Chapter 11
Gastrointestinal Disease and Levothyroxine Absorption

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Objectives
Describing common and uncommon gastrointestinal conditions associated with levothyroxine malabsorption.

Case

A 31-year-old woman sought endocrinology consultation because of profound hypothyroidism. The patient was initially diagnosed with metastatic (T3 N1b M1, stage II) papillary thyroid cancer at age 17 and underwent total thyroidectomy, bilateral neck dissection, and three radioactive iodine treatments. The patient has been free of disease since the last radioactive iodine treatment at age 20. She notes that since the initial surgery, she has experienced significant weight gain, cold intolerance, and dry skin. She notes that her TSH has never been normal since the surgery despite her levothyroxine dose has been increased several times. She currently takes 450 mcg of levothyroxine early in the morning with water. She assures she is adherent to the regimen, and the refill history is consistent with the levothyroxine regimen.

Her past medical history is significant for anxiety and depression, and she was told she has gluten intolerance, but is not following any specific diet.

Her family history is significant for a sibling affected by type 1 diabetes and her mother who has history of Graves' disease.

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Physical exam is remarkable for obesity grade I, 97 kg (BMI 34 kg/m^2), BP 102/70 mmHg, HR 76 bpm with periorbital edema, dry skin, delayed relaxation phase of deep tendon reflexes, and diffuse, nonpitting edema.

Laboratory data are reported below:

TSH 128 mcIU/ml (n.v. 0.4–4.5), free T4 < 0.4 ng/dl (n.v. 0.7–1.5), total T3 29 ng/dl (n.v. 60–181), thyroglobulin 0.3 ng/ml, anti-thyroglobulin antibodies <1 IU/ml; 25 OH vitamin D 9.2 ng/ml (n.v. 30–100), gastrin 19 pg/ml (n.v. 0–115), vitamin B 12383 pg/ml (n.v. 213–816), anti-gliadin IgA 21 A.U. (20–30 moderate positive), anti-gliadin IgG 21 A.U. (20–30 moderate positive), anti-tissue transglutaminase IgA 3 U/ml (negative <4), anti-tissue transglutaminase IgG 7 U/ml (negative <5), anti-endomysial IgA negative.

The provisional diagnosis of intestinal malabsorption due to celiac disease was made, and the patient was instructed to follow gluten-free diet while reducing levothyroxine dose to 300 mcg/day and starting 25 OH vitamin D 50,000 IU/week. One month later, the patient reported significant improvement of her symptoms.

Review of how the Diagnosis Was Made

This patient presented with severe clinical and biochemical hypothyroidism notwithstanding supraphysiologic dose of levothyroxine (>4.5 mcg/kg). Once nonadherence to the regime is ruled out, one should consider gastrointestinal malabsorption or drug interference with levothyroxine absorption. The historical data of "gluten intolerance" and the family history of autoimmune disease (mother with Graves' disease and sibling with type 1 diabetes) point to an immune-mediated gastrointestinal malabsorption. The very low 25-OH vitamin D levels effectively confirm gastrointestinal malabsorption (refusing the possibility that the severe hypothyroidism is entirely due to nonadherence). Normal gastrin and vitamin B12 levels rule out the diagnosis of atrophic gastritis. Finally, although weakly positive, the serologic markers for celiac disease, coupled with the clinical response to dietary modification, confirm the diagnosis of celiac disease–/gluten intolerance-induced levothyroxine malabsorption.

Lessons Learned

Nonadherence to Replacement Therapy Poor adherence to therapy is probably the most common cause of inability of achieving the target TSH in patients affected by hypothyroidism. This is particularly challenging in patients devoid of residual endogenous thyroid hormone production whereby the entire pool of circulating hormones derives from levothyroxine. Clinical suggestions for nonadherence include unexpected changes in free T4 and TSH over a short period of time or elevated TSH and free T4.

This latter condition likely reflects the patient attempt of "catching up" before the blood sampling. Causes of nonadherence include underlying psychiatric conditions, secondary gain, or polypharmacy with mix-up of prescriptions. This situation can be difficult to confirm with certainty, and confronting the patient is seldom useful. In these events, direct observation of weekly administration of levothyroxine is a viable therapeutic option. The patient refill history strongly supported, although did not confirm, good adherence to the therapeutic regimen. Occasionally the measurement of free T4 rise following a pharmacologic dose of levothyroxine can be used as a diagnostic test to distinguish malabsorption of levothyroxine vs. nonadherence [1].

Factors Affecting Levothyroxine Absorption Levothyroxine is the sodium salt of thyroxine (T4), and its absorption is function of tablet crushing and dissolution in the acidic environment of the stomach. Subsequently, the active drug is absorbed (60–80%) in the proximal intestine. In ability of dissolving the tablets, reduction of gastric acidity, binding of levothyroxine with interference substances (drugs or food), and anatomical or functional impairment of intestinal absorption are all causes of impaired levothyroxine absorption leading to low and inconsistent delivery of thyroid hormone replacement therapy [2].

Food, Interference on Levothyroxine Absorption Food and in particular items containing high concentration of calcium (milk and derivate), inhibit the absorption of levothyroxine. Coffee also inhibits the gastrointestinal absorption of levothyroxine [3], hence the recommendation of taking the levothyroxine only with water, at empty stomach, 30–60′ before breakfast [4]. The use of levothyroxine tablets in patients receiving enteral feeding represents a particular challenge since even if the crushed tablets may be sufficiently dissolved, calcium-containing feeding solution can still be present in the gastrointestinal tract, and often patients are treated with anti-acids.

Drug Interference on Levothyroxine Absorption Drugs can affect levothyroxine intestinal absorption by increasing the gastric pH (H_2 blockers, proton pump inhibitors), physically binding levothyroxine (calcium carbonate, magnesium oxide, phosphate binders, and sucralfate), or binding bile acids (cholestyramine) reducing the enterohepatic reabsorption of thyroid hormone.

Post-Surgical Levothyroxine Malabsorption Surgical procedures in the foregut affecting gastric acid secretion and diverting the gastric content from the jejunum significantly decrease the absorption of levothyroxine. In particular, bariatric procedures, either sleeve gastrectomy or Roux-en-Y, are associated with increased relative requirement (as expressed in mcg/kg) of levothyroxine and variability in absorption [5]. Patients are often treated with proton pump inhibitors to ameliorate gastroesophageal reflux, and the extent of the intestinal resection associated with the Roux-en-Y procedure also plays a role in the degree of levothyroxine malabsorption.

Gastrointestinal Diseases Affecting Levothyroxine Absorption Similar to surgical procedures, gastrointestinal conditions affecting the upper portion of the intestinal tract can have dramatic effects on the absorption of levothyroxine resulting in increased requirements or difficulties in controlling hypothyroidism. Importantly, some gastrointestinal diseases affecting levothyroxine absorption are also associated *per se* with thyroid autoimmunity, and a high index of suspicion should be kept when replacement therapy requires unusual dose of levothyroxine (above 2 mcg/kg) or multiple adjustments.

Atrophic Gastritis Irrespective of the etiology, this condition is associated with decreased gastric acid output resulting in elevated gastric pH and impaired levothyroxine absorption. Atrophic gastritis can be the result of *H. pylori* infection, and in this case, it is a reversible condition or secondary to an autoimmune state resulting in the physical destruction of the parietal cells resulting in permanent loss of acid production. This latter condition "thyrogastric syndrome" [6] is associated with vitamin B12 deficiency due to lack of intrinsic factor, autoimmune thyroid disease, and vitiligo [7] and can be part of the spectrum of polyglandular autoimmune syndrome.

Celiac Disease This autoimmune condition due to exposure to gluten in individuals with genetic predisposition results in submucosal lymphocyte infiltration and loss of intestinal villi, particularly in the proximal ileum with malabsorption, often associated with diarrhea and weight loss. Similar to autoimmune gastritis, this condition is associated with thyroid autoimmunity and type 1 diabetes. The diagnosis is based on the combination of serological markers (autoantibodies anti-gliadin, anti-tissue transglutaminase, and anti-endomysial) and the findings on the duodenal biopsy. Institution of gluten-free diet results in resolution of the malabsorption [8].

Lactose Intolerance This non-autoimmune condition, more prevalent in non-Caucasian populations, is due to (relative) lactase deficiency resulting in inability of digesting lactose. This in turn can cause bacterial overgrowth with malabsorption. Lactose intolerance is not associated with autoimmune thyroid disease [9].

Diabetic Gastroparesis This late and severe complication of diabetes results in delayed and unpredictable stomach emptying; hence, even in a fasting state, some significant gastric residue can be present with resultant binding of levothyroxine to food and consequent reduced absorption of the drug. Moreover, patients may experience bacterial overgrowth with additional malabsorption and are often treated with antacids. Collectively, diabetic gastroparesis can represent a major challenge in the delivery of adequate dose of levothyroxine.

The following table illustrates the characteristics of gastrointestinal conditions affecting levothyroxine absorption (Table 11.1).

Table 11.1 Gastrointestinal conditions associated with reduced levothyroxine absorption

Condition	Etiology	Associated with autoimmune thyroid disease	Diagnosis	Specific characteristics
Surgical causes	Loss of gastric acid production, loss of proximal ileum	No	History	
Atrophic gastritis	Autoimmune, *H. pylori* infection	Yes (autoimmune form)	Anti-parietal antibodies, *H. pylori*	High gastrin levels, B12 deficiency (autoimmune form)
Celiac disease	Autoimmune	Yes	Autoantibodies, biopsy	Associated with generalized malabsorption, vitamin D deficiency
Lactose intolerance	Relative lactase deficiency	No	History, enzyme measurement, biopsy	More prevalent in non-Caucasians
Diabetic gastroparesis	Autonomic neuropathy	Yes	History, gastric emptying studies	

Questions

1. A 23-year-old woman is referred for evaluation of hypothyroidism with complaints of fatigue, "mental fog," hair loss, and constipation. She weighs 52 kg and has been taking levothyroxine 125 mcg/day. Physical exam is remarkable for vitiligo. Her TSH is markedly elevated at 35 mcIU/ml (n.v. 0.4–4.5), her Hb is 10 g/dl, and the MCV is 102 fl (n.v. 80–96). Which is the most likely cause of poor levothyroxine absorption?

   (a) Poor adherence
   (b) Atrophic gastritis
   (c) Celiac disease
   (d) Food interference
   (e) Gastroparesis

2. A 73-year-old woman is referred from a nursing home for evaluation of hypothyroidism. She was transferred 1 month ago from the hospital following a stroke with residual hemiparesis and dysphagia. The patient is receiving continuous enteral feeding. She weighs 75 kg and has been taking levothyroxine 125 mcg/day. Her TSH is 75 mcIU/ml (n.v. 0.4–4.5), and her free T4 0.7 ng/dl (n.v. 0.7–1.5). Which is the most likely cause of her hypothyroidism?

   (a) Poor adherence
   (b) Atrophic gastritis
   (c) Celiac disease
   (d) Food interference
   (e) Gastroparesis

3. A 21-year-old man with 3 years history of diabetes is referred for evaluation of hypothyroidism with complaints of fatigue, weight loss, and skin rash. He weighs 70 kg and has been taking levothyroxine 150 mcg/day. Physical exam is remarkable for itchy symmetrical papular rash on the elbows. His TSH is 25 mcIU/ml (n.v. 0.4–4.5), HbA1c is 7.1%, and 25 OH vitamin D is 12 ng/ml (n.v. 30–100). Which is the most likely cause of poor levothyroxine absorption?

   (a) Poor adherence
   (b) Atrophic gastritis
   (c) Celiac disease
   (d) Food interference
   (e) Gastroparesis

Answers

1. (b) This patient is most likely affected by autoimmune atrophic gastritis resulting in reduction of gastric acid production with consequent impairment of levothyroxine absorption. The patient is also affected by vitamin B12 deficiency caused by lack of intrinsic factor. The clinical clues of these conditions are represented by the neuropsychiatric symptoms and the macrocytic anemia.
2. (d) Enteral feeding represents a major challenge in the delivery of levothyroxine due to the difficulties in dissolution of the tablets and the interference with feeding, particularly if continuous.
3. (c) This patient has celiac disease resulting in malabsorption (weight loss and vitamin D deficiency) and impaired levothyroxine absorption. Malabsorption due to diabetic gastroparesis is extremely unlikely since the diabetes is of recent onset and it is well controlled. Additionally, the patient has dermatologic manifestations (dermatitis herpetiformis) of celiac disease.

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