n

# Rapid levothyroxine absorption test for assessment of nonadherence to levothyroxine treatment: a case series of six patients

Farkhanda Gillani<sup>1\*</sup>, Muhammad Babar Imran<sup>1</sup>, Mariha Aslam<sup>1</sup>, Warda Ahmad<sup>2</sup>, Muhammad Shahzad Afzal<sup>1</sup>

#### **European Journal of Medical Case Reports**

Volume 8(6):118–121 DOI: 10.24911/ejmcr.173-1643087710



This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license: https://creativecommons.org/licenses/by/4.0/) which permits any use, Share — copy and redistribute the material in any medium or format, Adapt — remix, transform, and build upon the material for any purpose, as long as the authors and the original source are properly cited. © The Author(s) 2024

# ABSTRACT

**Background:** Failure to treat persistent hypothyroidism despite the use of adequately prescribed doses of levothyroxine should be evaluated for malabsorption and nonadherence to medication. Previous literature suggested that orally administered levothyroxine showed maximum absorption at or near 2 hours. This rapid absorption suggests the use of a 2-hour levothyroxine absorption test as an alternative to long, cumbersome protocols. Limited data are available measuring free thyroxine (FT4) levels at 2 hours after oral administration of 1,000 mcg of levothyroxine.

**Case Presentation:** Six patients who continued to have hypothyroidism despite taking ostensibly high doses of levothyroxine underwent a 2-hour protocol levothyroxine absorption test. All patients were given 1,000 mcg of levothyroxine, and serum levels of thyroid-stimulating hormone (TSH), FT4, and free triiodothyronine (FT3) were measured at 0, 60, and 120 minutes. All patients showed an increasing trend in FT4 in subsequent samples at 60 and 120 minutes, compared to baseline values, providing strong evidence of peak levothyroxine absorption at 2 hours. Five patients had raised baseline TSH levels, indicating nonadherence to treatment, and one had normal baseline TSH levels, indicating adherence to levothyroxine therapy on prior test scheduling, with increased FT3 and FT4 levels in subsequent samples at 60 and 120 minutes.

**Conclusion:** We conclude that the rapid levothyroxine absorption test, using a 2-hour protocol, is a more convenient method to differentiate nonadherence from malabsorption. Moreover, scheduling the patient will result in adherence to levothyroxine therapy in some patients.

Keywords: Levothyroxine absorption test, nonadherence, malabsorption, case series.

Received: 25 January 2022
Accepted: 10 February 2024
Type of Article: CASE REPORT
Specialty: Nuclear Medicine

Correspondence to: Farkhanda Gillani
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*
\*

# Background

Hypothyroidism is a common disorder, treated successfully with levothyroxine since 1927 [1,2]. The usual required dose of thyroid hormone replacement is 1.6-1.8  $\mu$ g/kg of body weight, and doses of more than 300  $\mu$ g/day are rarely required by the patient [3]. Refractory hypothyroidism, or persistent hypothyroidism, despite the administration of levothyroxine doses that seem adequate to treat hypothyroidism, mandates the use of levothyroxine absorption testing for the differentiation of nonadherence from malabsorption [4]. The primary site of absorption of levothyroxine is the small intestine, and its level rises linearly in the first 60-90 minutes before reaching a plateau [5]. The short protocol of levothyroxine absorption testing can therefore be adopted as an effective alternative to longer protocols for ruling out the malabsorption causes, i.e., intrinsic gastrointestinal disorders (celiac disease, atrophic gastritis, tropical sprue, resection of the small intestine, diabetic, and diarrhea), interference by food or supplements (e.g., calcium and iron), and concomitant medications (e.g., laxatives and antacids) [6].

# **Cases Presentation**

Six patients with persistent elevations in thyroid stimulating hormone, free thyroxine (TSH) levels despite the use of apparently higher doses of levothyroxine were evaluated using a short, 2-hour protocol of levothyroxine absorption tests. All patients were instructed not to take their usual dose of levothyroxine on the day of testing and to fast for 8 hours. In five patients, these instructions were given 2 days before testing. However, one patient was given the instructions 20 days before conducting the test. The patient's serum levels of TSH, free thyroxine (FT4), and free triiodothyronine (FT3) were measured at 0, 60, and 120 minutes after administration of 1,000 mcg of levothyroxine orally as 10 tablets of 100 mcg each, using the rapid levothyroxine absorption test protocol.

In all patients, both FT4 and FT3 levels increased substantially in subsequent samples at 60and 120 minutes, as shown in Figure 1, thereby excluding the poor levothyroxine absorption.

The baseline TSH level was raised in all patients who were scheduled 2 days before the test; however, a normal TSH level was seen in the patients scheduled 20 days before the test. The normal baseline TSH in that patient indicated that the patient had taken his prescribed dose of levothyroxine before the absorption test. However, despite the normal baseline TSH level, this patient also showed increased FT4 levels in subsequent samples at 60 and 120 minutes, as shown in Figure 2.

## Discussion

The absorption of levothyroxine occurs primarily in the jejunum and ileum of the small intestine. Approximately 80% of absorption takes place in the fasting state [7], with peak serum levels at or near 2 hours after oral administration [8].

A rapid levothyroxine absorption test at 2 hours is described in the literature in a small number of patients [9]. We describe the case series of six patients who had raised TSH levels over a period of 24-36 months despite the adequately prescribed doses of levothyroxine. We performed a rapid levothyroxine absorption test in these patients using a 2-hour protocol after administering 1,000  $\mu$ g of levothyroxine.

Five patients had raised baseline TSH levels; however, one had a normal baseline TSH level. The patient with a normal baseline TSH level was scheduled 20 days before the test; however, the remaining three with raised TSH levels were scheduled 2 days before the test. Therefore, the prolonged prior scheduling may let the patient adhere to his prescribed dose, resulting in normal TSH levels as

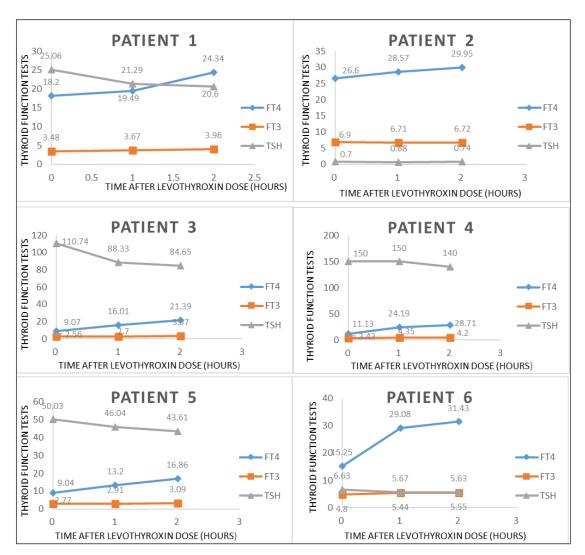


Figure 1. Two-hour levothyroxine absorption test in six patients.

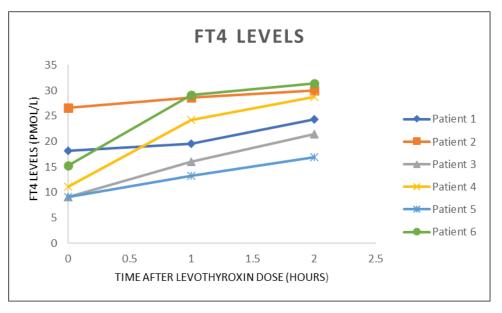


Figure 2. Two-hour levothyroxine absorption test in six patients, showing a substantial increase in FT4 levels in subsequent samples at 2 hours.

was reported previously by Balla [9]. The rapid 2-hour levothyroxine absorption test had been described previously [9], but only on 3 patients and all of them were euthyroid on baseline thyroid function testing. In our case series, we successfully performed a rapid levothyroxine absorption test on six patients, all of whom showed a subsequent increase in FT4 levels compared to baseline FT4 levels.

The possible explanation for the higher than usual levothyroxine dosage is reduced intestinal absorption, increased levothyroxine metabolism, and nonadherence to levothyroxine therapy. The intestinal absorption may be reduced in celiac disease, jejuno-ileal bypass procedures, severe hepatic cirrhosis, congestive heart failure, and the use of drugs such as sucralfate, calcium carbonate, ferrous sulfate, cholestyramine, and so on [5]. The drugs that mainly increase levothyroxine metabolism are carbamazepine, phenytoin, and phenobarbital [7]. Before evaluating a patient requiring an apparently high levothyroxine dose through cumbersome tests for malabsorption, one should consider the levothyroxine absorption testing to rule out nonadherence.

Once poor adherence to treatment is identified, different strategies can be adopted to improve treatment outcomes through a closer understanding of the patients' perspectives about illness, lifestyle modifications, and discussing health beliefs. All this can be achieved, including the elimination of false perceptions regarding the treatment, through an optimal doctor-patient relationship.

## Conclusion

In conclusion, our findings suggest that the rapid levothyroxine absorption test is a valuable diagnostic tool, capable of providing significant insights, within just 2 hours. This test effectively distinguishes between nonadherence and malabsorption in patients with persistent hypothyroidism. It can be conducted safely and cost-effectively in an outpatient setting. However, additional research is necessary to further substantiate these findings and reinforce their applicability in clinical practice.

## What is new?

Limited data are available about the safety and successful completion of a rapid 2-hour levothyroxine absorption test using 1,000  $\mu$ g of levothyroxine. This case series, comprising the data of six patients, strengthens the fact of safe and successful completion of rapid levothyroxine absorption test, used to rule out the nonadherence to levothyroxine treatment as the possible cause of persistent hypothyroidism.

#### **List of Abbreviations**

- FT3 Free triiodothyronine
- FT4 Free thyroxine
- TSH Thyroid stimulating hormone

## **Conflict of interests**

The authors declare that they have no conflict of interest regarding the publication of this case report.

#### Funding

None.

## **Consent for publication**

Written informed consent was obtained from the patient to publish this case in a medical journal.

#### **Ethical approval**

Ethical approval is not required at our institution for publishing a case series in a medical journal.

## **Author details**

Farkhanda Gillani<sup>1\*</sup>, Muhammad Babar Imran<sup>1</sup>, Mariha Aslam<sup>1</sup>, Warda Ahmad<sup>2</sup>, Muhammad Shahzad Afzal<sup>1</sup>

- 1. Nuclear Medicine Department, PINUM Cancer Hospital, Faisalabad, Pakistan
- 2. Consultant Radiologist, PINUM Cancer Hospital, Faisalabad, Pakistan

## References

- Harington CR, Barger G. Chemistry of thyroxine: constitution and synthesis of thyroxine. Biochem J. 1927;21(1):169–83. https://doi.org/10.1042/bj0210169
- 2. Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012 Aug;86(3):244–51.
- Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. American thyroid Association task force on thyroid hormone replacement. Guidelines for the treatment of hypothyroidism: prepared by the American thyroid Association task force on thyroid hormone replacement. Thyroid. 2014 Dec;24:1670–751. https:// doi.org/10.1089/thy.2014.0028
- Lips DJ, van Reisen MT, Voigt V, Venekamp W. Diagnosis and treatment of levothyroxine pseudomalabsorption. Neth J Med. 2004 Apr;62(4):114–8.

- Liwanpo L, Hershman JM. Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab. 2009 Dec;23(6):781–92. https://doi. org/10.1016/j.beem.2009.06.006
- Vita R, Santaguida MG, Virili C, Segni M, Galletti M, Mandolfino M, et al. Serum thyroid hormone antibodies are frequent in patients with polyglandular autoimmune syndrome type 3, particularly in those who require thyroxine treatment. Front Endocrinol (Lausanne). 2017 Aug;8(8):212. https://doi.org/10.3389/ fendo.2017.00212
- Surks MI, Sievert R. Drugs and thyroid function. N Engl J Med. 1995 Dec;333(25):1688–94. https://doi. org/10.1056/NEJM199512213332507
- Sun GE, Pantalone KM, Faiman C, Gupta M, Olansky L, Hatipoglu B. The clinical utility of free thyroxine in oral levothyroxine absorption testing. Endocr Pract. 2014 Sep;20(9):925–9. https://doi.org/10.4158/EP13487.OR
- Balla M, Jhingan RM, Rubin DJ. Rapid levothyroxine absorption testing: a case series of nonadherent patients. Int J Endocrinol Metab. 2015 Oct;13(4):e31051. https:// doi.org/10.5812/ijem.31051

#### Summary of the case report

1	Patient (gender, age)	Male, 27 years old
2	Final diagnosis	Nonadherence to levothyroxine therapy
3	Symptoms	Persistent hypothyroidisim
4	Medications (generic)	Levothyroxine
5	Clinical procedure	Levothyroxine absorption test