Tijana Lalić[1], 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]

MALAPSORPCIJA *VS* PSEUDOMALAPSORPCIJA U LEVOTIROKSIN APSORPCIONOM TESTU

SAŽETAK

Uvod: Najčešći razlog perzistentno povišenog TSH kod hipotiroidnih pacijenata na terapiji levotiroksinom je slaba saradnja pacijenata. Testom apsorpcije levotiroksina (LAT) najčešće se potvrđuje ovaj fenomen „pseudomalapsorpcije".

Prikaz slučaja: Pacijentkinja 60 godina, TT 60 kg, ITM 24,3 kg/m^2, požalila se na pospanost, umor, malaksalost i zaboravnost. Primetila je da joj je koža izrazito suva, perutava i slabije tolerisanje napora. Loš apetit uz oscilacije u težini oko 2 kg, konstipaciju i ponekad gorušicu. U hipotireozi deset godina posle terapijske doze J131 zbog Grejvsove bolesti. TSH je stalno povećan, 20–70 mIU/L, uprkos naporima (različiti preparati LT4) da se prilagodi doza. Poslednje dve godine oko 900 (15 µg/kg) LT4, prvo 3x300 µg, zatim 500+400 µg. Komorbiditeti: depresija, AP, HTA, paroksizmi apsolutne aritmije (neadekvatan INR poslednja dva meseca). Pre ispitivanja TSH 33,6 mIU/L, FT4<4,5 pmol/L. Urađen je standardni (1000 µg) LAT uz nadgledanje sa određivanjem TSH, T4 i FT4 2h, 4h, 6h i 24h nakon primene. Bazne vrednosti su bile TSH 26,92 mIU/L; FT4 4,4 pmol/L; T4 41,5 pmol/L. Izostanak pada TSH i minimalan porast FT4 i T4, značajno ispod AUC, ukazali su na neadekvatnu apsorpciju. Posle testa započela je sa 300 µg LT4 u obliku suspenzije. Prisustvo masti u stolici i pozitivna antiparijetalna antitela dodatno su upućivali na malapsorptivni sindrom. Urađena je EGDS, PH nalaz je ukazao na *H. pylori* hronični atrofični gastritis bez morfoloških elemenata za GSE. Uvedena je eradikaciona terapija i IPP. Tiroidni hormoni posle četiri nedelje: TSH 1,63 mIU/L, FT4 26,6 pmol/L, FT3 3,87 pmol/L.

[1] Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Klinički centar Srbije, Medicinski fakultet Univerziteta u Beogradu. tijana_lalic@yahoo.com

[2] Medicinski fakultet Univerziteta u Beogradu, Beograd.

Zaključak: Test apsorpcije levotiroksina je koristan za otkrivanje mnogo ređe malapsorpcije. Adekvatno lečenje omogućava odgovarajuću supstituciju i izbegavanje neracionalnog povećanja doze levotiroksina.

Ključne reči: malapsorpcija, TSH, hipotireoza, levotiroksin

ABSTRACT

Introduction: The most common cause for persistent elevation of TSH levels in hypothyroid patients treated with levothyroxine is poor compliance. The Levothyroxine Absorption Test (LAT) is usually confirmed this phenomenon called "pseudo-malabsorption".

Case report: 60-year-old female, weight 60kg, BMI 24.3kg/m^2, presented with sleepiness, tiredness, fatigue and forgetfulness. Her skin was very dry and flaky. She had low tolerance of effort, poor appetite with weight oscillation around 2kg, constipation and sometimes heartburn. Hypothyroid for ten years after radioiodine treatment of Graves´ disease. Her TSH levels were higher than normal, TSH 20-70mIU/L, in spite of efforts to adjust the dose (different LT4 preparations). In last two years her daily LT4 dose was 900 (15µg/kg), 3x300mcg, 500+400mcg. Comorbidities: depression, angina, hypertension, absolutely arrhythmias (with inadequate INR in last two months). Before testing TSH 33.6mIU/L, FT4 4.25 pmol/L. Standard (1000µg) LAT was performed under supervision. TSH, T4 and FT4 were measured 2h, 4h, 6h and 24h upon LT4 administration. Baseline values were TSH 26.92 mIU/L; FT4 4.4pmol/L; T4 41.5pmol/L. The lack of TSH fall with slight T4 and FT4 increase, significantly below expected AUC, pointed an inadequate absorption. It was started with 300 µg LT4 oral suspension, after testing. The presence of fat in the stool and positive antiparietal antibodies increased suspicion to malabsorptiv syndrome. EGDS was performed, PH finding confirmed *H.pylori* positive chronic atrophic gastritis, without morphological elements for GSE. Eradication treatment and IPP were introduced. After four weeks her thyroid hormones were TSH 1.63 mIU/L; FT4 26.6pmol/L, FT3 3.87pmol/L.

Conclusion: LAT is useful for identifying much rare malabsorption. The adequate treatment lead to proper substitution and avoidance of no rationale increase of levothyroxine dose.

Key words: malabsorption, TSH, hypothyreosis, levothyroxine

UVOD

Jedan od čestih kliničkih problema kod hipotiroidnih pacijenata je potreba za visokim dozama levotiroksina (LT4) zbog normalizacije TSH ili stalno povišen TSH uprkos visokim dozama. Najčešći razlog za neuobičajeno velike potrebe supstitucije je slaba saradnja pacijenata. Pojam „pseudomalapsorpcija" odnosi se na nepridržavanje (neadherentnost) terapijskom tretmanu. Ako se pitaju bez optuživanja i osuđivanja mnogi pacijenti će priznati da povremeno preskaču dozu. Problem je koliko često se to „povremeno" dešava. U jednom izveštaju stopa samoinicijativnog priznavanja nepridržavanja bila je 22 %. Razlozi za nepridržavanje mogu da budu mišljenje pacijenata o terapiji, odsustvo simptoma, strah od neželjenih efekata i poverenje u odnosu lekar–pacijent. Nasuprot tome, postoje različita stanja i poremećaji koji mogu da budu uzrok prave malapsorpcije.

Primarni metod za razlikovanje pseudomalapsorpcije od malapsorpcije je Test apsorpcije levotiroksina (Levothyroxine Absorption Test LAT).

PRIKAZ SLUČAJA

Pacijentkinja starosti 60 godina požalila se na izraženu pospanost, umor, malaksalost i zaboravnost mesec dana pre prijema u aprilu 2015. godine. Primetila je da joj je koža jako suva i perutava i slabo tolerisanje fizičkog napora. Imala je loš apetit uz oscilacije u težini oko 2 kg, tvrdu stolicu, na 4–5 dana uz čajeve i ponekad gorušicu. Hipertireoza u Grejvsovoj bolesti dijagnostikovana je 1994. godine. Definitivno izlečena terapijskom dozom J131 2005. godine. Nakon toga, navodno je TSH stalno povećan, 20–70 mIU/L, zbog čega je postepeno povećavana doza levotiroksina. Pokušano je sa različitim preparatima i navodi da sve vreme pravilno uzima terapiju. Poslednje dve godine njena dnevna doza LT4 je oko 900 (15 μg/kg), prvo 3x300 μg, zatim 500+400 μg. U martu je TSH 33,6 mIU/L, FT4 < 4,5 pmol/L.

Pored toga, leči se od angine pektoris, hipertenzije, paroksizama apsolutne aritmije (poslednja dva meseca INR uglavnom manji od dva na terapiji sa acenokumarolom) i depresije (paroksetin i klonazepam). Dobija OHB12 jednom mesečno. Navodi alergije na Penicillin, Novalgetol, Aspirin, Acetisal, Caffetin. Pored toga, u ličnoj anamnezi apendektomija i tonzilektomija. U porodici postoje bolesti štitaste žlezde, dijabetes, kardiovaskularne bolesti, ulkusna bolest duodenuma, fibroadenomi dojke i venski varikoziteti.

Objektivno, pacijentkinja je bila normalno uhranjena, TT 60 kg, ITM 24,3 kg/m^2, izrazito suve, perutave kože tela sa ekhimozama na podlakticama. Štitasta žlezda je bila tvrda, atrofična, nehomogena, lako bolno osetljiva pri palpaciji, nije bilo limfadenopatije. Srčana akcija je bila ritmična, frekvenca 60/min, srčani tonovi jasni, bez šumova, TA 147/82 mmHg. Kontraktura poslednja tri prsta desne šake (posledica

držanja u ledu). Bio je naglašen venski crtež na potkolenicama, a periferni pulsevi su simetrično palpabilni. Elektrokardiografski je verifikovan sinusni ritam, frekvence 60/min, AV blok I stepena, bez promene ST segmenta i T talasa.

U biohemijskim analizama, sem očekivane hiperlipidemije, ostali rezultati su bili u granicama normale (Tabela 1). Krvna slika je ukazala na blažu mikrocitnu anemiju sa urednim statusom gvožđa i povećanim vrednostima vitamina B12 zbog suplementacije. Test na okultno krvarenje bio je negativan (Tabela 2). Neadekvatan INR na tri četvrtine tablete acenokumarola (Tabela 3). U tri uzastopna uzorka stolice bili su pozitivni masti i skrob (Tabela 4). Tiroidni hormoni pri prijemu: TSH 29,11 (0,27–4,2 mIU/L, ECLIA); FT4 5,5 (12–22 pmol/L, ECLIA). Urađen je standardni Levotiroksin apsorpcioni test. Pacijentkinja je uz nadzor dobila 1000 μg LT4. Određivani su TSH, T4 i FT4 dva, četiri, šest i dvadesetčetiri sata posle primene. Svi rezultati su uneti u program za izračunavanje i prikazani su grafički. Bazne vrednosti su bile: TSH 26,92 mIU/L, FT4 4,4 pmol/L, T4 41,5 pmol/L. Najveća koncentracija (Cmax) T4 88,6 pmol/L postignuta je u 120. minutu. Vrednosti na kraju testa bile su TSH 29,37 mIU/L, FT4 7,2 pmol/L, T4 61,9 pmol/L. Izostanak pada TSH i minimalan porast FT4 i T4, značajno ispod AUC, ukazali su na neadekvatnu apsorpciju.

Imunološke analize su ukazale na pozitivna antiparijetalna antitela 1:80. Fekalni kalprotektin je bio negatiavn (≤ 100 μg/g). Zbog sumnje na malapsorptivni sindrom urađena je ezofagogstaroduodenoskopija. Patohistološki nalaz je odgovarao hroničnom fokalnom atrofičnom antralnom gastritisu, *H. pylori* visokopozitivnom (AAG, Houston): Grade III, Stage I; sa mikrofokalnom pojavom elemenata intestinalne metaplazije; bez morfološki evidentnih elemenata u prilog Gluten senzitivne enteropatije.

Posle testa pacijentkinja je dobijala 300μg levotiroksina u obliku suspenzije našte. Uvedena je eradikaciona terapija i inhibitor protonske pumpe. Posle četiri nedelje prilikom otpusta njen tiroidni status je bio: TSH 1,63 mIU/L, FT4 26,6 pmol/L, FT3 3,87 pmol/L. Postignut je adekvatan INR uz oralne antikoagulanse sa kojima je pacijentkinja otpuštena nakon što je tokom hospitalizacije bio uveden niskomolekularni heparin.

DISKUSIJA

Levotiroksin je osnova terapije hipotiroidizma, kao što se navodi u vodiču Američke tiroidne asocijacije. Prvi put je izolovan iz dehidratisanog tkiva tiroideje animalnog porekla u kristalnom obliku 1915. godine a sintetisan u obliku bolje apsorbujuće natrijumove soli 1927. godine. U proseku, oko 70–80 % doze tablete levotiroksina apsorbuje se u jejunumu i ileumu u optimalnim uslovima gladovanja. Dug poluživot (oko 7 dana) omogućava doziranje jednom dnevno (~14 % nedeljne doze). Propuštanje dnevne doze intermitentno imaće efekat na nivoe tiroidnih hormona tokom nekoliko dana ili nedelja, ali ne bi trebalo da utiče na nivoe tokom meseci i/ili godina. Postoji

prolazan pik koncentracija T4 i FT4 u serumu, veličine oko 15 %, između 2h i 4h od primene LT4. Prosečna doza za postizanje efikasne i optimalne supstitucije zavisi od telesne težine (idealne težine) i za većinu pacijenata iznosi 1,6–1,8 μ/kg, u nekim grupama 2,0–2,1 μ/kg. Preciznija supstituciona doza bolje korelira sa bezmasnim tkivom. Stabilno stanje T4 i TSH postiže se za šest nedelja generalno od započinjanja terapije. Praćenje restitucije simptoma hipotiroidizma je najbolje na osnovu TSH. Preporuka je da se LT4 uvek uzima 30–60 minuta pre doručka ili u vreme spavanja, 3 ili više sati od poslednjeg obroka. Za maksimalnu apsorpciju neophodno je da je želudac prazan, odnosno kiselost želudačnog pH je esencijalna za razlaganje tablete, uklanjajući Na i pretvarajući LT4 u lipofilni molekul. Malapsorpcija za tablete LT4 (*LT4 tablet malabsorption*) rezultat je slabijeg razlaganja u punom želucu ili vezivanja sekvestranata u intestinalnom lumenu. Kada se LT4 primenjuje istovremeno sa hranom apsorpcija se smanjuje na 40–64 % sa 80 % u poređenju sa apsorpcijom našte. Posebno se izdvaja uticaj dijetnih vlakana (musli, corn-flakes), kafe, grejpfruta, soje i papaje. Kafa deset minuta pre tablete vezuje LT4. Lekovi takođe mogu da interferiraju u apsorpciji LT4 (*drug-induced malabsorption*): IPP, $CaCO_3$, fero-sulfat, holestiramin i holestipol, antacidi koji sadrže aluminijum, estroegeni i androgeni, sucralfat, orlistat, multivitamini. Neki lekovi mogu da povećaju izlučivanje ili turnover: fenobarbital, fenitoin, karbamazepin, rifampicin, sertralin, imatinib i sunatinib (kinaza inhibitori). Inhibitori protonske pumpe promenom gastričnog pH mogu da uzrokuju smanjenje apsorpcije iako nema podataka o dužini tretmana koji je za to neophodan. Poznato je da se postiže brza i konzistentna supresija pH prvog dana primene. Studija sa Omeprazolom 20 i 40 mg u trajanju od 3 meseca pokazala je da nije bilo uticaja u klinički značajnom maniru kod hipotiroidnih pacijenata koji su prethodno bili eutiroidni. Savetuje se da se $CaCO_3$ uzima sa razmakom od 4h. Malapsorptivni sindromi povećavaju potrebe LT4 smanjenjem frakcije unete doze koja se apsorbuje. Najčešća bolest koja menja gastrični pH je *H. pylori* gastritis i atrofični gastritis zbog hipo/ahlorhidrije i produkcije amonijuma. To prouzrokuje promenu jonizujućeg statusa i konformacije LT4 molekula. Zbog toga se potrebe za LT4 mogu povećati do 37% (24–34%) kod pacijenta sa HP gastritisom i atrofičnim gastritisom (deficit B12) ili oba. Eradikacija *H. pylori* infekcije i započinjanje omeprazola udruženi su sa smanjenjem, zatim porastom TSH. Dodatno, veličina potrebne doze LT4 korelira sa prisustvom antiparijentalnih At, veće doze LT4 potrebne su kod onih koji imaju pozitivna antitela. Takođe, doza pozitivno korelira sa titrom antitela i težinom gastritisa. Celijakija zahteva povećanje doze tablete LT4 čak i u svom „atipičnom“ obliku, koji se karakteriše sa malo ili potpuno odsutnim gastrointestinalnim simptomima. Ako pacijenti nisu na strogoj dijeti bez glutena dnevna potreba LT4 može se povećati do 50%. U druge poremećaje spadaju: intolerancija laktoze, intestinalna đardijaza, ciroza i holestaza jetre, insuficijencija pankreasa, gastrointestinalna operacija i jejunostoma, jejunoilealni bypass, sindrom kratkog creva. Drugi faktori udruženi sa smanjenom apsorpcijom su starija životna dob i ekstremna gojaznost (ITM > 40 kg/m^2).

Levotiroksin apsorpcioni test izvodi se primenom specifične oralne doze LT4 u uslovima nadgledanja, merenjem T4 u određenim vremenima i poređenjem dobijenih i predviđenih Cmax i AUC vrednosti. Cmax i AUC značajno niže od očekivanih vrednosti govore u prilog neadekvatne (narušene) apsorpcije. U testu se koriste doze od 600 µg do 2000 µg (2mg) uz manje-više različite primene i interpretacije. Pokazano je da postoji visoko značajna korelacija FT4 i T4 i da FT4 može da se koristi naizmenično sa T4 u kvalitativnoj proceni testa. Potrebno je da postoji porast T4 i FT4 i pad TSH da bi se isključila malapsorpcija (apsorpcija adekvatna), odnosno potvrdila pseudomalapsorpcija. Savetuje se da se pacijentima koji, uz dozu LT4 2 µg/kg ili ≥ 300 µg dnevno, imaju stalno povećan TSH uradi LAT. U literaturi se mogu sresti uglavnom izveštaji o pojedinačnim slučajevima, jedan takav je za dozu terapije pre testa 1000 mcg, što je maksimalna vrednost, ili na manjim grupama pacijenata. Uobičajeno se izvodi tzv. visokodozni (high dose) LAT u kome se daje 1000 µg LT4 oralno u bolusu uz superviziju, posle prekonoćnog gladovanja, i mere T4 i TSH obično posle 2h (120'), 4h (240'), 6h (360') eventualno 24h (1440'). Može da se produži na drugi dan sa još 1000 µg. Osim efikasnosti visoke bolus doze, potvrđena je i bezbednost. Pored standardnog, postoje varijeteti u vidu brzog (rapid, 2h LAT), niskodoznog (low-dose LAT) i petodnevnog (5-day LAT). Brzi test (2h LAT) zasniva se na činjenici da FT4 dostiže maksimalne ili skoro maksimalne vrednosti 120 minuta od primene 1000 µg LT4 i podrazumeva određivanje TSH, FT4 i FT3 bazno, 60' i 120' od početka testa, čime je dokazana sposobnost razlikovanja pseudomalapsorpcije kod troje pacijenata. Modifikovani niskodozni (low-dose LAT) levotiroksin apsorpcioni test je efikasan i bezbedniji u odnosu na standardni kod kardioloških pacijenata. Podrazumeva primenu uz nadzor 300 µg dva puta dnevno (10 i 22h) tokom dva dana i određivanje TSH i FT4 svakog dana 2h posle davanja. Normalizacija FT4 upućuje na nepridržavanje i potvrđuje pseudomalapsorpciju. U petodnevnom testu (5-day LAT) pacijent dolazi u ambulantu od ponedeljka do petka i pod nadzorom uzima svoju uobičajenu dozu a TSH i FT4 se određuju prvog dana pre administriranja LT4 i petog dana 2h posle primene. Pokazalo se da je jednako efikasan kao standardni (1mg) test i da više odgovara za pacijente čije su dnevne doze manje od 500 µg. Posebna varijanta za dokazivanje neadherentnosti je nedeljna primena doze LT4 izračunate na osnovu telesne težine tokom 4 nedelje. S obzirom na to da se TSH i FT4 određuju na dan administriranja i to bazno, 60', 120' i 240' od primene i posle četiri nedelje predstavlja neku kombinaciju testa apsorpcije dnevno i praćenja posle četiri nedelje. Svake nedelje se daje ista doza LT4. Poznato je odranije da je maksimalna koncentracija T4 veća posle nedeljne primene LT4 u poređenju sa dnevnom supstitucijom. To je i preporuka vodiča ATA za tretman hipotiroidizma za prevazilaženje neadherentnosti. Pominju se i druge formulacije LT4, kao što je softgel kapsula i oralni rastvor u kojima je LT4 u obliku tečnosti za prevazilaženje ovog problema ili uzimanja uz hranu i druge lekove, ali to nije preporuka budući da ne postoje randomizovane kliničke studije. Nedovoljno

je istražena i primena parenteralnih oblika. Matematički model intramuskularne primene LT4 jednom ili dva puta nedeljno pokazao je neke fluktuacije T4, ali su ove vrednosti bile unutar referentnih. U našim uslovima najlakša je primena usitnjenih tableta u rastvoru.

Nedostaci LAT – ne postoji dobro dokumentovan standard sa kojim se rezultati individualnih pacijenata mogu porediti, posebno oni kod hipotiroidnih pacijenata sa normalnom apsorpcijom. Ako postoji dobra apsorpcija na visokoj dozi ostaje nedoumica da li je to normalna količina u nedostatku normalnih standardnih vrednosti. Težak hipotiroidizam sam može da umanji apsorpciju zbog edema mukoze tankog creva a to se ne može izmeriti testom.

ZAKLJUČAK

Levotiroksin apsorpcioni test je koristan za otkrivanje mnogo ređe malapsorpcije. Adekvatno lečenje omogućava odgovarajuću supstituciju i izbegavanje neracionalnog povećanja doze levotiroksina u lečenju hipotiroidizma.

Skraćenice:

LAT – Levotiroksin apsorpcioni test
AUC – površina ispod krive (eng. Area Under the Curve)
Cmax – maksimalna koncentracija
IPP – inhibitori protonske pumpe

Tabela 1. Biohemija

Glc 4.7mmol/L	Proteini 73g/L	Trigliceridi 2.05mmol/L	K 5.0mmol/L
HbA1c 6.2%	Albumin 45g/L	AST 28U/L	Cl 108mmol/L
Urea 8.1mmol/L	CRP 1.6	ALT 20U/L	Ca 2.53mmol/L
Kreatinin 96µmol/L	Holesterol 7.45mmol/L	ALP 33U/L	PO4 1.17mmol/L
ac. urricum 222µmol/L	HDL 1.50mmol/L	GGT 13U/L	
Uk. bilirubin 8.3µmol/L	LDL 5.02mmol/L	Na 141mmol/L	

Tabela 2. Krvna slika i sedimentacija

Hgb 119g/dl	MCH 33.8pg
Hct 0.35L/L	Tr 181x10^3
Er 3.51x10^6/L	Le 5.7x10^9
MCV 99-100fl	SE 44 /

Tabela 3. Dopunske hematološke analize

sFe 15.6µmol/L	B12 1745 (934)
UIBC 34.5µmol/L	Folat 8.12 (3.8-16)
TIBC 50.1µmol/L	FOBT negativan

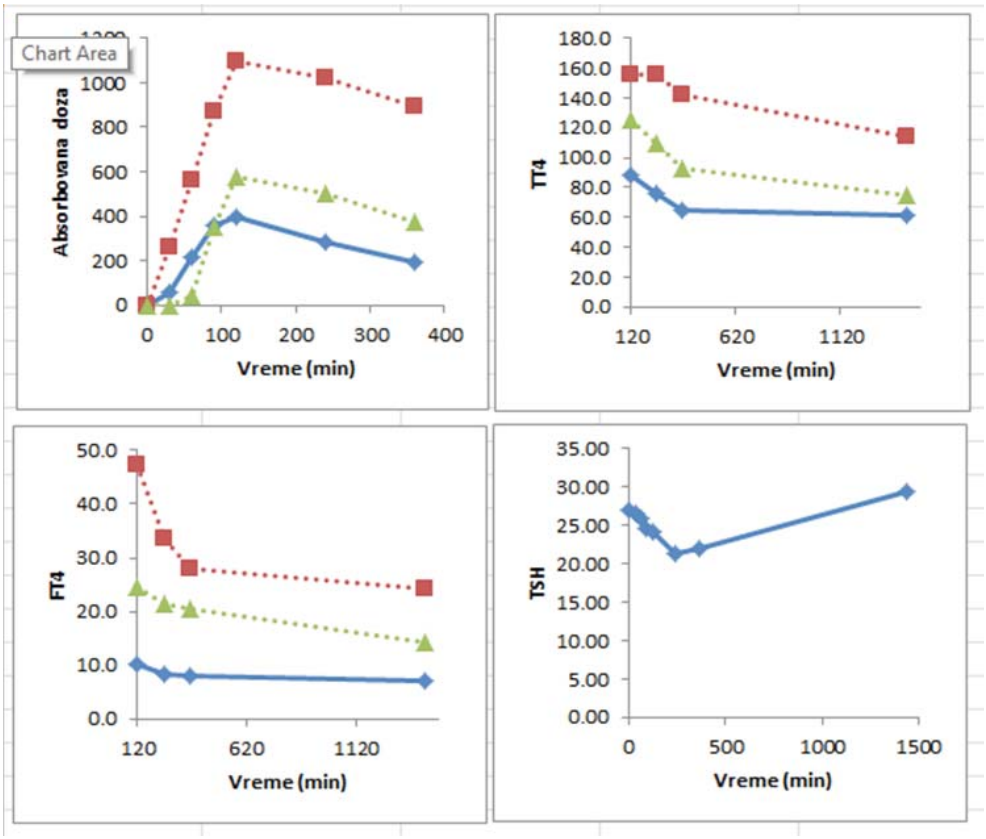
Tabela 4. Parametri hemostaze

aPT 41.7s	INR **1.07**
PT 12.6s	

Tabela 5. Pregled stolice na tri preparata

I	**skrob**	+	**mast-kvalitativno**	+	nesv. mišićna vlakna -
II	**skrob**	+	mast-kvalitativno	-	nesv. mišićna vlakna -
III	**skrob**	+	**mast-kvalitativno**	+	nesv. mišićna vlakna -

Grafik 1. Test apsorpcije levotiroksina: patološki nalaz



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 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 deter-

mnd 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.

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