Rapid Levothyroxine Absorption Testing: A Case Series of Nonadherent Patients

Mamtha Balla,1 Ram M. Jhingan,2 and Daniel J. Rubin3,*

1Abington Memorial Hospital, Abington, USA
2Einstein Medical Center Montgomery, East Norriton, USA
3School of Medicine, Temple University, Philadelphia, USA

*Corresponding author: Daniel J. Rubin, School of Medicine, Temple University, Philadelphia, USA. Tel: +1-2157074746, Fax: +1-2157075599, E-mail: djrubin@temple.edu

Received 2015 June 26; Revised 2015 July 28; Accepted 2015 August 22.

Abstract

Background: Nonadherence to levothyroxine therapy is one cause of persistent hypothyroidism. To distinguish nonadherence from malabsorption, a levothyroxine absorption test is required. Typically, this test measures the serum free thyroxine (FT4) response to 1000 mcg of oral levothyroxine over 4 to 24 hours. Published data indicate that serum levels of FT4 are at or near their peak 2 hours after levothyroxine ingestion.

Objectives: We present the successful completion of 2-hour levothyroxine absorption testing in 3 patients as a retrospective case series.

Patients and Methods: Serum levels of thyroid stimulating hormone (TSH), FT4, and free triiodothyronine (FT3) were drawn at 0, 60, and 120 minutes after 1000 mcg of oral levothyroxine.

Results: In all 3 cases, baseline thyroid function indicated the patients had taken their prescribed doses of levothyroxine prior to the absorption test. Despite high baseline levels both FT3 and FT4 increased during each absorption test, providing more evidence of adequate levothyroxine absorption. Subsequently, patients achieved normal TSH levels on lower doses of levothyroxine.

Conclusions: Levothyroxine absorption testing over 2 hours may offer a more rapid alternative to the commonly used longer protocols to rule out malabsorption. Scheduling a levothyroxine absorption test may induce some patients to start adhering to levothyroxine therapy.

Keywords: Levothyroxine, Medication Nonadherence, Case Studies

1. Background

Hypothyroidism is a common disorder (1). Patients with hypothyroidism require thyroid hormone replacement, and levothyroxine is the preferred therapy. Most patients require approximately 1.6 mcg/kg of levothyroxine daily (1). Occasionally, patients remain hypothyroid despite being prescribed very high levothyroxine doses. One cause of apparent levothyroxine therapy failure is poor gut absorption, a well-recognized phenomenon with numerous causes, including malabsorptive conditions (e.g. celiac, pancreatic insufficiency, jejuno-ileal bypass surgery), interference by food or supplements (e.g. calcium, iron) and concomitant medications (e.g. laxatives, antacids) (2-5). Another cause is nonadherence to levothyroxine therapy (3, 6, 7). An effective way to distinguish nonadherence from malabsorption is to perform levothyroxine absorption testing. This testing is typically performed by administering a single large oral dose of levothyroxine then measuring serum FT4 levels over the subsequent 4 to 24 hours (3, 7-12).

2. Objectives

Given that levels of FT4 are at or near their peak 2 hours after levothyroxine ingestion (7-14), we hypothesized that a levothyroxine absorption test could be completed in only 2 hours. We present the successful completion of 2-hour levothyroxine absorption testing in 3 patients found to be nonadherent to levothyroxine therapy.

3. Patients and Methods

We performed a retrospective case series of 3 patients. All patients were scheduled to have levothyroxine absorption testing approximately 3 weeks after they agreed to perform the test. Patients were instructed to skip their usual dose of levothyroxine on the day of the test. They were asked arrive at 8:00 AM for the test after at least an 8 hour fast. Serum levels of TSH, FT4, and FT3 were drawn at 0, 60, and 120 minutes after administration of 1000 mcg of levothyroxine orally as 5 tablets of 200 mcg each.

4. Results

4.1. Case 1

A 44-year-old, 70 kg female with a history of irritable bowel syndrome and primary hypothyroidism due to
Hashimoto's thyroiditis presented with severe hypothyroidism despite being prescribed 250 mcg (3.6 mcg/kg) of levothyroxine daily. She reported taking the levothyroxine regularly in the fasting state without other medications. TSH was 54.96 µU/mL (normal, 0.40 - 4.50, coefficient of variation [CV] 4.7 - 6.9%) and total thyroxine (T4) was 1.8 µg/dL (normal, 4.5 - 12.5, CV 4.2 - 6.2%). Prescribed levothyroxine doses and TSH levels over time are presented in Figure 1 A. TSH levels were variably high, normal, and low on doses of levothyroxine ranging from 175 to 400 mcg (2.5 to 5.7 mcg/kg) daily. After 3 years of attempted medical management, her TSH was 90.21 µU/mL on a levothyroxine dose of 300 mcg (4.2 mcg/kg) daily. Upon discussion with the patient, we increased the levothyroxine dose to 400 mcg daily and scheduled a 2-hour levothyroxine absorption test 3 weeks later. Despite a very high TSH level prior to the test, the patient was found to have low TSH and high FT3 and FT4 levels at baseline (Figure 2 A). Both FT3 and FT4 increased substantially during the test. Poor levothyroxine absorption was excluded, and we decreased the dose to 300 mcg daily while reinforcing the importance of adherence. Eight weeks later, the TSH was 0.01 µU/mL and FT4 was 3.2 ng/dL (normal, 0.8 - 1.8, CV 6.0 - 8.9%). Levothyroxine was further reduced to 150 mcg (2.1 mcg/kg) daily. TSH eventually normalized on 175 mcg daily of levothyroxine.

4.2. Case 2

A 42-year-old, 66 kg female with primary hypothyroidism due to Hashimoto's thyroiditis was referred to the Endocrinology Clinic for uncontrolled hypothyroidism. The patient reported taking levothyroxine every morning at the prescribed dose of 137 mcg (2.1 mcg/kg) in the fasting state without any other medications. She denied additional medications but did take iron supplements. Otherwise, she had no relevant medical history. Her family history was significant for primary hypothyroidism due to Hashimoto's in her mother, sister and brother. Review of old records revealed a TSH of 160 mIU/mL while taking 200 mcg daily. At this point, the patient presented to Endocrinology Clinic. We counselled the patient on adherence and increased the levothyroxine dose to 400 mcg daily then 600 mcg (6.9 mcg/kg) daily. After discussion with the patient, we increased the levothyroxine dose to 400 mcg daily then 600 mcg (6.9 mcg/kg) daily. TSH remained elevated (range 20.21 - 93.32 µIU/mL), the levothyroxine dose was increased to 400 mcg daily then 600 mcg (6.9 mcg/kg) daily.

Ten months after presentation (after 24 months of available follow-up data, Figure 1 C), he was admitted to the hospital with chest pain and symptomatic bradycardia. TSH was 52.50 mIU/L and total T4 was 2.78 mcg/dL.

4.3. Case 3

A 65-year-old, 87 kg male with a history of primary hypothyroidism secondary to TPO antibody-negative Hashimoto's thyroiditis presented to the Endocrinology Clinic with uncontrolled hypothyroidism. Other past medical history included hypertension, dyslipidemia, and gout. Medications in addition to levothyroxine included amlodipine, omeprazole, labetalol, allopurinol, colchicine, aspirin, and furosemide. The patient reported taking levothyroxine 200 mcg twice daily (400 mcg daily, 4.6 mcg/kg) on an empty stomach without any other medications. Laboratory studies showed a TSH of 54.26 mIU/L, a FT4 index of 1.0 (normal, 1.4 - 3.8) and total triiodothyronine (T3) of 70 ng/dL (normal, 76 - 181, CV 6.2 - 6.8%) (Figure 1 C). Review of old records revealed very high TSH levels on reported levothyroxine doses of 200 to 400 mcg daily. The patient was counseled on medication adherence and advised to take levothyroxine 200 mcg daily. Because the TSH was persistently elevated (range 20.21 - 93.32 µIU/mL), the levothyroxine dose was increased to 400 mcg daily then 600 mcg (6.9 mcg/kg) daily.

Each panel represents a single patient. The time of presentation to Endocrine clinic and the levothyroxine absorption test are indicated by arrows. TSH values were often elevated despite high prescribed doses of levothyroxine. TSH (normal 0.40 - 4.50 mIU/mL, CV 4.7 - 6.9%).
5. Discussion

We describe a rapid (2-hour) levothyroxine absorption test performed successfully in 3 patients. All 3 patients presented with high TSH levels over a period of 24 to 36 months despite high prescribed doses of levothyroxine. Much to our surprise, all 3 patients had low or low-normal TSH levels at baseline in the absorption test, compared to levels of more than 40 mIU/mL 3 to 8 weeks before the test. Furthermore, the baseline levels of FT3 and FT4 were high or high normal, indicating that these patients had started taking their levothyroxine prior to the absorption test. The decision to perform a levothyroxine absorption test may have motivated the patients to take their medication. We are unaware of previously published cases describing this phenomenon. In all 3 cases, subsequent TSH levels normalized after decreasing the levothyroxine dose.

Levothyroxine absorption takes place primarily in the jejunum and ileum of the small intestine. Approximately 80% of an orally administered dose is absorbed in the fasting state (2, 3). Serum levels of levothyroxine are at or near their peak 2 hours after administration of an oral dose (7-14). Typical levothyroxine doses in hypothyroidism are 1.5 to 1.6 mcg/kg/day (8, 15). Doses greater than 300 mcg/day are rarely required and should prompt consideration of nonadherence or malabsorption.

There are several possible explanations for higher than typical levothyroxine requirements, including decreased gut absorption, increased metabolism, and nonadherence. Decreased gut absorption is observed in any condition that causes malabsorption, such as celiac disease, jejuno-ileal bypass procedures, severe hepatic cirrhosis, and congestive heart failure (3, 16, 17). Several drugs impair intestinal absorption of the levothyroxine including sucralfate, calcium carbonate, ferrous sulfate, and cholestyramine (2, 17). Drugs such as carbamazepine, phenytoin and phenobarbital increase the metabolism of levothyroxine, leading to higher dose requirements (2). All of these possibilities should be considered in the evaluation of a patient with an apparently high levothyroxine dose.
Study concept and design: Daniel J. Rubin. Critical revision of the manuscript: Mamtha Balla and Daniel J. Rubin. Drafting of the manuscript: Mamtha Balla and Daniel J. Rubin. Critical revision of the manuscript for important intellectual content: Daniel J. Rubin.

Footnotes

Authors’ Contributions: Study concept and design: Daniel J. Rubin. Acquisition of data: Mamtha Balla, Ram M. Jhingan, and Daniel J. Rubin. Analysis and interpretation of data: Mamtha Balla and Daniel J. Rubin. Drafting of the manuscript: Mamtha Balla and Daniel J. Rubin. Critical revision of the manuscript for important intellectual content: Daniel J. Rubin.

References

1. Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244–51.
2. Surks MI, Sievert R. Drugs and thyroid function. N Engl J Med. 1995;333(25):1688–94.
3. Ains KB, Reifert S, Fein HG, Weintraub BD. Pseudomalabsorption of levothyroxine. JAMA. 1991;266(5):218–20.
4. Mersebach H, Rasmussen AK, Kirkegaard L, Feldt-Rasmussen U. Intestinal adsorption of levothyroxine by antacids and laxatives: case stories and in vitro experiments. Pharmacol Toxicol. 1999;84(3):107–9.
5. Azizi F, Belur R, Albano J. Malabsorption of thyroid hormones after jejunoileal bypass for obesity. Ann Intern Med. 1979;90(6):941–2.
6. Illedrisi MS, Szymajda A, Alshanti M, Urban RJ. Noncompliance with medical treatment: pseudomalabsorption of levothyroxine. South Med J. 2009;94(8):833–6.
7. Lips DJ, van Reisen MT, Voigt V, Venekamp W. Diagnosis and treatment of levothyroxine pseudomalabsorption. Neth J Med. 2004;62(4):114–8.
8. Srinivas V, Oyibo SO. Levothyroxine pseudomalabsorption and thyroxine absorption testing with use of high-dose levothyroxine: case report and discussion. Endocr Pract. 2008;14(6):1012–5.
9. Sun GE, Pantalone KM, Faiman C, Gupta M, Olanisky I, Hatipoglu B. The clinical utility of free thyroxine in oral levothyroxine absorption testing. Endocr Pract. 2014;20(9):925–9.
10. Vita R, Benveniga S. Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule. Endocr Pract. 2014;20(3):338–41.
11. Livadariu E, Valdes-Socin H, Burlacu MC, Vulpoi C, Daly AF, Beckers A. Pseudomalabsorption of thyroid hormones: case report and review of the literature. Ann Endocrinol (Paris). 2007;68(6):460–1.
12. Ogawa D, Otsuka F, Mimura U, Ueno A, Hashimoto H, Kishida M, et al. Pseudomalabsorption of levothyroxine: a case report. Endocr J. 2000;47(1):45–50.
13. Walker JN, Shillo P, Ibbotson V, Vincent A, Karavitaki N, Weetman AP, et al. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. Eur J Endocrinol. 2013;168(6):913–7.
14. Goichot B, Vinzio S, Luca F, Sirlin X, Sapin R, Schlienger JL. In vivo evidence for a direct ultra-fast negative feedback of thyroxine on TSH secretion in humans: a case of L-thyroxine pseudomalabsorption. Clin Endocrinol (Oxf). 2007;67(6):952–3.
15. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med. 1993;119(6):492–502.
16. Morris JC. How do you approach the problem of TSH elevation in patients with thyroid disease. Ann Intern Med. 1999;131(6):819–20.
17. Liwanpo L, Hershman JM. Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab. 2009;23(6):781–92.
18. Benveniga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed intestinal absorption of levothyroxine. Thyroid. 1995;5(4):249–51.
19. Kubota S, Fukata S, Matsuzuka F, Kuma K, Miyachi A. Successful management of a patient with pseudomalabsorption of levothyroxine. Int J Psychiatry Med. 2003;33(2):183–8.