LT4 are overtreated (low TSH); most common in women

Stott DJ et al. TRUST Study Group. N Engl J Med. 2017:376(26):2534-2544.

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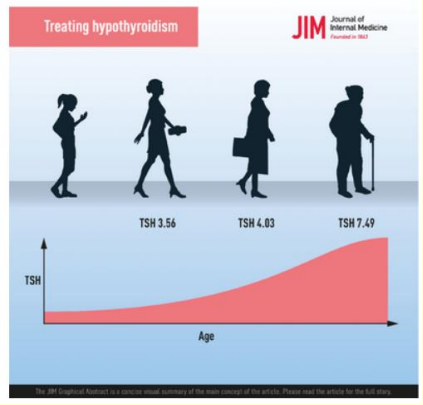
When to Treat Subclinical Hypothyroidism



	Age less than 65–70 years	Age greater than 65–70 years
TSH under 7.0 mIU/L	Monitoring recommended Consider treatment trial, if significant symptoms	Do not treat-age appropriate
TSH 7.0–10 mIU/L	Treat	Monitoring recommended Consider treatment trial, if significant symptoms
TSH above 10 mIU/L	Treat	Treat

Ross DS. J Intern Med.2022;291:128–140.

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Hypothyroidism in the Elderly: Who Should Be Treated and How?

- A "natural" trend in a slight TSH increase has been documented in the older population, even in subjects without documentable thyroid diseases, but an age-related TSH reference range is not available yet.
- Thus, it is worth the performance of an extensive thyroid evaluation in older subjects with a circulating TSH rise, especially in the oldest olds, including either laboratory tests (free thyroid hormone levels and antithyroid autoantibody titers) or thyroid ultrasound examination.
- This diagnostic process is aimed to assess the presence of an actual thyroid disease (Hashimoto thyroiditis, gland atrophy, *etc.*), which may lead to the diagnosis of subclinical hypothyroidism, rather than a physiological age-related TSH elevation, although circulating TSH values >10 mIU/L should be considered clinically relevant.
- The choice of treatment should also depend on the presence of clinical signs and symptoms consistent with hypothyroidism, as well as concomitant comorbidities and patient compliance.
- Nonetheless, several data from literature warn the clinician to be extremely cautious in treating older patients, especially the oldest olds (>80 years).

Calsolaro V et al. J Endocr Soc. 2019 Jan 1; 3(1): 146–158.

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Follow-up Testing

- For routine primary hypothyroidism, TSH is all that is required unless there is something that does not make sense
- In most circumstances, there is very little information gained from checking FT4 or FT3 once the patients have started thyroid hormone therapy
  - Patients (and Dr. Google) will very frequently disagree

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Case 4

- 72-year-old man recently hospitalized for exacerbation of congestive heart failure and atrial fibrillation
- Thyroid function tests obtained in the hospital were:
  - TSH 0.175 uU/mL (0.4-5.5)
  - FT4 1.0 ng/dL (0.7-1.8)
  - FT3 2.2 pg/mL (2.6-4.6)
- Endocrinology was consulted
  - Diagnosis was euthyroid sick syndrome/non-thyroidal illness
  - Discharged after 2-week hospital stay
  - Recommendation was to repeat the tests in 6-12 weeks once the patient had fully recovered from their underlying condition

Follow-up

- Patient is reassessed approximately 6 weeks from hospitalization
- Doing well, no shortness of breath, kidney function at baseline, BP well-controlled
- Repeat TFTs are obtained:
  - TSH 7.5 uU/mL (0.4-5.5)
  - FT4 0.9 ng/dL (0.7-1.8)
  - FT3 2.4 pg/mL (2.6-4.6)

What Do You Do Now?

A. Start levothyroxine
B. Repeat TFTs in another 6—8 weeks
C. Thyroid ultrasound
D. Nuclear Medicine Uptake and Scan

TFTs in Euthyroid Sick Syndrome (ESS)/Non-thyroidal Illness (NTI)

CHANGES IN THYROID HORMONE DURING ILLNESS

	Hormone			
Severity of Illness	**Free T_3**	**Free T_4**	**Reverse T_3**	**TSH**
Mild	↓	N	↑	N
Moderate	↓↓	N, ↑ ↓	↑↑	N, ↓
Severe	↓↓↓	↓	↑	↓↓
Recovery	↓	↓	↑	↑

A low FT3 with normal FT4 and low-normal TSH are the most common abnormalities seen in ESS

Although the FT3 is usually low in ESS; in severe cases, the FT4 can also be low

Melmed S et al J Clin Endocrinol Metab. 1982 Feb;54(2):300-6.
Franklyn JA et al. J Clin Endocrinol Metab. 1994 Jun;78(6):1368-71.
Williams Textbook of Endocrinology, 11th Edition, Table 10.9

ESS/NTI

- The TSH levels have been reported
  - -Normal in approximately 50%
  - -Decreased in about 30%
  - -Increased in approximately 12%
  - -Level varies based on severity of illness
- The TSH levels are markedly suppressed (<0.1 µIU/mL) in about 7% of patients
  - Predominantly in those patients treated with corticosteroids

Spencer C et al. Clin Chem. 1987;33(8):1391-6.

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TFTs During Recovery from ESS/NTI

- A mild elevation of TSH is seen in patients who are recovering from their illness
  - However, serum levels > 25 to 30 µU/mL strongly suggests the diagnosis of primary hypothyroidism
- TSH >30 µU/mL is rarely seen
  - TSH >20 µU/mL is found in <3%
- TFTs should return to baseline with resolution of underlying illness

Bacci VJ et al. Clin Endocrinol Metab 1982;54:1229-1235.
Kaptein EM et al. Clin Lab Med 1993;13:653-672.
Brent GAJ et al. Clin Endocrinol Metab 1986;63:1-8.

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Severe ESS/NTI

- Some advocate treatment, especially when FT4 is low
- A low FT4 is a significant predictor of mortality
- Sometimes a full assessment of pituitary function testing and pituitary MRI are required to differentiate ESS from central hypothyroidism
  - Check Reverse T3 (controversial)
- Literature suggests some improvement in clinical parameters with treatment of ESS/NTI (e.g. cardiac output) but no mortality benefit
  - Most studies have demonstrated an increase in mortality with treatment

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Bonus Case

- A 42-year-old woman presents to your office complaining of worsening fatigue for the past 4 years
- She has a history of sarcoidosis, which has been under control since the time of her diagnosis 10 years ago
- She reports her TSH has been checked at least 5 times, and all of them were in the normal range (she brings these records for your review)
- On further review of her laboratory test results, you note FSH (follicle stimulating hormone) and LH (luteotropic hormone) levels that are within the reference range, and an estradiol level that is very low

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Bonus Case

TSH checked by PCP:

	10/02	11/05	7/06	10/06	1/09
TSH0.400-5.500 uU/mL	3.720	2.440	4.810	3.890	4.390

All within the normal range, over 7 years

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She Reports She Has Not Had Any Periods for 8 Years, and That She Was Told By Her Previous Doctor That She Had Premature Ovarian Failure. What Would Be the Next Best Step in Her Evaluation?

A. Order free T4 and free T3
B. Order microsomal antibodies
C. Complete an evaluation of each of her hypothalamic-pituitary-axes
D. Check a serum angiotensin-converting-enzyme (ACE)

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Data

Component	Reference Range	1/22/2009	2/13/2009	3/10/2009
Cortisol Basal	ug/dL			<1.0
Cortisol 30 min	ug/dL			1.5
Cortisol 60 min	ug/dL			<1.0
CK	30-220 U/L	757 (H)		
Aldolase	2.0-8.0 U/L	3.8		
Prolactin	2.0-17.4 ng/mL	10.8		
FSH	mU/mL	1.9		
LH	mU/mL	0.9		
TSH	0.400-5.500 uU/mL		5.580 (H)	
Free T4	0.7-1.8 ng/dL		0.2 (L)	
T3	94-170 ng/dL		42 (L)	
ACTH	8-42 pg/mL			10
Estradiol 17B	pg/mL			<12

MRI was consistent with sarcoidosis involvement of the hypothalamus/pituitary

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Answer

- Central Hypothyroidism/Panhypopituitarism
- Patient was too young for menopause
- LH/FSH would be high in menopause or premature ovarian failure
  - This should have been tip off for possible central process
  - If concerned for central process, must get FT4/FTI with TSH
  - If patient has symptoms, should get TSH/FT4, TSH is only indicated as a screening test
  - Screening tests are those that are completed to detect disease in asymptomatic patients, she was clearly not asymptomatic
- She has a history of an infiltrative disorder which can involve pituitary/hypothalamus

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Central Hypothyroidism

- Low or “normal range” TSH, in setting of Low FT4/FT3
  - Rarely a slightly high TSH can be observed
- Pituitary or Hypothalamic Process
  - Mass lesions
  - Infiltrative disorders
  - Pituitary irradiation history
  - Pituitary surgery
  - Infarction/Apoplexy (Sheehan Syndrome)
  - Genetic diseases - pit-1 mutation
  - Empty sella syndrome

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Central Hypothyroidism

- Isolated central hypothyroidism would be very unlikely
- Usually occurs with other anterior pituitary hormone deficiencies
- If a diagnosis of central hypothyroidism is suspected
  - Complete an evaluation of the remaining hypothalamic/pituitary axes
  - Refer to an endocrinologist
  - Likely will require pituitary imaging (MRI)

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