Thyroid Hypofunction I - Part Three

Let's use that case as a springboard to talk about autoimmune hypothyroidism, or Hashimoto's.

Hashimoto's is the most common cause of hypothyroidism in the U.S. by far. Estimates vary depending on the study, but they range from 50 to 90 percent of cases of hypothyroidism caused by Hashimoto's, and most studies are closer to 90 percent. Thyroid antibodies are detected in 10 to 12.5 percent of the general population, depending on the study you look at, again. Antibody production does not guarantee progression to thyroid dysfunction. That's really important to understand, and, in fact, most people who produce thyroid antibodies don't go on to develop hypothyroidism, and that should be obvious given that up to 12.5 percent of the population produces antibodies, whereas only about 4.6 percent of the population has hypothyroidism.

In one study, when both TPO and thyroglobulin antibodies were present, the odds ratio for overt hypothyroidism was 23.5 and for subclinical hypothyroidism was 11.7. These were higher for TPO alone than for overt hypothyroidism, which the odds ratio was 6.9 in that case, and for subclinical hypothyroidism, the odds ratio was 4.0 in that case. Thyroglobulin alone, at least in that particular study, was not a risk factor for overt hypothyroidism or subclinical hypothyroidism, but it has been in other studies.

TPO is more commonly elevated in Hashimoto's and considered to be more diagnostic, but thyroglobulin can be elevated, and when they both are, it strengthens the likelihood that the patient will progress to both overt and subclinical hypothyroidism.

Note that TPO and thyroglobulin antibodies can also be elevated in Graves' disease, so if you see elevated antibodies and low TSH, it may be more likely Graves', and we'll talk more about this in the next unit, though in some cases, that can also be a condition called Hashimoto's thyrotoxicosis, which is that early stage of Hashimoto's where you sometimes get a transient hyperthyroid state. The takeaway from this is that 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% of the risk of developing Hashimoto's is genetic.

What determines whether a patient progresses or doesn't? This is a great question that we don't fully understand yet. We do know that genes play a strong role because we have studies of identical twins that suggest that about 70 percent of the risk of developing hypothyroidism, Hashimoto's hypothyroidism, is genetic, and only 30 percent is environmental. Siblings of patients with autoimmune thyroid disease are clearly at risk, as evident from sibling risk ratios ranging from 5.9 to higher than 10. We also know that the appearance of thyroid antibodies precedes the risk of developing autoimmune thyroid disease by many years, sometimes by decades. The onset of Hashimoto's is usually between 30 and 50 years old, but antibodies can show up as early as the teenage years. This suggests the possibility that intervening early to balance and regulate the immune system may prevent the development of clinical thyroid disease later, and this is why it is important to test for antibodies. It's also why it's important to ask in the intake paperwork if there is a family history of thyroid disease.

If only clinical and serum findings are used to diagnose Hashimoto's, at least half of patients would be missed.

However, clinically, part of the issue is that up to 20 percent of patients with autoimmune thyroid disease don't produce antibodies, and 13 percent have only really low levels of antibodies. In fact, if only clinical and serum findings were used to diagnose Hashimoto's, the diagnosis would be missed in at least half of patients. Also, antibody production varies considerably intraindividually. This means that a single negative antibody test cannot rule out Hashimoto's, especially with the initial onset of Hashimoto's with that relapsing-remitting pattern of immune dysfunction we talked about. This can lead to some pretty weird lab results. Antibodies can vary from high to normal. TSH can range from low to normal to high, and the same is true for thyroid hormones. As I mentioned on the last slide,

there is a condition called Hashimoto's thyrotoxicosis that presents a lot like Graves' disease, but those patients eventually progress to clinical hypothyroidism, not hyperthyroidism.

We usually test patients two to three times for thyroid antibodies over the course of several months to get a better idea, but again, since 20 percent never test positive for thyroid antibodies, you can't look at negative antibody tests and rule out Hashimoto's that way.

If antibody tests are negative, and you really suspect Hashimoto's is present, thyroid ultrasound can be performed to confirm a suspected Hashimoto's diagnosis. Ultrasound findings in Hashimoto's cases would be a diffusely enlarged thyroid gland, coarsened parenchymal echogenicity, more hypoechoic than normal, and often hypervascular on color Doppler sonography. Diverse multinodular goiter is also indicative of Hashimoto's with a positive predictive value of 95 percent.

Studies have shown that properly performed thyroid ultrasound has a sensitivity of 90 percent, specificity of about 85 percent, positive predictive value of 84 percent, negative predictive value of 91 percent, and an accuracy of 87 percent for the diagnosis of Hashimoto's patients in those patients with positive TPO antibodies.

Some patients with positive thyroid ultrasound don't produce antibodies, and some patients with antibodies have a negative ultrasound. The ideal clinical approach, for this reason, is to do both forms of testing, if possible. Run antibodies on at least three occasions separated by a period of a few months and also a thyroid ultrasound.

The next patient is a really interesting case. This is a 65-year-old female with slight fatigue, and hypothyroidism was her only complaint. She had never been tested for Hashimoto's, and I ran a follow-up test with thyroid antibodies, and this is what came back.

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					

Her thyroglobulin antibodies were 194 in a range of 0 to 0.9. This is, I think, one of the highest, if not the highest, levels of thyroglobulin that I've ever seen. Note that her TPO antibodies are normal, 24 in a range of 0 to 34. 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 does have Hashimoto's, but she was taking thyroid medication, and the dose was perhaps a little bit too high given her suppressed TSH and her high free T4. Note that her free T3 is not high at 2.7. We're going to talk a little bit more about this later. This is somewhat controversial when you're treating with thyroid medication whether you should treat for adequate T3 levels or whether you should treat for normal TSH levels, and we'll come back to this.

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
Renal Panel (10)					
Glucose, Serum	83		mg/dL	65 - 99	01
BUN	16		mg/dL	8 - 27	01
Creatinine, Serum	0.86		mg/dL	0.57 - 1.00	01
eGFR If NonAfricn Am	72		mL/min/1.73	>59	
eGFR If Africn Am	83		mL/min/1.73	>59	
BUN/Creatinine Ratio	19			11 - 26	
Sodium, Serum	139		mmol/L	134 - 144	01
Potassium, Serum	4.1		mmol/L	3.5 - 5.2	01
Chloride, Serum	100		mmol/L	97 - 108	01
Carbon Dioxide, Total	23		mmol/L	18 - 29	01
Calcium, Serum	9.2		mg/dL	8.7 - 10.3	01
Phosphorus, Serum	4.0		mg/dL	2.5 - 4.5	01
Albumin, Serum	4.0		g/dL	3.6 - 4.8	01
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					

This 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 don't convert T4 to T3 well. That's common. Her thyroglobulin antibodies dropped from 194 to 118, which is an improvement, of course, but still quite high.

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					

Here's another follow-up test after more treatment. Now her TSH, free T4, and free T3 are all normal, 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	**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

Here's what a textbook case of Hashimoto's hypothyroidism looks like. Patient is a 52-year-old female with afternoon fatigue, low-grade headaches four days a week, and bloating. Here is what she wrote in her intake paperwork: "I was diagnosed with Hashimoto's 12 years ago after the birth of my second child." Here's my note about that. That's the most common time for onset of Hashimoto's in women is after childbirth because there is a profound immune shift that happens in the second and third trimester and then again in the postnatal period. Okay, back to her account. "I was given a script for Armour. Took a little bit and then stopped. I'm not very good at remembering to take pills. I've always thought there was a more natural way for me to get my thyroid back to optimal levels, but I have not had it checked in many years." Well, as you can see, her TSH is 57. Her free T3 is 1.9. Her free T4 is 0.65, and her TPO antibodies were 378. This is what hypothyroidism looks like when it is untreated.

That said, her symptoms were somewhat mild, which is probably why she didn't take it seriously, but part of your job as a clinician is to educate patients on the risks of hypothyroidism, such as increased cardiovascular risk, risk of metabolic disease, poor pregnancy outcomes, etc., above and beyond the symptoms it produces. Every cell in the body needs thyroid hormone, and even if the patient has subclinical hypothyroidism, as we discussed, they are at increased risk for these conditions, but when the hypothyroidism is frank and extreme, like it is here, they are at even higher risk.

Comprehensive Stool Analysis / Parasitology x3

BACTERIOLOGY CULTURE

Expected/Beneficial flora	Commensal (Imbalanced) flora	Dysbiotic flora
4+ Bacteroides fragilis group		3+ Enterobacter cloacae complex
3+ Bifidobacterium spp.		3+ Klebsiella oxytoca
4+ Escherichia coli		3+ Klebsiella pneumoniae ssp pneumoniae
3+ Lactobacillus spp.		
3+ Enterococcus spp.		
3+ Clostridium spp.		
NG = No Growth		

BACTERIA INFORMATION

Expected /Beneficial bacteria make up a significant portion of the total microflora in a healthy & balanced GI tract. These beneficial bacteria have many health-protecting effects in the GI tract including manufacturing vitamins, fermenting fibers, digesting proteins and carbohydrates, and propagating anti-tumor and anti-inflammatory factors.
Clostridia are prevalent flora in a healthy intestine. Clostridium spp. should be considered in the context of balance with other expected/beneficial flora. Absence of clostridia or over abundance relative to other expected/beneficial flora indicates bacterial imbalance. If *C. difficile* associated disease is suspected, a Comprehensive Clostridium culture or toxigenic *C. difficile* DNA test is recommended.
Commensal (Imbalanced) bacteria are usually neither pathogenic nor beneficial to the host GI tract. Imbalances can occur when there are insufficient levels of beneficial bacteria and increased levels of commensal bacteria. Certain commensal bacteria are reported as dysbiotic at higher levels.
Dysbiotic bacteria consist of known pathogenic bacteria and those that have the potential to cause disease in the GI tract. They can be present due to a number of factors including: consumption of contaminated water or food, exposure to chemicals that are toxic to beneficial bacteria; the use of antibiotics, oral contraceptives or other medications; poor fiber intake and high stress levels.

YEAST CULTURE

Normal flora	Dysbiotic flora
	2+ Candida inconspicua
	2+ Candida krusei

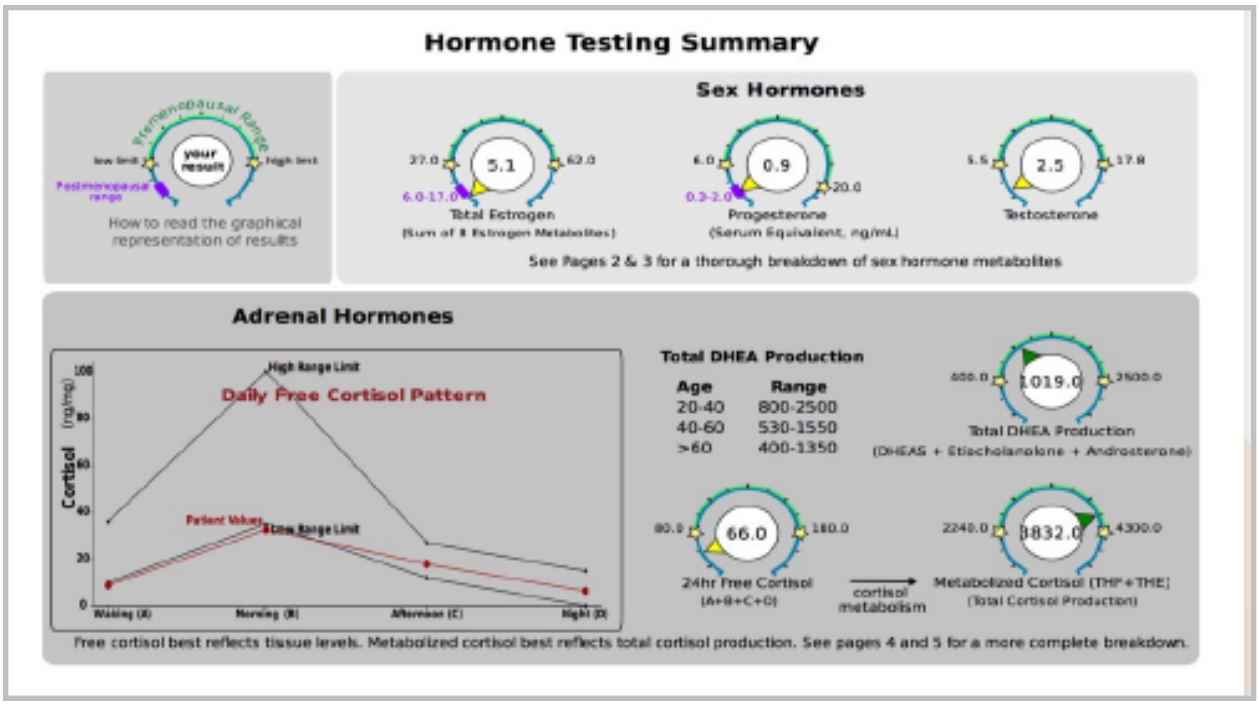
MICROSCOPIC YEAST

Result:	Expected:
Rare	None - Rare

The microscopic finding of yeast in the stool is helpful in identifying whether there is proliferation of yeast. Rare yeast may be normal; however, yeast observed in higher amounts (few, moderate, or many) is abnormal.

YEAST INFORMATION

Yeast normally can be found in small quantities in the skin, mouth, intestine and mucocutaneous junctions. Overgrowth of yeast can infect virtually every organ system, leading to an extensive array of clinical manifestations. Fungal diarrhea is associated with broad-spectrum antibiotics or alterations of the patient's immune status. Symptoms may include abdominal pain, cramping and irritation. When investigating the presence of yeast, disparity may exist between culturing and microscopic examination. Yeast are not uniformly dispersed throughout the stool, this may lead to undetectable or low levels of yeast identified by microscopy, despite a cultured amount of yeast. Conversely, microscopic examination may reveal a significant amount of yeast present, but no yeast cultured. Yeast does not always survive transit through the intestines rendering it unviable.



This patient had significant bacterial and fungal dysbiosis and also HPA axis dysregulation with quite low free cortisol, and these were both likely contributing to immune dysregulation. Notice that her free cortisol is low, while her metabolized cortisol is high-normal. This is a pattern you more often expect to see in hyperthyroidism rather than hypothyroidism, if you recall from the HPA axis unit, and she is far from hyperthyroid. This is just a reminder that the urine results and all the results in the panel won't always fit the textbook definition.