Tijana Lalić, Biljana Beleslin[1,2], Mirjana Stojković[1,2], Slavica Savić[1], Tanja Nišić[1], Miloš Stojanović[1,2], Marija Barać[1], Jasmina Ćirić[1,2], Miloš Žarković[1,2]

MALABSORBTION *VS* PSEUDO-MALABSORPTION IN LEVOTHYROXINE ABSORPTION TEST

INTRODUCTION

One of the most common clinical problems in hypothyroid patients is need for high doses of levothyroxine (LT4) for normalization of TSH or permanently elevated TSH despite high LT4 doses. The most common cause for unusually large amounts of supstitution is poor compliance of patients. The term "pseu-domalabsorption" refers to a non compliance (nonadherence) to therapeutic treatment. If you ask patients without judgmental and accusation many of them will admit skiping a dose occasionally. The problem is how often "occasionally" happens. In one report, the rate of self admitted non compliance was 22%. Reasons for non compliance may be patients belief of therapy, the absence of symptoms, fear of side effects and trust in the doctor-patient relationship. On contrary, there are differente conditions which can cause true malabsorption.

The primary method of distinguishing pseu-domalabsorption from malabsorption is the Levothyroxine Absorption Test - LAT.

CASE STUDY

A sixty year old female patient complained to the expressed drowsiness, fatigue, weakness and forgetfulness one month before admission in April 2015. She noticed that her skin was very dry, flacky and poor tolerance of physical exertion. She had a poor appetite with fluctuations in weight around 2kg, hard stool, every 4-5 days after teas and sometimes heartburn. Hyperthyroidism in Grave's disease was diagnosed in 1994. Definitely cured after radioiodine treatment in 2005. After it, apparently the TSH constantly was increased, 20-70mIU/L, which is why doses of levothyroxine

[1] Clinic for Endocrinology, Diabetes and Metabolic diseases, Clinicala Center of Serbia, Belgrade, Dr Subotica street 13, 11000 Belgrade

[2] School of Medicine, Belgrade University, Belgrade

was progressively increased. It was attempted with different forms of levo-thyroxine and she claimd properly taking of drug all the time. The last two years her daily dose of LT4 was about 900 (15μg/kg), the first 3x300μg than 500 + 400μg. In March, the TSH 33.6mIU / L, FT4 < 4.5pmol/L.

In addition, she was under treatment for angina, hypertension, paroxysmal arrhythmias (the last two months INR generally less than two with acenocoumarol treatment) and depression (paroxetine and clonazepam). Vitamin B12 was administerd once a month. She was allergic to Penicillin, Novalgetol, Aspirin, Acetisal, Caffetin. In the personal history she had appendectomy and tonsillectomy. In the family, there were thyroid disease, diabetes, cardiovascular disease, duodenal ulcer disease, fibro-adenoma of the breast and venous varices.

Objectively, the patient was normally nourished, TT 60kg, BMI 24,3kg / m^2, very dry, flaky body skin with ecchymoses on forearms. Thyroid gland was firm, atrophic, non-homogeneous, easy-sensitive painful on palpation, there was no lymphadeno-pathy. Heart rate was rhythmic, frequency 60/min, heart sounds clear, low-noise, TA 147/82mmHg. Contracture last three fingers of the right hand (the result of keeping in the ice). She had pronounced venous drawing on the shins, and peripheral pulses were symmetrical palpable. In ECG was sinus rhythm, frequency 60/min, AV block first degree, without changing the ST segment and T wave.

In biochemical analysis exept expected hyperlipidemia other results were within normal ranges (Table 1). Blood work pointed to a less severe microcytic anemia with normal iron status and high levels of vitamin B12 due to supplementation. Occult blood test was negative (Table 2). Inadequate INR to three-quarters of acenocoumarol tablet (Table 3).

In three consecutive stool samples were positive fats and starches (Table 4). Thyroid hormones on admission: TSH 29.11 (0,27-4,2mIU/L, ECLIA); FT4 5.5 (12-22pmol/L, ECLIA). Standard levothyroxine absorption test was performed. The patient received 1000μg LT4 under the supervision. TSH, T4 and FT4 were determnd two, four, six and twenty four hours after application. All results are entered into the program to calculate and are presented graphically. Base values were: TSH 26,92 mIU/L, FT4 4,4 pmol/L, T4 41,5pmol/L. Maximum concentration (Cmax) of T4 88,6pmol/L was achieved in 120 minutes. The values at the end of the test were TSH 29,37 mIU/L, FT4 7,2 pmol/L, T4 61,9pmol/L. The absence of the fall of TSH and the minimal increase in FT4 and T4, significantly below the AUC, have pointed to inadequate absorption.

Immunological analysis showed the positive 1:80 antiparietal antibody. Fecal calprotectin was negativ (≤ 100μg/g). Because of suspicion of malapsorptiv syndrome gastroscopy was made. Pathohistological finding was consistent with chronic atrophic antral focal gastritis, H. pylori highly positive (AAG, Houston): Grade III Stage I; with micro focal intestinal metaplasia; no obvious morphological elements supporting Gluten-sensitive enteropathy.

After the test the patient received 300 μg of levothyroxine in the form of oral suspension in fasting state. H. pylori treatment was introduced as well as a proton pump inhibitor. After four weeks on discharge her thyroid status was: TSH 1,63 mIU/L, FT4 26,6 pmol/L, FT3 3,87 pmol /L. There has been an adequate INR with oral anticoagulants with whom the patient was discharged after low molecular weight heparin was introduced during hospitalisation.

DISCUSSION

Levothyroxine is the mainstay of treatment of hypothyroidism, as stated in the American Thyroid Association Guidelines for tretment of hypothyroidism. It was first isolated in crystal form from dehydrated thyroid tissues of animal origin in 1915 and synthesized in the form of better absorbing sodium salts in 1927. On average, about 70-80% of the dose of levothyroxine tablets is absorbed in the jejunum and ileum in optimal fasting conditions. Long half-life (approximately 7 days) is adecvate for once daily dosing (~14% of the weekly dose). Leakage daily dose intermittently will have effect on the levels of thyroid hormones for a few days or weeks but should not affect the levels in the months and/or years. There is a weak peak of T4 and free T4 concentration in the serum, approximately 15%, between 2 and 4 hours from the application of LT4. The average dose for achieving the efficient and optimal substitution depends on the body weight (ideal body weight) and for the majority of patients is 1,6-1,8 μ/kg, in some groups, 2,0-2,1 μ/kg. Advanced replacement dose better correlates with lean-mass. Generally, steady state of T4 and TSH is achieved in six weeks of initiation of therapy. Folloup and monitoring of restitution symptoms of hypothyroidism is best based on TSH. The recommendetion is always to take LT4 30-60 minutes before breakfast or at bedtime, 3 or more hours after the last meal.

For maximum absorption, it is necessary that the stomach is empty, the acidity of the gastric pH is essential for the dissolution of the tablet, removing sodium and transforming LT4 in a lipophilic molecule. Levo-thyroxine tablet malabsorption is the result of lesser decomposition in full stomach or sequestrants binding in the intestinal lumen. When LT4 is administered with food absorption decreases to 40-64% from 80% in comparison with the absorption in fasting state. Especially interesting is the effect of dietary fiber (muesli, corn-flakes), coffee, grapefruit, soy and papaya. Coffee ten minutes before the tablet is influences LT4 absorption. Medications can also interfere with the absorption of LT4 (drug-induced malabsorption): IPP, $CaCO_3$, ferrous sulfate, cholestyramine and colestipol, antacids containing aluminum, estroegeni and androgens, sucralfate, orlistat, multivitamins. Some drugs can increase the LT4 ecscretion or turnover: phenobarbital, phenytoin, carbamazepine, rifampicin, sertraline, and imatinib sunatinib (kinase inhibitors). Proton pump inhibitors changing gastric pH

can cause a decrease in absorption, although no data on the length of treatment that is necessary for this. It is known that provides for rapid and consistent suppression of pH on the first day of application. A study with omeprazole 20 and 40 mg for 3 months showed that there was no clinically significant influence in the hypothyroid patients who were previously euthyroid. It is advisable to take CaCO3 after 4 hours. Malabsorption syndromes increase the LT4 need reducing the fraction of the dose that is absorbed. The most common illness that alters gastric pH is H. pylori gastritis and atrophic gastritis due to hypo/achlorhydria and production of ammonium. This causes a change of ionized status and LT4 molecule conformation. Therefore, the need for LT4 may result in up to 37% (24-34%) in patients with H. pylori gastritis and atrophic gastritis (B12 deficit) or both. Eradication of H. pylori infection and the start of omeprazole are associated the first with a reduction than a elevation of TSH. Further, the size of the LT4 required dose correlates with APA antibodies, larger LT4 doses are required in those who have had positive antibodies. Also, the dose positive correlate with the antibody titer and severity of gastritis. Celiac disease requires increasing the LT4 dose even in its "atypical" form that is characterized by little or completely absent gastrointestinal symptoms. If patients are not on a strict gluten-free diet daily needs of LT4 can be increased to 50%. In other disorders include: lactose intolerance, intestinal giardiasis, cholestasis and cirrhosis of the liver, pancreatic insufficiency, gastrointestinal surgeries and jejunostomy, jejunoilealni bypass, short bowel syndrome. Other factors associated with reduced absorption are the older age and extreme obesity (BMI> 40kg/m^2).

Levothyroxine absorption test is performed under the supervision using the specific oral doses of LT4, measuring T4 at certain times and comparing the obtained and predicted Cmax and AUC values. Cmax and AUC significantly lower than the expected values pointed to inadequate (disturbed) absorption. The test used a dose of 600 μg to 2000 μg (2mg) with more or less different applications and interpretations. It was shown that there was a highly significant correlation FT4 and T4 and FT4 may be used interchangeably with the T4 to a qualitative assessment of the test. There needs to be an increase in T4 and FT4 and TSH fall to rule out malabsorption (adequate absorption) or confirmed pseudo-malabsorption. It is advisable to performd LAT to patients with a LT4 dose of 2 μg/kg or ≥300 μg per day who have continuously increased TSH. The literature can be encountered mainly reports on individual cases, in one such LT4 dose before the test was1000mcg which is the maximum value, or smaller groups of patients. Typically performed the so-called high (high dose) LAT in which it is administered 1000μg LT4 oral bolus under supervision, after an overnight fast, and measures T4 and TSH usually after 2h (120 '), 4h (240'), 6h (360 ') possibly 24h (1440 '). It can be extended for another day with another 1000μg. In addition to high efficiency of a bolus dose and safety has been confirmed. Beside standard test varieties exist in the form of rapid (2h LAT), low-dose LAT and the five-day (5-day LAT). Rapid test (2h LAT) is based on the

fact that FT4 reaches a maximum or near the maximum value of 120 minutes of application 1000μg LT4 and involves the determination of TSH, FT4 and FT3 at the 0', 60' and 120' from the beginning of the test, which is a proven ability to distinguish pseudo-malabsorption at three patients. The modified low dose (low-dose LAT) levothyroxine absorption test is an effective and safer than the standard for cardiac patients. Involves the use under the supervision of 300μg twice daily (10 am and 22 pm) for two days and the determination TSH and FT4 every day 2h after administration. The normalization of FT4 indicates non-compliance and confirms pseudo-malabsorption. The five-day test (5-day LAT) patient comes to the clinic from Monday through Friday to take under the supervision usual dose of LT4, TSH and FT4 are determined on the first day before the administration of LT4 and fifth day 2 hours after application. It proved to be as effective as standard (1mg) test and more convenient for patients whose daily doses are less than 500μg. Special variant for proving noadherence is the weekly application of LT4 doses calculated based on body weight for 4 weeks. With regard to TSH and FT4 determination on the day of administration base, 60', 120' and 240 'of the application and after four weeks represents a combination of daily absorption test and monitoring after four weeks. Every week is given the same dose of LT4. It is known from before that the maximum concentration of T4 is higher after weekly application in comparison with LT4 daily substitution. This is a recommendation from ATA Guidelines for treatment of hypothyroidism for overcoming nonadherence. Reference is also made to other formulations of LT4 such as softgel capsules and oral solution wherein the LT4 is in the form of a liquid to overcome the problem of taking with food or other drugs, but it is not recommended because there are no randomized clinical trials. Insufficiently researched parenteral application forms. Mathematical model of LT4 intramuscular administration once or twice a week showed some T4 fluctuations but these values were within the reference. In our conditions the easiest is the use of crushed tablets in solution.

Disadvantages LAT - there is no a well documented standard with which the results of individual patients are comparable especially those in hypothyroid patients with normal absorption. If there is good absorption of high doses remains the question as to whether this is a normal amount in the absence of normal standard values. Heavy hypothyroidism alone can reduce the absorption due to edema of the mucosa of the small intestine and this can not be measured by test.

CONCLUSION

Levothyroxine absorption test is useful for detecting much rare malabsorption. Adequate treatment lead to the appropriate substitution and avoid and prevent irrational increase in the dose of levothyroxine in the treatment of hypothyroidism.

Reference:

1. American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement.Thyroid. 2014 Dec;24(12): 1670–751.
2. Balla M, Jhingan RM, Rubin DJ. Rapid Levothyroxine Absorption Testing: A Case Series of Nonadherent Patients. Int J Endocrinol Metab. 2015 Oct 13; 13(4): e31051.
3. Lewandowski KC, Dąbrowska K, Komorowska-Dudek I, Lewiński A. A single bolus of high dose levothyroxine (L-T4) as a test in cases of suspected poor compliance to L-T4 therapy. Thyroid Res. 2015 Dec 1; 8: 16.
4. Morelli S, Reboldi G, Moretti S, Menicali E, Avenia N, Puxeddu E. Timing of breakfast does not influence therapeutic efficacy of liquid levothyroxine formulation. Endocrine. 2015 Nov 4.
5. Srinivas V1, Oyibo SO. Levothyroxine pseudomalabsorption and thyroxine absorption testing with use of high-dose levothyroxine: case report and discussion. Endocr Pract. 2010 Nov-Dec;16(6): 1012–5.
6. Walker JN1, Shillo P, Ibbotson V, Vincent A, Karavitaki N, Weetman AP, Wass JA, Allahabadia A. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. Eur J Endocrinol. 2013 May 10; 168(6): 913–7.
7. John C. Morris How do You Approach the Problem of TSH Elevation in a Patient on High-dose Thyroid Hormone Replacement? Int J Qual Health Care. 2009; 70(5): 671–673.
8. Abi-Abib Rde C, Vaisman M. Is it necessary to increase the dose of levothyroxine in patients with hypothyroidism who use omeprazole? Arq Bras Endocrinol Metabol. 2014 Oct; 58(7): 731–6.
9. Sun GE, Pantalone KM, Faiman C, Gupta M, Olansky L, Hatipoglu B. The clinical utility of free thyroxine in oral levothyroxine absorption testing. Endocr Pract. 2014 Sep; 20(9): 925–9.
10. Thynne TR, Doogue MP. A dose of paracetamol for the levothyroxine absorption test. Clin Endocrinol (Oxf). 2013 Jun; 78(6): 968–9.
11. Walker JN, Shillo P, Ibbotson V, Vincent A, Karavitaki N, Weetman AP, Wass JA, Allahabadia A. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. Eur J Endocrinol. 2013 May 10; 168(6): 913–7.
12. Yue CS, Scarsi C, Ducharme MP. Pharmacokinetics and potential advantages of a new oral solution of levothyroxine vs. other available dosage forms. Arzneimittelforschung. 2012 Dec; 62(12): 631–6.
13. Virili C, Bassotti G, Santaguida MG, Iuorio R, Del Duca SC, Mercuri V, Picarelli A, Gargiulo P, Gargano L, Centanni M. Atypical celiac disease as cause of increased need for thyroxine: a systematic study. J Clin Endocrinol Metab. 2012 Mar; 97(3): E419–22.