

Investigating Unstable Thyroid Function

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A 43-year-old man presents for his thyroid checkup. He has known hypothyroidism secondary to Hashimoto thyroiditis, also known as *chronic lymphocytic thyroiditis*. He is taking levothyroxine (LT4) 250 µg (two 125-µg tablets once per day). Review of his prior lab results and notes (see Table 1) reveals frequent dose changes (about every three to six months) and a high dosage of LT4, considering his weight (185 lb).

Patients with little or no residual thyroid function require replacement doses of LT4 at approximately 1.6 µg/kg/d, based on lean body weight.¹ Since the case patient weighs 84 kg, the expected LT4 dosage would be around 125 to 150 µg/d.

This patient requires a significantly higher dose than expected, and his thyroid levels are fluctuating. These facts should trigger further investigation.

Important historical questions I consider when patients have frequent or significant fluctuations in TSH include

- Are you consistent in taking your medication?
- How do you take your thyroid medication?
- Are you taking any iron supplements, vitamins with

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TABLE 1
Lab Results for the Case Patient

	5/27/15	4/10/15	2/11/15	9/21/14	3/6/14	Reference range
TSH (µIU/mL)	6.6	4.3	0.13	1.3	4.7	0.45-4.5
Free T4 (ng/dL)	0.9		1.8		1.1	0.9-2.4

iron, or contraceptive pills containing iron?

- Has there been any change in your other medication regimen(s) or medical condition(s)?
- Did you change pharmacies, or did the shape or color of your pill change?
- Have you experienced significant weight changes?
- Do you have any gastrointestinal complaints (nausea/vomiting/diarrhea/bloating)?

MEDICATION ADHERENCE

It is well known but still puzzling to hear that, overall, patients' medication adherence is merely 50%.² It is very important that you verify whether your patient is taking his/her medication consistently. Rather than asking "Are you taking your medications?" (to which they are more likely to answer "yes"), I ask "How many pills do you miss in a given week or month?"

For those who have a hard time remembering to take their medication on a regular basis, I recommend setting up a routine:

Keep the medication at their bedside and take it first thing upon awakening, or place it beside the toothpaste so they see it every time they brush their teeth in the morning. Another option is of course to set up an alarm as a reminder.

RULES FOR TAKING HYPOTHYROID MEDICATIONS

Thyroid hormone replacement has a narrow therapeutic index, and a subtle change in dosage can significantly alter the therapeutic target. Hypothyroid medications are absorbed in the jejunum/ileum, and an acidic pH in the stomach is optimal for thyroid absorption.³ Therefore, taking the medication on an empty stomach (fasting) with a full glass of water and waiting at least one hour before breakfast is recommended, if possible. An alternate option is to take it at bedtime, at least three hours after the last meal. Taking medication along with food, especially high-fiber and soy products, can decrease absorption of thyroid hormone, which may result in an unstable thyroid function test.

There are supplements and

medications that can decrease hypothyroid medication absorption; it is recommended that patients separate these medications by four hours or more in order to minimize this interference. A full list is available in Table 2, but the most commonly encountered are iron supplements, calcium supplements, and proton pump inhibitors.²

In many patients—especially the elderly and those with multiple comorbidities that require polypharmacy—it can be very challenging, if not impossible, to isolate thyroid medication. For these patients, recommend that they be “consistent” with their routine to ensure they achieve a similar absorption rate each time. For example, a patient’s hypothyroid medication absorption might be reduced by 50% by taking it with omeprazole, but as long as the patient consistently takes the medication that way, she can have stable thyroid function.

NEW MEDICATION REGIMEN OR MEDICAL CONDITION

In addition to medications that can interfere with the absorption of thyroid hormone replacement, there are those that affect levels of thyroxine-binding globulin. This affects the bioavailability of thyroid hormones and alters thyroid status.

Thyroid hormones such as thyroxine (T4) and triiodothyronine (T3) are predominantly bound to carrier proteins, and < 1% is unbound (so-called *free hormones*). Changes in thyroid-binding proteins can alter free hormone levels and thereby change TSH levels. In disease-free euthyroid subjects, the body can compensate by adjusting hormone production for changes in binding proteins

to keep the free hormone levels within normal ranges. However, patients who are at or near full replacement doses of hypothyroid medication cannot adjust to the changes.

In patients with hypothyroidism who are taking thyroid hormone replacement, medications or conditions that increase binding proteins will decrease free hormones (by increasing bound hormones) and thereby raise TSH (hypothyroid state). Vice versa, medications and conditions that decrease binding protein will increase free hormones (by decreasing bound hormones) and thereby lower TSH (thyrotoxic state). Table 3 lists commonly encountered medications and conditions associated with altered thyroid-binding proteins.¹

It is important to consider pregnancy in women of child-bearing age whose TSH has risen for no apparent reason, as their thyroid levels should be maintained in a narrow therapeutic range to prevent fetal complications. Details on thyroid disease during pregnancy can be found in the April 2015 Endocrine Con-

TABLE 2
Medications That Reduce Levothyroxine Absorption

Aluminum-containing antacid
Calcium
Cation exchange resin
Cholestyramine
Colesevelam
Ferrous sulfate (iron)
Orlistat
Proton pump inhibitor
Raloxifene
Sevelamer
Sucralfate

Source: Jonklaas. 2014.²

sult, “Managing Thyroid Disease in Pregnancy” (<http://bit.ly/1Q6lh3g>).

In women treated for hypothyroidism, starting or discontinuing estrogen-containing medications (birth control pills or hormone replacement therapy) often results in changes in thyroid status. It is a good practice to inform the patient about these changes and

TABLE 3
Conditions and Medications Associated With Altered Thyroid-binding Proteins

Increased binding protein	Decreased binding protein
<i>Conditions</i>	<i>Conditions</i>
Hepatitis	Hepatic failure
Pregnancy	Nephrosis
<i>Medications</i>	Severe illness
Estrogens (birth control pills, hormone replacement therapy)	<i>Medications</i>
Methadone	Anabolic steroids
Selective estrogen receptor modulators	Androgens
	Glucocorticoids
	Nicotinic acid

Source: Garber et al. 2013.¹

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to recheck her thyroid labs four to eight weeks after she starts or discontinues estrogen, adjusting the dose if needed.

CHANGES IN MANUFACTURER/BRAND

There are currently multiple brands and generic manufacturers supplying hypothyroid medications and reports that absorption rates and bioavailability vary among them.² Switching products can result in changes in thyroid status and in TSH levels.

Once a patient has reached euthyroid status, it is imperative to stay on the same dose from the same manufacturer. This may be challenging, as it can be affected by the patient's insurance carrier, policy changes, or even a change in the pharmacy's medication supplier. Although patients are supposed to be informed by the pharmacy when the manufacturer is being changed, you may want to educate them to check the shape, color, and dose of their pills and also verify that the manufacturer listed on the bottle is consistent each time they refill their hypothyroid medications. This is especially important for those who require a very narrow TSH target, such as young children, thyroid cancer patients, pregnant women, and frail patients.³

WEIGHT CHANGES

As mentioned, thyroid medications are weight-based, and big changes in weight can lead to changes in thyroid function studies. It is the lean body mass, rather

than total body weight, that will affect the thyroid requirement.³ A quick review of the patient's weight history needs to be done when thyroid function test results have changed.

GASTROINTESTINAL DISTURBANCES

Hypothyroid medications are absorbed in the small intestine, and gastric acidity levels have an impact on absorption. Any acute or chronic conditions that affect these areas can alter medication absorption quite significantly. Commonly encountered diseases and conditions are *H pylori*-related gastritis, atrophic gastritis, celiac disease, and lactose intolerance. Treating these diseases and conditions can improve medication absorption.

I went through the list with the patient, but there was no applicable scenario. I adjusted his medication but went ahead and tested for tissue transglutaminase antibody IgA to rule out celiac disease; results came back mildly positive. The patient was referred to a gastroenterologist, who performed a small intestine biopsy for definitive diagnosis. This revealed "severe" celiac disease. A strict gluten-free diet was started, and the patient's LT4 dose was adjusted, with regular monitoring, down to 150 µg/d.

Common symptoms of celiac disease include bloating, abdominal pain, and loose stool after consumption of gluten-con-

taining meals. It should be noted that this patient denied all these symptoms, even though he was asked specifically about them. After he started a gluten-free diet, he reported that he actually felt "very calm" in his abdomen and realized he did have symptoms of celiac disease—but he'd had them for so long that he considered it normal. As is often the case, presence of symptoms would raise suspicion ... but lack of symptoms (or report thereof) does not rule out the disease.

CONCLUSION

Most patients with hypothyroidism are fairly well managed with relatively stable medication dosages, but there are subsets of patients who struggle to maintain euthyroid range. The latter require frequent office visits and dosage changes. Carefully reviewing the list of possible reasons for thyroid level changes can improve stability and patient quality of life, prevent complications of fluctuating thyroid levels, and reduce medical costs, such as repeated labs and frequent clinic visits. **CR**

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