KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Thyroid Hypofunction

More than one in 10 individuals will develop a thyroid condition in their lifetime.

- However, most will be unaware of their condition.

Women are five to eight times more likely than men to have thyroid problems.

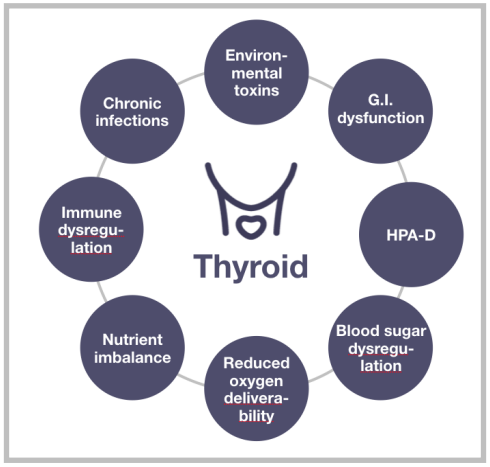
- One woman in eight will develop a thyroid disorder during her lifetime.

Undiagnosed thyroid disease may put patients at risk for certain serious conditions such as cardiovascular disease, osteoporosis, and infertility.

Pregnant women with undiagnosed or inadequately treated hypothyroidism have an increased risk of miscarriage, preterm delivery, and severe developmental problems in their children.

FUNCTIONAL APPROACH TO THYROID DYSFUNCTION

Interactions between the thyroid gland and the rest of the body.



Thyroid dysfunction is often a symptom or result of a deeper underlying problem.

On the case review panel, the following markers are included:

TSH	Reverse T3
Total T4	Free Thyroxine Index
Free T4	T3 Uptake
Total T3	TPO and Thyroglobulin antibodies
Free T3	

T3 uptake:

- More of a marker of estrogen and testosterone levels.
- Affected by medication use.
- Not as relevant in thyroid diagnosis, but useful as part of the overall picture.

Free thyroxine index:

- Often out of range in hypothyroid or hyperthyroid states.
- Not a reliable marker on its own.

Free T4 and free T3 are better indicators of what's happening at the cellular level than total T4 and total T3.

Antibody production

- Precedes the development of clinical thyroid disease by many years.
- Identifying patients with positive antibodies and normal TSH and thyroid hormones can prevent future problems.

ADJUNCT MARKERS

Alkaline phosphatase
MCV
Urine iodine (24-hour, spot)
Hair iodine

Other markers can also be useful in establishing the diagnosis of hypothyroidism. Alkaline phosphatase and MCV are part of the Case Review blood panel. Urine iodine and hair iodine can be ordered separately. These markers will be discussed in their respective sections in the ADAPT course.

The current TSH reference range is 0.5–4.5 … **but is it too broad?**

The current reference range for thyroid-stimulating hormone, or TSH, is based on the 2002 NHANES III study that looked at individuals without evidence of thyroid dysfunction or positive thyroid peroxidase (TPO) antibodies and/or thyroglobulin (TG) antibodies. They took the 95 percent reference range, made a bell curve, and came up with a TSH range of 0.45 to 4.12.

Concerns over how the reference range was developed:

1. Although the NHANES study excluded patients with positive TPO antibodies (in an attempt to exclude patients with thyroid disease from the reference range calculation), studies have shown that up to 20 percent of Hashimoto's patients do not produce antibodies to TPO.

    a. In these patients, autoimmune thyroid disease must be confirmed by thyroid ultrasound even in the absence of antibody production.

    b. This suggests that the TSH range determined by NHANES III was probably skewed upward because the study population included people with occult thyroid dysfunction.

2. Recent studies that did a better job excluding patients with existing thyroid disease found that TSH ranges from 0.5–2.0 in patients with a normally functioning thyroid gland.

3. Numerous studies have shown that slightly elevated TSH levels, for example 3 to 4.5, are associated with increased risk of cardiovascular disease.

4. Replacement with thyroxine has a beneficial effect on atherogenic lipid profile and impaired vascular function in patients with TSH levels between 2.5 and 4.5.

Defining the functional range:

- The Whickham Survey demonstrated that the chance of developing future clinical hypothyroidism is increased when TSH rises above 2.0.
- The American Association of Clinical Endocrinologists now suggests an upper limit for TSH of 3.0.
- Endocrine Society suggests an upper limit of 2.5.
- Data suggests considerable intra-individual variability with serum TSH, indicating that there may be an individual setpoint for TSH, determined by genetic and environmental factors.
- TSH can vary with age and ethnicity.

Given this, **I've defined the functional reference range for TSH as 0.5 to 2.0**.

- That does not mean that everyone with a TSH above 2.0 requires treatment, but we should start looking more carefully when you see TSH above that level.

FUNCTIONAL RANGES FOR THYROID MARKERS

The functional ranges below for T4, T3, free T4, and free T3 have been set based on clinical experience, since there is much less data published on these markers.

Marker	Functional range
TSH	0.5–2.0 mU/L
Total T4	6.0–12 ug/dL
Total T3	100–180 ng/dL
Free T4	1.0–1.5 ng/dL
Free T3	2.5–4.0

We use the normal lab range for thyroid antibodies.

Thyroid peroxidase (TPO) Ab	0–34
Thyroglobulin (TG) Ab	0.0–0.9

Subclinical hypothyroidism:

- Defined by elevated TSH but normal thyroid hormone levels.
- Estimated prevalence in the U.S. adult population of 4.3 percent.
- Prevalence of subclinical hypothyroidism increases with age and is approximately 10 percent in women over 60 years old and somewhat lower in men.
- Many studies have found that subjects with subclinical hypothyroidism have higher total cholesterol, LDL, and C-reactive protein than euthyroid subjects.
- **May increase the risk of cardiovascular disease by 60 percent.**
    - Treatment of subclinical hypothyroidism has been shown to improve cardiovascular markers.
- There is a risk of overtreatment.
    - Approximately 20 percent of patients are currently overtreated by thyroid replacement, with increased risk of hyperthyroidism that has been associated with atrial fibrillation, reduced bone mineral density, and cardiac dysfunction.

Secondary hypothyroidism:

- Low TSH due to low pituitary output and low T4 or T3.
- Caused by a dysfunction of the hypothalamus or pituitary gland, leading to decreased activity of the thyroid gland.
- Also will have low growth hormone, LH, FSH, and ACTH.
- Rare, 46 cases out of 100,000 people, so less likely to see it in clinical practice.

HASHIMOTO'S THYROIDITIS

- High TSH, low T3 and T4, and high TPO antibodies as seen in the example below is textbook Hashimoto's.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
TSH+T4F+T3Free					
TSH	57.040	High	uIU/mL	0.450 - 4.500	01
Triiodothyronine,Free,Serum	1.9	Low	pg/mL	2.0 - 4.4	01
T4,Free(Direct)	0.65	Low	ng/dL	0.82 - 1.77	01
Thyroid Peroxidase (TPO) Ab	378	High	IU/mL	0 - 34	01

- Is the cause of hypothyroidism in **up to 90 percent of cases.**

- **Patients with elevated thyroid antibodies are far more likely to develop hypothyroidism,** whether overt, clinical, or subclinical.
- **However, the presence of thyroid antibodies alone does not guarantee progression to clinical disease.**
- **70 percent** of the risk of developing Hashimoto's **is genetic**
    - Ask if there is a family history of thyroid disease.
- The appearance of thyroid antibodies precedes the risk of developing autoimmune thyroid disease by many years.
    - This highlights the importance of testing for thyroid antibodies.
- **Most common time of onset in women is after childbirth.**
- Up to 20 percent of patients with autoimmune thyroid disease don't produce antibodies, and 13 percent have only low levels of antibodies.
- **If only clinical and serum findings were used to diagnose Hashimoto's, the diagnosis would be missed in at least half of patients.**
- TSH and antibody levels can vary considerably intra-individually and can fluctuate significantly, largely due to the relapsing–remitting nature of the immune attack.
    - Antibodies can vary from high to normal.
    - TSH can range from low to normal to high, and the same is true for thyroid hormones.
- Thyroid ultrasound can be performed to confirm a suspected Hashimoto's diagnosis.
- **Ideal testing might include running antibodies on at least three occasions separated by a period of a few months and also a thyroid ultrasound.**

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
TSH+T4F+T3Free					
TSH	**0.122**	**Low**	uIU/mL	0.450 - 4.500	01
Triiodothyronine,Free,Serum	2.7		pg/mL	2.0 - 4.4	01
T4,Free(Direct)	**1.80**	**High**	ng/dL	0.82 - 1.77	01
Thyroid Antibodies					
Thyroid Peroxidase (TPO) Ab	24		IU/mL	0 - 34	01
Thyroglobulin, Antibody	**194.0**	**High**	IU/mL	0.0 - 0.9	01
Please Note:					01
Low positive Thyroglobulin antibodies are seen in a portion of the asymptomatic populations.					
Antithyroglobulin antibodies measured by Beckman Coulter Methodology					

Above are lab results for a 65-year-old female whose only complaint was slight fatigue and hypothyroidism. Her thyroglobulin antibodies were 194. Her TSH is low at 0.122, and her free T4 is high. This is **facetious hyperthyroidism**, which is hyperthyroidism caused by excess thyroid medication. She also has Hashimoto's.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
TSH+T4F+T3Free					
TSH	**7.140**	**High**	uIU/mL	0.450 - 4.500	01
Triiodothyronine,Free,Serum	2.0		pg/mL	2.0 - 4.4	01
T4,Free(Direct)	1.23		ng/dL	0.82 - 1.77	01

Below is what her labs looked like after reducing her thyroid medication dose and addressing some of her immune dysfunction. **T4 is now normal, but free T3 is borderline low. Most Hashimoto's patients have low T4-to-T3 conversion.** Her thyroglobulin antibodies dropped from 194 to 118, which is an improvement, but still quite high.

Thyroid Antibodies					
Thyroid Peroxidase (TPO) Ab	18		IU/mL	0 - 34	01
Thyroglobulin, Antibody	**118.4**	**High**	IU/mL	0.0 - 0.9	01
Please Note:					01
Low positive Thyroglobulin antibodies are seen in a portion of the asymptomatic populations.					
Antithyroglobulin antibodies measured by Beckman Coulter Methodology					

Here's another follow-up test after more treatment. Now her TSH, free T4, and free T3 are allnormal, although free T3 is still a little low in the functional range. Her thyroglobulin antibodies are still high, but about 70 percent lower than they were after the first test.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
TSH+T4F+T3Free					
TSH	0.676		uIU/mL	0.450 - 4.500	01
Triiodothyronine,Free,Serum	2.4		pg/mL	2.0 - 4.4	01
T4,Free(Direct)	1.31		ng/dL	0.82 - 1.77	01
Thyroglobulin Antibody	**58.8**	**High**	IU/mL	0.0 - 0.9	01
Thyroglobulin Antibody measured by Beckman Coulter Methodology					

Reverse T3 is another marker on the full thyroid panel.

- Inactive form of T3
- In emotional, psychological, or physiological stress, the body will convert excess T4 to reverse T3 as a means of conserving energy for healing and repair.

Ratio of reverse T3 to free T3:

- Above 20 for optimal ratio.

Ratio of reverse T3 to total T3:

- Above 10 for optimal ratio.

Low T4-to-T3 conversion, high reverse T3, or a high RT3-to-free T3 or -total T3 ratio, can be a **sign of inflammation, HPA axis dysfunction, or nutrient imbalance.**

For example, thyroid markers may normalize after **treating underlying conditions such as gut issues and heavy metal toxicity. Thus, we recommend addressing those underlying conditions prior to considering replacement thyroid hormone.**

Note that some studies have shown a link between elevated mercury levels and thyroid antibody production, and removal of dental amalgams has been shown to reduce thyroid antibody levels.

Thyroid				
TSH	0.800		uIU/mL	0.450 - 4.500
Thyroxine (T4)	**4.2**	**Low**	ug/dL	4.5 - 12.0
T3 Uptake	**40**	**High**	%	24 - 39
Free Thyroxine Index	1.7			1.2 - 4.9
Triiodothyronine (T3)	**66**	**Low**	ng/dL	71 - 180

The above result is from a 26-year-old patient with chief complaints of fatigue, tachycardia spells, and digestive distress, including constipation. Her TSH is on the low end, but her T4 and T3 are also low. In a classic hypothyroid presentation, you expect to see high TSH when T4 and T3 are low, but that's not the case here. This is central hypothyroidism.

Central hypothyroidism:

- Due to insufficient stimulation by TSH of an otherwise normal thyroid gland.
- Can be secondary to hypothyroidism caused by pituitary malfunction or tertiary hypothyroidism caused by hypothalamic malfunction.
- Usually due to pituitary macroadenomas, pituitary surgeries, or post-radiation.
- This presentation can also occur in Hashimoto's, especially in the early stages when the immune attack is relapsing and remitting.
- Confirmed by a TSH stimulation test.

The above patient also had high T3 uptake. This is likely due to her PCOS with high testosterone levels.

T3 uptake:

- Elevated T3 uptake can be caused by high testosterone.
- Chronic insulin surges and blood sugar problems can also lead to elevated T3 uptake, particularly in women.
- Low T3 uptake can be caused by high estrogens, and you most often see this in women taking oral contraceptives.

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
TSH+T4F+T3Free					
TSH	1.780		uIU/mL	0.450 - 4.500	01
Triiodothyronine,Free,Serum	2.4		pg/mL	2.0 - 4.4	01
T4,Free(Direct)	**0.69**	**Low**	ng/dL	0.82 - 1.77	01
Thyroid Antibodies					
Thyroid Peroxidase (TPO) Ab	**184**	**High**	IU/mL	0 - 34	01
Thyroglobulin, Antibody	<1.0		IU/mL	0.0 - 0.9	01
Please Note:					01
Low positive Thyroglobulin antibodies are seen in a portion of the asymptomatic populations.					
Antithyroglobulin antibodies measured by Beckman Coulter Methodology					

Above is an example of another presentation to be aware of. TSH is normal. Free T3 is normal in the reference range but borderline low in the functional range. Positive TPO antibodies and low free T4. This patient had Hashimoto's and was taking Armour Thyroid. When the patient is taking a medication that contains T3, you'll often see low T4 and normal T3. This is due to negative feedback inhibition. The body sees plenty of T3 in the bloodstream and reduces the output of T4. In this situation, consider treating TSH and free T3 and ignore total T4 and free T4.

Other markers common in hypothyroidism:

- Alkaline phosphatase is often low.
  - Thyroid hormone induces the production of alkaline phosphatase.
  - Alkaline phosphatase enzymes are anti-inflammatory and have evolved to help us tolerate our resident microbes by making us less reactive to them.
  - Think of alkaline phosphatase as a marker of immune tolerance.
- Both iron deficiency and overload can adversely affect the HPA axis and contribute to autoimmune thyroid disease and hypothyroidism.
- Vitamin D deficiency
  - This affects the thyroid in several ways.
    - It influences T-regulatory cells and plays important role in balancing TH1, which is cell mediated, and TH2, which is humoral immunity.

- It regulates insulin secretion and sensitivity and balances blood sugar.

There is a connection between autoimmune thyroid disease and gluten intolerance.

- Prevalence of celiac disease is much higher in patients with autoimmune thyroid disease.
- Antigliadin antibodies are more likely to be present in patients with autoimmune thyroid disease.

NUTRIENTS FOR THYROID HEALTH

So far, we've been talking about hypothyroidism due to immune dysfunction, or Hashimoto's; inflammation; or gut imbalances or toxins, but the thyroid needs several nutrients to function properly, including iodine, selenium, iron, zinc, vitamin B12, vitamin B2, vitamin C, vitamin A, vitamin D, and magnesium.

Iodine	B2
Selenium	Vitamin C
Iron	Vitamin A
Zinc	Vitamin D
B12	Magnesium

Iodine:

- An essential nutrient required for reproduction and growth; its only known function is the synthesis of thyroid hormone.
- Recent data indicates that iodine deficiency may be a bigger issue in our patient population than conventional wisdom suggests, and this is especially true for **at-risk populations such as children, women of childbearing age, pregnant and nursing women, African Americans, and individuals on diets** that do not include bread, dairy, iodized salt, sea vegetables, or fish heads.
- Iodine supplementation can be helpful to normalize TSH and improve thyroid symptoms.

Testing for iodine:

- Spot urine test

  - Studies have shown that urine iodine and even 24-hour urine collections are not accurate for individuals because of significant intra-individual day-to-day variations in iodine intake.
  - About 10 spot urine collections are needed to estimate iodine intake with acceptable precision.
- A study in 2014 indicated that hair iodine may be a better marker of longer-term iodine intake and current iodine status.
- Serum iodine is not considered to be a very accurate indicator of iodine levels.
  - However, serum thyroglobulin level, not thyroglobulin antibodies but thyroglobulin itself, is considered to be a fairly sensitive marker of iodine status.
  - High thyroglobulin indicates low iodine status, and levels above 40 mcg/L are suggestive of deficiency.

If you have a patient with hypothyroidism, two to three negative antibody tests, and a negative thyroid ultrasound, **consider iodine deficiency.**

Some studies have shown that **increased iodine intake, especially in supplement form, can increase the autoimmune attack on the thyroid**. Iodine reduces the activity of thyroid peroxidase, and TPO is required for proper thyroid hormone production.

Selenium may protect against the harmful effects of iodine. Other studies have shown that selenium prevents the triggering and flaring of autoimmune disease that excess iodine without selenium can cause.

You can begin **iodine supplementation with or without testing.**

For testing, based on the above, **I suggest combining serum thyroglobulin with 24-hour urine and possibly hair as well, and you can run hair iodine** with Doctor's Data Essential Toxic Hair Elements profile.

- If the test results are **normal**, and the patient is not in any of the groups that are at high risk for iodine deficiency, do not supplement with iodine.
- If iodine is low and/or if they are in any of the **high-risk groups for deficiency, and there is no evidence of Hashimoto's**, supplementing with doses up to 1,100 mcg per day appears to be safe, but I would still **monitor thyroid antibodies and other thyroid markers closely.**

- If iodine is low and/or they are in a high-risk group for deficiency, and the **patient does have Hashimoto's**, you can try supplementing at a very low dose such as maybe 100 mcg or just increase intake of foods with iodine.

Selenium Supplementation:

- Long-term high dose selenium supplementation can lead to complications such as gastrointestinal upset, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability, and mild nerve damage.
- Some studies have shown that supplementing with selenium in the context of low iodine status may actually aggravate hypothyroidism.
- A large clinical trial with 35,000 men found that selenium supplementation when selenium levels were adequate at baseline significantly increased the risk of prostate cancer.
- **I usually recommend that patients obtain adequate selenium intake through their diet and possibly to use testing for selenium levels at baseline to determine whether selenium supplementation is warranted.**

Iron:

- Deficiency reduces heme-dependent thyroid peroxidase activity in the thyroid, resulting in impaired production of thyroid hormone.
- Iron-deficiency anemia during pregnancy can result in both higher TSH and lower T4 concentrations.
- Treat iron deficiency.
- Monitor iron level, being careful to avoid iron overload.

Other nutrients required for proper thyroid function are:

Nutrient	Function
Magnesium, B12 and zinc	Required for synthesis of TSH
Riboflavin and vitamin C	Required by iodine symporter
Vitamins A & D	Required to activate the nuclear thyroid receptor

Supplement as necessary, since many individuals are deficient in these nutrients.