KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

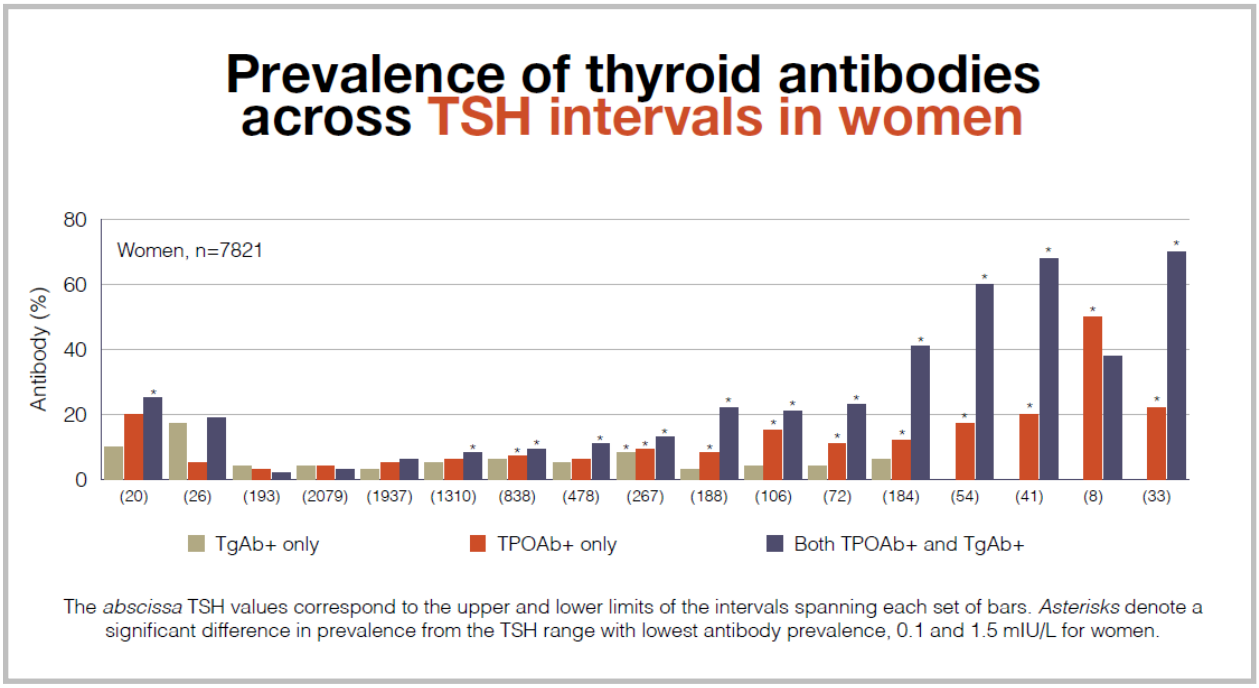
Thyroid Hypofunction I - Part Two

The current thyroid-stimulating hormone, or TSH, reference range is based on the 2002 NHANES III study cohort that looked at individuals without evidence of thyroid dysfunction or positive thyroid peroxidase antibodies, 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. Today, the range is 0.5 to 4.5 for most labs. Some have a slightly lower end, such as 0.4, and others such as Kaiser have a higher top end of 5 or even 5.5 in some cases.

The reference range for TSH is still highly controversial and frequently debated in the scientific literature, but there are some significant problems in how it was developed. For example, in the NHANES study, although they did measure TPO antibodies in an attempt to exclude patients with thyroid disease, some studies have shown that 20 percent of patients with mild TSH elevations and cytological evidence of autoimmune thyroid disease do not produce thyroid antibodies ever, so you could test their thyroid antibodies several times, and they would never test positive, but they still do have autoimmune thyroid disease.

In these studies, autoimmune thyroid disease was confirmed by thyroid ultrasound even in the absence of antibody production, so this means that the range determined by NHANES III was probably skewed upward because the study population included people with occult thyroid dysfunction. More rigorous recent studies that more carefully excluded patients with both known and unknown thyroid disease have found a TSH reference range that is much narrower than the standard laboratory range.

What's more, numerous studies have shown that even slightly elevated TSH levels at a range currently considered to be normal, for example, 3 to 4.5, are associated with increased risk of cardiovascular disease. Other studies have found that thyroid dysfunction may worsen the prognosis of diabetes, kidney dysfunction, and metabolic syndrome, and also worsen pregnancy outcomes, neurological and psychological problems, and heart failure.



The Whickham Survey demonstrated that the chance of developing future clinical hypothyroidism is increased when TSH rises above 2.0. An ideal TSH concentration is at or slightly below that level. It found that thyroid antibody production is associated with TSH levels above 2.0, with 80 percent of people with TSH over 20 producing antibodies. Finally, replacement with thyroxine has been found to exert beneficial effect on atherogenic lipid profile and impaired vascular function in patients with TSH levels between 2.5 and 4.5. This was, in fact, a more common treatment for high cholesterol prior to the development of cholesterol-lowering drugs such as statins.

The American Association of Clinical Endocrinologists now suggests an upper limit for TSH of 3.0, while the Endocrine Society suggests an upper limit of 2.5. Arguably, given the Whickham data, the upper limit should be 2.0, but at that level, there is more concern about overtreatment.

Given all this, I've defined the functional reference range for TSH of 0.5 to 2.0. That doesn't mean that everyone with a TSH above 2.0 requires treatment, but it does mean that we should start looking more carefully when you see TSH above that level.

That said, there are some things you need to know about this functional range. First, like all functional or even lab ranges, it isn't necessarily a guideline for treatment. It's just one variable for consideration in the overall clinical diagnosis. It's an invitation to look deeper, and we'll talk about this more as we

go through case studies. Second, the data suggests considerable intraindividual variability with serum TSH in that there may be an individual setpoint, almost like a thermostat for TSH, that is determined by genetic and environmental factors. The setpoint reflects characteristics of each individual's negative feedback loop, including the responsiveness of thyroid follicular cells to TSH stimulation and the sensitivity of TRH neurons and thyrotropes to thyroid hormone feedback.

Third, it's well established that TSH can vary with age and ethnicity. For example, in one study, normal TSH for African Americans was 3.6 versus 4.2 for Mexican Americans or Caucasians. Now, of course, that study wasn't excluding people with thyroid antibodies, so you probably need to revise those numbers downward if they had been, but the main point here is that the values can differ based on ethnicity.

The upper limit for TSH in one study was 3.5 for people 20 to 29 years old, 4.5 in people 50 to 59 years old, and 7.5 in those older than 80 years. As we discussed in the case of 25(OH)D, or vitamin D, it's likely that the optimal TSH range should vary based on ethnicity, age, and perhaps other factors, but we don't yet have enough info to accurately quantify this.

Functional ranges for core thyroid 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

What about functional ranges for T4, T3, free T4, and free T3? There is far less data published on this, and most clinicians, including me, have simply narrowed the lab range based on clinical experience, so you'll get the functional ranges as part of the individual biomarker reference sheets for thyroid, and I've also put them on this slide.

Reference ranges for thyroid antibodies

Marker	Range (IU/mL)
Thyroid peroxidase (TPO) Ab	0–34
Thyroglobulin (TG) Ab	0.0–0.9

What about thyroid antibodies? I don't have a functional range for thyroid antibodies. You just use the normal lab range, and I don't agree with people who say that any antibody production to TPO or thyroglobulin is abnormal. Autoantibodies that occur in healthy individuals, which are referred to as natural autoantibodies, are usually of the IgM isotype, and they bind to several unrelated antigens with moderate affinity. They play a role in the development of the B-cell repertoire and the homeostasis of the immune system. For example, rheumatoid factor has been suggested to enhance the binding of low-affinity IgG antibodies to their antigens, potentially assisting in first-line immunological defense against foreign pathogens before the development of specific higher-affinity antibodies, so something similar could be going on when you see very low levels of TPO or thyroglobulin antibody, and it does not mean that the patient has Hashimoto's if they have levels that are above zero but within the reference range.

All right, let's just dive right into some cases, and then we'll cover some of the remaining points within the context of these cases.

Marker	Value	Functional Range	Lab Range
Glucose	97	75 – 90	65 - 99
Hemoglobin A1c	5.2	4.4 – 5.4	4.8 - 5.6
Uric Acid	5.8	3.2 - 5.5	2.5 - 7.1
BUN	17	13 – 18	6 - 24
Creatinine	0.71	0.85 – 1.1	0.57 - 1
Sodium	141	135 – 140	134 - 144
Potassium	3.9	4.0 – 4.5	3.5 - 5.2
Chloride	102	100 – 106	97 - 108
C02	26	25 – 30	18 - 29
Calcium	9.3	9.2 – 10.1	8.7 - 10.2
Phosphorus	4.1	3.5 – 4.0	2.5 - 4.5
Magnesium	1.9	2.0 – 2.6	1.6 - 2.6
Protein, total	6.6	6.9 – 7.4	6.0 - 8.5
Albumin	4.6	4.0 – 5.0	3.5 - 5.5
Globulin	2.0	2.4 – 2.8	1.5 - 4.5
A/G ratio	2.3	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.3	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	56	42 – 107	39 - 117
LDH	144	140 - 180	119 - 226
AST	15	10 - 30	0 - 40
ALT	13	10 - 22	0 - 32
GGT	11	0 - 28	0 - 60
TIBC	267	250 – 350	250 - 450
UIBC	192	150 - 375	150 - 375
Iron	75	85 – 135	35 - 155
Iron saturation	28	15 – 45	15 - 55
Ferritin	177	MW: 30 - 150	15 - 150
Cholesterol, total	230	150 – 250	100 - 199
Triglycerides	91	50 – 100	0 - 149
HDL	71	55 – 85	> 39
LDL	141	0 – 175	0 - 99
T. Chol / HDL Ratio	3.2	< 3	0 - 4.4
Triglycerides / HDL Ratio	1.28	< 2	< 3.8
TSH	6.060	0.5 – 2.5	0.45 - 4.50
T4, total	6.2	6.0 – 12	4.5 - 12.0
T3 Uptake	32	28 - 35	24 - 39
T3, Total	100	100 – 180	71 - 180
Vitamin D, 25-hydroxy	47.3	35 - 60	30.0 - 100.0

Marker	Value	Functional Range	Lab Range
WBC	5.3	5.0 – 8.0	3.4 - 10.8
RBC	4.91	4.4 – 4.9	3.77 - 5.28
Hemoglobin	13.8	13.5 - 14.5	11.1 - 15.9
Hematocrit	42.5	37 - 44	34.0 - 46.6
MCV	87	85 – 92	79 - 97
MCH	28.1	27.7 – 32.0	26.6 - 33.0
MCHC	32.5	32 – 35	31.5 - 35.7
RDW	13.5	11.5 – 15.0	12.3 - 15.4
Platelets	201	150 – 415	150 - 379
Neutrophils	63	40 – 60	
Lymphocytes	29	25 – 40	
Monocytes	6	4.0 – 7.0	
Eosinophils	2	0.0 – 3.0	
Basophils	0	0.0 – 3.0	
Additional Tests:			
T3, Free	3.1	2.5 - 4.0	2 - 4.4
T4, Free	1.06	1 - 1.5	0.82 - 1.77
Thyroid – TPO Ab	<6		0 - 34
Thyroid – TGA	<1.0		0 - 0.9
CRP-hs	1.23	< 1.0	0.00 - 3.00
Homocysteine	12.1	< 9.0	0.0 - 15.0
Vitamin B-12	374	450 – 2000	211 - 946
Copper	122		72 - 166
Zinc	125		56 - 134
Zinc / Copper Ratio	1.02	> 0.85	
Serum Methylmalonic Acid (MMA)	160	0 - 325	0 - 378

The first patient is a 57-year-old female with overall concern to resolve or at least improve gut dysbiosis and, in her words, specifically, "I'd like to lose some weight, 15 to 20 pounds, improve energy enough to exercise more, improve the rosacea on my cheeks, and have more normal bowel movements. I have ongoing loose stools with occasional urgency that is stressful and affects quality of life, and I cannot eat most grains." If we look at her labs, her TSH is 6, which is even outside of the lab reference range. However, her total T4, T3, and thyroid antibodies were all in range. She had been diagnosed with Hashimoto's in the past, but her antibodies were normal here. This is just a reminder that they can fluctuate significantly, and antibody production doesn't always progress to clinical disease. In fact, most often it doesn't.

When TSH is elevated but thyroid hormone levels are normal, that's called subclinical hypothyroidism. Subclinical hypothyroidism is common, with an estimated prevalence in the U.S. adult population of 4.3 percent in a recent analysis of the NHANES III data, but again, that's using the standard upper limit for TSH. Of patients with subclinical hypothyroidism, 80 percent of them have a

serum TSH of less than 10. The prevalence of subclinical hypothyroidism increases with age and is approximately 10 percent in women aged more than 60 years old and somewhat lower in men.

Sublinical hypothyroidism may increase the risk of cardiovascular disease by 60%.

There is considerable controversy over whether subclinical hypothyroidism is indicative of a problem and should be treated. Despite some conflicting results, many studies have found that subjects with subclinical hypothyroidism have higher total cholesterol, LDL, and C-reactive protein than euthyroid subjects. As mentioned, subclinical hypothyroidism is associated with increased risk of cardiovascular disease and many other conditions. For example, one study found a 60 percent increase in cardiovascular disease risk in patients with subclinical hypothyroidism. An adjustment for traditional CVD risk factors in these studies didn't decrease this risk. Also, treatment of subclinical hypothyroidism has been shown to improve cardiovascular markers. One study found a significant 10 percent decrease in average intima-media thickness after six months of thyroxine replacement, with a decrease of similar magnitude in the 18 participants with TSH less than 10.

On the other hand, there is a risk of overtreatment. Approximately 20 percent of patients are currently overtreated by thyroxine replacement, with an increased risk of hyperthyroidism that has been associated with atrial fibrillation, reduced bone mineral density, and cardiac dysfunction. Moreover, thyroxine replacement might have adverse effects on mortality, in the elderly particularly. We'll talk about this more when we get to the treatment section, but as you might suspect, the decision to treat subclinical hypothyroidism depends on the individual case, and I'll give you an algorithm to help you make that decision.

Marker	Value	Functional Range	Lab Range
Glucose	82	75 – 85	65 – 99
Hemoglobin Alc	5.2	4.4 – 5.4	4.8 – 5.6
Uric Acid	3.9	W: 3.2 – 5.5	2.5 - 7.1
BUN	15	13 – 18	6 – 20
Creatinine	1.01	0.85 – 1.1	0.57 - 1.00
Sodium	143	135 – 140	134 – 144
Potassium	4.5	4.0 – 4.5	3.5 – 5.2
Chloride	102	100 – 106	97 – 108
C02	24	25 – 30	18 - 29
Calcium	10.0	9.2 – 10.1	8.7 – 10.2
Phosphorus	3.8	3.5 – 4.0	2.5 – 4.5
Magnesium	2.1	2.0 – 2.5	1.6 – 2.6
Protein, total	7.2	6.9 – 7.4	6.0 – 8.5
Albumin	4.9	4.0 – 5.0	3.5 – 5.5
Globulin	2.3	2.4 – 2.8	1.5 – 4.5
A/G ratio	2.1	1.5 – 2.0	1.1 – 2.5
Bilirubin, total	1.1	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	65	42 – 107	39 - 117
LDH	159	140 - 180	119 – 226
AST	33	W: 10-30	0 – 40
ALT	42	W: 10-22	0 – 32
GGT	15	10 -26	0 -60
TIBC	289	250 – 350	250 – 450
UIBC	211	150 - 375	150 – 375
Iron	78	85 – 135	35 – 155
Iron saturation	27	15 – 40	15 – 55
Ferritin	167	W: 10-122	15 – 150
Cholesterol, total	207	150 – 250	100 – 199
Triglycerides	41	50 – 100	0 – 149
HDL	82	55 – 85	> 39
LDL	117	0 – 175	0 – 99
Triglycerides / HDL Ratio	0.5	< 2	< 3.8
TSH	1.020	0.5 – 2.5	0.450 – 4.500
T4, total	5.7	6.0 – 12	4.5 – 12.0
T3 Uptake	31	W: 28-35	24 – 39
T3, Total	60	100 – 180	71 – 180
Vitamin D, 25-hydroxy	77.4	35 - 60	30.0 - 100.0
WBC	4.9	5.0 – 8.0	3.4 - 10.8
RBC	5.07	4.4 – 4.9	3.77 - 5.28
Hemoglobin	15.0	W: 13.5-14.5	11.1 - 15.9

	Value	Functional Range	Lab Range
Hematocrit	45.5	W: 37-44	34.0 - 46.6
MCV	90	85 – 92	79 - 97
MCH	29.6	27.7 – 32.0	26.6 - 33.0
MCHC	33.0	32 – 35	31.5 - 35.7
RDW	13.3	11.5 – 15.0	12.3 - 15.4
Platelets	327	150 – 415	150 -379
Neutrophils	54	40 – 60	
Lymphocytes	38	25 – 40	
Monocytes	5	4.0 – 7.0	
Eosinophils	2	0.0 – 3.0	
Basophils	1	0.0 – 3.0	
B-12	1540	450 – 2000	211 - 946
Additional Tests:			
CRP-hs	0.12		0.00 – 3.00
Homocysteine	7.4		0.00 – 15.0
Sed Rate (Westergren)			0 – 32
T3, Free	2.1		2.0 – 4.4
T4, Free	0.95		0.82 – 1.77
Thyroid Peroxide (TPO)	108		0 - 34
Thyroglobulin, Antibody	<1.0		0.0 - 0.9
TGF-B1			344 - 2382

Here's the flip side of a case we just discussed. Here we see normal TSH at 1 but functionally low T4, free T4, and free T3. This is an old lab before I was using functional range for free T3. Then we also see elevated TPO antibodies. This patient is a 34-year-old female with anovulation, migraines, and a prior diagnosis of Hashimoto's. In Hashimoto's, TSH levels can fluctuate significantly, especially in the early stages of disease, and this is largely due to the relapsing-remitting nature of the immune attack. When the immune attack is strong, that can destroy tissue and actually lead to a release of thyroid hormone into the system, which can lead to a transient hyperthyroid state and depressed TSH, but then after that passes, the thyroid has lost more capacity to produce hormone, which can lead to hypothyroidism, so you'll see TSH go up. If this is happening, I've seen TSH go from 30 to below 0.5 in the same patient in a matter of weeks.

Another possible cause of normal TSH and low T4 or T3 is secondary hypothyroidism. This is caused by a dysfunction of the hypothalamus or pituitary, leading to decreased activity of the thyroid gland. Most often in these cases, TSH will be low due to low pituitary output, but in some cases, it can be normal or low-normal as it is here. In this case, we know she has Hashimoto's, so that's the most likely cause, and treatment would focus on immune regulation first by addressing underlying causes of immune dysfunction and then possibly replacement if T4 and T3 continue to be below the range.