

## RESEARCH

# Levothyroxine malabsorption or pseudomalabsorption? A question in the management of refractory hypothyroidism

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## Abstract

**Purpose:** The levothyroxine absorption test (LT4AT) is an important tool for distinguishing hypothyroidism due to malabsorption from 'pseudomalabsorption' conditions. Our aim was to review our institution's LT4AT results and assess its role in the management of patients with refractory hypothyroidism.

**Methods:** We performed a retrospective study of all patients evaluated for refractory hypothyroidism who underwent LT4AT in our tertiary center between 2014 and 2020. Its results and the impact on thyroid function management during follow-up were assessed.

**Results:** Ten female patients were included with a mean age of 40 years (min-max: 26–62). Mean weight was 72 kg (min-max: 43–88) and baseline LT4 dosage ranged from 2.5 to 5.3 µg/kg/day. The most common causes of hypothyroidism were postsurgical in 50% ( $n = 5$ ) and autoimmune in 20% ( $n = 2$ ). During LT4AT, normal LT4 absorption was found in all but one individual (mean FT4 increase of 231%, min-max: 85–668). The only patient with objective LT4 absorption impairment (maximal increase of 48% by hour 5) presented also *Helicobacter pylori* gastritis and prior history of 'intestinal surgery' during childhood. No adverse events were reported during any of the LT4ATs. During follow-up (median 11.5 months (IQR 23)), three patients obtained euthyroidism and six had improved their hypothyroidism state.

**Conclusions:** The LT4AT is an effective and safe way to assess refractory hypothyroidism and provides valuable information to distinguish LT4 malabsorption from 'pseudomalabsorption'. Our data suggest that most patients with suspicious LT4 malabsorption perform normally during LT4AT. This test provides relevant information for better management of patients with refractory hypothyroidism.

## Key Words

- ▶ levothyroxine absorption test
- ▶ refractory hypothyroidism
- ▶ thyroid-stimulating hormone
- ▶ thyroxine

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## Introduction

Oral levothyroxine (LT4) is the mainstay therapy for hypothyroidism. Absorption of oral LT4 occurs primarily in the small intestine within the first 3 h of ingestion, with an absorption rate of 60–80% (1). Initial LT4 dosing is traditionally performed using a weight-based calculation; thus, most patients with minimal endogenous thyroid function require approximately 1.6–1.8 µg/kg/day (2, 3).

Refractory hypothyroidism is not uncommon in clinical practice, even if its prevalence has not been fully established, and may be defined as a thyroid-stimulating hormone (TSH) level above the upper limit of the reference range, under a daily LT4 dose of  $\geq 1.9$  µg/kg (4). Actually, some patients still exhibit refractory hypothyroidism despite reported adherence to large doses of LT4 even in

the absence of known conditions or medications which might impair LT4 absorption, namely gastrointestinal disorders (gastroparesis, atrophic gastritis, celiac disease, *Helicobacter pylori* infection, lactose intolerance, pancreatic insufficiency, short-bowel syndrome), systemic medical conditions (cirrhosis, cardiomyopathy, nephrotic syndrome), concomitant use of other drugs (proton pump inhibitor, ferrous salts, calcium carbonate, laxatives, anticonvulsants) and dietary interferences (2, 4, 5, 6). Levothyroxine absorption test (LT4AT) constitutes an important tool for distinguishing hypothyroidism due to malabsorption from other ‘pseudomalabsorption’ conditions or non-adherence (7, 8). This is a noninvasive and safe method, although seldom used for the evaluation of patients with refractory hypothyroidism.

Our aim was to review our institution’s experience with the LT4AT and assess its role in the management of patients with refractory hypothyroidism, namely distinguishing malabsorption from other ‘pseudomalabsorption’ conditions or non-adherence.

## Materials and methods

We performed a retrospective study of all patients evaluated for refractory hypothyroidism that were submitted to LT4AT in our tertiary center between January 2014 and December 2020. Inclusion criteria were age over 18 years at the time of testing, evidence of primary or secondary hypothyroidism and completion of the LT4AT based on our institution’s protocol. Ages over 65 years, cardiac arrhythmias or known coronary artery disease were considered exclusion criteria for LT4AT for safety reasons. In addition, patients who had undergone LT4AT outside of our tertiary center were excluded.

First, we excluded all potential causes of malabsorption, such as celiac disease, pernicious anemia and concomitant use of drugs known to impair LT4 absorption. Underlying comorbidities, namely other gastrointestinal disorders (gastroparesis, *Helicobacter pylori* infection, pancreatic insufficiency, short-bowel syndrome, gastric bypass surgery) and systemic medical conditions (cirrhosis, heart failure, nephrotic syndrome) were also documented. In addition, the timing of daily LT4 oral administration and adherence to therapy were also reported. Outpatient thyroid functions previous to LT4AT and during follow-up were assessed.

Prior to performing the test, patients were instructed to fast overnight and to hold their usual LT4 dose that day. They were also advised not to take any medications

known to affect LT4 absorption (namely proton pump inhibitor, ferrous salts, calcium carbonate, laxatives) at least 24 h prior to the test. Our current LT4AT protocol was derived from previous publications and is based on a 6-h test following 1000 µg of oral LT4 intake (9, 10, 11). At the patient’s admission, a peripheral i.v. catheter was inserted and a baseline blood sample was collected for TSH, free thyroxine (FT4) and free triiodothyronine (FT3) measurements. Then, 1000 µg of LT4 was administered orally. Blood specimens were collected at baseline and hourly for 6 h with TSH (reference range 0.27–4.2 µIU/mL), FT4 (reference range 0.93–1.7 ng/dL) and FT3 (reference range 2.0–4.4 pg/mL) measurements. The LT4AT was performed under supervision, during which blood pressure and heart rate were evaluated hourly during the test. The FT4 levels increase rate was calculated using the formula: % FT4 increase = (maximum FT4 – baseline FT4 (µg/dL)) / baseline FT4 (µg/dL) × 100. Adequate LT4 absorption was considered when FT4 levels increased at least 50% over baseline at any of the six data points (10).

This study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto (205-DEFI/213-CE). Consent to participate was waived by the Ethics Committee due to the retrospective nature of the study and full data anonymization.

## Results

Ten female patients were included with a mean age of 40 years (min–max: 26–62). The mean weight was 72 kg (min–max: 43–88) and the baseline LT4 requirement ranged from 2.5 to 5.3 µg/kg/day. The most common cause of hypothyroidism was postsurgical in 50% ( $n=5$ ), followed by autoimmune thyroiditis (20%,  $n=2$ ), postpartum thyroiditis (10%,  $n=1$ ), central hypothyroidism (10%,  $n=1$ ) and idiopathic (10%,  $n=1$ ). Six patients (60%) had previously undergone evaluation for causes associated with malabsorption, including testing for celiac disease ( $n=5$ ), pernicious anemia ( $n=4$ ) and *Helicobacter pylori* infection ( $n=2$ ). The only patient (I) with known comorbidities associated to a putative malabsorptive condition had a history of *Helicobacter pylori* gastritis and prior ‘intestinal surgery’ during childhood. Three patients (30%) were under potential interfering medications: proton pump inhibitor (two), ferrous sulfate (two) and calcium carbonate (one), all taken separately from LT4, with at least a 4-h interval. Table 1 summarizes the baseline characteristics of the ten patients included.

## LT4 absorption test results

Six patients (60%) had an FT4 increase rate above 100% and in all but one individual, normal LT4 absorption was found (mean FT4 increase of 231%, min–max: 85–668). The only patient (I) with LT4 absorption impairment (maximal increase of 48% by hour 5) had previous history of *Helicobacter pylori* gastritis and prior ‘intestinal surgery’ during childhood. Table 2 and Fig. 1 resume LT4AT results.

Eight patients reached peak FT4 levels after 1–4 h, with an absolute increment ranging from 0.97 to 2.92 ng/dL. One of these individuals achieved an increase above 50% by hour 1; three did so by hour 2; three by hour 3 and one by hour 4. Patient I, who failed to reach a 50% FT4 increase, continued to show a rise in FT4 by hour 5, with a maximal absolute FT4 increment of 0.88 ng/dL. On the other hand, changes in FT3 levels were minimal and they remained below the reference upper limit during all LT4ATs.

Four patients (C, E, G and I) had a normal baseline TSH value during the LT4AT and a suppressed baseline TSH value was found in patient H. TSH levels declined from baseline to hour 6 in seven out of nine (78%) patients with primary hypothyroidism. The two patients (C and H) who had a stable TSH during the test presented nevertheless an adequate LT4 absorption. The only patient that revealed a low FT4 increase (I) did present a slight TSH decrease from baseline (1.83  $\mu$ IU/mL) to hour 6 (0.94  $\mu$ IU/mL), despite an insufficient rise in FT4. No adverse events were reported during any of the LT4ATs and there was no significant increase in blood pressure and heart rate.

## Clinical follow-up

At post-LT4AT follow-up (median 11.5 months, min–max: 1–68), 3 patients (A, F and H) progressed to the euthyroid state. A single weekly oral dose of LT4 was started under supervision in patient A, achieving a stable euthyroid state within 1 year with a dose of 800  $\mu$ g LT4 per week. Two patients (F and H) obtained euthyroid state with the same or even lower LT4 dose than previously. The remaining six patients with normal absorption (B, C, D, E, G and J) maintained persistent hypothyroidism but with thyroid function tests improvement under the same dose of LT4. Although patients C and G had a normal baseline TSH value during the LT4AT, they continued to present hypothyroidism during follow-up, in spite of some TSH decreasing values. All patients with normal absorption achieved normalization or near-normal TSH levels but did so by requiring larger doses of LT4, ranging

from 2.3 to 4.5  $\mu$ g/kg/day. Lastly, patient I with a probable malabsorptive condition (maximal increase of 48% by hour 5 of LT4AT) maintained a hypothyroid state, even after further increase in LT4 dose. Table 3 summarizes clinical follow-up.

## Discussion

According to our data, LT4AT seems to be an effective and safe way to assess refractory hypothyroidism and provides valuable information to distinguish LT4 malabsorption from ‘pseudomalabsorption’. Most of the patients with suspected LT4 malabsorption perform normally during LT4AT with only one patient with objective LT4 absorption impairment who already presented medical conditions supporting a malabsorption hypothesis. No adverse events were reported during any of the LT4ATs. During follow-up, most patients achieved either normalization or improvement of TSH with the same or slightly more than the previous LT4 dosage.

Robust evidence regarding the use of oral LT4AT in the management of refractory hypothyroid patients is scarce, with only a few case series reported. Heterogeneity between the various protocols constitutes also an important limitation for comparing published data (2, 6, 8, 10, 12, 13, 14, 15, 16). Currently, in our institution, all patients submitted to LT4AT receive a full dose of LT4 1000  $\mu$ g, regardless of weight or BMI, which may be excessive and needless to demonstrate adequate absorption. This fixed dose also limits the use of LT4AT in patients with major comorbidities, such as cardiac arrhythmias or known coronary artery disease. Several patients had an FT4 increase above 100%, supporting the idea that this dosage may be excessive in some individuals. On the other hand, thyroxine absorption appears to be paradoxically increased in hypothyroid patients, when compared to euthyroid patients, which could partly explain these findings (17). While some institutions also adopted the use of 1000  $\mu$ g of LT4 (2, 8, 10, 12, 13), others performed LT4AT effectively with lower dosages such as 600  $\mu$ g, in order to limit potential adverse effects, especially when considering elderly and/or frail individuals (14, 15, 18). However, we strongly believe that the best strategy for LT4AT should probably include an individualized protocol; the 1000  $\mu$ g protocol was safe and in agreement with the LT4 dose calculated based on the patient’s age, weight and average expected total weekly amounts of LT4.

Our protocol takes into account the FT4 increase rate (%), based on baseline and maximum FT4 levels. Adequate LT4 absorption is interpreted according to the

**Table 1** Baseline characteristics of the ten patients.

Patient	Age (years)	Weight (kg)	BMI (kg/m <sup>2</sup> )	LT4 requirement (µg/kg/day)	TSH <sup>a</sup> (µIU/mL)	FT4 <sup>b</sup> (ng/dL)	Cause of hypothyroidism	Evaluation for malabsorption	Comorbidities	Potential interfering medications
A	54	43.0	19.6	3.5	88.1	0.73	Postsurgical	None	None	PPI; FS
B	28	80.5	32.7	2.5	182.0	0.55	Unknown	None	None	None
C	36	70.5	27.5	5.3	58.5	0.95	Autoimmune thyroiditis	Celiac disease; pernicious anemia	None	None
D	40	82.0	31.3	3.7	NA	0.37	Central	None	None	None
E	26	52.5	20.5	4.3	100.0	0.60	Postsurgical	Celiac disease; pernicious anemia; <i>H. pylori</i> infection	None	None
F	30	84.0	32.4	3.6	44.9	1.18	Postsurgical	None	None	None
G	28	66.0	23.4	3.8	24.2	0.65	Postpartum thyroiditis	Celiac disease; pernicious anemia	None	FS
H	42	73.0	23.9	3.9	9.0	0.91	Postsurgical	Celiac disease	None	None
I	62	88.0	29.4	3.4	33.5	0.85	Postsurgical	<i>H. pylori</i> infection	<i>H. pylori</i> gastritis; 'intestinal surgery'	PPI; CC
J	52	82.0	30.6	3.1	6.0	1.61	Autoimmune thyroiditis	Celiac disease; pernicious anemia	None	None

<sup>a</sup>Reference range of TSH level is 0.27–4.2 µIU/mL.

<sup>b</sup>Reference range of FT4 level is 0.93–1.7 ng/dL.

CC, calcium carbonate; FS, ferrous sulfate; FT4, free thyroxine; LT4, levothyroxine; NA, not available; PPI, proton pump inhibitor; TSH, thyroid-stimulating hormone.

trend of increase in FT4 during the procedure. Absolute and relative increments in either FT4 and total T4 have been positively correlated with LT4 absorption, supporting their utility in determining normal absorption (9, 16). Ghost *et al.* proposed that a mean increment in FT4 from baseline to 3 h of at least 0.8 ng/dL suggests normal absorption (18). Based on previous studies which emphasize that at least a relative 50–100% increase in FT4 level should be obtained to demonstrate adequate absorption, we have endorsed this 50% increase cut-point (10, 19). Nevertheless, our small sample size is underpowered for determining the best LT4 doses, FT4 cut-off values and time-sampling duration for evaluating normal absorption. Based on our data, the LT4AT time length could be reasonably reduced to 4 h while still providing all its relevant information.

Interesting data were also obtained when observing TSH trends during the test. Although our 6-h test period may be short to evaluate the full effects of LT4 on thyrotrophic production of TSH, its levels did not reliably decline by 6 h in all patients, which is probably related to the kinetics of TSH release and formation. Thus, we recognize that TSH measurements during LT4AT do not provide relevant information. Yet, Giochot *et al.* demonstrated a potential utility of a 6-h TSH measurement, reporting a 39% reduction in TSH within 2 h of oral thyroxine ingestion (20). We can not explain these contrasting results, although a rapid inhibition of release of pre-formed TSH from the anterior pituitary, which is then followed by a delayed inhibition of TSH synthesis by thyrotrophs, may help justify some of our results (21).

In our cohort, most patients with suspected LT4 malabsorption presented normal LT4AT results. Surprisingly, four patients (C, F, G and I) presented a normal baseline TSH value during LT4AT and one (patient H) had a suppressed baseline level, suggesting increased LT4 adherence prior to the scheduled test. This pre-test 'effect' is also highly informative about prior LT4 compliance and helped further therapeutic enforcement. Moreover, the full LT4AT data of these patients are also relevant. For example, when reviewing the complete LT4AT results, despite presenting normal TSH at baseline, patient I did not achieve an FT4 increase above 50%, suggesting a probable malabsorptive condition. In fact, this patient had a previous history of *Helicobacter pylori* gastritis and prior 'intestinal surgery' during childhood, probably due to an intussusception, which can both affect LT4 absorption associated with proton pump inhibitor and calcium carbonate. We theorize that this 'intestinal surgery' can

**Table 2** Levothyroxine absorption test (LT4AT) results.

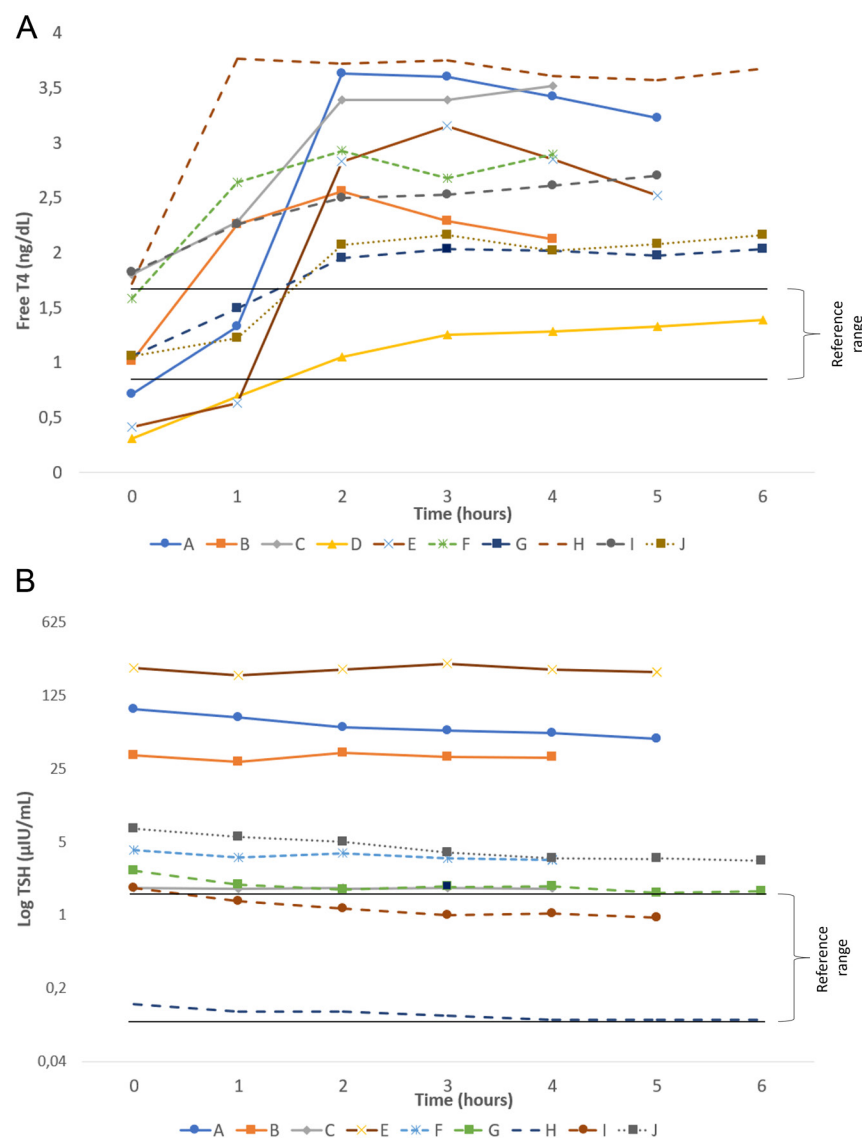
Patient	Baseline TSH <sup>a</sup> ( $\mu$ IU/mL)	Final TSH ( $\mu$ IU/mL)	Baseline FT4 <sup>b</sup> (ng/dL)	Maximum FT4 (ng/dL)	FT4 increase (ng/dL)	% FT4 increase	Baseline FT3 <sup>c</sup> (pg/mL)	Final FT3 (pg/mL)
A	93.1	48.4	0.71	3.63 (hour 2)	2.92	411	1.54	2.59
B	33.3	32.1	1.01	2.56 (hour 2)	1.55	153	2.62	2.98
C	1.83	1.81	1.80	3.52 (hour 4)	1.72	96	3.38	3.65
D	NA	NA	0.31	1.39 (hour 6)	1.08	348	1.65	1.93
E	228.0	209.5	0.41	3.15 (hour 3)	2.74	668	1.43	2.01
F	4.16	3.35	1.58	2.93 (hour 2)	1.35	85	2.69	3.17
G	2.66	1.69	1.06	2.03 (hour 3)	0.97	92	2.72	3.01
H	0.14	0.10	1.72	3.77 (hour 1)	2.05	119	3.62	4.30
I	1.83	0.94	1.82	2.70 (hour 5)	0.88	48	3.05	3.11
J	6.69	3.28	1.06	2.16 (hour 3)	1.10	104	2.72	2.92

<sup>a</sup>Reference range of TSH level is 0.27–4.2  $\mu$ IU/mL.

<sup>b</sup>Reference range of FT4 level is 0.93–1.7 ng/dL.

<sup>c</sup>Reference range of FT3 level is 2.0–4.4 pg/mL.

FT3, free triiodothyronine; FT4, free thyroxine; NA, not available; TSH, thyroid-stimulating hormone.



**Figure 1**

Levothyroxine absorption test (LT4AT) results.

(A) Free thyroxine trends during LT4AT.

(B) Logarithmic TSH trends during LT4AT. LT4AT, levothyroxine absorption test; FT4, free thyroxine;

TSH, thyroid-stimulating hormone. \*Note:

Patients B, C and F finished LT4AT at hour 4 and

patients A, E and I finished at hour 5, due to loss

of venous access.



**Table 3** Last follow-up evaluation.

Patient	Follow-up (months)	TSH <sup>a</sup> (μIU/mL)	FT4 <sup>b</sup> (ng/dL)	Overall thyroid function	LT4 requirement (μg/kg/day)
A	68	0.99	1.86	Euthyroidism	2.3
B	33	40.2	2.07	Improved hypothyroidism	2.5
C	25	32.3	0.91	Improved hypothyroidism	4.5
D	12	NA	0.79	Improved hypothyroidism	3.7
E	16	28.4	0.93	Improved hypothyroidism	4.2
F	1	3.58	1.49	Euthyroidism	3.5
G	4	25.0	0.60	Improved hypothyroidism	3.8
H	11	3.01	1.65	Euthyroidism	2.3
I	8	53.3	0.60	Hypothyroidism	3.0
J	9	12.3	1.31	Improved hypothyroidism	3.1

<sup>a</sup>Reference range of TSH level is 0.30–3.94 μIU/mL.

<sup>b</sup>Reference range of FT4 level is 0.95–1.57 ng/dL.

FT4, free thyroxine; NA, not available; TSH, thyroid-stimulating hormone.

adversely affect LT4 absorption by reducing exposure of the drug to the intestinal mucosa. In addition, gastrointestinal disorders, namely *Helicobacter pylori* gastritis, are a major known issue in patients with thyroxine malabsorption. This gastric infection affects approximately 30–50% of the population worldwide and it is a well-known factor interfering with LT4 absorption by increasing local pH and mucosa inflammation (1, 22).

A comprehensive evaluation for contributory comorbidities was undertaken for most patients. In fact, unless clinically indicated, an LT4AT seems to avoid an extensive evaluation for patients with refractory hypothyroidism. In these cases, adherence can be easily assessed and modifications to the therapeutic plan can be openly dealt with the patient when LT4 adherence issues are discussed. Despite a proper malabsorption investigation, mistrust and frustration between the patient and clinician may arrive. In these situations, LT4AT is highly recommended, as it represents an additional tool that can guide objective refractory hypothyroidism management (16).

During follow-up, many of our patients achieved either normalization or improvement of TSH over time, although still requiring larger doses of LT4 than previously. Nonadherence in the setting of chronic disease may explain much of our results (23). Thereby, a close follow-up of these patients with refractory hypothyroidism is essential. Strategies for enhancing compliance, namely supervised oral ingestion and/or once weekly intake of LT4, seem to be an effective and well-tolerated way to overcome this issue. When malabsorption is found, distinct LT4 formulations have been used with success (24, 25, 26). LT4 soft gel and LT4 liquid contain predissolved LT4 and are claimed to improve bioavailability, presumably by facilitating absorption. Despite these options, a recent study concluded that the evidence in favor of using LT4 soft gel

or LT4 liquid in clinical practice over LT4 traditional tablet formulation is somewhat weak (27). In order to help LT4 absorption in lactose intolerance cases, currently a free-lactose LT4 formulation is available. Finally, when other conditions are present, such as severe gastroparesis, the parenteral formulation should be considered (16).

The risk of administering a large single-week LT4 dose is low. This may result from the fact that, despite serum T4 increases after weekly LT4 ingestion, T4 is in fact bound by circulating thyroxine-binding globulin and has to be converted to triiodothyronine (T3) to be biologically active, so that acute changes in T3 levels are usually minimal (10). In fact, we have confirmed during LT4AT that changes in FT3 levels were minimal and that they remained within the reference range throughout the test. This may help explain the absence of side effects observed during LT4ATs. Nevertheless, most clinicians when treating a patient with a single weekly dose administration pursue with caution in patients with underlying cardiac arrhythmias or coronary artery disease (6).

This study has some limitations, mainly due to its retrospective design and small sample size. This relatively modest size reflects how infrequently this test is performed in our clinical practice. Despite its overall safety, the probably excessive fixed LT4 dose may have restrained LT4AT use and prevented some patient evaluations for safety concerns. Individualizing LT4AT protocol by adjusting LT4 dose to the average expected total weekly amounts of LT4, weight, height and age should be considered in future studies.

This case series constitutes one of the largest cohorts published to date presenting LT4AT data. Given that robust evidence regarding the use of oral LT4AT in the management of refractory hypothyroid patients is scarce, we consider that our study adds valuable data. Moreover, the addition of FT3 levels during LT4AT was essential to

help explain the safety and absence of side effects observed during the test. Lastly, the inclusion of a follow-up period allowed us to assess clinical performance after LT4AT and these data were included on patient's management.

In summary, LT4AT is an effective and safe way to assess refractory hypothyroidism that provides important clinical information to distinguish LT4 malabsorption from 'pseudomalabsorption'. Our data suggest that most patients with suspected LT4 malabsorption do present adequate LT4AT absorption results. Valuable information obtained during this test was linked to thyroid function improvement in all patients most probably by providing a better understanding of the underlying causes associated with each refractory hypothyroidism case.

#### Declaration of interest

The authors have no conflicts of interest to declare.

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#### Ethical approval

This study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto (205-DEFI/213-CE).

#### Informed consent

Consent to participate was waived by the Ethics Committee of Centro Hospitalar Universitário do Porto (205-DEFI/213-CE) due to the retrospective nature of the study and full data anonymization.

#### Author contribution statement

SSM and ACC designed the study. SSM acquired the data. SSM, TSS and ACC interpreted the data. SSM and TSS drafted the work and all authors revised it critically for important intellectual content. All authors approved the final version submitted and are accountable for all aspects of the work. All authors read and approved the final manuscript.

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