

Refractory Hypothyroidism in Pediatrics: Insights from Levothyroxine Absorption Test

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Abstract

Hypothyroidism is a common endocrine disorder characterized by insufficient production of thyroid hormones and its management poses significant challenges in clinical practice, particularly in childhood. The most common cause of pediatric hypothyroidism is congenital hypothyroidism, resulting from thyroid dysgenesis or thyroid hormone biosynthesis defects. Acquired hypothyroidism may also occur secondary to autoimmune thyroiditis, thyroid surgery or radiation therapy. Levothyroxine (LT4), a synthetic form of thyroxine, constitutes the cornerstone of thyroid hormone replacement therapy

Keywords: Hypothyroidism; Pediatrics; Levothyroxine Absorption Test; thyroid dysgenesis; Graves' disease

Introduction

Hypothyroidism is a common endocrine disorder characterized by insufficient production of thyroid hormones and its management poses significant challenges in clinical practice, particularly in childhood. The most common cause of pediatric hypothyroidism is congenital hypothyroidism, resulting from thyroid dysgenesis or thyroid hormone biosynthesis defects. Acquired hypothyroidism may also occur secondary to autoimmune thyroiditis, thyroid surgery or radiation therapy. Levothyroxine (LT4), a synthetic form of thyroxine, constitutes the cornerstone of thyroid hormone replacement therapy. Despite its narrow therapeutic window, LT4 is acknowledged to be a safe and effective treatment for hypothyroidism, where effectiveness is judged by an appropriate serum concentration of thyroid free hormones and thyrotropin (TSH) according to age-specific reference intervals [1]. However, achieving optimal therapeutic outcomes can be challenging in case of refractory hypothyroidism (RH), a condition characterized by persistently high thyrotropin levels despite adequate or high doses of LT4 therapy. RH may be caused by true malabsorption due to an organic cause [2], which alters the LT4 pharmacokinetics, or by pseudomalabsorption due to poor adherence to treatment.

The levothyroxine absorption test (LT4AT) is increasingly recognized as a valuable diagnostic tool for assessing LT4 absorption and guiding treatment decisions. The LT4AT is a non-invasive and safe method to potentially differentiate LT4 malabsorption from pseudomalabsorption [3]. Although extensively investigated in adults, the standardization of LT4AT remains still not defined [3-8]. Moreover, the application of LT4AT in pediatric patients is notably lacking in published literature, highlighting a significant gap in clinical practice. In pediatric patients, an accurate diagnosis of refractory hypothyroidism is crucial. It requires careful consideration of factors such as age-specific TSH reference intervals, the etiology of hypothyroidism, and potential interfering factors. This is essential to avoid inappropriate increases in LT4 dosage and to identify children who would benefit from further investigations for malabsorption. Here we describe

three cases of LT4AT conducted in our department in pediatric patients affected by hypothyroidism, highlighting its importance in the diagnosis of LT4 pseudomalabsorption, with the aim of optimizing therapeutic strategies.

Materials and Methods

We have conducted LT4AT on three pediatric patients affected by refractory hypothyroidism followed in our center (Pediatric Department, IRCCS San Raffaele University Hospital, Milan). Two patients were affected by primary hypothyroidism and one with secondary hypothyroidism due to thyroidectomy for Graves' disease. Individual charts were reviewed to document that appropriate workups for malabsorption were previously performed. These included serum evaluations for celiac disease, atrophic gastritis, and vitamin deficiencies. Medications known to interfere with LT4 absorption were ruled out by careful medical history. Adherence and correct drug assumption were evaluated as well. LT4AT was performed in a hospitalization setting in order to supervise LT4 effective administration and to monitor eventual side effects. Patients were not allowed to eat the night before the test and during the test. A single dose of LT4 was administered at 8:00 am, followed by serial measurements of free thyroxine (FT4) and TSH at specific intervals over a six-hour period (0', 60', 120', 180', 240', 360' minutes).

The LT4 dose was individualized based on the patient's current therapeutic requirement, previous effective LT4 dosage, and the expected physiological needs according to age and etiology of hypothyroidism [9]. In our cohort, the individualized daily doses ranged approximately between 2.0 and 3.5 µg/kg/day. The daily dose was then multiplied by seven corresponding to the estimated weekly LT4 intake, up to a maximum total dose of 1000 µg. This approach was intended to ensure sufficient pharmacological challenge for the evaluation of LT4 absorption, while maintaining safety parameters comparable to those applied in adult protocols. Thyroid function tests were performed using electro-chemiluminescence immunoassay (ECLIA). Our Centre's laboratory reference range during childhood for TSH is 0.25

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- 5 $\mu\text{U/L}$, and for FT4 is 0.93 - 1.7 ng/dL.

An FT4 increment >0.40 ng/dL at 3 hours from baseline had been considered the cutoff to exclude true malabsorption, as proposed in literature [6].

Results

Case 1: A 5-year and 1-month-old male child, weighting 19.8 kg (48th percentile) with a BMI of 17.09 kg/m² (80th percentile), diagnosed at birth with primary severe hypothyroidism due to thyroid agenesis. Moreover, at the age of 22 months he was diagnosed with autism spectrum disorder.

During the first year of life, an excellent response to therapy was observed, with FT4 stably in range and with progressively decreasing doses of levothyroxine. However, over time, TSH levels were found variably elevated and fluctuated despite dose adjustments from a minimum of 3.60 to a maximum of 6.02 $\mu\text{g/kg/day}$. After five years of challenging medical management, the TSH resulted markedly elevated (217 $\mu\text{IU/mL}$) with a FT4 at the lower limits of the reference range (0.98 ng/dL), with a daily levothyroxine dose of 5.60 $\mu\text{g/kg/day}$. Despite the good adherence to the therapy reported by the parents, due to the persistence of poor hormonal control, the patient was admitted to our Center to prompt a levothyroxine absorption test two weeks later.

Blood tests were performed, and biochemical malabsorption was ruled out. After administration of LT4 by the nurses, a lower TSH level was observed (76.6 $\mu\text{IU/mL}$), but still marked elevated, accompanied by an FT4 level of 1.62 ng/dL. A supervised dose of levothyroxine (500 μg , based on a weekly dose of 25.2 $\mu\text{g/kg}$, corresponding to 3.6 $\mu\text{g/kg/day}$) was administered. The test was well tolerated. FT4 increased substantially throughout the test reaching a peak of 2.75 ng/dL within the first three hours, ruling out levothyroxine malabsorption. No side effects were observed in the following 24 hours. After the test, the levothyroxine dose was reduced to 5.05 $\mu\text{g/kg/day}$. Once week later, the patient's TSH level decreased significantly to 17.5 $\mu\text{IU/mL}$, while the FT4 level increased to 1.89 ng/dL. As a result, the levothyroxine dosage was further reduced to 4.40 $\mu\text{g/kg}$. One year later, the dosage was further reduced by an additional 5% to 3.86 mcg/kg/day, as the thyroid function test showed TSH below normal limits and a high FT4 (TSH 0.02 $\mu\text{IU/m}$ and FT4 1.92 ng/dl).

Case 2: A 14-year and 9-month-old girl, weighting 68 kg (95th percentile) with a BMI of 23.8 kg/m² (75th percentile) affected with secondary hypothyroidism due to thyroidectomy for Graves's disease (onset at 11 years of age).

After thyroid surgery, thyroid function values were fluctuating and were not well controlled, with TSH elevated despite adequate doses of LT4. LT4 doses were gradually increased from a minimum of 1.28 $\mu\text{g/kg/day}$ to a maximum of 4.07 $\mu\text{g/kg/day}$. A change in the formulation of LT4 (from tablets to soft capsules) was not effective in improving hormone control. The patient was questioned about adherence to pharmacological treatment. She reported taking levothyroxine every day, 20 minutes before breakfast, without any other medications. Biochemical malabsorption was ruled out. The patient practiced competitive swimming, therefore, we expected that she would be very motivated to follow the therapy in order to maintain high sports performance. Latest laboratory tests revealed a high level of TSH (122 $\mu\text{IU/mL}$) with low FT4 (0.59 ng/mL) despite a levothyroxine dose of 4.07 $\mu\text{g/kg/day}$. In consideration of the persistence of poor hormonal control despite the ongoing high-dose therapy, a levothyroxine absorption test was scheduled. Upon admission the physical examination was unremarkable, in particular there were no signs or

symptoms of hypothyroidism, neither clinical nor reported by the patient or her parents.

5 days after admission and administration of LT4 by the nurses, TSH level demonstrated a decrease to 43.5 $\mu\text{IU/mL}$, with an FT4 level of 1.44 ng/mL. A dose of LT4 (1000 μg , considering a weekly dose of 14,7 $\mu\text{g/kg}$, corresponding to 2,1 $\mu\text{g/kg/day}$) was administered under medical supervision. The test was well tolerated. An increase in FT4 of 1.68 ng/mL was observed three hours from baseline which allowed us to exclude malabsorption of levothyroxine. The recommended LT4 dosage was reduced to 3.91 $\mu\text{g/kg/day}$. After one week, TSH had decreased to 4.71 $\mu\text{IU/mL}$ and FT4 normalized to 1.74 ng/dL on a slightly adjusted LT4 dose of 3.70 $\mu\text{g/kg/day}$. Subsequent reductions were implemented over the following weeks, with a consistent emphasis on the importance of therapy adherence. One year later TSH and FT4 were within the target range on a levothyroxine dose of 1.63 $\mu\text{g/kg/die}$.

Case 3: A 7-year and 10-month-old girl, weighting 49 kg (>97 th percentile) with a BMI of 27.37 kg/m² (>97 th percentile), diagnosed at birth with primary hypothyroidism resulting from thyroid agenesis.

Despite consistent adjustments of her levothyroxine dosage over the years, her TSH levels have persistently hovered above the upper limit of normal. At her last assessment, she exhibited alarming high TSH levels and a very low FT4 value (TSH 284 $\mu\text{IU/mL}$ and FT4 0.47 ng/dL), while receiving a daily levothyroxine dose of 3.0 $\mu\text{g/kg/day}$. Blood tests showed severe dyslipidemia with high levels of both triglycerides (>95 th bp) and total cholesterol (>95 th bp). Biochemical malabsorption was ruled out. Baseline measurements, after administration of LT4 by our nurses, revealed a notably elevated TSH of 264.0 $\mu\text{IU/mL}$ and an FT4 of 1.32 ng/dL. Following the supervised administration of 700 μg of LT4 (equal to a daily dosage of 2 $\mu\text{g/kg/die}$ and based on a weekly dose of 14,2 $\mu\text{g/kg}$), we meticulously tracked her hormone levels hourly for six hours. Remarkably, her FT4 levels peaked at 3.29 ng/dL three hours post-levothyroxine intake, confirming effective LT4 absorption. No adverse effects were observed. After one week, TSH improved to 3.59 $\mu\text{IU/mL}$ and FT4 was 1.34 ng/dL. Given the satisfactory improvement in thyroid function parameters, and the FT4 value within the reference range, the LT4 dosage was maintained unchanged at 3.00 $\mu\text{g/kg/day}$. One year after the test, her thyroid function was within limits with a TSH level of 2.47 $\mu\text{IU/mL}$ and FT4 of 1.43 ng/dl on a dose of LT4 of 2.56 μg per day, reflecting the efficacy of our approach.

Table 1 summarizes the characteristics of the patients, their pre- and post-test thyroid function results, and those during follow-up.

Table 1: Patients characteristics and thyroid function values before, during, and after the Levothyroxine absorption test (LT4AT). TFT: Thyroid function test; FT4: free thyroxine; FT3: free tri-iodothyronine; TSH: thyroid stimulating hormone; LT4: levothyroxine; BMI: body mass index

		Case 1	Case 2	Case 3
Demographic and clinical characteristics	Age at LT4AT	5 years 1 month	14 years 9 months	7 years 10 months
	Gender	Male	Female	Female
	Diagnosis	Congenital hypothyroidism (thyroid agenesis)	Secondary hypothyroidism (thyroidectomy for Graves disease)	Congenital hypothyroidism (thyroid agenesis)
	Comorbidities	Autism spectrum disorder	Allergic asthma IgA immunoglobulins deficiency	Overweight
	Interfering medications	No	No	No
	Weight (at LT4AT)	19.8 kg (48° p.le)	68 kg (95° p.le)	49 kg (>97° p.le)
	Height (at LT4AT)	105,8 cm (13° p.le)	169 cm (88° p.le)	133,8 cm (87° p.le)
	BMI (at LT4AT)	17.09 kg/m2 (80° p.le)	23.8 kg/m2 (75° p.le)	27.3 kg/m2 (>97° p.le)
Pre-test clinical information in outpatient clinic	TSH μ IU/ml (nv 0.25 - 5.00)	217	122	284
	FT4 ng/dL (nv 0.93 - 1.7)	0.98	0.59	0.47
	LT-4 dose (mcg/kg/die)	5.60	4.07	3.00
	Hypotiroidism duration	5 years 1 month	2 years	7 years 10 months
Test results	Basal TSH μ IU/ml (nv 0.25 - 5.00)	76.6	43.5	264.0
	Basal FT4 (nv 0.93 - 1.7 ng/dL)	1.62 ng/dl	1.44 ng/dl	1.32 ng/dl
	LT-4 test dose	500 μ g	1000 μ g	700 μ g
	- weekly dose (μ g/kg/week)	25.2	14.7	14.2
	- daily dose (μ g/kg/die)	3.6	2.1	2.0
	- recommended daily dose for age and etiology	3.2–3.7	1.7–2.2	2.0–3.0
TFT after one week post test	Peak FT4 at 3 h (ng/dl)	2.75	3.12	3.29
	FT4 increment at 3 h from baseline	1.13	1.68	2.17
TFT after one week post test	TSH μ IU/ml (nv 0.25 - 5.00)	17.5 μ IU/mL	4.71	3.59
	FT4 ng/dL (nv 0.93 - 1.7)	1.89	1.74	1.34
	LT-4 dose (mcg/kg/die)	4.40	3.70	3.00
Follow up data (1 year after)	Test side effects	No	No	No
	TSH μ IU/ml (nv 0.25 - 5.00)	0.02	1.09	2.47
	FT4 ng/dL (nv 0.93 - 1.7)	1.92	1.56	1.43
	LT-4 dose (mcg/kg/die)	3.2	1.63	2.56

Discussion

In clinical practice, cases of refractory hypothyroidism (RH) despite the referred administration of adequate doses of LT4, also among pediatric patients are not uncommon. In these cases, it is essential to establish the differential diagnosis among the causes of RH: malabsorption versus pseudomalabsorption. Pathological causes of LT4 malabsorption include gastrointestinal disorders such as celiac dis-

ease, lactose intolerance, atrophic gastritis and small intestinal resection, as well as other rare conditions such as nephrotic syndrome, Addison's disease, and cystic fibrosis.

Nonpathological causes such as inadequate compliance, change of formulation, physiological increased demands (ex. puberty), immunoassay interferences, and interaction with supplements or medica-

tions, must be ruled out. Drugs as proton pump inhibitors (PPI), aluminum hydroxide, ferrous sulfate, cholestyramine, and calcium can impair absorption of the LT4 [7]. Rifampicin, phenytoin, phenobarbital, and carbamazepine can accelerate the metabolism of thyroxine [7,13]. Dietary factors as fiber, grape, soy, and coffee may also alter the LT4 absorption [7].

LT4AT is precious in evaluating cases suspected for pseudomalabsorption due to poor adherence to LT4 treatment. Unfortunately, the lack of standardization across institutions and laboratories poses a significant obstacle to the clinical utility of LT4AT. While various LT4AT protocols have been described in literature, they often differ in terms of methods, variables and criteria used for interpretation [3,6,8]. However, this issue is further exacerbated in the pediatric population due to the absence of recommendations, highlighting a critical gap in clinical practice. Above all, defining RH in childhood could be the first challenge for the pediatric endocrinologist: proper LT4 doses in pediatric population differ according on age and underlying etiology with individual variability between patients with the goal of maintaining an optimum biochemical control. In our experience, the LT4AT was taken in consideration when the prescribed daily dose exceeded the upper limit of the expected maintenance range for the patient's specific age and etiology and especially when LT4 requirements were progressively increasing without obtaining a satisfying hormonal control. In children with thyroid agenesis, the expected LT4 requirement is approximately 3.0-4.0 µg/kg/day; in cases of thyroid ectopy slightly lower doses are required with estimated needs around 2.0-3.0 µg/kg/day; for patients with a normally located thyroid gland but affected by dysmorphogenesis or partial gland dysfunction, the maintenance dose tends to be lower typically around 1.5-2.0 µg/kg/day; finally, in patients with autoimmune thyroiditis or following total thyroidectomy maintenance LT4 requirements are generally around 1.5-2.0 µg/kg/day [9]. These proposed LT4 requirements should be considered as an empiric guide for the clinician rather than a rigid criterion, allowing an individualized assessment based on patient age, growth, comorbidities and treatment context.

Once the indication for LT4AT has been confirmed, the test dose has been individualized considering both patient's previous effective LT4 dose and expected posology according to age and etiology. A single oral dose corresponding approximately to the patient's weekly LT4 requirement, defined as previously mentioned, with a maximum of 1000 mcg, was administered. Subsequently, thyroid function values - TSH, FT3, and FT4 - are collected at baseline and hourly over the next six hours. Optimal levothyroxine absorption is confirmed by a 0.40 ng/dL increase in FT4 levels at 3 hours with a sensitivity of 97% and specificity of 80%, as described by Ghosh et al. [6] This timeframe can be explained by the specific pharmacodynamics of the drug [10]: infact after oral ingestion, LT4 tablet disintegration and dissolution occur primarily in the stomach, requiring an acidic gastric pH (1.0-3.0) to remove the sodium ion and convert LT4 into a lipophilic molecule [9]. LT4 is predominantly absorbed in the jejunum and ileum, with absorption rates of 70% to 80% when taken on an empty stomach, and reaching its peak concentration in approximately 3 h, with a bioavailability of 70% to 80% [6,7]. The 3 hours cut-off is consistent with the other findings present in literature [5]. For example, Kubota et reported an FT4 increment by 0.6 ng/dL in a case of pseudomalabsorption [11]. Conversely, Jauk et al described an FT4 increment of only 0.1 ng/dL in a patient with real malabsorption [12].

threshold is dependent on the baseline value. Thus, since some patients may actually take LT4 for some days before the scheduled day of the test, falsely raising the FT4 value, we prefer taking into consideration the absolute increment of FT4 levels instead of multiple of increment from baseline values.

Furthermore, some other authors suggest adding the evaluation of the volume of distribution (Vd) to estimate the amount of drug absorbed [3,5]. The Vd is measured in liters and obtained by calculating: $Vd = 0,442 \times BMI$. Based on this, the percentage of drug absorption can be estimated by the formula: $LT4 \text{ absorbed (\%)} = \frac{\text{peak total thyroxine (TT4)} (\mu\text{g/dL}) \times Vd (\text{dL})}{\text{administered dose of LT4} \times 100}$ [3,5]. Besides not being easy to manage, this formula considers total T4, since original absorption studies for LT4 were validated using TT4 measurements. With the purpose of evaluating the use of FT4 in the oral LT4AT, a recent study compared the dosage of total or free T4 after 1000µg of LT4. The authors found a strong correlation between measures of TT4 and FT4 ($r = 0.88$, $p < 0.001$), suggesting that FT4 may be used instead of TT4.

Consistently, in our cohort, all three patients showed an FT4 increment exceeding 0.4 ng/dL at three hours, with the expected pharmacokinetic response, confirming adequate intestinal absorption. Therefore, given the practical difficulties in obtaining and maintaining venous access for serial sampling in young children, a simplified protocol focusing on a two key time points - baseline and three hours post-administration - may be sufficient in most cases to confirm adequate absorption and should be considered in pediatric patients in order to minimize the procedural burden.

In the post-test phase, monitoring for adverse effects related to elevated thyroid hormone levels is essential. All our patients presented with significant reductions in TSH values, supporting the diagnosis of pseudo malabsorption and validating the clinical utility of LT4AT in guiding therapeutic management. Upon discharge, strong emphasis must be placed on the importance of compliance, and patients should be closely reevaluated until thyroid function is normalized. In Figure 2, is presented a schematic synthesis of the LT4AT protocol used in our center and proposed for pediatric patient with RH [14-18].

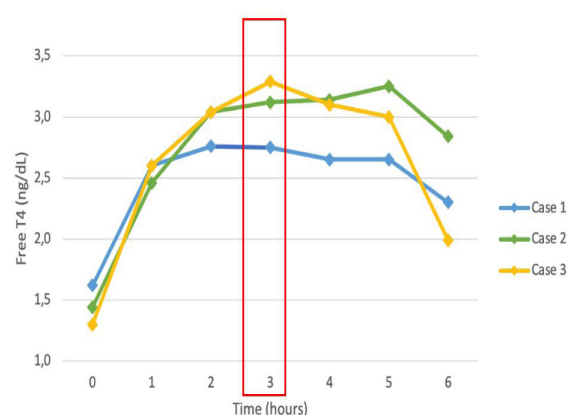
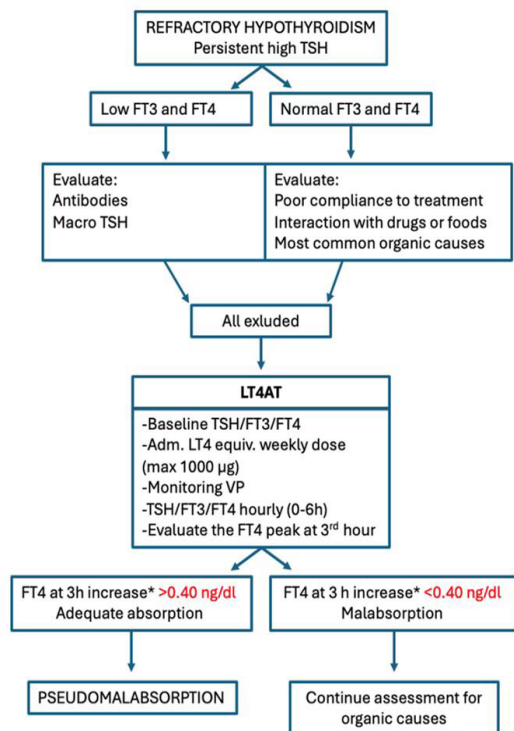


Figure 1: Comparison between the curves resulting from the levothyroxine absorption test (LT4AT) conducted in the three patients described.

Instead Santos Monteiro et al considered a FT4 increment over the baseline of more than 50% consistent with pseudomalabsorption and observed absolute increments from 0.97 to 2.92 ng/dL [13]. However, as suggested also by Soares et al, achieving this relative



*FT4 increase refers to the difference between the peak and basal values of FT4.

Figure 2: Diagnostic-therapeutic algorithm for refractory hypothyroidism proposed. VP: vital parameters. Adm. LT4 equiv.: administration of LT4 equivalent to the weekly dose.

Conclusion

In pediatric patients with refractory hypothyroidism, distinguishing between true malabsorption and poor adherence remains a major clinical challenge. Our experience highlights the utility of LT4AT as a valuable tool in clinical practice to guide diagnosis and optimize long-term management, by reducing the risks of overtreatment and associated complications [16]. Further clinical studies are needed to establish standardized pediatric protocols with validated cutoffs, thereby strengthening the application of the LT4AT in routine pediatric endocrinology.

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