

ACOI Annual conference 2022, Baltimore, MD

My thyroid tests are normal.  
Could it still be my thyroid?

ACOI annual convention 10/2022

Baltimore, MD

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# Conflicts of interest

- Speaker bureau
  - Abbott
  - Dexcom

# Case 1

- 45 year old Caucasian male with aches. Has had thyroidectomy for a 2 cm papillary thyroid cancer 8 years earlier. Thyroglobulin level is undetectable. No evidence of thyroid cancer recurrence. On a reasonable weight based dose of levothyroxine and TSH is low-normal at 0.5. Works as a scientist with marine life.
- Has aches that are worsening over a year or two.
- Thyroid dose has been increased and decreased slightly over 2 years at his request to see if this improves the aches as he is convinced the thyroid is the cause. TSH is close to normal with each dosage change. He notes that after each dosage change his aches improve but for only 2 weeks.
- Are the aches from the thyroid?

# Case 2

- 70 year old with what he describes as a “mystery malady” for about 15 years. Has sweats, heat sensation, flushing, and intermittent feeling of just being unwell, and having brain fog. The providers kept focusing on thyroid, but ordered many tests over many years.
- Has had multiple and frequent thyroid blood tests (TSH and free T4), all in the normal range, but sometimes top normal TSH to low normal TSH.
- He is not on thyroid medications
- Levothyroxine supplementation, and in fact, anti-thyroid medication, used briefly in the past, have not helped as far as he can tell, as the symptoms are only intermittent, but increasing over the years without diagnosis.
- Is this thyroid disease?

# Case 3

- 25 year old Caucasian female with near-syncope spells for 5 years.
- Has positive TPO, but TSH has always been mid-normal. Free T4 is normal. These tests have been repeated frequently.
- She thinks she has thyroid disease and hypoglycemia causing her symptoms (shakes, sweats, hunger, anxiety, palpitations) and she is eating small, frequent meals with occasional relief when eats she thinks, but but not consistently.
- Is this thyroid disease?

# Case 4

- 16 year old male with no signs of puberty.
  - Tired, lightheaded, achy, nausea, weakness. Cold, mild LE edema.
  - Mildly overweight.
  - TSH: 1.0.
- 
- Is this thyroid disease?



# Case 5

- 52 year old menopausal woman (menses stopped two years ago) with 20 year history of hypothyroidism. Weight: 80 kg. Relaters no other medical history. Thyroxine dose generally stable at 50 mcg daily. TSH is 0.75 and Free T4 is mid-normal.
- c/o tired, all day. Also, can't lose weight despite a "reasonable" diet.
- Her PCP added liothyronine (T3) 10 mcg AM and 10 mcg at 3 pm. Initially she lost a few pounds and had more energy. TSH is 0.75 still.
- Did the T3 (liothyronine) seem to help because it helped the thyroid situation or because it added a rapid-acting stimulant or some other reason? However a few months later it didn't help any more.

# Purpose of thyroid replacement

- To re-establish euthyroid state. But what does that mean?
- Thyroid replacement's function is not primarily to cause weight loss in overweight individuals or treatment of fatigue, since many other factors can cause weight concerns and fatigue and metabolism issues.

# Symptoms: generally non-specific

- Weight concerns (can't gain can't lose)
- Energy (tired, hyper)
- Hair thinning
- Brittle nails
- Cold
- Hot
- Sweats

# Symptoms

- Cardiac palpitations or heart racing sensation
- Brain fog, concentration issues, memory issues
- Nervous feeling/tremors
- Diarrhea/Constipation/Nausea/Vomiting/change in bowel frequency
- Aches
- Swelling
- Compressive symptoms: swallowing, breathing, hoarseness
- Etc.

# Symptoms

- Can be Vague?
- Can be Multifactorial?
- Do they Come and go?
- Are they Constant?
- Are they Mixed symptoms (some of hypo- and some of hyperthyroidism)?
- Are they Affected by change in thyroid dose? And if so, how soon after any change in thyroid dose do the symptoms change? Does the change last long?
- Are the symptoms Out of proportion to the thyroid situation?

# Laboratory issues

- TSH: is it correct? Is it sensitive enough?
- Free T4: is it needed? Is it sensitive enough?
- Are there random fluctuations in TSH or absorption of thyroxine?
- Is the reference range correct?
- Could the patient have central hypothyroidism (TSH not accurate)?
- Could the patient have resistance to thyroid hormone, which is probably rare (central or peripheral resistance)?
- Could they feel better with the TSH in the low-normal, mid-normal, or high-normal range? Or doesn't it matter? And is the TSH expected to be totally stable from time to time?

# Levothyroxine (T4)

- Is it the right treatment?
- Is it the best treatment?
- Is T3 (lithyronine) needed instead or in addition to levothyroxine?
  - What are the benefits/risks of T3?
  - Is there a long-acting form of T3?

- If a person feels better on T3, does it mean that the thyroid situation needed T3 to adequately treat the patient or are they feeling better due to a relatively rapid stimulatory effect of T3 (similar to caffeine's effect)?
- Could they feel better on T3 since it might treat depression or some other underlying non-thyroidal issue ("burst effect")?
- Is thyroid USP/Armour thyroid (T4 and T3 together) physiologic?



# REMEMBER...

- As an endocrinologist, it is my responsibility to be open-minded toward the patients' concerns and various possibilities; BUT to also not focus exclusively on the thyroid as the cause of the symptoms so as to neglect other possible causes of the "thyroid-like" symptoms
- The patient is often so focused on the thyroid being THE cause of the symptoms, often supported by internet and social media searches, that they can convince the provider the thyroid must be the problem.
- Explain to the patient that a TSH of 5 or 7 is often not a big change from a TSH of 2 and a TSH of 0.4 is often not a big change from a TSH of 2.
- Reassure your patient that you are not writing off their symptoms or their concerns about their thyroid.

- Do the symptoms briefly improve and then return after adjusting the thyroid dose?
  - patients often interpret this as indicating that the thyroid IS the cause of their symptoms.
  - providers often interpret this as indicating that the thyroid IS NOT the cause of their symptoms.

- Are the symptoms out of proportion to the TSH levels?
- Do the symptoms wax and wane despite a stable or normal TSH level?
- Does the patient focus on the exact TSH level?
- Does the patient note that a mild change in TSH compared to the prior TSH level is a “huge” change?
- Does the patient misinterpret a low TSH as meaning their thyroid dose is too little or that their thyroid is underactive?

# Terminology confusion

- Don't tell a patient that the thyroid is high or low: this is vague and can lead to misinterpretation:
  - Such as: does “a low thyroid” mean that
    - the thyroid is underactive or on too little thyroid hormone (in other words, a high TSH);
    - or that the TSH is low meaning the thyroid is overactive or on too much thyroid hormone?

# What dose is the patient on?

- Be aware of a typical replacement dose of thyroxine in someone that is on levothyroxine:  $1.7 \times \text{wt. in kg}$ .
- If the patient is on less than a calculated replacement dose, then maybe they will eventually need a higher dose. Or maybe only part of their thyroid was burned out and the process stopped destroying the thyroid. Or maybe they never had permanent thyroid disease (might have initially had transient thyroiditis).
- If a patient is on more than a calculated replacement, could they not be absorbing the thyroxine due to interfering substances (iron, calcium, antacids, PPI's, caffeine, etc.) or due to malabsorption syndrome (celiac disease, etc.)? Or is the patient missing doses? Or could they have the rare syndrome of thyroid hormone resistance?

- Could the patient have central hypothyroidism (due to pituitary/hypothalamic disease), in which case the TSH will not be accurate and Free T4 must be followed to roughly dose the thyroid supplementation (along with a knowledge of a usual weight-based replacement dose).

- Is the patient iodine deficient, iodine replete, or does the patient have excess iodine intake?
- Kelp, seaweed, and other iodine supplements might cause excessive iodine intake.
- This might or might not make a difference.

# LITERATURE

- Often contradictory or fail to answer the question
- Might yield different result in patients of different age, ethnicity, sex, iodine sufficiency status, cause of hypothyroidism, etc.



# Oregon Health and Science University, 2018

- In patients (138) treated for hypothyroidism, “altering doses of levothyroxine in hypothyroid patients to vary the TSH level in and near the reference range does not affect the quality of life, mood, or cognition” but “subjects preferred perceived higher doses despite a lack of objective benefit”
- Does this vary by cause of hypothyroidism, age, sex, ethnicity, etc.?
- Would different tests of mood, cognition, and QoL change these results?

# Oregon Health and Science University, 2018

(QoL studies used: 36-item short form health survey, underactive thyroid-dependent QoL questionnaire; mood: profile of mood states, affective lability scale; cognition: executive function, memory, they also had general intelligence testing)

Billewicz scale of hypothyroid-related symptoms

References:

- Samuels, Kolobova, Niederhausen, Janowsky, Schuff. Effects of altering levothyroxine (L-T4) doses on quality of life, mood, and cognition in L-T4 treated subjects. 2018. The Journal of Clinical Endocrinology & Metabolism. 103(5): 1997-2008. <https://doi.org/10.1210/jc.2017-02668>.
- Billiewicz, Chapman, Crooks, Day, Gossage, Wayne, Young. 1969. Statistical methods applied to the diagnosis of hypothyroidism. QJ Med 38(150): 255-266.

# Differentiated thyroid cancer patients

- “TSH suppressive doses are more effective in improving the QoL in differentiated thyroid cancer patients after thyroidectomy.”
- 208 patients
- ThyPRO questionnaire for QoL
- QoL most related to Free T3 and after that by sex (females had lower QoL)
- Italy, The Netherlands

Reference: Monzani, Piccinini, Boselli, Corleto, Margiotta, Peeters, Simoni, Brigante (2022) Journal of Endocrinological Investigation. <https://doi.org/10.1007/s40618-022-01903-6>.

# S. Korea

- Increased mortality in treated hypothyroid patients in S. Korea
- Hypothyroid patients also had more comorbidities
- TSH values not necessarily known at various times

Reference: Risk of all-cause mortality in levothyroxine-treated hypothyroid patients: a nationwide Korean cohort study. 2021. Sohn, Seo, Chung. *Frontiers Endocrinology*. <https://doi.org/10.3389/fendo.2021.680647>

Combination thyroid hormone replacement: knowns and unknowns. Taylor, Eligar, Muller, Scholz, Dayan, Okosieme. 2019. Frontiers of Endocrinology. <https://doi.org/10.3389/fendo.2019.00706>

- “10-15% of patients on levothyroxine do not feel their health is entirely restored” and some want to add liothyronine
- Clinical trials have not demonstrated superiority of combination therapy (T3 plus T4) compared to T4 therapy
- Serum T4 is the main source of intracellular T3 via D2 deiodinase
- The concentration of circulating T4 is about 5 times higher than T3
- There are rare mutations in transporter and thyroid hormone receptor which cause tissue specific hypothyroidism. However, more common variants have uncertain effects.

Combination thyroid hormone replacement: knowns and unknowns. Taylor, Eligar, Muller, Scholz, Dayan, Okosieme. 2019. Frontiers of Endocrinology. <https://doi.org/10.3389/fendo.2019.00706>

- Even in the 1970s, when higher levothyroxine doses were often used, it was recognized that some people seemed to feel better with T3. (could be related to co-existing disease such as depression or due to imperfect replacement with T4 alone?)
- The number of people having their TSH tested is growing, but not representative of the entire population. In the UK, the 3 most common reasons for TSH testing are: depression, fatigue, weight gain and are more likely to be: female, over 60, and have higher psychologic diagnosis.
- In the UK, the patients with persistent symptoms despite low TSH were more likely to be prescribed T3.
- TSH range is not adjusted for age, sex, ethnicity, etc.
- TSH might not fully reflect thyroid hormone concentration in all tissues.

Combination thyroid hormone replacement: knowns and unknowns. Taylor, Eligar, Muller, Scholz, Dayan, Okosieme. 2019. Frontiers of Endocrinology. <https://doi.org/10.3389/fendo.2019.00706>

- T4:T3 ratio in humans: about 14:1. (armour thyroid has a higher % of T3)
- Which affects TSH most: T4 or T3?
- T3 is short-acting: peaks in 2-4 hours and wears off by 12 hours.
- There is no long-acting T3 supplementation.
- Reference ranges for Free T4 and Free T3 (and total levels) are not adjusted for age, sex, ethnicity, etc.
- T3 might signal health status in the brain.
- Trials have not shown superiority of T3 combined with T4 over T4 therapy alone.

- In a cohort study, individuals on levothyroxine had 15-20% lower T3:T4 ratios on levothyroxine than healthy or matched controls”.

Reference:

Peterson, McAninch, Bianco. 2016. Is a normal TSH synonymous with “euthyroidism” in levothyroxine monotherapy? J Clin Endocrinology Metabolism. 101:4964-73. <https://doi.org/10.1210/jc.2016-2660>.



# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Infectious (UTI, Tick borne diseases, COVID 19, Mononucleosis, other viral, etc.....)
- Inflammation (vasculitis, other autoimmune conditions, etc.)
- Mental health Conditions (Personality factors, ADHD, mood disorders, depression, PTSD, stress, anxiety, panic attacks, bipolar, eating disorders, etc.)
- Cardiac (POTS, NMH, other autonomic insufficiencies, CHF, CAD, arrhythmia, etc.). Remember: people with diabetes and other conditions might not get typical symptoms of heart disease

# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Pulmonary conditions (COPD, sarcoid, etc.)
- Liver conditions
- Renal conditions
- Rheumatologic/Orthopedic conditions: Chronic Fatigue Syndrome, Polymyalgia Rheumatica, Fibromyalgia Syndrome, Bone disease, Bone cancer, nerve impingement syndromes (carpal tunnel, etc.), etc.
- Neurologic conditions (partial/temporal lobe seizures, MS, Parkinson disease, dementia, memory loss, traumatic brain injury, paraplegia, myasthenia gravis, etc.)

# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Hematologic/Oncologic: anemia, polycythemia, cancers, paraneoplastic syndrome, Monoclonal gammopathy, leukemia, lymphoma (can cause sweats and neck adenopathy, etc.), etc.
- Sleep disturbances (sleep apnea, many other causes, etc.)
- Neuroendocrine tumors (Pheochromocytoma, Carcinoid, etc.): palpitations, hotness, diarrhea, etc.
- Mastocytosis, other allergy/immunologic conditions (angioedema, etc.)
- Side effects of medications
- GI: celiac disease, IBS, inflammatory bowel disease, etc.

# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Non-compliance with thyroid medications (too much or too little)
- Over-stimulation from T3 for those on T3 preparations
- Menopause
- Hypogonadism (male or female)
- Other endocrine issues: Pituitary/adrenal insufficiency, pheochromocytoma, carcinoid, MTC, glucocorticoid excess (don't forget frequent pain shots can cause cortisol excess syndrome and then withdrawal can cause adrenal insufficiency!)
- Autoimmune conditions
- Diabetes mellitus, diabetic neuropathy (autonomic or peripheral)

# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Other medical conditions that affect metabolism such as insulin resistance/metabolic syndrome, diabetes mellitus, etc.)
- Nutritional: B12 deficiency, etc. (numbness/tingling, weakness, fatigue, memory issues): don't forget: metformin, especially at high doses, can cause B12 deficiency; so can celiac disease.
- Dehydration
- Vascular: circulatory issues, etc.

# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Lymphedema, venous insufficiency
- Neck nodules: any head/neck cancer, metastatic disease, lymphadenopathy from any cause
- Poor conditioning (“out-of-shape”)
- Obesity

# Conditions that can mimic thyroid disease (this list is certainly not exhaustive)

- Caffeine use or excess
- Illicit substances
- Narcotic use (for many reasons including they can endocrine hormones)
- Tobacco use
- Endocrine disruptors (which can cause thyroid disease also)
- Neuroendocrine tumors
- Etc., etc., etc.

# Don't forget transient thyroiditis

- Temporary abnormality of thyroid function tests
  - Often hyperthyroid first for about 2 months
  - Then euthyroid briefly (1 month or so)
  - Then hypothyroid for about 2 months
  - Then usually become euthyroid



# Autoimmune link

- Remember that hypothyroidism due to Hashimoto's and Hyperthyroidism due to Graves' disease are autoimmune conditions, therefore, other autoimmune diseases are likely to occur in these patients.

# Thoughts to remember

- Providers must use clinical and laboratory assessment to appropriately adjust (or not adjust) the thyroid dose with a goal of maintaining euthyroidism while helping the patient avoid consequences of over- or undertreatment.
- Thyroid dose might change over time based on patient's weight, age, estrogen/testosterone status, medications, medical conditions, pregnancy.

Reference: Duntas and Jonklaas. Levothyroxine dose adjustment throughout a patient's lifetime. *Advances in Therapy* 2019; 36(suppl 2): 30-46. <https://doi.org/10.1007/s12325-019-01078-2>.

# Detection of hypothyroidism by symptoms

- The number hypothyroid symptoms reported were directly related to TSH level. Stronger association when more symptoms were reported and for symptoms that changed in the past year (compared to symptoms reported to be present at the time of testing).

## Reference:

Canaris, Steiner, Ridgway. Do traditional symptoms of hypothyroidism correlate with biochemical disease? J Gen Internal Medicine. 1997.12(9): 544-550. <https://doi.org/10.1046/j.1525-1497.1997.07109.x>.

- ThyPRO QoL assessment might be one of the best assessments to use

- Try to avoid excessive changes in thyroid hormone dosing: looks bad and can make a patient's symptoms go back and forth
- Remember: small changes in levothyroxine can have a large impact on TSH (narrow therapeutic index)
- Free T4 is often a ballpark number
- Some biotinylated assays of Free T4 yield a falsely high Free T4 level in a patient using high biotin doses

- Be an advocate for your patient.
- Empathize with the patient and acknowledge their concerns.
- Suggest and pursue other conditions that can mimic thyroid symptoms and can cause their symptoms to educate them.
- Suggest possible solutions: See nutritionist, exercise program, sleep study, counseling, etc.

- Reinforce that all hypothyroid people are not overweight and tired and all hyperthyroid patients are not thin and energetic
- Reinforce that just because they might feel better on a certain regimen of too much thyroxine or using T3, that it doesn't mean they feel better because their thyroid is better treated
- Remember that the function of thyroid treatment is to normalize the thyroid status, not to make someone lose weight or gain energy, etc.
- Remind people that thyroid hormone of all types is stimulating in a non-specific manner: it stimulates everything!

- Work with the patient: if the TSH allows a change in dose and the patient wants to try it, it might be very reasonable to do this.
- If the TSH is mildly abnormal once although generally is normal, don't have to change the dose of thyroxine based on one blood test if the patient feels very well; but might just want to repeat TSH level in a few months.
- Sometimes decreasing the dose of levothyroxine helps the patient to feel better. Not always looking to increase the dose.



# Remind patients of complications of over-treatment with thyroid hormone

These worsen with age and length of time over-treated.

- Cardiac dysrhythmia
- Bone loss
- Anxiety
- Poor sleep
- Hot
- Diarrhea/increased bowel frequency
- Etc.

# Tests to consider

- Sed rate, CRP, CBC with diff, chemistry panel
- Urinalysis
- Tryptase
- ANA
- Tick borne panel
- B12 level
- Celiac panel
- Catecholamine testing
- Cortisol testing
- Sleep study

Consider referral to appropriate specialist: but don't just turf the uncertainty to another provider

- Neurologist
- Heme/Onc
- Rheumatologist
- Immunologist
- Rehab/Physiatry
- Nephrologist
- Cardiologist

# Case 1

- 45 year old Caucasian male with aches. Has had thyroidectomy for a 2 cm papillary thyroid cancer 8 years earlier. Thyroglobulin level is undetectable. No evidence of thyroid cancer recurrence. On a reasonable weight based dose of levothyroxine and TSH is low-normal at 0.5. Works as a scientist with marine life.
- Has aches that are worsening over a year or two.
- Thyroid dose has been increased and decreased slightly at his request to see if this improves the aches. TSH is close to normal with each dosage change. He notes that after each dosage change his aches improve but for only 2 weeks.
- Are the aches from the thyroid?

What did it turn out was really causing his symptoms?

- Lyme disease

# Case 2

- 70 year old with what he describes as a “mystery malady” for about 15 years. Has sweats, heat sensation, flushing, and intermittent feeling of just being unwell, and having brain fog. The providers kept focusing on thyroid, but ordered many tests over many years.
- Has had multiple and frequent thyroid blood tests (TSH and free T4), all in the normal range, but sometimes top normal TSH to low normal TSH.
- He is not on thyroid medications
- Levothyroxine supplementation, and in fact, anti-thyroid medication, used briefly in the past, have not helped as far as he can tell, as the symptoms are only intermittent, but increasing over the years without diagnosis.
- Is this the thyroid?

# Case 2

- He had mastocytosis

# Case 3

- 25 year old Caucasian female with near-syncope spells for 5 years.
- Has positive TPO, but TSH has always been mid-normal. Free T4 is normal. These tests have been repeated frequently.
- She thinks she has thyroid disease and hypoglycemia causing her symptoms and she is eating small, frequent meals with occasional relief, but this is not consistently helping her.
- Was this thyroid disease?



# Case 3

- She was found to have NMH/POTS on a tilt table test. Treating this improved her symptoms markedly

# Case 4

- 16 year old male with no signs of puberty.
- Tired, lightheaded, achy, nausea, weakness. Cold, mild LE edema.
- Mildly overweight body weight.
- TSH normal at 1.0.
  
- Is this thyroid disease?

# Case 4

- YES! And more...
- His free T4 was eventually checked and was undetectably low.
- His testosterone and free testosterone levels were nearly zero.
- LH level was very low.
- His ACTH stimulation test was abnormal (60 minute post-stimulation cortisol level was 10). ACTH level was low at baseline.
- MRI of the pituitary revealed an empty sella.
- He had pan-hypopituitarism with central hypothyroidism. The “normal” TSH level was inappropriately normal for the low Free T4 level. (TSH was inaccurate in him.)

# Case 5

- 52 year old menopausal woman (menses stopped two years ago) with 20 year history of hypothyroidism. Weight: 80 kg. Relates no other medical history. Thyroxine dose generally stable at 50 mcg daily. TSH is 0.75 and Free T4 is mid-normal.
- c/o tired, all day. Also, can't lose weight despite a "reasonable" diet.
- Her PCP added liothyronine (T3) 10 mcg AM and 10 mcg at 3 pm. Initially she lost a few pounds and had more energy. TSH is 0.75 still.
- Did the T3 (liothyronine) seem to help because it helped the thyroid situation or because it added a rapid-acting stimulant or some other reason?

# Case 5

- T3 might have helped or might not have helped the symptoms. Hard to be sure. T3 is also a stimulant and can treat depression.
- She has been on a low dose of levothyroxine based on her weight, so did she really have permanent hypothyroidism 20 years ago?  
UNKNOWN. Is TPO positive now?
- Does she need further evaluation for sleep apnea. PROBABLY
- Should she see a dietitian? YES
- Should she have a thorough work-up for other potential causes? YES