Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 63; Numer/Number 4/2012
ISSN 0423–104X

The influence of lactose intolerance and other gastro-intestinal tract disorders on L-thyroxine absorption

Wpływ nietolerancji laktozy i innych zaburzeń organicznych oraz czynnościowych przewodu pokarmowego na wchłanianie L-tyroksyny

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Abstract

The preferred treatment for hypothyroidism is oral levothyroxine (LT4) ingestion, in doses that ensure a sustained state of hormonal balance. Many different factors may significantly influence the absorption of LT4, including: interval between the ingestion of the drug and the last meal, eating habits, and different functional and organic pathologies of the gastro-intestinal tract.

The main purpose of this paper is to review and systematise the available literature on the subject of the influence of different malabsorption syndromes on the effectiveness of LT4 preparations.

The need to use high LT4 doses in the substitutional treatment of hypothyroidism is often the very first sign of one of the pathologies that are connected with malabsorption syndrome, which might have been asymptomatic and undiagnosed previously. Patients who require more than 2 μg/kg body weight of LT4 per day, with constantly increased thyrotropin level, should be diagnosed with the suspicion of pseudomalabsorption or real absorption disorder. An LT4 absorption test, using high doses of LT4, may be useful in the diagnosis of pseudomalabsorption. After excluding non-compliance, the differential diagnosis should include such disorders as lactose intolerance, coeliac disease, atrophic gastritis, *Helicobacter pylori* infection, bowel resection, inflammatory bowel disease, and parasite infection.

Where there is a diagnosis of lactose intolerance, both a low lactose diet and a lactose-free LT4 preparation should be administered to restore euthyroidism or make it possible to decrease the dose of the LT4 preparation. In coeliac disease, a gluten-free diet usually allows a normalisation of the need for LT4, as do eradication of the *H. pylori* infection or parasite colonisation. In cases of atrophic gastritis or inflammatory bowel disease, treating the underlying diseases and regaining the state of remission may improve the absorption of LT4. In patients after gastro-intestinal tract surgery, a dose of LT4 higher than that typically used is needed to restore euthyroidism. **(Endokrynol Pol 2012; 63 (4): 318–323)**

Key words: *hypothyroidism, L-thyroxine, malabsorption, lactose intolerance, coeliac disease*

Streszczenie

Metodą z wyboru w leczeniu niedoczynności tarczycy jest doustne podawanie L-tyroksyny (LT4) w dawkach pozwalających na utrzymanie u pacjenta stanu równowagi hormonalnej. Wymienia się wiele czynników, które mogą w istotny sposób wpływać na wchłanianie preparatu LT4, do których należą między innymi: korelacja czasowa przyjęcia leku i ostatniego posiłku, niektóre nawyki żywieniowe, a także różne organiczne i czynnościowe patologie przewodu pokarmowego. Głównym celem niniejszej pracy jest przegląd i usystematyzowanie literatury dotyczącej wpływu różnorodnych zaburzeń wchłaniania na skuteczność podawanych preparatów LT4.

Konieczność stosowania dużych dawek LT4 w leczeniu substytucyjnym niedoczynności tarczycy często jest pierwszym objawem jednego z zespołów chorobowych, przebiegających z zaburzeniami wchłaniania, które mogą być skąpoobjawowe i wcześniej mogły pozostawać nierozpoznane. Pacjenci otrzymujący LT4 w dawce większej niż 2 μg/kg mc./dobę, z przetrwale podwyższonymi stężeniami tyreotropiny, powinni być poddani diagnostyce w kierunku pozornych lub rzeczywistych zaburzeń wchłaniania LT4. Test wchłaniania LT4 z wykorzystaniem jej dużej dawki jest przydatny w diagnozie pozornych zaburzeń wchłaniania. Po wykluczeniu braku współpracy ze strony pacjenta w diagnostyce różnicowej należy uwzględnić takie patologie, jak: nietolerancja laktozy, celiakia, zanikowe zapalenie błony śluzowej żołądka, infekcja *Helicobacter pylori*, stan po resekcji jelita, nieswoiste zapalenie jelita czy, wreszcie, infekcje pasożytnicze.

W przypadku potwierdzenia nietolerancji laktozy należy zastosować preparat LT4 pozbawiony laktozy oraz dietę bezlaktozową w celu uzyskania eutyreozy bądź możliwości zmniejszenia dawki preparatu LT4. W celiakii zastosowanie diety bezglutenowej zwykle skutkuje normalizacją zapotrzebowania na LT4, podobnie jak eradykacja infekcji bakteryjnej *H. pylori* czy pasożytniczej. W przypadku zanikowego zapalenia błony śluzowej żołądka czy nieswoistego zapalenia jelita leczenie choroby podstawowej i uzyskanie remisji może doprowadzić do poprawy wchłaniania LT4. U chorych po operacjach jelit zwykle konieczne jest stosowanie ponadstandardowych dawek LT4 w celu uzyskania eutyreozy. **(Endokrynol Pol 2012; 63 (4): 318–323)**

Słowa kluczowe: *niedoczynność tarczycy, L-tyroksyna, zaburzenia wchłaniania, nietolerancja laktozy, celiakia*

Introduction

Irrespective of the cause, the external replacement of hormonal deficiency constitutes the basic method of hypothyroidism treatment. Oral preparations available commercially contain as an active substance either L-thyroxine (LT4) sodium or its combination with L-triiodothyronine. The method of choice in hypothyroidism treatment is oral administration of LT4 in doses that enable the patient's hormonal balance to be maintained [1].

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There are many difficulties in obtaining and sustaining euthyroidism in a hypothyroid patient that a practicing clinician may come across. In patients treated with a standard LT4 dose, when a state of compensation is not achieved, two potential causes of the phenomenon should be considered: firstly, patient non-compliance, and secondly, drug malabsorption in the alimentary tract.

Patient non-compliance, also referred to as pseudomalabsorption, remains the most frequent cause of failure to achieve euthyroidism despite large doses of LT4 (> 2 μg/kg body weight).

L-thyroxine is absorbed from the lumen of the alimentary tract within hours from the moment of administration, mainly in the jejunum and ileum and, to a lesser degree, in the duodenum. Of crucial importance is the role of acidity of gastric juice; therefore, it is recommended that preparations be taken on an empty stomach to maximise the dose absorbed [2, 3].

There are many factors that can significantly affect LT4 absorption, such as the time elapsed between the drug administration and the last meal, certain eating habits, as well as various organic and functional pathologies of the alimentary tract.

It has been proven that absorption is optimal when LT4 is taken on an empty stomach, whereas it is not so effective when the preparation is administered directly with a meal [4–6].

As a standard, LT4 should be taken at least 30 minutes before breakfast; such a recommendation can be found on the leaflets contained in medicine boxes. There have also been studies suggesting a similar efficacy of the dose taken before going to sleep; the data available, however, is not definitive [7, 8].

Drug interactions must also be taken into consideration. Some medications, such as raloxifene, drugs binding bile acids, cholestyramine, colestipol, proton pump inhibitors, orlistat, sevelamer, and preparations containing aluminium, iron or calcium can significantly reduce LT4 absorption. Thus it is important that those drugs and LT4 should be administered a few hours apart [9–15].

A replacement LT4 dose should always be adjusted individually. The dose, once established, can be changed during treatment, even in the same patient. The factors significantly influencing LT4 requirement in a given patient include: progress of the disease, an increase or decrease in body weight, pregnancy, and the use of hormonal drugs such as oral contraception or hormone replacement therapy. Moreover, various additional ingredients found in different LT4 preparations can have an impact on their absorption; therefore, when the absorption of the LT4 drug is disturbed, it is well worth trying to replace it with another one made by a different manufacturer. Studies have shown that LT4 preparations made by different manufacturers can have different bioavailability [16–18]. However, interpreting some of these studies can be difficult owing to, among other things, the heterogeneity and the small size of the group investigated, a single measurement of drug concentration in the blood, a different level of hypothyroidism, and a lack of correlation in reference to endogenous free thyroxine (FT4) concentration. It is because of this last-named factor that labelling of the products as bioequivalent is not justified. Ignorance of the above fact in the procedures recommended by the FDA can result in iatrogenic hyper- or hypothyroidism when a preparation is replaced without further screening and the establishment of a new dose. The differences in bioavailability of preparations of various brands do not result from those in the active substance (which is LT4) but from the so-called inert ingredients. These, by definition, should not have an impact on a patient's body but, at the same time, can considerably modify drug absorption. Lactose is frequently used as an adjuvant [19].

The other factors responsible for LT4 absorption are eating habits, which result in increased LT4 doses in such patients. Grapefruit juice minimally slows down LT4 absorption [20], while papaya consumed in large amounts has a significantly negative influence on the degree of drug bioavailability [21], as does a diet rich in fiber [22]. *In vitro* studies have shown dose-dependent, non-specific LT4 absorption by wheat bran and soya preparations [23]. On the other hand, it is interesting to note that excessive coffee consumption results in decreased LT4 absorption [24].

As has already been said, the bioavailability of the preparations administered is significantly influenced by concomitant organic and functional alimentary tract disorders.

The main aim of this paper is a review and systematisation of the literature concerning the impact of different malabsorption phenomena on the effectiveness of LT4 preparations.

Lactose intolerance

The frequency of lactose intolerance among adult Caucasian patients ranges in the literature from 7% to as much as 20% of a population, which makes it a relatively common pathology. In Poland, according to different studies, hypolactasia in adults occurs in 17.39–37.50% of the population. Lactose intolerance (due to intestinal lactase deficiency) can be primary (genetics-related) or secondary (concomitant with many gastrointestinal tract diseases, very often coeliac disease); persistent or transient when remission of the main disease can reinstate the enzyme's normal activity and eliminate the symptoms of intolerance.

Primary lactose intolerance occurring in adults is inherited autosomally recessively and is the most frequent form of lactose deficiency. The activity of the enzyme decreases in proportion to age, though total lack of lactose production is rare. The presenting symptoms (e.g. abdominal discomfort or pain, nausea, vomiting, diarrhoea, constipation, flatulence, borborygmus, body weight loss) are diverse and non-specific. They are derived from lactose fermentation by colon bacteria and can often resemble the symptoms of irritable colon syndrome. It is worth remembering that irritability to lactose is very individual and changes with age [19, 25, 26].

It should be particularly borne in mind that lactose often is the so-called auxiliary ingredient (indifferent, as a rule, to the body) used in many commercially available medicaments [27], and also in those preparations in which LT4 is an active substance. Even small amounts of lactose in patients with intolerance can result in local digestion and absorption disorders, which is unfavourable for the absorption of the active substance itself. The amount of lactose consumed can be substantial and give clinical symptoms, especially in the elderly, in whom polypragmasy is not uncommon.

The diagnosis of lactose intolerance is made using interview data, an elimination diet and various tests (hydrogen test, glucose concentration assessment after standardised lactose dose administration, as well as small intestine biopsy) [25].

The literature data provides examples of a negative impact of lactose in medical preparations on absorption of various drugs, including psychoactive drugs [19]. One example is that of a female patient with LT4 malabsorption related to lactose intolerance. She had primary hypothyroidism with permanently elevated thyrotropin (TSH) levels. When it comes to gastrointestinal symptoms, she complained only of diarrhoea occurring sporadically over the previous 7–8 years. Increasing the dose to 900 μg and additional therapy with triiodothyronine did not result in the restoration of euthyroidism. Malabsorption diagnostic tests, including lactose absorption test, revealed lactose intolerance. LT4 intravenous therapy resulted in the normalisation of thyroid hormones concentrations; then, an LT4 lactose-free preparation and a lactose-free diet were used. Three months later, the symptoms regressed and biochemical euthyroidism was achieved [3].

Coeliac disease

Coeliac disease, an autoimmune ailment of the small intestine found in genetically predisposed patients, is characterised by chronic dietary gluten intolerance. It can manifest itself at any age [26] and the literature provides numerous examples of cases in which coeliac disease resulted in LT4 malabsorption.

One of the first such cases was a female patient after thyreoidectomy who was diagnosed with coeliac disease at 68 years of age while being investigated for the causes of LT4 and alphacalcidol malabsorption [28]. The patient's history revealed persistent hypocalcaemia, chronic diarrhoea, anaemia and hypoalbuminaemia. There are also cases of patients in whom LT4 malabsorption was concomitant with non-specific symptoms of coeliac disease such as body weight loss, anaemia, electrolyte disorders (hypocalcaemia, hypomagnesaemia) or osteopenia [29, 30]. In some hypothyroid patients 'resistance' to LT4 treatment is the first, and practically only, symptom suggestive of malabsorption in coeliac disease, with normal haemoglobin, electrolyte and albumin levels and the absence of any clinical indicators in the form of gastrointestinal symptoms [31, 32]. In all those cases, when a gluten-free diet was employed, daily LT4 requirement was reduced and TSH levels returned to normal.

A study by Jiskra et al. showed that patients with hypothyroidism related to autoimmune thyroiditis, in whom the replacement daily LT4 dose was 125–200 μg, presented higher concentrations of anti-gliadin IgA antibodies than those in whom the daily LT4 dose was lower (50–100 μg) [33].

Virili et al. carried out the first systematic assessment of an LT4 dose in replacement treatment of patients with diagnosed hypothyroidism in the course of chronic thyroiditis and coeliac disease. The study group consisted of 35 patients with hypothyroidism in the course of Hashimoto's thyroiditis and non-classic coeliac disease. The analysis focused on the LT4 dose necessary to obtain target TSH values before the introduction of a gluten-free diet (in all patients) and then in 21 patients on a gluten-free diet (the remaining ones were non-compliant). The LT4 requirement was compared to a control group of 68 patients with hypothyroidism in the course of Hashimoto's disease, in whom coeliac disease and other ailments that might contribute to malabsorption were excluded. In patients with isolated hypothyroidism, target TSH values (median 1.02 mIU/L) were obtained in all persons after 5 ± 2 months of treatment, with a median daily LT4 dose of 1.31 μg/kg body weight. At the same time, using a similar LT4 dose, patients with hypothyroidism and coeliac disease manifested higher TSH values (median 4.2 mIU/L). In 21 patients, target TSH values (median 1.25 mIU/L) were obtained over a period of 11 ± 3 months of a gluten-free diet; there was no need to increase the LT4 dose (median 1.32 μg/kg body weight daily). In the remaining 14 patients, who were not on

a diet, target TSH values (median 1.54 mIU/L) were obtained following an LT4 dose increase (median 1.96 μg/kg body weight daily, +49%, $p < 0.0002$) compared to patients with hypothyroidism but without coeliac disease. The study showed that non-classic coeliac disease increased LT4 requirement in replacement therapy and that target TSH values can be attained by the introduction of a gluten-free diet or an increase of LT4 dose. It is worth noting that LT4 malabsorption can be the first signal of coeliac disease [34].

The problem of concomitant hypothyroidism related to chronic thyroiditis and coeliac disease is quite common, because the underlying factor in both cases is an autoimmune process as well as a genetic predisposition. Thyroid diseases are often accompanied by the presence of specific antibodies, including those against thyroglobulin, thyreoperoxidase, and TSH receptor, as well as such endogenous substances as myosin, troponin, tropomyosin and myoglobin [35]. It has been shown that coeliac disease occurs significantly more often in patients with Hashimoto's disease compared to the overall population, whereas Hashimoto's disease, in turn, is diagnosed in as many as 21% of patients with coeliac disease [36]. Suspected coeliac disease must be verified using serological (tissue transglutaminase and antiendomysial antibodies) and morphologic tests (endoscopic and histopathological confirmation of enteral villi atrophy) [26]. The estimated LT4 requirement in total hypothyroidism is 1.0–2.0 μg/kg body weight daily. The values quoted in the paper by Virili et al. come within this range, but in patients with concomitant coeliac disease they are significantly higher compared to those without malabsorption. While increasing the LT4 dose in malabsorption patients is not a big problem, we think that from a clinical point of view it is important to stress the finding that is potentially indicative of a diagnosis of non-classic coeliac disease, the first noticeable clinical manifestation of which can be LT4 malabsorption. Making a diagnosis of classic coeliac disease is not usually difficult; however, it is the non-classic form, especially without concomitant typical gastrointestinal symptoms, diagnosed only in adulthood, that does create problems, and very often the disease goes undiagnosed for a long time. One should remember that in adults with coeliac disease, parenteral symptoms are prevalent such as dermal symptoms (herpetiform dermatitis), anaemia, genito-urinary tract symptoms (delayed puberty, fertility disorders, early menopause), neurological symptoms (epilepsy, migraine, depression, ataxia) and other (muscle weakness, osteoporosis, tetany, short stature, low body weight, enamel hypoplasia). Estimates put the ratio of asymptomatic coeliac disease at 1:100–1:300 in a given population, whereas the classic form of the disease with gastrointestinal symptoms is more than ten times less frequent [34].

In patients with autoimmune hypothyroidism and with no other indications, screening for coeliac disease is not recommended. In those, however, in whom euthyreosis is attained only after a daily LT4 dose of more than 2 μg/kg body weight, tests for coeliac disease should be carried out.

In a recent study, Collins et al. compared the LT4 requirement in replacement therapy in patients with hypothyroidism and concomitant coeliac disease, against the requirement in those with isolated hypothyreosis. The study showed that the LT4 requirement in the former group, before introduction of a gluten-free diet, was 2.6 μg/kg body weight compared to 1.3 μg/kg body weight in the latter group, with coeliac disease treatment resulting in a significant decrease in LT4 requirement to 1.89 μg/kg body weight [37].

Atrophic gastritis and *Helicobacter pylori* infection

Chronic atrophic gastritis is another common factor modifying LT4 absorption. It is connected with gastric mucosa colonisation by *H. pylori*, and could affect as much as 50% of the world's population. The main source of LT4 malabsorption in this case is the reduced acidity of gastric juice. During *H. pylori* infection, urease produced by the microorganisms neutralises the acidity of gastric juice [38]. Centanni et al. have proven that patients with multinodular goitre and *H. pylori* infection (a 22% increase), with atrophic gastritis (a 27% increase), or with both diseases occurring simultaneously (a 34% increase), require LT4 doses that are 22–34% higher to obtain the target TSH values. In a prospective observation in patients who developed *H. pylori* infection at that time, LT4 requirement increased significantly, the effect being almost completely reversible when the infection was eradicated. A similar phenomenon was observed in patients treated with proton pump inhibitor (omeprazole); in order to maintain target TSH values, it was necessary to increase the LT4 dose by 37% [39].

In a recent study, Bugdaci et al. assessed the impact of *H. pylori* infection eradication on TSH and thyroid hormone levels in patients with hypothyroidism who did not respond earlier to large doses of LT4. All patients manifested a significant decrease in TSH concentrations; 21% of them, however, developed iatrogenic hyperthyroidism. This leads us to conclude that in patients taking high LT4 doses in replacement therapy of hypothyroidism, *H. pylori* infection eradication can result in a significant improvement of LT4 absorption which, therefore, necessitates a further LT4 dose adjustment (reduction) [40].

Bowel resections

In recent years, owing to the so-called epidemic of obesity, there has been a growing amount of bariatric surgery, the aim of which is to facilitate body weight reduction in the most obese patients. The method has become increasingly popular following the development of laparoscopic techniques. Its effectiveness has also been confirmed by numerous literature reports [41]. Studies have also shown that such surgical procedures have an influence on drug absorption. Evidence pointing to a decreased absorption of various preparations was presented in 15 out of 22 investigations dealing with an analysis of patients who underwent jejunoileostomy (Kremen's operation), and in one out of three studies concerning an analysis of patients after gastroplasty. In one study, no malabsorption symptoms were reported in patients after biliopancreatic diversion. Therefore, it is necessary to individually adjust the dosage and monitor the patient postoperatively [42].

LT4 malabsorption occurs also in patients after other bowel resection surgeries (in the course of so-called short bowel syndrome). Such patients manifest an increased postoperative requirement for LT4 preparations. However, no direct correlation has been observed between the length of the bowel left and the LT4 dose absorbed [43].

A recent study by Rubio et al. concerning the LT4 absorption test has shown that in patients who underwent gastric bypass according to the Roux-en-Y method, LT4 absorption does not decrease, only that the process becomes slower [44].

Other causes

There are literature reports of a negative impact of Giardia lamblia infection and that of non-specific bowel inflammations on LT4 absorption [45–47]. The case of a 57 year-old female patient is presented, with well-controlled hypothyroidism over a period of six years, who developed gastrointestinal symptoms with a co-existing marked deterioration of hormonal balance. An adequate control of hypothyroidism using routine LT4 doses was restored after *Giardia lamblia* infection eradication with metronidazole [46].

Conclusions

The need to use high LT4 doses in replacement therapy of hypothyroidism can be the first symptom of malabsorption syndrome, which can be oligosymptomatic and previously undiagnosed. Patients taking LT4 in a dose of more than 2 μg/kg body weight daily, with persistently elevated TSH values, should be diagnosed with reference to pseudomalabsorption or real LT4 malabsorption. The LT4 absorption test, using a high LT4 dose, plays a role in the diagnosis of pseudomalabsorption which is the commonest cause of difficulties in obtaining euthyreosis in hypothyroid patients [48, 49]. With patient non-compliance excluded, and real LT4 malabsorption confirmed, a differential diagnosis must take into consideration such pathologies as lactose intolerance, coeliac disease, atrophic gastritis, *H. pylori* infection, bowel resection postoperative state, inflammatory bowel disease and, finally, parasite infections.

Once lactose intolerance has been confirmed via a lactose absorption test, a lactose-free LT4 preparation and a lactose-free diet should be used in order to attain euthyreosis or reduce the dose of LT4 preparation. In coeliac disease, a gluten-free diet usually results in the normalisation of LT4 requirement, as does the eradication of *H. pylori* infection or one caused by parasites. When it comes to atrophic gastritis or inflammatory bowel disease, treatment of the main disease and its remission can improve LT4 absorption. Patients after bowel surgery usually require higher than standard doses of LT4 to attain euthyreosis.

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