

Diagnosis and treatment of levothyroxine pseudomalabsorption

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ABSTRACT

Many causes of malabsorption of levothyroxine in patients with hypothyroidism have been thoroughly described in literature. Pseudomalabsorption, poor compliance of the patient with the therapy regime, is the most common cause of failure of levothyroxine therapy. Pseudomalabsorption is characterised by a deficient diagnostic process, patient denial and difficulties in treatment. The present article provides guidelines in diagnosing and treating pseudomalabsorption in hypothyroidism.

INTRODUCTION

Thyroid diseases are common in the endocrinology clinic.¹ Well-documented clinical trials on therapeutic options are available in the case of hypothyroidism.^{2,3} Prevalence of hypothyroidism amongst adults is 15.9 out of 1000 persons.¹ As a result of dysfunction of the thyroid gland, the free thyroxine (fT₄) is characteristically low, sometimes even reduced to undetectable concentrations. The thyroid-stimulating hormone (TSH) serum value is elevated as a result of the regulatory negative feedback mechanism. Patients with hypothyroidism are supplemented with synthetic thyroxine hormone (i.e. levothyroxine, LT₄) in oral doses to achieve physiological fT₄ serum levels. The mean treatment dosage LT₄ is 1.6 µg/kg bodyweight a day.⁴ The results with this dosage are adequate and reproducible. When, however, large amounts of LT₄ are needed for hypothyroidism treatment, the cause should be investigated by the clinician. Many causes of LT₄ malabsorption are known and discussed in literature (table 1 on the next page).

Common causes are gastrointestinal diseases, liver diseases, pancreatic diseases, certain gastrointestinal surgical procedures, drugs and dietary interactions, heart disease or pregnancy.⁵⁻³⁰ By far the most common cause of malabsorption is, however, poor or noncompliance with oral LT₄ treatment by the patient.^{31,32} Even with this knowledge, the above-mentioned possible causes should initially be considered.

The aim of the article is to provide guidelines for the physician for the investigation of malabsorption of LT₄. Probable causes and their specific investigations are discussed. In addition, possible techniques to detect pseudomalabsorption are proposed. For this purpose a typical case of pseudomalabsorption is presented.

CASE PRESENTATION

A 33-year-old female patient presented to the outpatient endocrinology clinic with the typical symptoms of hyperthyroidism (i.e. agitation, weight loss, increased sense of hunger and diarrhoea). Initial laboratory blood investigations showed an increased fT₄ serum concentration (108.3 pmol/l) and TSH concentrations below detection level (<0.05 mE/l) (figure 1). Ultrasonography of the thyroid gland showed inhomogeneous lobes without cysts or nodules. The right lobe measured 2.4 x 2.1 x 4 and the left lobe 1.5 x 2.0 x 3.0 cm. Laboratory tests for thyroid-stimulating immunoglobulins were positive and the diagnosis of Graves hyperthyroidism was made. Treatment was started with thiamazole and propranolol in daily doses. After four months of treatment normalisation of fT₄ and

Table 1
Biological causes of levothyroxine malabsorption

HYPOTHYROIDISM	
Gastrointestinal diseases	Coeliac disease ³⁸
	Lactose intolerance ³⁹
	Vitamin B ₁₂ deficiency ⁴⁰
Liver diseases	Intestinal infections (<i>Giardia lamblia</i>) ⁴¹
	Cirrhosis
	Obstructive liver disease ⁴²
Pancreatic diseases	Pancreatic insufficiency ^{5,6}
Previous gastrointestinal surgery	Jejunostomy ⁹
	Jejunioileal bypass ^{7,8}
	Short bowel syndrome ¹⁰
Medication interference	Cholestyramine ¹⁴
	Colestipol ¹⁵
	Aluminum hydroxide- containing antacids ¹⁶
	Ferrous sulphate ^{17,18}
	Sucralphate ¹⁹
	Propranolol ²⁰
	Laxatives ²¹
	Calcium carbonate ^{22,23}
	Lovastatin ²⁴
	Bile acid sequestrants ¹⁴
	Activated charcoal ⁴³
	Anion exchange resins ⁵
	Phenytoin ²⁶
	Phenobarbital ²⁶
	Carbamazepine ²⁷
	Rifampin ²⁸
	Amiodarone ²⁹
	Oestrogen therapy ¹¹
Dietary interference	Walnuts ¹²
	Soybean ¹³
	Prunes ¹²
Heart disease	Herbal remedies ³⁰
	Congestive heart failure ⁵
Pregnancy ¹¹	

Biological causes of levothyroxine malabsorption as discussed in medical literature.

TSH to the physiological level had still not been reached. The decision was made to inhibit thyroid functioning with radioactive iodine. Scintigraphic visualisation showed a relatively enlarged thyroid gland with intense homogeneous activity and a 24-hour radioactive iodine ¹³¹I (J131) uptake of 74%. The patient was given 15 mCi radioactive iodine orally. Concordantly, the patient developed hypothyroidism with low fT₄ and high TSH serum concentrations concomitant with the characteristics of attenuated thyroid gland functioning: weight gain, fatigue, myxoedema,

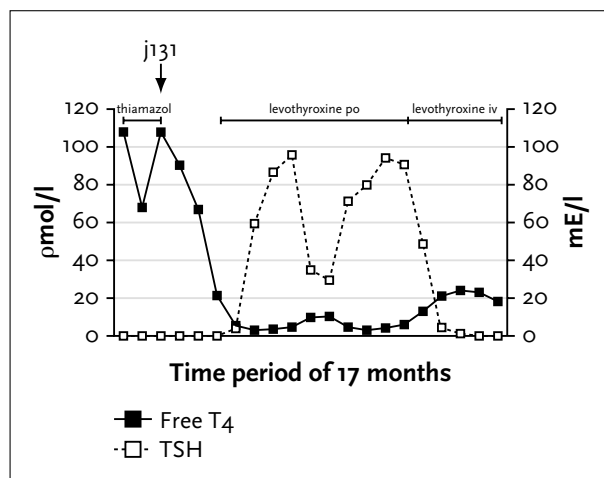


Figure 1
Serum concentrations free T₄ and TSH

muscle cramps and constipation. The patient was treated with LT₄ orally for the acquired endocrine dysregulation. Normalisation of the fT₄ and TSH concentrations was not reached during treatment with oral LT₄. Even high dosages of 400 µg per day were not successful. Malabsorption of LT₄ through adjunctive medicine or supplement use was excluded. Gastrointestinal, liver or pancreas diseases were excluded through laboratory investigations. Additionally, the patient had not had previous gastrointestinal surgery. Congestive heart failure and pregnancy were not present either. Consequently, the patient was admitted to hospital to investigate the cause of the unsuccessful treatment more thoroughly. Intravenous LT₄ treatment was started to treat the symptoms of hypothyroidism and, additionally, investigate the option of an autoimmune action against thyroxine hormone. Immunological investigations targeted on intestinal malabsorption, such as lactose intolerance or lactase deficiency, were negative. Antibodies against gliadine and endomysium were not present. Intestinal germs as *Giardia lamblia* were excluded. Normal fT₄ and TSH serum levels were reached with 200 µg LT₄ intravenously within 12 days. Moreover, the symptoms diminished within this period. The physical state of the patient improved greatly and oral LT₄ treatment was tried once more. However, in one week the endocrinological state of hypothyroidism was reached again. The possibility of malabsorption by defective compliance (i.e. pseudo-malabsorption) was the most probable cause at this stage. To prove pseudomalabsorption an LT₄ absorption test was performed. After an overnight fast the patient was not allowed to ingest anything except fluids during the duration of the test. An oral dose of 1000 µg LT₄ was given under the auspices of the physician. The patient was observed by a trained nurse throughout the test. Blood samples were obtained prior to, and two, four and six hours following

the bolus ingestion to investigate total T_4 (TT_4), fT_4 and TSH serum levels. *Figure 2* shows the results of the absorption test as performed in the presented case. The patient started with laboratory signs coinciding with hypothyroidism. Immediate fT_4 serum increase is seen following LT_4 ingestion, with the maximum serum level within the first 120 minutes, known to be a normal time interval.³³ The results therefore showed a normal absorption of LT_4 by the small intestines, and malabsorption was excluded; pseudomalabsorption was proven.

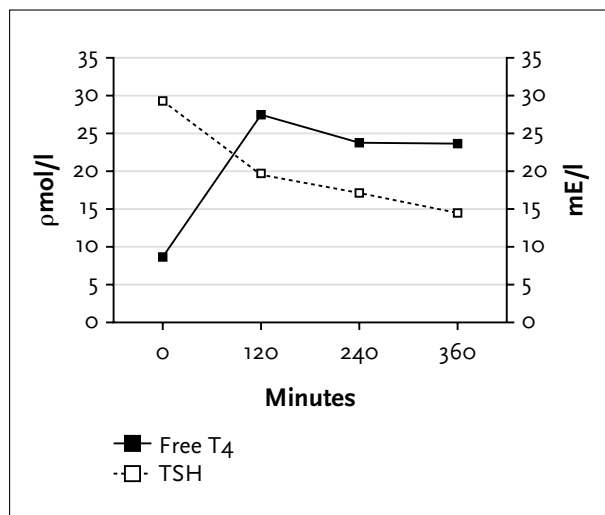


Figure 2
Serum free T_4 and TSH response to bolus levothyroxine administration

DISCUSSION

A case such as this is rarely seen in the endocrinology clinic, although it is typical in its essence. The clinician was challenged with a situation of hyperthyroidism, which did not respond to treatment. The choice was made to improve the condition of the patient by treatment with radioactive iodine, after which hypothyroidism developed. This endocrinological dysregulation did not improve despite much effort from the clinician and high dosages of oral LT_4 . Pseudomalabsorption is part of the differential diagnosis of every doctor, although the great disadvantages of hypothyroidism for the patient (such as fatigue, constipation, weight gain up to 27 kg in 12 months) would seem reason enough for therapy compliance. However, from the Munchausen syndrome it is known that patients are capable of low compliance and exposure to serious complications of unnecessary medical and surgical

procedures for doubtful reasons.³⁴ Before the diagnosis pseudomalabsorption can be made, all possible causes for malabsorption should be investigated (*table 2*). The combination of clinical presentation, thorough history taking, exploration of diet and drugs and primary laboratory investigations is able to exclude most known causes of LT_4 malabsorption. For the most common cause, pseudomalabsorption, an LT_4 absorption test is diagnostic. The absorption test is performed with 1000 to 2000 μg LT_4 orally with control of proper ingestion and possible surreptitious regurgitation.^{4,33,35} LT_4 uptake is greater when fasting, so patients are kept fasting in advance of the absorption test.⁴ Normally 70 to 100% of the administered dose is absorbed within the gastrointestinal tract, with maximal serum levels reached within two to four hours following ingestion.^{4,33,35} It should be noted that the intestinal uptake of LT_4 is variable among euthyroid subjects.^{4,33,35} A TT_4 distribution volume of 13 to 17% and a maximum TT_4 serum level rise of 116 nmol/l (1 nmol T_4 is about 750 ng) reveals nearly 100% LT_4 absorption in our patient.^{4,35} However, even the normalisation of fT_4 and TSH serum levels following LT_4 ingestion prove the absence of an intrinsic absorption defect. An absorption test as performed is able to distinguish between pseudo and real malabsorption, even between different forms of intrinsic absorption defects.^{33,36} From our results, we concluded that the hypothyroid state of our patient could be explained by pseudomalabsorption of LT_4 , i.e. poor treatment compliance.

Treatment of LT_4 pseudomalabsorption is hampered by the general poor compliance and absence of recognition of the patient. The poor compliance is often due to psychiatric

Table 2
Diagnostic process of pseudomalabsorption

HYPOTHYROIDISM	
Exclude	Gastrointestinal diseases
	Liver diseases
	Pancreatic diseases
	Previous gastrointestinal surgery
	Medication interference
	Dietary interference
	Intraluminal germs
	Congestive heart failure
	Pregnancy
Test pseudomalabsorption	Levothyroxine absorption test
	Intravenous levothyroxine treatment

In the case of untreatable hypothyroidism, unresponsive to high-dose levothyroxine treatment, the possibility of a biological cause should be explored. If no indications for biological causes are found, the possibility of poor patient compliance should come forward, and could be tested through a levothyroxine absorption test or intravenous levothyroxine treatment.

disorders of a depressive nature, which are not uncommon in severe hypothyroidism, although few patients exhibit true psychopathology.^{4,35,37} Treatment, therefore, needs unusual measures. Psychiatrists recommend that patients presenting the psychopathological features of a Munchhausen syndrome or factitious disorder should be observed conservatively.³⁴ Confronting the patient with the doubts of the clinician about the level of compliance could mark and mutilate the patient for life, without improvement in the treatment. Subtle handling of the patient is required. On the other hand, the state of hypothyroidism should be improved. Several treatment strategies are possible. Parenteral infusion of LT_4 has shown to be useful in (pseudo)malabsorption.³⁶ Supervised oral LT_4 ingestion is a less invasive alternative. Patients are prone to drop out of both treatment regimes. Informing the patient about the effects of poor compliance does improve the five-year compliance follow-up in some patients though.⁴ Our first objective was to diminish the disadvantages of hypothyroidism by intravenous LT_4 treatment. We prepared the patient for a restart of oral LT_4 intake within the process of feeling better physically. When this proved to be unsuccessful an absorption test was performed. The dose given was in line with a one-week dose. The patient was therefore subscribed one dose of LT_4 weekly. The fT_4 and TSH serum levels normalised and the patient continued to do well during follow-up. In conclusion, pseudomalabsorption is characterised by a troubled diagnosis process, absence of recognition of the patient and difficulty in treatment. The present article provides guidelines in diagnosing and treating LT_4 pseudomalabsorption in hypothyroidism.

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