Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

The importance of sequential evaluation of refractory hypothyroidism cases

A importância da avaliação sequencial de casos de hipotiroidismo refratário

La importancia de la evaluación secuencial de los casos de hipotiroidismo refractario

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ABSTRACT

Objective: To identify causes of refractoriness to oral levothyroxine (LT4) and propose a sequential investigation protocol including gastrointestinal and psychiatric assessments and the LT4 absorption test. **Methods:** A prospective case series included adults (18–65 years) using ≥2.5 µg/kg/day or ≥250 µg/day of LT4. Ten patients completed full evaluation: medical interview, empirical antiparasitic therapy, upper endoscopy with biopsies, tests for malabsorption and lactose intolerance, psychiatric screening (M.I.N.I. Plus), and a standardized 4-hour LT4 absorption test applying four diagnostic criteria. **Results:** Most participants were women (80%), mean BMI 28.6 kg/m². At least one contributing factor was identified in 90%. Endoscopic abnormalities were common (80%); half were *Helicobacter pylori* positive, 40% lactose intolerant, 40% screened positive for depression, and 60% used interfering medications. Based on absorption criteria, three patients had true malabsorption, while most showed adequate LT4 absorption, suggesting pseudo malabsorption linked to nonadherence. Total T4-based criteria yielded the highest concordance, while free T4 and TSH changes were more variable. **Conclusion:** Refractory hypothyroidism is typically multifactorial. Drug interactions, gastrointestinal disorders, and psychiatric comorbidities frequently impair control. Most patients demonstrated adequate LT4 absorption, highlighting nonadherence as a major cause. A structured, multidisciplinary approach optimizes diagnostic accuracy.

Keywords: Refractory hypothyroidism, Levothyroxine absorption test, Levothyroxine malabsorption, Pseudo malabsorption.

RESUMO

Objetivo: Identificar as causas de refratariedade à levotiroxina oral (LT4) e propor um protocolo de investigação sequencial, incluindo avaliações gastrointestinais e psiquiátricas e o teste de absorção de LT4. **Métodos:** Uma série de casos prospectiva incluiu adultos (18-65 anos) em uso de ≥2,5 µg/kg/dia ou ≥250 µg/dia de LT4. Dez pacientes completaram a avaliação completa: anamnese, terapia antiparasitária empírica, endoscopia digestiva alta com biópsias, testes para má absorção e intolerância à lactose, triagem psiquiátrica (M.I.N.I. Plus) e um teste de absorção de LT4 padronizado de 4 horas, aplicando quatro critérios diagnósticos. **Resultados:** A maioria dos participantes era do sexo feminino (80%), com IMC médio de 28,6 kg/m². Pelo menos um fator contribuinte foi identificado em 90% dos casos. Anormalidades endoscópicas foram comuns

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SUBMETIDO EM: 12/2025 | **ACEITO EM: 1/2022** | **PUBLICADO EM: 3/2026**

(80%); metade dos pacientes apresentou positividade para *Helicobacter pylori*, 40% intolerância à lactose, 40% triagem positiva para depressão e 60% uso de medicamentos que interferiam no tratamento. Com base nos critérios de absorção, três pacientes apresentaram má absorção verdadeira, enquanto a maioria apresentou absorção adequada de levotiroxina (LT4), sugerindo pseudomáabsorção associada à não adesão ao tratamento. Os critérios baseados no T4 total apresentaram a maior concordância, enquanto as alterações no T4 livre e no TSH foram mais variáveis. **Conclusão:** O hipotireoidismo refratário é tipicamente multifatorial. Interações medicamentosas, distúrbios gastrointestinais e comorbidades psiquiátricas frequentemente comprometem o controle. A maioria dos pacientes demonstrou absorção adequada de LT4, destacando a não adesão ao tratamento como uma das principais causas. Uma abordagem estruturada e multidisciplinar otimiza a precisão diagnóstica.

Palavras-chave: Hipotireoidismo refratário, Teste de absorção de levotiroxina, Má absorção de levotiroxina, Pseudo má absorção.

RESUMEN

Objetivo: Identificar las causas de refractariedad a la levotiroxina oral (LT4) y proponer un protocolo de investigación secuencial que incluye evaluaciones gastrointestinales y psiquiátricas y la prueba de absorción de LT4. **Métodos:** Una serie de casos prospectiva incluyó adultos (18-65 años) que usaban ≥2,5 µg/kg/día o ≥250 µg/día de LT4. Diez pacientes completaron la evaluación completa: entrevista médica, terapia antiparasitaria empírica, endoscopia superior con biopsias, pruebas de malabsorción e intolerancia a la lactosa, cribado psiquiátrico (M.I.N.I. Plus) y una prueba estandarizada de absorción de LT4 de 4 horas aplicando cuatro criterios diagnósticos. **Resultados:** La mayoría de los participantes fueron mujeres (80%), IMC medio 28,6 kg/m². Se identificó al menos un factor contribuyente en el 90%. Las anomalías endoscópicas fueron comunes (80%); La mitad presentó *Helicobacter pylori* positivo, el 40% intolerancia a la lactosa, el 40% presentó resultados positivos para depresión y el 60% consumía medicamentos que interferían. Según los criterios de absorción, tres pacientes presentaron malabsorción verdadera, mientras que la mayoría mostró una absorción adecuada de LT4, lo que sugiere una pseudomalabsorción relacionada con la falta de adherencia. Los criterios basados en T4 total arrojaron la mayor concordancia, mientras que los cambios en T4 libre y TSH fueron más variables. **Conclusión:** El hipotiroidismo refractario suele ser multifactorial. Las interacciones farmacológicas, los trastornos gastrointestinales y las comorbilidades psiquiátricas con frecuencia dificultan el control. La mayoría de los pacientes mostraron una absorción adecuada de LT4, destacando la falta de adherencia como una causa principal. Un enfoque estructurado y multidisciplinario optimiza la precisión diagnóstica.

Palabras clave: Hipotiroidismo refractario, Prueba de absorción de levotiroxina, Malabsorción de levotiroxina, Pseudo malabsorción.

INTRODUCTION

Hypothyroidism, defined by a deficiency of thyroid hormone, is a common condition worldwide (ROBERTSON HM, et al., 2014; CHAKER L e PAPALEONTIOU M, 2025). In Brazil, data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) indicate an annual incidence of overt and subclinical hypothyroidism of approximately 0.5% and 1%, respectively (MAZETO GM, et al., 2022).

The disease affects the function of almost every organ and system and has a highly heterogeneous presentation; it can manifest with few or many symptoms (CHAKER L e PAPALEONTIOU M, 2025). In iodine-sufficient countries the principal etiology is autoimmune (JONKLAAS J, et al., 2014).

Since 1927, synthetic levothyroxine has been the gold standard treatment for hypothyroidism (HARRINGTON CR e BARGER G, 1927; CHAKER L e PAPALEONTIOU M, 2025). It is primarily absorbed in the jejunum

and ileum with absorption rates between 62% and 82%, and absorption can be optimized by fasting administration, making oral use effective for most patients (MAZETO GM, et al., 2022; JONKLAAS J, et al., 2014; VAN WILDER N, et al., 2017). In addition, its long half-life permits once-daily dosing. The efficacy and safety of its use are well documented in the literature (JONKLAAS J, et al., 2014).

Despite being common and easily treated in many cases, hypothyroidism also presents challenges. Although the recommended dose of 1.6–1.8 µg/kg/day is sufficient for good control in most cases, many patients require atypically high doses (MAZETO GM, et al., 2022; VAN WILDER N, et al., 2017; SHIMBA R, et al., 2025).

While there is no universally accepted definition, many authors consider patients refractory when using doses above 1.9–2.5 µg/kg or greater than 250–300 µg/day (JONKLAAS J, et al., 2014; GONZALES KM, et al., 2019).

Numerous causes may be related to lack of response to treatment, including gastrointestinal diseases, drug interactions and dietary factors (ROBERTSON HM, et al., 2014; SHIMBA R, et al., 2025). However, administration errors remain the principal cause of need for high doses of the medication (MAZETO GM, et al., 2022; VAN WILDER N, et al., 2017).

Considering hypothyroidism is a systemic disease and that severe cases may lead to important cardio and neurological repercussions (COUTO B, et al., 2024) it is recommended that every suspected case of refractoriness be investigated seriously and persistently (GONZALES KM, et al., 2019; NUGURU, SP et al., 2022).

Unfortunately, there is a large scarcity of standardized protocols for investigating refractory patients, and practical tools such as the levothyroxine absorption test have been explored little in research; therefore, interpretation has proven heterogeneous among authors (MAZETO GM, et al., 2022; GONZALES KM, et al., 2019).

In this context, the present study aims to evaluate the causes of refractoriness to oral levothyroxine treatment in hypothyroid patients and to propose an investigation protocol for these cases, including assessment for gastrointestinal disease, psychiatric evaluation, and the levothyroxine absorption test.

METHODS

A prospective case series study was conducted and approved by the Institution's Ethics and Research Committee, nº 1.619.188 and CAAE nº 56982616.5.0000.0096. All patients were recruited from a tertiary thyroid outpatient clinic, where they were being regularly followed for hypothyroidism while using levothyroxine doses considered elevated.

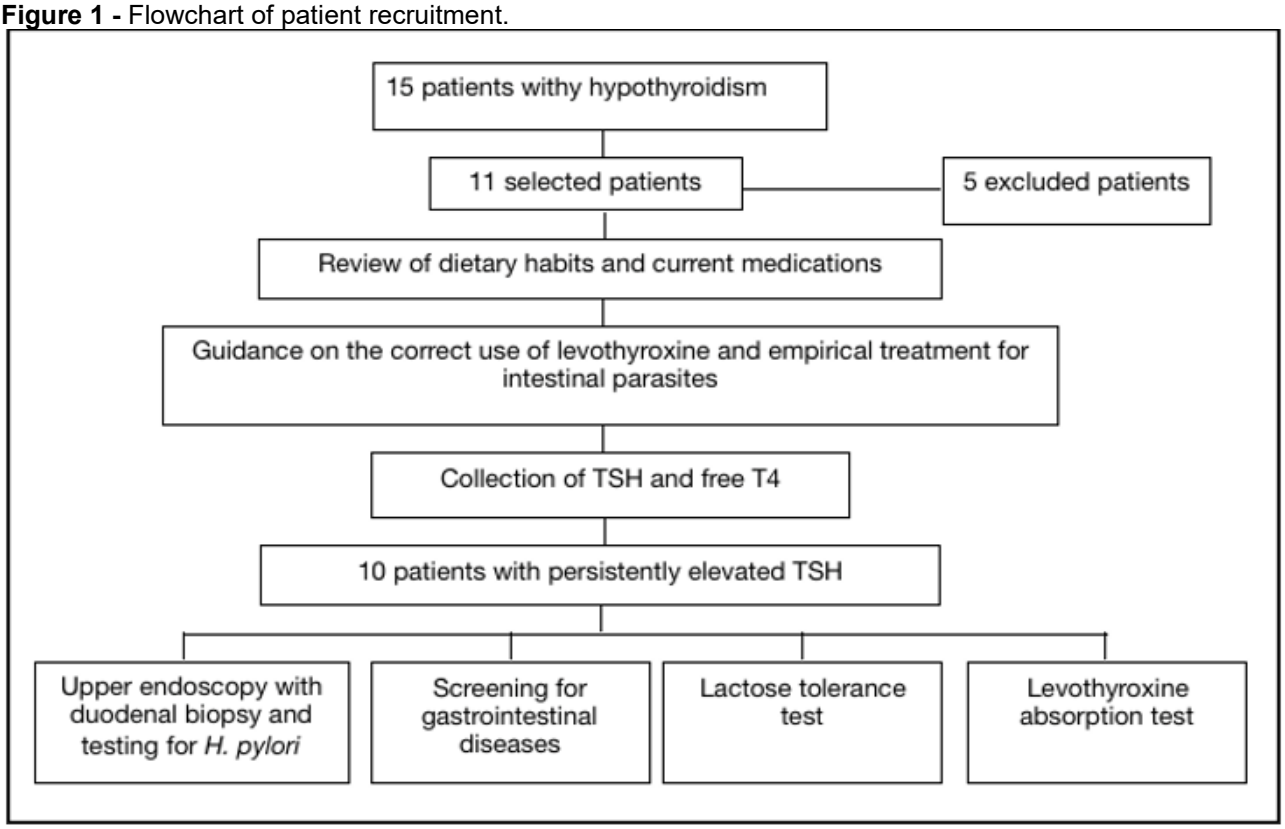
Men and women aged 18 to 65 years with refractory hypothyroidism on levothyroxine (defined as dose ≥ 2.5 µg/kg or ≥ 250 µg/day) who agreed to participate were included. Patients with significant cardiovascular disease or coronary artery disease were excluded. All participants signed an informed consent form (ICF).

A total of 15 patients were recruited, of whom 5 were excluded (2 of them due to normalization of TSH and free T4 values after correct administration counseling, 1 patient due to stable angina, 1 patient who refused to participate and 1 patient who could not be located).

All participants underwent a sequential evaluation that included an initial medical interview (including information on the method of levothyroxine administration, brand, presence of gastrointestinal symptoms, history of diseases and surgeries, among other information).

At this time patients were instructed about correct medication use and all received empirical treatment for intestinal parasitosis with albendazole 400 mg once daily for 3 days. All current medications were reviewed. Baseline venous blood samples were collected for TSH and free T4 measurement. **Figure 1** shows the participant recruitment protocol.

Figure 1 - Flowchart of patient recruitment.



Source: Rebolho ACO, et al., 2026.

Next, all patients underwent upper digestive endoscopy, screening for gastrointestinal diseases, an oral lactose tolerance test, the levothyroxine absorption test and psychiatric evaluation, as detailed below.

Upper digestive endoscopy (esophagogastroduodenoscopy — EGD)

Procedures were performed by the Digestive Endoscopy Service of a reference hospital in Paraná. Exams were carried out after fasting, under topical anesthesia with lidocaine spray in the oropharynx. *Helicobacter pylori* was investigated in all patients using the urease test.

Gastric and duodenal biopsy

All patients underwent gastric mucosal biopsy and at least two duodenal biopsies to investigate atrophic gastritis and celiac disease, respectively. Slides were stained with hematoxylin-eosin and evaluated and reviewed by the Pathology Service of the same hospital.

Screening for malabsorptive disease

Complete blood counts were evaluated using light absorbance/impedance/flow cytometry equipment CAL-8000 NINDRAY to detect anemia. Anti-parietal cell antibodies were measured by chemiluminescence (CMIA) and considered negative if < 7 U/mL, indeterminate between 7 and 10 U/mL, and positive if > 10 U/mL. Vitamin B12 was measured by chemiluminescence (CMIA) and considered normal for values between 187 and 883 pg/mL.

To investigate celiac disease, in addition to duodenal biopsies obtained during EGD, anti-endomysial antibodies and total immunoglobulin A (IgA) were measured by indirect immunofluorescence on human umbilical cord substrate and turbidimetry, respectively.

The lactose tolerance test consisted of administration of 50 g lactose under medical supervision with serial blood glucose measurements at 0, 30, 60 and 90 minutes. A test was considered positive for lactose intolerance if the increment in blood glucose was less than 20 mg/dL above baseline at any time point.

Levothyroxine oral absorption test

The test was performed by administering levothyroxine sodium (Puran T4®) under medical supervision after absolute fasting for 8 hours and omission of the patient's usual daily levothyroxine dose on the day of the test. The dose administered was adjusted according to age and BMI, following protocols accepted in the literature, and is described below (**Figure 2**). Serum TSH, free T4 and total T4 were measured at times 0, 2 and 4 hours.

Figure 2 - Levothyroxine dose adjusted by BMI.

Age 18–65 years, BMI < 40 kg/m²: 1000 mcg
Age 18–65 years, BMI ≥ 40 kg/m²: 1500 mcg
Age ≥ 65 years: 600 mcg

Source: Rebolho ACO, et al., 2026.

For test interpretation, four parameters were used according to criteria cited by several studies and available guidelines: levothyroxine percentage absorption (Criterion 1), percentage increase in total T4 during the test (Criterion 2), increase in free T4 during the test (Criterion 3), and percentage decline in TSH during the test (Criterion 4).

Malabsorption was considered present if 3 of the 4 criteria were positive. The abnormal thresholds were: levothyroxine absorption percentage < 50% (Criterion 1), increase in total T4 < 50% (Criterion 2), increase in free T4 less than 2–3 times basal value relative to the peak at 2 hours (Criterion 3), and reduction in TSH < 40% after 2 hours (Criterion 4). The formula used to calculate the percentage absorption of levothyroxine is shown below (**Figure 3**). Cases with results different from those described above were interpreted as pseudo malabsorption.

Figure 3 - Formula for calculation of levothyroxine percentage absorption.

% Absorption = [[Increase in total T4 (µg/dL) × 10 / total LT4 dose administered (µg)]] × Vd (L) × 100
Increase in total T4 = peak total T4 − basal total T4
Vd (volume of distribution) = 0.442 × BMI

Source: Rebolho ACO, et al., 2026.

Psychiatric evaluation

Patients were evaluated by the Psychiatry Service of the same hospital using the M.I.N.I. PLUS (Mini International Neuropsychiatric Interview). This questionnaire is a psychiatric interview with an approximate duration of 15 minutes and is considered a short, structured and accurate screening tool for psychiatric disorders in clinical or research settings.

RESULTS

Of the participants, 2 were men (20%) and 8 were women (80%). Mean age was 44.4 years and mean BMI was 28.6 kg/m²; 80% of patients were overweight or obese (60% overweight and 20% obese). The median daily levothyroxine dose was 400 µg/day and the dose adjusted per kg was 5.03 µg/kg. Sample characteristics are shown in **Table 1**.

Table 1 - Sample characteristics.

Characteristics	Men	Women	All
Number (%)	2 (20%)	8 (80%)	10 (100%)
Mean age	49.5 (49–50)	43.13 (21–56)	44.4 (21–56)
Mean weight, kg (range)	95.8 (85–106.6)	71.06 (41–87)	76.01 (41–106.6)
Mean height, m (range)	1.77 (1.75–1.79)	1.58 (1.51–1.72)	1.62 (1.51–1.79)
Mean BMI, kg/m² (range)	30.5 (27.75–33.27)	28.12 (17–33.56)	28.6 (17–33.56)
Median LT4, µg (range)	600 (300–900)	400 (225–1200)	400 (225–1200)
Median LT4, µg/kg	5.98 (3.52–8.44)	5.03 (3.21–29.26)	5.03 (3.21–29.26)
Median TSH, mU/L	19.05 (4.45–33.62)	8.08 (2.45–53.77)	8.08 (2.45–53.77)

Source: Rebolho ACO, et al., 2026.

Regarding hypothyroidism etiology, 1 case (10%) was secondary to total thyroidectomy for malignant thyroid neoplasm, 6 cases (60%) secondary to therapeutic radioactive iodine for Graves' disease, and 3 cases (30%) secondary to Hashimoto's thyroiditis.

At the initial interview, 6 patients (60% of the sample) were taking a medication known to interfere with levothyroxine absorption or metabolism. Among these, proton pump inhibitor use (omeprazole) was the most prevalent (used by 4 of 10 patients — 40%), followed by ferrous sulfate (20%) and calcium carbonate (10%).

Eight of the 10 patients (80%) had abnormal findings on EGD: 3 with esophagitis (30%), 4 with gastritis (40%) and 1 with duodenitis (10%); 50% of patients tested positive for *Helicobacter pylori.*

No patient was diagnosed with celiac disease. Only 1 patient (10%) had an initially positive anti-parietal cell antibody measurement, and the lactose tolerance test was positive in 4 patients (40%). Similarly, 40% of patients screened positive for depression. In 90% of cases one or more conditions known to be associated with refractoriness were identified (**Table 2**). Only one case (denominated case 5) initially screened negative for all pathologies.

Table 2 - Summary of the investigation, by case.

Case	Hypothyroidism etiology	LT4 dose (mcg/kg)	EGD findings	*H. pylori* screen	Lactose intolerance	M.I.N.I. Plus
1	Hashimoto's thyroiditis	11,25	Erosive Esophagitis	Positive	No	Positive
2	Post-surgical	4,59	Moderate Chronic Duodenitis	N/A	Yes	Negative
3	I-131 for Graves' disease	5,91	Erosive distal esophagitis and gastric polyp	Positive	No	Negative
4	I-131 for Graves' disease	4,65	Normal	N/A	Yes	Positive
5	Hashimoto's thyroiditis	14,63	Normal	Positive	No	Negative
6	I-131 for Graves' disease	36,56	Chronic Moderate Antral Gastritis	Positive	Yes	Positive
7	I-131 for Graves' disease	3,21	Oxyntic Chronic Gastritis	Positive	No	Negative
8	I-131 for Graves' disease	5,42	Chronic Antral Gastritis and Duodenitis	Negative	No	Positive
9	Hashimoto's thyroiditis	4,28	Oxyntic Chronic Gastritis	Positive	No	Negative
10	I-131 for Graves' disease	3,52	Chronic Antral Gastritis and Duodenitis	Negative	Yes	N/A

Legend: LT4 = levothyroxine. I-131 = iodine-131. N/A = test not applied or unavailable.
Source: Rebolho ACO, et al., 2026.

Regarding the levothyroxine absorption test, one patient did not complete the test and was therefore excluded from the analysis, and another patient lacked data for calculation of Criterion 1. After applying the 4 criteria, three of the 10 cases were considered to have malabsorption. Criterion 1 was positive in 3 cases, concordant with Criterion 2. Fifty-five percent of patients were positive for Criterion 3, and 66.66% of cases were positive for Criterion 4 (**Table 3**).

Table 3 - Levothyroxine absorption test results.

Case	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Result
1	**46,89%**	**18%**	1,13	**22,03%**	**Anormal**
2	115,82%	74,8%	**1,76**	**26,47%**	Normal
4	84,48%	79,56%	**1,45**	**31,47%**	Normal
5	**4,37%**	**13,39%**	**1,11**	55,08%	**Anormal**
6	106,97%%	297%	3,4	40,33%	Normal
7	**43,81%**	**12,51%**	**0,98**	**5,08%**	**Anormal**
8	107,12%	95,43%	2,09	52,42%	Normal
9	72,63%	187,68%	2,73	**31,52%**	Normal
10	N/A	80,95%	**1,39**	**24,72%**	Normal

Legend: Criterion 1 = percentage absorption of levothyroxine. Criterion 2 = percentage increase of total T4 during the test. Criterion 3 = increase in free T4. Criterion 4 = percentage decline in TSH. N/A = test not applied or unavailable. Abnormal = malabsorption by positivity of three or more criteria. Normal = adequate levothyroxine absorption. Altered results are highlighted. **Source:** Rebolho ACO, et al., 2026.

Selected case descriptions

Case 1: Male, 41 years old, hypothyroidism secondary to Hashimoto's thyroiditis. Medical history included diabetes mellitus, hypertension, dyslipidemia and depression. Initially on levothyroxine 75 mcg (Puran T4). Over follow-up the patient had progressive worsening of hypothyroid symptoms (dry skin, depressed mood, marked somnolence), depression and diarrhea 6–8 times daily. Multiple concomitant gastroenterology consultations were performed; aside from mild erosive gastritis found on EGD, other causes of malabsorptive GI disease were excluded. Notably, as depressive symptoms worsened, TSH values rose concomitantly despite progressively higher levothyroxine doses. After 3 years of follow-up the patient required psychiatric hospitalization and was diagnosed with bipolar affective disorder; following adjustment of psychiatric treatment, subsequent suppressed TSH values were documented, allowing reduction of levothyroxine dose from 1350 µg/day to 1000 µg/day. The patient was lost to follow-up six months after psychiatric hospitalization.

Case 5: Female, 30 years old, hypothyroidism due to Hashimoto's since age 12, using 600 mcg/day levothyroxine (≈14.66 mcg/kg). At study evaluation EGD, lactose tolerance test, anti-parietal cell antibodies, stool parasitology and duodenal biopsy were all negative, with only a positive *H. pylori* urease test. Despite this, the levothyroxine absorption test was positive for malabsorption. The patient had no comorbidities, was not taking oral medications, and did not screen positive for depression; intravenous levothyroxine was therefore indicated, with excellent control of hypothyroidism and symptoms. After 5 years of gastroenterology follow-up the patient was retested for gastrointestinal malabsorptive diseases and both the lactose tolerance test and investigation for atrophic gastritis became positive.

Case 7: Female, 32 years old, had Graves' disease without ophthalmopathy and received 30 mCi I-131 after two years of titrated tapazole therapy. She developed hypothyroidism 6 months after radioiodine and was started on levothyroxine 75 mcg, gradually increased to 225 mcg/day with highly variable TSH values. EGD showed mild chronic oxyntic gastritis; the remainder of the investigation was negative except for a positive levothyroxine absorption test indicating malabsorption. After eight years of follow-up she was diagnosed with congestive heart failure and pericardial effusion and was transferred to cardiology care, interrupting endocrinology follow-up.

Case 6: Male with hypothyroidism secondary to iodine therapy for Graves' disease, with the highest levothyroxine dose per kg in the series (36 µg/kg). This patient had multiple positive investigations: gastritis, positive *H. pylori* test, lactose intolerance and positive screen for depression. Notably, despite these findings the patient preserved levothyroxine absorption by all measured parameters, demonstrating the multifactorial nature present in many cases.

DISCUSSION

Although uncommon, refractory hypothyroidism causes considerable distress to both physicians and patients. A coherent and targeted evaluation of these patients is therefore essential. Despite the distress these

cases cause, publications offering a logical and sequential recommendation for investigation are scarce (ROBERTSON HM, et al., 2014). Furthermore, there is considerable heterogeneity in information and recommendations, as much of the literature derives from case reports or series (MAZETO GM, et al., 2022; VAN WILDER N, et al., 2017).

Intestinal parasitosis is a known factor interfering with levothyroxine absorption (ROBERTSON HM, et al., 2014). Considering its prevalence in developing countries, and because this condition is endemic in Brazil, all patients in this study received empirical treatment for intestinal parasitosis with albendazole (KATZ N, 2018; TORTORA A, et al., 2019). This measure was individualized to the reality of our population and there is no formal recommendation to perform such treatment in other contexts, especially without parasitological stool testing. However, there is recommendation that this condition be investigated in refractory cases because intestinal parasites activate gut T lymphocytes, which can disrupt the epithelial barrier and increase permeability, causing malabsorption and diarrhea, and may also interfere with gastric acidity and consequently the ability to dissolve levothyroxine (ROBERTSON HM, et al., 2014; TORTORA A, et al., 2019).

Our sample consisted predominantly of women, with 80% above normal weight and a mean BMI of 28.6 kg/m², a finding common to other studies (ROBERTSON HM, et al., 2014; GONZALES KM, et al., 2019). Gonzales, et al. (2019) re-viewed refractory hypothyroidism cases at the Mayo Clinic over four years, reporting a similar profile: 94% female with mean BMI 32.5 kg/m² (GONZALES KM, et al., 2019; CARON P, et al., 2025).

Regarding etiology of refractory hypothyroidism, the literature does not show clear pre-dominance of any single cause (VAN WILDER N, et al., 2017). Our sample comprised mainly patients with hypothyroid-ism secondary to iodine therapy for Graves' disease (6 of 10 patients). However, other authors found other etiologies as predominant (autoimmune cause in 37.6% of cases in Robertson et al. and 37.5% post-surgical cases in Gonzales et al. (ROBERTSON HM, et al., 2014; GONZALES KM, et al., 2019; KATZ N, 2018; CARON P, et al., 2025).

Our study showed that after empirical treatment for intestinal parasitosis, 90% of cases still had some factor interfering with levothyroxine response: 60% were using medications that interfere with absorption or metabolism of levothyroxine and 80% had some abnormality on upper endoscopy. This supports that cases of refractoriness without a defined cause are rare (MAZETO GM, et al., 2022; JONKLAAS J, et al., 2014; VAN WILDER N, et al., 2017).

Another interesting finding, lacking comparable data in other studies, was the importance of psychiatric evaluation. Although considered a screening tool, the M.I.N.I. Plus detected that 4 of 10 patients met screening criteria for depression (SHEEHAN DV, et al., 1998). While it is known that inadequately controlled hypothyroidism negatively affects mood, depressive disorders may also reflect adherence problems. This relationship is suggested by the finding that among the four patients with positive depression screening, only one was considered to have malabsorption by the levothyroxine absorption test (MAZETO GM, et al., 2022; VAN WILDER N, et al., 2017; LIPS DJ, et al., 2004; BALLA M, et al., 2015).

Approaching suspected nonadherence can be delicate and problematic, and a non-confrontational approach is recommended (ROBERTSON HM, et al., 2014; SHEEHAN DV, et al., 1998). Extensive counseling about correct and regular use of medication and discussion of the deleterious effects of inadequate treatment are essential. When diagnostic doubt remains, the levothyroxine tolerance/absorption test (LT4 absorption test) is recommended (MAZETO GM, et al., 2022; VAN WILDER N, et al., 2017, LIPS DJ, et al., 2004; BALLA M, et al., 2015).

Although the levothyroxine absorption test is known as an ancillary tool in diagnosing mal-absorption or pseudo malabsorption, the best methodology for performing it and interpreting results is uncertain. The dose administered can vary according to patient weight or be a fixed 1000 µg dose (GHOSH S, et al., 2020). Tests last from 4 to 24 hours (MAZETO GM, et al., 2022; GONZALES KM, et al., 2019; CARON P, et al., 2025; VAN WILDER N, et al., 2017). While it seems established that total T4 rises during the test (generally at the second hour after administration), the role of the free T4 curve and especially TSH behavior are much debated (MAZETO GM, et al., 2022; CARON P, et al., 2025; VAN WILDER N, et al., 2017; WALKER JN, et al., 2013).

Gonzales KM, et al. (2019) suggest using the percentage absorption of total T4 calculated by a specific formula that adjusts for BMI and the test dose (GONZALES KM, et al., 2019; CARON P, et al., 2025); this formula was initially suggested by Sherman et al. in 1994 (SHERMAN SI, et al., 1994). By this parameter, a normal percentage absorption of T4 is suggested to be > 60%. Several authors cite this reference as appropriate, although no prospective randomized study on the topic exists (GONZALES KM, et al., 2019).

Comparing the criteria, both levothyroxine percentage absorption and percentage increase in total T4 (Criteria 1 and 2) yielded similar results: all cases of malabsorption were positive for both. The free T4 increase (Criterion 3) and especially the TSH behavior (Criterion 4) were very variable and discrepant.

Interestingly, regarding TSH behavior during the test, a reduction was observed in all patients even though the test lasted only 4 hours. While some studies suggest that TSH may be used as a parameter and some authors recommend a percentage reduction of 40% as a cutoff, it cannot be stated that this is statistically robust since TSH is known to take 4–6 weeks to decrease after levothyroxine administration. Moreover, there are few studies on TSH behavior during the test (MAZETO GM, et al., 2022; VAN WILDER N, et al., 2017). Therefore, the lack of a statistically tested and globally accepted protocol limits its uncontextualized use.

The application of four criteria in interpreting the levothyroxine absorption test aimed to broaden understanding of hormonal dynamics during the test. Although statistical significance cannot be asserted due to study methodology and the small sample size, our results suggest that using multiple criteria is a broad and coherent way to differentiate pseudo from true malabsorption, a finding consistent with other data in the literature (WALKER JN, et al., 2013).

It is important to note that most published studies focus on a single contributing factor for refractoriness, whether gastrointestinal disease, pseudo malabsorption, drug influence or comorbidities (BENSEÑOR IM, et al., 2021; GHOSH S, et al., 2020). Similarly, many publications describe different ways to perform the levothyroxine absorption test, each with its own protocol and interpretation. Studies that take a multicausal approach are rare. Our study shows that in a single case one or more factors may be involved in lack of clinical response, highlighting the seriousness and complexity of this type of investigation and supporting the importance of multidisciplinary management involving gastroenterologists, endocrinologists and even psychiatrists.

CONCLUSION

In our case series, refractory hypothyroidism displayed a multifactorial character, with frequent association of more than one factor contributing to inadequate TSH control. Although nonadherence remains the principal cause, other factors, such as drug interferences and gastrointestinal conditions, often coexist, reinforcing the importance of an individualized, multidisciplinary approach that addresses all possible etiologic contributors. Analysis of the different criteria used for the levothyroxine absorption test showed that the first two evaluated parameters present greater concordance with each other, while the later criteria showed greater variability and therefore lower reproducibility. Finally, systematic application of the absorption test revealed that most patients have adequate levothyroxine absorption, reinforcing the hypothesis that inadequate adherence to therapy remains the principal determinant of refractory hypothyroidism in clinical practice.

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