CASE REPORT

Levothyroxine sodium oral solution to control thyroid function in a patient with hypothyroidism and celiac disease

Author: Ernest Asamoah, MD

Institutional mailing address: Community Physicians Network, Diabetes & Endocrinology Care, 8435 Clearvista Place, Suite 101, Indianapolis, IN 46256, USA

Email address: eoasamoah@mac.com

Target Journal: *Clinical Case Reports*

Word count limit: 3000

Number of tables/figures/references allowed: not specified

Key words: case report, celiac disease, levothyroxine sodium oral solution (L-T4 oral solution), malabsorption, Hashimoto's thyroiditis

Abstract (limit, 50 words): 50

Abstract (Key Clinical Message)

A patient with hypothyroidism, Addison's disease, and celiac disease had persistent hypothyroid symptoms, and frequent fluctuations in TSH, prompting transition to L-T4 sodium oral solution (Tirosint®-SOL). Implementing a gluten-free diet and switching to the oral solution significantly improved malabsorptive and subsequent hypothyroid symptoms without the need to increase L-T4 dosage.

Introduction

Levothyroxine (L-T4) is a synthetic hormone that is structurally identical to T4 and it is used as a therapeutic substitute in conditions associated with hypothyroidism.[1] Treatment of hypothyroidism with L-T4 sodium tablets often requires multiple dose adjustments and can be complicated by patients with conditions that limit absorption.[1,2]

Capsule and tablet formulations of L-T4 are absorbed throughout the small intestine, and mainly at the jejunum and upper ileum.[2] Successful treatment relies on drug delivery to the small intestine and on consistent full daily absorption. Malabsorption of L-T4 is an important medical problem in patients with hypothyroidism.[2] Comorbid conditions, including celiac disease, have been known to limit L-T4 absorption.[1-3]

This case report describes a 62-year-old female patient who was followed for over 12 years. Initially she presented with hypothyroidism, followed by the diagnosis of Addison's disease and, subsequently, celiac disease. During this period, despite continued L-T4 treatment, her thyroid stimulating hormone (TSH) remained suboptimal prompting transition to L-T4 oral solution. The switch to L-T4 oral solution, subsequently led to optimal TSH attainment and symptom relief.

The case demonstrates the utility of L-T4 oral solution following a switch from L-T4 tablet formulations in a patient with celiac disease, a comorbid malabsorptive disorder.

Case History

The patient was suffering from general malaise, nausea, vomiting, and >20-lb weight loss over 2 months. She started treatment with L-T4 sodium tablets (Synthroid®) 75 μg in October 2007, after her TSH had been measured by her primary care physician at 34.34 mIU/L (normal range [NR] 0.34–4.82 mIU/L) (**Table 1**). The symptoms of fatigue, nausea, and vomiting abated at that time.

A few weeks later, in early December 2007, the patient was again suffering from nausea and vomiting along with a continued weight loss. Further testing revealed cortisol level at 38.62 nmol/L (NR 165.53-689.70 nmol/L) and prolactin level at 0.126 μg/L (NR 0.006-0.076 μg/L), while no pituitary tumor was observed on the CT scan and MRI performed. An

adrenocorticotropic hormone (ACTH) stimulation test showed 30 minutes of cortisol at 49.66 nmol/L (NR 496.58-551.76 nmol/L), confirming adrenal insufficiency (**Table 1**).

On December 12, 2007, the patient was referred for endocrine consultation. Additional medical history included hypertension and cholecystectomy. The patient worked as a cook and had a family history of thyroid disease (mother on thyroid hormone therapy); no other family history of thyroid disease or endocrinopathy was reported. Based on the initial work-up presentation and treatment, the patient's diagnosis of hypothyroidism (Hashimoto's thyroiditis [HT]) was confirmed, and she was also diagnosed with autoimmune adrenal failure (Addison's disease). Two or more concurrent autoimmune diseases qualified the patient for the diagnosis of polyglandular autoimmune syndrome II. To confirm the new diagnoses, several diagnostic tests were performed (**Table 2**). The patient continued L-T4 sodium tablets 75 μg daily for hypothyroidism. Concomitant treatments included prednisone 5 mg daily and fludrocortisone acetate (Florinef®) 0.1 mg daily for adrenal insufficiency (**Table 1**).

One month later, on January 16, 2008, the patient's TSH levels were measured at 6.16 mIU/L (NR 0.34–4.82 mIU/L), resulting in regular subsequent dose increments of the L-T4 sodium tablets every 1–3 months (until October 2008 [**Table 1**]); changes in L-T4 dosage continued for approximately 10 years. During this time, thyroid hormone replacement therapy was changed every 3–6 months and treatment with L-T4 sodium tablets (Synthroid®) was alternated with generic L-T4.

Further Investigations and Treatment

In August 2018, the patient presented with GI symptoms and was further diagnosed with celiac disease following a series of tests (**Table 3**). The patient was switched from generic L-T4 to L-T4 sodium tablets (Synthroid®) and the dose was increased from 125 μg to 137 μg due to hypothyroid symptoms of fatigue and mental 'fogginess' (**Table 4**). In addition, the patient was advised to stay on a gluten-free diet, one month after initiation of which, she felt better, as her GI symptoms significantly improved, but were not completely resolved.

In May 2019, despite TSH levels within normal range they continued to fluctuate and the patient again presented with persistent hypothyroid symptoms, including malaise, fatigue, and mental 'fogginess' (**Table 4**). The patient was very frustrated because of her persistent

symptoms and the frequent changes to her therapy. After a thorough discussion on L-T4 oral solution, and considering its reliable absorption, more consistent TSH levels and possibly hypothyroid symptoms improvement, the patient was switched from L-T4 sodium tablets 137 μg to L-T4 oral solution 125 μg (**Table 4**). Concomitant treatment with fludrocortisone acetate 0.1 mg, prednisone 5 mg, and calcium plus vitamin D supplements was continued.

Outcome and Follow-up

Two and a half months following the switch to L-T4 oral solution, the patient's symptoms finally resolved without any need for L-T4 dose increase. The gluten-free diet significantly reduced her GI symptoms and, along with the switch to L-T4 oral solution, enhanced the absorption of the thyroid hormone therapy, controlled fluctuations in TSH levels and resolved persistent hypothyroid symptoms.

Discussion

Celiac disease is characterized by a permanent intolerance to gluten, causing damage to the small intestine mucosa.[4] Mucosal damage in the proximal small bowel consists of inflammation, crypt hyperplasia, and villous atrophy that have been seen to regress upon withdrawal of gluten from the diet.[5]

A strong association between celiac disease and HT has been documented. Celiac and autoimmune thyroid diseases share multiple clinical features, and patients with celiac disease have exhibited a prevalence of autoimmune thyroid disease ~4 times higher than that in the general population.[6] An increased prevalence of celiac disease-associated antibodies has been seen in patients with HT, thus, screening these patients for celiac autoimmunity is recommended.[6]

L-T4 is absorbed primarily at the jejunum and upper ileum and patients with malabsorptive disorders such as celiac disease can have limited L-T4 absorption, requiring increased L-T4 therapy.[1-3] Interestingly, it has been shown that increases in L-T4 doses have not been required in some patients with HT and celiac disease on a gluten-free diet while those not on such diet required increases of L-T4 therapy by 50%.[7] Patients with malabsorption on L-T4

therapy presenting with poor TSH control, disorders such as celiac disease should be considered as differential diagnoses.[4,8]

Addison's disease (adrenal insufficiency) may also cause treatment-refractory hypothyroidism.[2,9] In this case report, following diagnosis of Addison's disease, the patient was prescribed treatment with fludrocortisone and prednisone. Glucocorticoid agents may suppress TSH secretion and such patients should be referred to endocrinologists.[9]

It has been shown that patients with HT on tablet L-T4 whose TSH levels were poorly controlled, improved after switching to liquid L-T4 formulation without increasing the L-T4 dose.[10] Fluctuating TSH levels were reflected in this patient's frequent dose adjustments along with the deterioration of hypothyroidism symptoms. L-T4 has a narrow therapeutic index, so bioequivalence differences exist between various available products.[11] A pH-dissolution profile study on L-T4 tablet products showed that dissolution of L-T4 was limited thus limiting the rate of absorption.[11] Dissolution is considered a contributing factor to the bioequivalence problems between various L-T4 products.[11] L-T4 oral solution contains only L-T4, glycerol, and water;[12] it does not require a gastric phase of dissolution thus it is more readily absorbed than tablets.[13]

Patients with autoimmune thyroid disease have a higher risk for other autoimmune disorders, including celiac disease.14,15 The patient described here suffered from 3 concurrent autoimmune conditions (HT, Addison's disease, and celiac disease), symptoms of which overlapped. Fatigue is a common presentation in both hypothyroidism and Addison's disease. The patient's fluctuating thyroid function test results and the new GI symptoms of bloating, abdominal discomfort and intolerance of certain foods led to further testing and diagnosis of celiac disease. Implementation of a gluten-free diet improved GI symptoms and, along with the switch to L-T4 oral solution, enhanced L-T4 absorption and led to more stable TSH levels without the need to regularly increase L-T4 dosage. Patients with malabsorption on L-T4 therapy, presenting with fluctuating TSH levels (prompting L-T4 dose changes should be assessed for concurrent autoimmune conditions such as celiac disease.4,5 Tirosint®-SOL may provide an alternative formulation to tablets and should be considered to yield more stable TSH levels and provide symptomatic control.

Concluding Remarks

This case report showed L-T4 oral solution to stabilize thyroid function and improve hypothyroidism symptoms in a patient with 3 autoimmune disorders, including celiac disease, which, until diagnosed and treated, negatively affected L-T4 absorption, resulting in significant fluctuations of TSH levels and frequent L-T4 dose adjustments (mostly with incremental doses). Following implementation of a gluten-free diet and a switch to L-T4 oral solution, patient's GI and hypothyroid symptoms improved significantly without the need to increase L-T4 dosage. Tirosint®-SOL is a highly absorbable and effective option for patients with HT and celiac disease when standard tablets and capsules are inefficiently absorbed in the small intestine.

Author Contributions

Author: Ernest Asamoah, MD

The author provided the case report, final approval of the version to be published, and is accountable for the integrity of the content and for addressing questions.

Institutional mailing address: Community Physicians Network, Diabetes & Endocrinology Care, 8435 Clearvista Place, Suite 101, Indianapolis, IN 46256, USA

Email address: eoasamoah@mac.com

References

1. Fallahi P, Ferrari SM, Ruffilli I, Ragusa F, Biricotti M, Materazzi G, Miccoli P, Antonelli A. Advancements in the treatment of hypothyroidism with L-T4 liquid formulation or soft gel capsule: an update. *Exp Opin Drug Deliv*. 2017;14(5):647–655.
2. Centanni M, Benvenga S, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: an expert consensus report. *J Endocrinol Invest*. 2017;40**(**12):1289–1301.
3. McMillan M, Rotenberg KS, Vora K, Sterman AB, Thevathasan L, Ryan MF, Mehra M, Sandulli W. Comorbidities, concomitant medications, and diet as factors affecting levothyroxine therapy: results of the CONTROL Surveillance Project. *Drugs R&D*. 2016;16(1):53–68.
4. de Carvalho GA, Fighera TM. Effect of gastrointestinal disorders in autoimmune thyroid diseases. *Transl Gastrointest Cancer*. 2015;4(1):76–82.

5. Sedhom R, Katz K. Celiac disease and treatment of hypothyroidism: an unappreciated problem. *Am J Gastroenterol*. 2016;111:S978, Abstract 2049.
6. Lerner A, Jeremias P, and Matthias T. Gut-thyroid axis and celiac disease. *Endocr. Connect.*, 2017;6(4):R52–R58.
7. Virili C, Bassotti G, Santaguida MG, Iuorio R, Del Duca SC, Mercuri V, Picarelli A, Gargiulo P, Gargano L, and Centanni M. Atypical celiac disease as cause of increased need for thyroxine: a systematic study. *J Clin Endocrinol Metab*. 2012;97(3):E419–E422.
8. Ruchala M, Szczepanek-Parulska E, and Zybek A. The influence of lactose intolerance and other gastro-intestinal tract disorders on L-thyroxine absorption. *Endokrynol Pol*. 2012;63(4):318–323.
9. Ramadhan A, Tamilia M. Treatment-refractory hypothyroidism. *CMAJ*. 2012;184(2):205–209.
10. Virili C, Giovanella L, Fallahi P, Antonelli A, Santaguida MG, Centanni M, Trimboli P. Levothyroxine therapy: changes of TSH levels by switching patients from tablet to liquid formulation. a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2018;9:10.
11. Pabla D, Akhlaghi F, Zia H. A comparative pH-dissolution profile study of selected commercial levothyroxine products using inductively coupled plasma mass spectrometry. *Eur J Pharm Biopharm*. 2009;72(1):105–110.
12. Institut Biochimique SA (IBSA). Tirosint®-SOL (levothyroxine sodium) oral solution prescribing information. Revised June 2018. Accessed May 20, 2020. http://www.ibsa-pharma.us/dam/jcr:f49295b7-e0d8-4ab9-a41b-5a5091b8fe18/Tirosint_SOL_USPI_2018-06.pdf.
13. Yue CS, Scarsi C, Ducharme MP. Pharmacokinetics and potential advantages of a new oral solution of levothyroxine vs. other available dosage forms. *Arzneimittelforschung*. 2012;62(12):631–636.
14. Antonelli A, Benvenga S. Editorial: the association of other autoimmune diseases in patients with thyroid autoimmunity. *Front Endocrinol (Lausanne)*. 2018;9:540.
15. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, Manji N, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med*. 2010;123(2):183 e1-9.

List of Tables

Table 1. Diagnostic tests and treatment timeline from 2007 until 2018

Date	TSH (mIU/L)	Free T4 (pmol/L)	Additional tests	Dose of L-T4 (µg)/ action taken
	NR 0.34–4.82	NR 10.30–23.17	-	L-T4 sodium tablets (Synthroid®)
Oct 2007	34.34	Not evaluated	-	75
Dec 5, 2007	-	-	Cortisol: 38.62 nmol/L (NR 165.53–689.70 nmol/L)	75

			Prolactin: 0.126 μg/L (NR 0.006–0.076 μg/L) CT scan/MRI: no pituitary tumor ACTH 30 minutes cortisol: 49.66 nmol/L (NR 496.58–551.76 nmol/L)	
Dec 12, 2007	0.79	15.45	ACTH: 848.32 pmol/L (NR 1.10–5.94 pmol/L) 21-Hydroxylase antibody: Positive, 47.4 kU/L (NR <1.0 kU/L) TPO: 538000 IU/L (NR 0.0–34900 IU/L)	75 **Started on concomitant treatment:** prednisone 5 mg, fludrocortisone acetate 0.1 mg
Jan 16, 2008	6.16	10.17	-	88
Apr 4, 2008	3.26	14.42	-	100
May 19, 2008	3.24	Not evaluated	-	112
Aug 28, 2008	0.28	14.80	-	112
Oct 10, 2008	3.36	11.46	-	125
Apr 8, 2009	1.57	13.39	-	125
Dec 29, 2009	1.04	10.04	-	125
Oct 12, 2010	0.65	13.51	-	125
2010–2018	Not available	Not available	-	The patient was followed up with her primary care physician from 2010–2018. During this time, the patient reported significant changes to her thyroid hormone therapy almost every 3–6 months on L-T4 sodium tablets and, at times, generic L-T4.

Abbreviations: ACTH, adrenocorticotropic hormone; CT, computed tomography; L-T4, levothyroxine; MRI, magnetic resonance imaging; NR, normal range; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone

Table 2. Diagnostic tests performed on December 12, 2007

Diagnostic test	Result
Adrenocorticotropic hormone (ACTH)	848.32 pmol/L (NR 1.10-5.94 pmol/L)
21-Hydroxylase antibody	Positive, 47.4 kU/mL (NR <1.0 kU/mL)
Thyroid peroxidase (TPO) antibody	538000 IU/L (NR 0. 0-34900 IU/L)
Thyroid-stimulating hormone (TSH)	0.79 uIU/mLmIU/L (NR 0.4–4.5 uIU/mLmIU/L)
Free thyroxine (T4)	15.45 pmol/L (NR 10.30-23.17 pmol/L)

Abbreviations: NR, normal range

Table 3. Diagnostic tests performed on August 28, 2018

Diagnostic test	Result
Gliadin IgG	Positive, 20.6 kU/L (NR 0.0–14.9 kU/L; positive for >14.9 kU/L)
Gliadin IgA	Positive, 18.3 kU/L (NR 0.0–14.9 kU/L)
Gliadin TTG	Positive, 15 kU/L (NR 0.0–14.9 kU/L)

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; NR, normal range; TTG, tissue transglutaminase

Table 4. Diagnostic tests and treatment timeline from August 28, 2018 until January 7, 2020

Date	TSH (mIU/L) NR 0.34–4.82	Free T4 (pmol/L) NR 10.30–23.17	Additional tests	Dose of L-T4 (µg)/ action taken
Aug 28, 2018	3.57	11.97	Gliadin IgG: Positive, 20.6 kU/L (NR 0.0–14.9 kU/L; positive for >14.9 kU/L) Gliadin IgA: Positive, 18.3 kU/L (NR 0.0–14.9 kU/L) Gliadin TTG: Positive, 15 kU/L (NR 0.0–14.9 kU/L)	Generic L-T4 changed to Synthroid® and dose raised to 137 µg due to hypothyroid symptoms of fatigue and mental fogginess **Concomitant intervention: gluten-free diet**

Nov 6, 2018	0.77	13.13	-	137
May 30, 2019	3.20	13.26	-	**Switched to L-T4 oral solution** (Tirosint®-SOL) 125 µg due to persistent hypothyroid symptoms
Aug 13, 2019	0.45	14.80	-	125 (symptoms improved significantly)
Sep 18, 2019	0.37	14.67	-	125
Jan 7, 2020	0.51	15.06	-	125 (patient continues to feel fine)

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; L-T4, levothyroxine; NR, normal range; T4, free thyroxine; TSH, TSH, thyroid-stimulating hormone; TTG, tissue transglutaminase

Acknowledgements

The author wishes to acknowledge Diane Kwiatkoski and Chrysi Petraki of IQVIA for assistance in preparation of this manuscript. Funding for preparation of this manuscript was provided by IBSA, Pharma Inc., Parsippany, NJ.

Conflicts of Interest

The author declares that he has no conflicts of interest.

Data Availability

The data that support this case report are available from the author upon reasonable request.