Submitted: 14.06.2022
Accepted: 21.07.2022
Early publication date: 06.10.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0078
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 5/2022

Liquid levothyroxine improves thyroid control in patients with different hypothyroidism aetiology and variable adherence — case series and review

Marek Ruchała[1*], *Artur Bossowski*[2], *Magdalena M. Brzózka*[3*], *Małgorzata Gietka-Czernel*[4], *Alicja Hubalewska-Dydejczyk*[5], *Beata Kos-Kudła*[6], *Andrzej Lewiński*[7], *Anhelli Syrenicz*[8], *Wojciech Zgliczyński*[4]

[1]*Department of Endocrinology, Metabolism, and Internal Medicine, University of Medical Sciences, Poznań, Poland*
[2]*Department of Paediatrics, Endocrinology, and Diabetes with a Cardiology Division, Medical University of Białystok, Białystok, Poland*
[3]*Medical Department, IBSA Poland*
[4]*Department of Endocrinology, Medical Centre of Postgraduate Education, Warsaw, Poland*
[5]*Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland*
[6]*Department of Endocrinology and Neuroendocrine Tumours, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*
[7]*Department of Endocrinology and Metabolic Disorders, Medical University of Łódź, Poland, Polish Mother's Memorial Hospital — Research Institute, Łódź, Poland*
[8]*Department of Endocrinology, Pomeranian Medical University, Szczecin, Poland*
**These authors contributed equally.*

Abstract

It is estimated that hypothyroidism treatment may be either suboptimal or excessive in about 32–45% patients treated with L-thyroxine (LT4). There are multiple possible causes of poor control of hypothyroidism, including narrow LT4 therapeutic index, food and drug interactions, comorbidities, and patient non-adherence. Some of these obstacles could possibly be overcome with the novel liquid LT4 formulation. Liquid LT4 reaches maximum blood concentration about 30 minutes faster than the tablet form. Faster pharmacokinetics might lead to more efficient LT4 absorption, as suggested by a recent real-world study in patients with primary and central hypothyroidism. Liquid LT4 treatment led to increased free thyroxine (FT4) and sex hormone binding globulin (SHBG) with decreased low-density lipoprotein (LDL) cholesterol concentration and substantially improved quality of life for the patients. Herein we present a series of 31 patients with hypothyroidism of different aetiologies treated with the novel liquid LT4 formulation in standard clinical care in light of the latest scientific publications on liquid LT4 formula. We observed normalization of thyroid function tests shortly after introduction of liquid LT4, irrespective of concurrent diseases or concomitant medications that could diminish LT4 absorption. In more detail, the treatment with liquid LT4 managed to normalize thyroid-stimulating hormone (TSH) concentrations in patients without any known causes of LT4 absorption disturbances, as well as in those with malabsorption: with gastric bypass, partial small and large intestine resection, scleroderma, gluten intolerance, celiac disease, atrophic gastritis, and polytherapy. In conclusion, considering many factors disturbing LT4 absorption, hypothyroidism therapy with liquid LT4 seems to be a particularly effective option. **(Endokrynol Pol 2022; 73 (5): 893–902)**

Key words: *hypothyroidism; Hashimoto's thyroiditis; liquid levothyroxine; compliance; adherence; drug absorption; drug formulation; malabsorption; quality of life (QoL)*

Introduction

Hypothyroidism is a common endocrine disorder affecting about 5% of the population [1, 2]. The standard of care involves long-term substitution therapy with synthetic thyroid hormone, L-thyroxine (LT4). Even though there are treatment guidelines available for multiple clinical scenarios, LT4 therapy is either suboptimal or excessive in about 32–45% of cases [3]. Further, more than three-quarters of patients on tablet LT4 therapy complain about poor quality of life (QoL) and low treatment satisfaction [4–6].

There are numerous possible causes of poor control of hypothyroidism. LT4 has a narrow therapeutic index, i.e. the difference between the minimum effective concentration and the minimum toxic concentration

Marek Ruchała, Department of Endocrinology, Metabolism, and Internal Medicine, University of Medical Sciences, Poznań, Poland; e-mail: mruchala@ump.edu.pl
Magdalena M. Brzózka, Medical Department, IBSA Poland; e-mail: magdalena.brzozka@ibsapoland.pl

in the blood is small; therefore, even small dose alterations may result in significant clinical effects. Moreover, drug absorption may be altered by many factors, such as the patient's concurrent conditions (*H. pylori* infection, celiac disease, lactose intolerance, gastroparesis), concomitant drugs (proton-pump inhibitors, calcium-, magnesium-, and aluminium-containing compounds, ferrous sulphate, tricyclic antidepressants, β-blockers, ciprofloxacin, simethicone, sucralfate, raloxifene, orlistat), and food intake (milk, soy, coffee, papaya, grapefruit juice, fibre) [7]. Therefore, prescribing information of most marketed LT4 products advises taking the drug at least 30 minutes before breakfast; however, the American Thyroid Association and the European Thyroid Association recommend administration at least 60 minutes prior to breakfast or at bed-time at least 3 hours after the last meal [8, 9].

It is not surprising that many patients find this treatment regimen challenging. Gastrointestinal disorders restricting LT4 absorption may affect more than 60% of the global population [10]. Moreover, in a large survey among 1000 patients treated for hypothyroidism, about half of the respondents reported taking dietary supplements that could interfere with LT4 absorption, about 60% consumed such food, and more than 40% of patients reported taking their medication less than 30 minutes before breakfast, sometimes even during the day [11].

To overcome pharmacokinetic barriers, novel LT4 formulations have been developed, including gel capsule and liquid forms. A study of 3 different LT4 formulations revealed that liquid LT4 reaches maximum blood concentration about 30 minutes faster than the tablet form [12], probably because the phase of tablet disintegration is omitted. Notably, liquid LT4 displays similar bioavailability whether administered 30 min or 15 min before a high-fat, high-calorie breakfast [13]; thus, this formulation might substantially improve treatment outcomes in hypothyroid patients. Faster pharmacokinetics might lead to better LT4 absorption [12], as suggested by a real-world study in which liquid LT4 treatment led to increased free thyroxine (FT4) and sex hormone binding globulin (SHBG) with decreased low-density lipoprotein (LDL) cholesterol concentration and substantially improved QoL in patients with primary and central hypothyroidism [14].

Patient management with liquid levothyroxine

This is the first multicentre study describing outcomes of liquid, alcohol-free LT4 formulation therapy in patients with hypothyroidism, who struggled to achieve euthyroidism with previous therapy with LT4 tablets.

Data were gathered in 2020–2021 at 7 endocrinology centres in Poland by 8 endocrinologists during routine clinical practice and retrospectively extracted from medical records. The choice of which patient data to include in the study was an independent physician's decision, to illustrate typical everyday practice. Patients with poor hypothyroidism control, who had been either switched from LT4 tablet formulation to liquid LT4 Tirosint-SOL or prescribed Tirosint-SOL as the first LT4 preparation, were included and followed-up for several weeks up to achievement of euthyroidism. There were no exclusion criteria applied, to reflect the outcomes in real-world setting. To measure the outcomes, we analysed the results of laboratory tests, relief of symptoms, and patient-reported satisfaction.

We analysed the data of 31 patients (30 females and one male). Most of the patients had hypothyroidism due to Hashimoto's disease (n = 12), post-operative hypothyroidism (n = 9), or needed therapy optimization due to pregnancy (n = 5). Two patients had hypothyroidism due to treatment for Graves' disease (one with concurrent neuroendocrine tumour [NET] grade 2), and one newborn had congenital hypothyroidism. Two of the described cases displayed panhypopituitarism (n = 2) after pituitary surgery.

Patient characteristics and clinical data are presented in Table 1.

Hashimoto's disease

Patient 1

A 38-year-old woman with a busy lifestyle due to a challenging job was diagnosed with Hashimoto's disease at the age of 24; she had no concurrent diseases. She reported having problems achieving euthyroidism during the past year and complained of dry skin and fatigue. She was treated with 100 μg LT4 in tablet form. In February 2021, her TSH was 6.423 mIU/L. Her LT4 dose was increased to 100 μg 5 days a week and 125 μg twice a week; however, in April 2021 her TSH increased to 8.18 mIU/L and FT4 was 11.8 pmol/L. The patient did not report any new symptoms; her body weight was stable (50 kg); complete blood test, ferritin, vitamin B12, and albumin were within normal ranges. Antibodies against gliadin, tissue transglutaminase, and gastric parietal cells were negative. *Helicobacter pylori* stool test was negative.

At the end of April 2021, it was decided to switch from LT4 tablets to a liquid formulation at a dose of 112 μg. In June 2021, her TSH was 0.287 mIU/L and FT4 was 19.6 pmol/L. Subsequently, the dose was adjusted to 100 μg daily, and in September 2021 her TSH was normalized at 1.33 mIU/L. The patient felt well and was satisfied with the new treatment.

Table 1. *Patients' characteristics and clinical data*

	Sex, age [years]	Therapy with tablet LT4		Therapy with liquid LT4		Further management
		LT4 daily dose [μg]	TSH [μU/mL]	LT4 daily dose [μg]	TSH [μU/mL]	
Hashimoto's disease						
Patient 1	Female, 38	100 × 5/125 × 2/week	8.18	100	1.33	Continuation of the reduced dose of liquid LT4
Patient 2 + RYGB	Female, 55	200	9.8	175	1.2	Continuation of the reduced dose of liquid LT4
Patient 3 + gluten intolerance + inflammatory bowel disease	Female, 50	150	33.7	137	0.051	Dose reduction to 112 μg
Patient 4 + patient preference	Female, 35	137	2.3	125	2.1	
Patient 5	Female, 37	50	5.46	50	2.43	Continuation of liquid LT4
Patient 6	Female, 47	75/100	4.17	88	1.37	Continuation of liquid LT4
Patient 7 + Alzheimer's disease	Female, 77	50	20.11	100	3.7	
Patient 8	Female, 41	125	4.89	150	0.21	Dose reduction to 137 μg
Patient 9 + Addison's disease + celiac disease	Female, 14	100/175	8–22	125	3.5	Dose reduction to 100 μg
Patient 10 + type 1 diabetes mellitus	Female, 8	50	21	50/38	4.5	
Patient 11	Female, 58	125	36	150/175	6.8	TSH value after 7-day post switch. No follow-up
Patient 12	Female, 51	50	4.38	50 × 6/75 × 1/week	1.98	
Thyroidectomy						
Patient 13 + MEN 2a + adrenalectomy	Male, 26	125	5.6–12	125	1.8	Continuation of treatment with the same dose of liquid LT4
Patient 14 + partial small and large intestine resection	Female, 76	250	73.7	75	Within normal ranges	TSH normalized after 10 days of therapy
Patient 15 + parathyroid insufficiency	Female, 31	200 + 25	1.0	200	0.073	
Patient 16 + scleroderma	Female, 43	250	5.26	275	0.068	
Patient 17	Female, 52	137	50.92	137/150	5.46	Measured after 2 months post-switch Liquid LT4 dose increased to 150 μg
Patient 18 + adenocarcinoma	Female, 71	75/100	48.01	100	4.6	Measured 20 days after the switch
Patient 19 + parathyroid insufficiency + polytherapy	Female, 35	175	34.2	175	16.4	Liquid LT4 dose increased to 175 μg five times a week and 200 μg twice a week

→

Table 1. *Patients' characteristics and clinical data*

	Sex, age [years]	Therapy with tablet LT4		Therapy with liquid LT4		Further management
		LT4 daily dose [μg]	TSH [μU/mL]	LT4 daily dose [μg]	TSH [μU/mL]	
Patient 20	Female, 48	187.5	6.11	200	0.1	After 6 weeks of treatment
Patient 21	Female, 17	–	3.2	125	0.08	
Pregnancy						
Patient 22 + post-operative hypothyroidism	Female, 38	175 × 4/200 × 3 per week	6.6	175 × 4/200 × 3 per week	1.4	Continuation of treatment with the same dose of liquid LT4
Patient 23 + celiac disease	Female, 26	125	5.2	125 × 5/150 ×2/week	1.6	
Patient 24 + lifestyle issue	Female, 34	200	3.9	175/200	2.51	
Patient 25 + vomiting	Female, 36	75	2.3 (I trimester)	50	2.31 (II trimester)	
Patient 26	Female, 36	125/150	3.9	137	0.98	
Graves' Disease						
Patient 27 + NET G2 + polytherapy	Female, 44	75	4.9	75	1.89	
Patient 28	Female, 15	–	21.08	25	3.08	Liquid LT4 dose reduction to 13 μg
Newborn with congenital hypothyroidism						
Patient 29	Female, newborn	–	294.9 (10 days after birth)	50	2.31 (3 weeks after birth)	Liquid LT4 dose reduction to 25/13 μg at 8 weeks resulting in TSH 3.03 at 12 weeks of age
Central hypothyroidism						
	Sex, age [years]	**Tablet LT4 daily dose [μg]**	**FT3 and FT4 concentration**	**Liquid LT4 daily dose [μg]**	**FT3; FT4 concentration**	
Patient 30 Pituitary tumour and post-surgery multihormonal insufficiency + ischemic stroke + COVID-19 complications	Female, 60	112	FT3 — 0.87 pmol/L; FT4 — 10.0 pmol/L	112	FT4 — 16.6 pmol/L	FT3 and FT4 increase within a few days
Patient 31 + acromegaly + post-surgery multihormonal pituitary insufficiency	Female, 65	100	FT3 — 1.33 pg/mL; FT4 — 1.04 ng/dL	88	FT3 — 2.2 pg/mL; FT4 — 1.68 ng/dL	FT3 and FT4 increase within a few weeks

LT4 — L-thyroxine; THS — thyroid-stimulating hormone; RYGB — Roux-en-Y gastric bypass; FT3 — free triiodothyronine FT4 — free thyroxine

Patient 2

A 55-year-old woman with Hashimoto's disease underwent bariatric surgery (Roux en Y Gastric Bypass) due to morbid obesity with body mass index (BMI) of 44 kg/m^2. Before the surgery, she was taking LT4 in tablet form at a daily dose of 200 μg; her TSH was 3.5 mU/L and FT4 was 12.4 pmol/L. After the surgery, the patient lost 30 kg in 10 months, and her LT4 dose was not weight-adjusted. Her laboratory parameters worsened; TSH was 9.8 mU/L and FT4 was 10.5 pmol/L.

The patient reported muscle cramps and a slower rate of body mass reduction.

It was decided to introduce liquid LT4 at the same dose. After 2 months, her TSH was 3.1 mU/L and FT4 was 13.8 pmol/L, and she felt much better. Three months later, TSH dropped to 0.5 mIU/L; therefore, the liquid LT4 dose was decreased to 175 μg daily. After 2 months, TSH normalized to 1.2 mIU/L.

Patient 4

A 35-year-old woman with Hashimoto's disease had been undergoing treatment for 10 years with the tablet form of LT4 at a dose of 137 μg. Her TSH was normalized at 2.3 mIU/L; however, she was willing to try the novel alternative liquid drug form due to the possibility of administration without regard to food. After 3 months of liquid LT4 125 μg daily, TSH was 2.1 mIU/L.

Patient 12

A 51-year-old female was diagnosed with subclinical hypothyroidism 10 years ago, at the same time when an abnormal oral glucose tolerance was confirmed during pregnancy. Thyroid ultrasonography (US) was suggestive of autoimmunological thyroid inflammation; thyroglobulin antibodies (aTg) were 22.49 IU/mL (normal value < 4.11 IU/mL). She was treated with LT4 in tablet form at a dose of 50 μg with the following results: TSH — 5.56 mIU/L, FT4 — 13.5 pmol/L. After giving birth, the patient interrupted the treatment due to increased appetite. Her TSH was 2.02 mIU/L.

Three years ago, the patient presented to the endocrinology unit due to fatigue, weakness, feeling cold, and joint pain. TSH was 7.7 mIU/L, FT4 was 11.9 pmol/L, and aTg was 57.25 IU/mL. LT4 was re-introduced in tablet form at a dose of 50 μg. After 3 months, the drug was changed to another LT4 tablet preparation; however, the patient did not tolerate this drug well either. Her TSH was 4.38 mIU/L. The patient asked to switch the drug once again; therefore, liquid LT4 at a dose of 50 μg was introduced. The drug was well tolerated, but the patient continued feeling tired despite her TSH being within normal range (2.52 mIU/L). The liquid LT4 dose was increased to 75 μg given once a week and 50 μg given 6 times a week. Finally, her TSH reached 1.98 mIU/L and she felt well.

Thyroidectomy

Patient 13

A 26-year-old male had multiple endocrine neoplasia (MEN) type 2A and post-operative thyroid and adrenal insufficiency. As a child, he underwent prophylactic thyroidectomy. Over time, he developed pheochromocytomas of both adrenal glands, each followed by adrenalectomy. Establishing a therapeutic LT4 dose was difficult due to the patient's non-compliance. His TSH fluctuated between 5.6 and 12 mIU/L while on the LT4 tablet at a dose of 125 μg. The patient complained of fatigue. Unfortunately, after attempting to increase the LT4 dose to 137 μg, the patient presented with signs of thyrotoxicosis factitia (palpitations).

Fluctuations of thyroid hormones were particularly dangerous in this patient due to his underlying condition. His elevated thyroid hormones increased the metabolism of hydrocortisone, resulting in decreased hydrocortisone blood concentration, which could be life-threatening. On the other hand, the uncontrolled hypothyroidism resulted in hyponatremia and disabled adrenal hormone substitution monitoring.

It was decided to switch from tablet to liquid LT4 at a daily dose of 125 μg. After 6 weeks of therapy, the patient's TSH was 2.3 mU/L, and after 12 weeks it was 1.8 mU/L. Liquid LT4 was continued, and the patient felt well.

Patient 16

A 43-year-old female presented to the endocrinology unit complaining of generalized oedema and hot flashes. On 9 June 2020, she was diagnosed with bifocal papillary carcinoma (Bethesda group V). On 30 July 2020, she underwent thyroidectomy and was subsequently treated with LT4 in tablet form at a dose of 150 μg (1.49 μg/kg). Post-operative histopathological examination revealed multifocal papillary thyroid carcinoma. On 11 August 2020, her TSH was 14.8 mIU/L and FT4 was 1.3 ng/dL. The LT4 dose was gradually in-creased, reaching 250 μg (2.7 μg/kg) on 17 November 2020, but TSH was still not suppressed (5.26 mIU/L). At that time, the patient was diagnosed with scleroderma.

It was decided to switch the drug to the liquid LT4 formulation at the same dose. On 10 February 2021, TSH was 3.89 mIU/L and the liquid LT4 dose was increased to 275 μg in order to achieve a recommended TSH concentration of 0.1–0.5 mIU/L [15]. On 12 April 2021, TSH was suppressed at 0.04 mIU/L, aTg was 11.4 IU/mL, and thyroglobulin (Tg) was < 0.04 ng/mL. The drug was continued at a dose of 275 μg. On 8 June 2021 TSH was 0.068 mIU/mL.

Patient 20

A 48-year-old woman presented to the endocrinology unit due to poor control of post-operative hypothyroidism. Her thyroid was removed during papillary carcinoma treatment. Even though the patient was taking high LT4 doses (187.5 μg, body weight 56 kg; 3.35 μg/kg), TSH was not suppressed (TSH — 6.11 mIU/L) while the recommended TSH concentration was between 0.1 and 0.5 mIU/L [15]. She admitted non-com-

pliance with taking the medicine at least 30 minutes before breakfast. Liquid LT4 was introduced at a dose of 200 μg daily. After 6 weeks of treatment, TSH decreased to 0.1 mIU/L.

Pregnancy

Patient 22

A 38-year-old woman was in the 23rd week of her third pregnancy (with a history of one caesarean section and one miscarriage) with post-operative hypothyroidism. Before the pregnancy, her BMI was 29 kg/m^2; she was treated with LT4 tablets at a dose of 125 μg.

During the current pregnancy, she was diagnosed with gestational hypertension and treated with methyldopa. The LT4 dose was increased to 175 μg three times a week and 200 μg four times a week (2.7 μg/kg); however, TSH was still elevated at 6.6 mIU/L and FT4 was 9.2 pmol/L. The goal TSH concentration while treating hypothyroidism in pregnancy is below 2.5 mIU/L as recommended by the Polish Endocrine Society [16] and the American Thyroid Society [17]. Thus, it was decided to switch from tablet LT4 to liquid form at the same dose. After 4 weeks, TSH decreased to 2.0 mIU/L and FT4 was 13.6 pmol/L. After another 4 weeks (31st week of pregnancy) TSH was 1.4 mIU/L and FT4 was 12.3 pmol/L.

Patient 25

A 36-year-old woman was undergoing treatment for Hashimoto's disease for 14 years. During her first pregnancy in 2015, she was treated with LT4 in tablet form at a dose of 75–100 μg. After delivery, her LT4 dose was decreased to 75 μg and her thyroid hormones were within normal ranges.

In 2021, during the first trimester of her second pregnancy, her TSH was 2.3 mIU/L. She complained of nausea and vomiting complicating drug intake. Therefore, the LT4 tablet dose was switched to a liquid formulation at a dose of 50 μg daily. At the 20th week of the pregnancy, the patient's TSH was 2.31 mIU/L.

Graves' disease

Patient 27 — Graves' disease with neuroendocrine tumour (NET) G2

On 2 February 2021, a 44-year-old woman attended the clinic due to intermittent abdominal pain and postprandial fullness in the epigastrium. Her medical history included type 1 diabetes mellitus diagnosed when she was 9 years old, Graves' disease diagnosed in 1999 and treated with ^{131}I isotope twice in 2000 and 2003, chronic kidney disease, and arterial hypertension. At gastroscopy, chronic atrophic gastritis and several polyps in the lower gastric body were noticed. Five polyps were removed; in histopathological examination, 2 of them, sized 2–3 mm, were diagnosed as neuroendocrine tumour (NET) G1 (Ki-67 1%) and 3 of them, sized 5–7 mm, as NET G2 (Ki-67 5%).

On 6 April 2021, the patient was hospitalized. She complained of chronic fatigue, weight gain, and dry skin. Computed tomography (CT) of the abdomen revealed nodular thickening of the gastric body sized 5 × 2.5 mm, hypodense lesions in the caudate lobe of the liver sized 5.5 mm, and post-COVID ground-glass opacity of the lungs. On 8 April 2021, laboratory tests showed increased chromogranin and gastrin concentrations, while urine serotonin and 5-hydroxyindoloacetic acid (5-HIO) concentrations were within normal ranges. Thyrotropin was 4.9 μIU/mL and FT4 was 1.34 ng/dL. Additionally, the patient had vitamin B12 deficiency. She was discharged from the hospital on 9 April 2021.

The patient was switched from LT4 tablets to liquid LT4 at the same dose of 75 μg daily. She was concomitantly treated with alfacalcidol, insulin aspart, insulin degludec, furosemide, and pentoxifylline. After 2 months of treatment, on 1 June 2021, TSH was 1.89 mIU/L and FT4 was 1.44 ng/dL. The patient reported improvement in well-being, body mass stabilization, and better diabetes control.

Patient 28

A 15-year-old girl with Graves' disease [TSH — 0.01 μIU/mL; FT4, 4.5 ng/dL; free triiodothyronine (FT3) — 8.62 pg/mL; TSH receptor antibodies (TRAb) — 18 IU/L at diagnosis] presented to the endocrinology department in November 2020 with the following control test results: TSH — 21.08 μIU/mL; FT3 — 3.15 pg/mL; FT4 — 0.615 ng/dL; TRAb — 12 IU/L. She had been treated with thiamazole for 2 months, at that time at a dose of 5 mg twice daily, orally.

To avoid drug-induced hypothyroidism, the thiamazole dose was reduced to 5 mg once daily and liquid LT4 25 μg was started. After 6 weeks, a significant improvement was observed: TSH was 5.08 μIU/mL and FT4 was 1.615 ng/dL. After another 3 months of therapy, her clinical condition was stable; TSH was 3.08 μIU/mL; FT4 was 1.43 ng/dL; TRAb was 4.5 IU/L. The patient was further treated with thiamazole 5 mg and liquid LT4 13 μg daily.

Newborn with congenital hypothyroidism

Patient 29

A girl born on 18 February 2021, with a birth weight of 3250 g and body length of 54 cm, with no family history of thyroid dysfunction, underwent a screening test 3 days after birth; her TSH was 78 μIU/mL (normal range:

1.38–12 μIU/mL). Ten days after birth, TSH reached 294.9 μIU/mL, FT4 was 0.134 ng/dL (normal ranges: 1.1–2.0 ng/dL), FT3 was 1.1 pg/mL (normal ranges: 2.0–5.2 pg/mL), thyroid peroxidase antibodies [aTPO] were > 5 IU/mL, creatinine was 0.71 mg/dL, and bilirubin was elevated at 11.08 mg/dL. Ultrasonography showed slightly enlarged thyroid with increased blood flow in colour and power Doppler. The baby had hearing impairment; Pendred syndrome was presumed.

Liquid LT4 was introduced at a dose of 25 μg for 2 days, then the dose was increased to 50 μg for 10 days. On 8 March 2021, laboratory tests were as follows: profound decrease in TSH to 2.31 μIU/mL, FT4 — 3.17 ng/dL, FT3 — 6.04 pg/mL, thyroglobulin > 500.0 ng/mL, total bilirubin — 10.47 mg/dL, and creatinine — 0.5 mg/dL. Thyroid autoantibodies were within normal ranges (aTPO — 7.8 IU/mL; aTg — 14.0 IU/mL). The LT4 dose was subsequently decreased to 38 μg. On 15 March 2021, when the baby was 4 weeks old, TSH was 1.11 μIU/mL, FT4 — 2.19 ng/dL, FT3 — 5.1 pg/mL, total bilirubin — 6.57 mg/dL, and creatinine — 0.32 mg/dL. On 17 March 2021, the drug dose was reduced to 25 μg. During the next 4 weeks, TSH concentration gradually decreased, reaching 0.85 μIU/mL on 13 April 2021; LT4 was 1.66 ng/dL, LT3 — 4.62 pg/mL, aTPO — 5.5 IU/mL, total bilirubin — 1.77 mg/dL, creatinine — 0.3 mg/dL, and vitamin D3 was 40 ng/mL. The baby showed noticeable psychomotor improvement and reacted to auditory stimuli. There were no auditory system abnormalities revealed in audiological evaluation; therefore, the initial diagnosis of Pendred syndrome was excluded.

On 14 April 2021, the LT4 dose was decreased to 25/13 μg administered every other day. On 12 May 2021, when the baby was 12 weeks old, TSH was normalized at 3.03 μIU/mL, LT4 was 1.62 ng/dL, and FT3 was 4.23 pg/mL. The drug dosage was maintained at 25/13 μg administered every other day. Thyroid hormones were normalized, and the baby was developing properly. After one year of therapy the patient is euthyroid with normal psychomotor development (75th and 50th centiles of body length and mass, respectively).

Central hypothyroidism

Patient 30

A 60-year-old female with multihormonal hypopituitarism, ischemic stroke of the right hemisphere, and post-stroke dementia syndrome was hospitalized due to SARS-CoV-2 infection-induced pneumonia. After stabilization, the patient was transferred to the endocrinology department due to a life-threatening condition evoked by hormonal insufficiency.

In 1985 the patient had been operated due to a large chromophobic pituitary tumour, followed in 1986 by radiotherapy. Before hospitalization for COVID-19, she was treated with a morning hydrocortisone dose of 10 mg and desmopressin 60 μg twice a day, and an oral tablet LT4 112 μg daily.

Upon hospitalization, the patient was in a moderately severe general condition, circulatory and respiratory compensation, without verbal contact, fed with an industrial diet through a gastric tube. She received intravenous hydrocortisone, a preparation of LT4, and desmopressin by gavage. Thyroid hormone results were as follows: FT3 0.87 pmol/L (3.1–6.8), FT4 — 10.0 pmol/L (12.0–22.0), and TSH — 0.035 μIU/mL (0.27–4.20). A liquid LT4 preparation was implemented, achieving FT4 normalization of 16.6 pmol/L (12.0–22.0) within a few days.

Patient 31

A 65-year-old female patient after surgical removal (June 2020) of pituitary macroadenoma, compressing the pituitary stalk, modelling the optic chiasm, and causing symptoms of acromegaly and hyperprolactinemia. In September and October 2020, during her stay at the Department of Endocrinology and Metabolic Diseases, postoperative multi-hormonal pituitary insufficiency was confirmed, and no biochemical indicators of active acromegaly were found. In addition to substitution treatment with hydrocortisone (15 mg at 8.00 a.m. and 10 mg around 2:00 p.m.) and desmopressin (60 μg daily), the patient received LT4 substitution with tablets (75 μg/day, and then after 5 weeks the dose was increased to 100 μg/day). Regardless of the LT4 dose, the TSH concentration remained significantly decreased (0.13 IU/L), which confirmed secondary hypothyroidism; the level of free thyroxine (FT4) was in the low normal range (1.04 ng/dL, normal range: 0.93–1.7 ng/dL), while the level of FT3 was clearly decreased (1.14 pg/mL, normal range: 2.0–4.4 pg/mL). Increasing the dose of LT4 tablets to 100 μg did not have any significant effect on the hormonal constellation, and the very low level of FT3 (1.33 pg/mL) remained the most characteristic. Therefore, after 6 months of treatment with LT4 in tablet form, it was decided to switch to a liquid LT4 preparation (liquid LT4, 88 μg/day). This change resulted in normalization of FT3 concentration after a few weeks (low normal values — 2.2 pg/mL) and an increase in FT4 concentration (high normal values — 1.68 ng/dL). TSH levels remained consistently low (< 0.05 IU/L), which is typical of hypopituitarism. However, from the start of taking liquid LT4, the patient reported a significant improvement in general well-being and QoL, which was directly related to the intake of the LT4 liquid preparation. This proves that in cases of secondary hypothyroidism and TSH deficiency or lack thereof, faster absorption of the liquid LT4 preparation ensures more

effective T3 formation in the monodeiodination process, which gradually leads to the normalization of this hormone concentration.

Safety

The patients did not report any adverse events during therapy with liquid LT4. One patient complained of the unpleasant taste of the drug.

Discussion and literature review

We present 31 cases of patients who managed to achieve euthyroidism with liquid LT4 formulation. This group is largely heterogenous, with different hypothyroidism aetiologies, multiple or no comorbidities, polytherapy, and lifestyle and adherence issues that could have negatively influenced the outcomes of treatment with tablet LT4.

The effects of switching from tablet to an equal dose of liquid LT4 have been examined in numerous prospective studies concerning patients without factors that could alter LT4 absorption [18], as well as those with such conditions [19–23]. These studies have been selected and analysed in a meta-analysis by Virilli et al. [24]. In all studies, TSH significantly dropped after switching from tablet to liquid drug formulation. Of note, the mean difference between TSH values obtained during tablet and liquid LT4 therapy was most pronounced in patients who underwent bariatric surgery (5.7) [19] and in patients with LT4 malabsorption caused by calcium and iron supplements (5.53) [20], showing measurable clinical benefits yielded by improved pharmacokinetic properties of liquid LT4 formulation. However, another meta-analysis [25] of 8 studies, including 4 studies not analysed by Virilli et al., showed superiority of liquid LT4 in patients on replacement or suppressive therapy with malabsorption, while no significant differences were observed in those without malabsorption. In contrast, Fallahi et al. [18] showed significant TSH reduction in patients with Hashimoto's disease and post-operative hypothyroidism without LT4 malabsorption.

Indeed, in our study, liquid LT4 managed to normalize TSH concentrations in patients without any known causes of LT4 absorption disturbances, as well as in those with malabsorption: with gastric bypass (Patient 2), partial small and large intestine resection (Patient 14), scleroderma (Patient 16), gluten intolerance (Patient 3), celiac disease (Patient 9, Patient 23), atrophic gastritis (Patient 27), and polytherapy (Patient 19, Patient 27, Patient 29). Among numerous causes of LT4 malabsorption, intolerance to tablet excipients should also be mentioned [7, 26]. Tirosint-SOL is the first alcohol-free liquid LT4 formulation, containing only the active substance, glycerine, and water, thus minimizing the risk of excipient allergy or intolerance. Given that many patients might display diagnosed and undiagnosed gastrointestinal disorders, intolerances, and allergies, detailed medical history before LT4 therapy initiation is of crucial importance [27].

Importantly, problems in achieving good control of thyroid hormones concern not only patients with comorbidities or concomitant therapies, but also those who are unable to be compliant with drug administration 30–60 min before breakfast. Pseudomalabsorption (patient non-compliance) is increasingly acknowledged as the main cause of therapy failure despite high LT4 doses [27]. Trimboli et al. found that softgel and liquid LT4 formulations were effective regardless of the interval between drug administration and breakfast, and suggested considering them as the first-line therapy in patients with hypothyroidism [28]. Recent pharmacokinetic data showed that liquid LT4 displays similar bioavailability whether taken 30 min or 15 min before a high-fat, high-calorie breakfast [13], which might substantially improve treatment outcomes in hypothyroid patients, especially those with adherence issues. This approach is reflected in Patient 4, who preferred the novel liquid drug formulation and achieved the same clinical result with a decreased liquid LT4 dose compared to tablet form. Virilli et al., based on a comprehensive literature search, proposed a treatment algorithm advising liquid LT4 formulations according to patient preference, but also to patients treated with multiple drugs, with gastrointestinal disorders, intolerant to excipients, and to special populations (infants, unconscious, enterally fed, unable to swallow, and pregnant women) [29].

Notably, the issue of patients' QoL is drawing increasing attention as the main goal of the therapy. Dissatisfaction with LT4 treatment has been described repeatedly [6], and overall QoL has been reported as low by patients suffering from hypothyroidism [4, 5]. This suggests a growing need for the development of new treatments [4], which is confirmed by the results of a study conducted among Polish endocrinologists [30]. Therapy with novel liquid LT4 could improve patients QoL in several aspects. First, recent real-world data showed that euthyroid patients with hypothyroidism treated with liquid LT4 displayed (besides increased FT4 and SHBG and decreased LDL cholesterol concentration) an increase in QoL assessed with the ThyPRO questionnaire when compared with the QoL they perceived during therapy with tablet-form LT4 [14]. ThyPRO has been described as the most relevant and reliable QoL questionnaire for hypothyroidism [6], and it has been validated in Polish language [31]. The QoL was improved in 12 of 12 investigated catego-

ries in patients with primary hypothyroidism, and in 10 of 12 in patients with central hypothyroidism [14]. Second, as suggested by Ducharme et al., treatment with liquid LT4 could allow a shorter interval between administration of LT4 and food intake from 30 to 15 min because the pharmacokinetics of liquid LT4 is similar between both intake regimens [13]. Thus, increased convenience of therapy could improve patients' adherence and compliance.

Pregnant women are a particularly important population due to an increased demand for LT4 caused by hormonal factors, potential pregnancy complications and infant developmental delays resulting from decreased fT4 concentration, and nausea/vomiting that can restrict drug ingestion. In a retrospective study among pregnant woman with hypothyroidism, those who were treated with liquid LT4 needed dose adjustments significantly less often than those on tablet LT4 [32].

Liquid LT4 formulation may also be helpful in personalized congenital hypothyroidism therapy in infants [33]. As a drug with a narrow therapeutic index, LT4 dosing should be exceptionally precise in babies due to their low body mass. However, the minimal dose of 13 μg LT4 in liquid form could be challenging to divide in precisely defined smaller doses when needed in premature newborns. On the other hand, drug formulation should enable convenient administration. LT4 preparations compounded at pharmacies may not provide accurate and stable drug concentrations [34]; therefore, optimal solutions are still needed.

In a study of 78 infants with congenital hypothyroidism, liquid LT4 resulted in lower TSH values at 7–10 days and 6–8 months of therapy compared to tablet formulation [35]. Another study in a smaller group of patients showed faster TSH normalization but also suggested higher risk of overtreatment in newborns with severe hypothyroidism treated with liquid LT4 compared to tablets, highlighting the need for an individualized approach and increased therapy monitoring [33]. In our study, liquid LT4 managed to decrease TSH concentrations from 294.9 mIU/L to 2.31 mIU/L in just less than 2 weeks in a newborn with congenital hypothyroidism.

Although liquid LT4 formulation safety and efficacy has been investigated in numerous studies and clinical scenarios, this is one of the first reports on the new, alcohol-free liquid LT4 composition, containing only L-thyroxine, glycerol, and water. To date, outcomes of therapy with alcohol-free liquid LT4 have been described in a single-centre study in patients with primary and central hypothyroidism [14] and case studies concerning a newborn with congenital hypothyroidism and 21 trisomy [37], a patient with celiac and Addison's disease [38], patients with celiac disease, a pregnant patient with post-operative hypothyroidism, a patient with post-operative hypothyroidism due to Graves' disease [39], and in a patient with malabsorption due to multiple gastrointestinal disorders [40]. Our results seem to be in line with the previous reports, suggesting potential benefits of treatment with novel LT4 formulation.

This study has some limitations. Our study population is highly heterogenous in terms of hypothyroidism aetiology, age, comorbidities, and duration of follow-up; therefore, we were unable to perform statistical analysis of the obtained data. Moreover, lack of a comparative group disables drawing any firm conclusions about effectiveness and safety of the intervention. On the other hand, such a study design reflects real-world clinical practice and is free of selection bias, which is present in some studies with strict inclusion and exclusion criteria.

Conclusions

Considering many factors disturbing LT4 absorption, such as patient non-compliance, concurrent gastrointestinal diseases, infections, allergies (diagnosed or undiagnosed), and interactions with food or concomitant medicines, or poor QoL, hypothyroidism therapy with liquid LT4 seems to be a particularly effective option and can be considered as the treatment of choice.

Funding
This research received no external funding.

Institutional Review Board Statement
The study was approved by the Ethics Committee of the Polish Mother's Memorial Hospital — Research Institute in Lodz (no. 72/2021).

Acknowledgements
The authors would like to thank IBSA Poland and Proper Medical Writing for their support with manuscript preparation.

Disclosures
The following authors have received honoraria from companies: M.R. — Novartis, Pfizer, Ipsen, Berlin-Chemie Menarini, Genzyme, Merck, IBSA; A.B. — Pfizer, Ipsen, IBSA, NovoNordisk, Eli Lilly, Sandoz; M.G.C. — Berlin-Chemie Menarini, Merck, IBSA; A.H.D. — IBSA, Pfizer, Ipsen, Recordati, Merck, Berlin-Chemie/Menarini; B.K.K. — Novartis, Pfizer, Ipsen, Recordati, Merck, IBSA; A.S. — Berlin-Chemie Menarini, IBSA, Ipsen, Recordati, Merck; W.Z. — Novartis, Pfizer, Ipsen, Recordati, Merck, IBSA; M.M.B. is employee of Medical Department at IBSA Poland; A.L. — declares no conflict of interests.

References

1. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, et al. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014; 99(3): 923–931, doi: 10.1210/jc.2013-2409, indexed in Pubmed: 24423323.
2. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin

Endocrinol Metab. 2002; 87(2): 489–499, doi: 10.1210/jcem.87.2.8182, indexed in Pubmed: 11836274.
3. 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, doi: 10.1007/s40618-017-0706-y, indexed in Pubmed: 28695483.
4. Peterson SJ, Cappola AR, Castro MR, et al. An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction. Thyroid. 2018; 28(6): 707–721, doi: 10.1089/thy.2017.0681, indexed in Pubmed: 29620972.
5. Mitchell AL, Hegedüs L, Žarković M, et al. Patient satisfaction and quality of life in hypothyroidism: An online survey by the british thyroid foundation. Clin Endocrinol (Oxf). 2021; 94(3): 513–520, doi: 10.1111/cen.14340, indexed in Pubmed: 32978985.
6. Hegedüs L, Bianco AC, Jonklaas J, et al. Primary hypothyroidism and quality of life. Nat Rev Endocrinol. 2022; 18(4): 230–242, doi: 10.1038/s41574-021-00625-8, indexed in Pubmed: 35042968.
7. Virili C, Antonelli A, Santaguida MG, et al. Gastrointestinal Malabsorption of Thyroxine. Endocr Rev. 2019; 40(1): 118–136, doi: 10.1210/er.2018-00168, indexed in Pubmed: 30476027.
8. Jonklaas J, Bianco AC, Bauer AJ, et al. 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; 24(12): 1670–1751, doi: 10.1089/thy.2014.0028, indexed in Pubmed: 25266247.
9. Pearce SHS, Brabant G, Duntas LH, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J. 2013; 2(4): 215–228, doi: 10.1159/000356507, indexed in Pubmed: 24783053.
10. Castellana M, Castellana C, Giovanella L, et al. Prevalence of gastrointestinal disorders having an impact on tablet levothyroxine absorption: should this formulation still be considered as the first-line therapy? Endocrine. 2020; 67(2): 281–290, doi: 10.1007/s12020-019-02185-4, indexed in Pubmed: 31953721.
11. McMillan M, Rotenberg KS, Vora K, et al. Comorbidities, Concomitant Medications, and Diet as Factors Affecting Levothyroxine Therapy: Results of the CONTROL Surveillance Project. Drugs R D. 2016; 16(1): 53–68, doi: 10.1007/s40268-015-0116-6, indexed in Pubmed: 26689565.
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; 62(12): 631–636, doi: 10.1055/s-0032-1329951, indexed in Pubmed: 23154888.
13. Ducharme M, Scarsi C, Bettazzi E, et al. A Novel Levothyroxine Solution Results in Similar Bioavailability Whether Taken 30 or Just 15 Minutes Before a High-Fat High-Calorie Meal. Thyroid. 2022; 32(8): 897–904, doi: 10.1089/thy.2021.0604, indexed in Pubmed: 35469428.
14. Bornikowska K, Gietka-Czernel M, Raczkiewicz D, et al. Improvements in Quality of Life and Thyroid Parameters in Hypothyroid Patients on Ethanol-Free Formula of Liquid Levothyroxine Therapy in Comparison to Tablet LT4 Form: An Observational Study. J Clin Med. 2021; 10(22), doi: 10.3390/jcm10225233, indexed in Pubmed: 34830515.
15. Jarząb B, Dedecjus M, Lewiński A, et al. Diagnosis and treatment of thyroid cancer in adult patients — Recommendations of Polish Scientific Societies and the National Oncological Strategy. 2022 Update [Diagnostyka i leczenie raka tarczycy u chorych dorosłych — Rekomendacje Polskich Towarzystw Naukowych oraz Narodowej Strategii Onkologicznej. Aktualizacja na rok 2022]. Endokrynol Pol. 2022; 73(2): 173–300, doi: 10.5603/EP.a2022.0028, indexed in Pubmed: 35593680.
16. Hubalewska-Dydejczyk A, Trofimiuk-Müldner M, Ruchala M, et al. Thyroid diseases in pregnancy: guidelines of the Polish Society of Endocrinology [Choroby tarczycy w ciąży: zalecenia postępowania Polskiego Towarzystwa Endokrynologicznego]. Endokrynol Pol. 2021; 72(5): 425–488, doi: 10.5603/EP.a2021.0089, indexed in Pubmed: 34855189.
17. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017; 27(3): 315–389, doi: 10.1089/thy.2016.0457, indexed in Pubmed: 28056690.
18. Fallahi P, Ferrari SM, Antonelli A. Oral L-thyroxine liquid versus tablet in patients with hypothyroidism without malabsorption: a prospective study. Endocrine. 2016; 52(3): 597–601, doi: 10.1007/s12020-015-0836-y, indexed in Pubmed: 26721663.
19. Fallahi P, Ferrari SM, Camastra S, et al. TSH Normalization in Bariatric Surgery Patients After the Switch from L-Thyroxine in Tablet to an Oral Liquid Formulation. Obes Surg. 2017; 27(1): 78–82, doi: 10.1007/s11695-016-2247-4, indexed in Pubmed: 27272506.
20. Benvenga S, Di Bari F, Vita R. Undertreated hypothyroidism due to calcium or iron supplementation corrected by oral liquid levothyroxine. Endocrine. 2017; 56(1): 138–145, doi: 10.1007/s12020-017-1244-2, indexed in Pubmed: 28155174.
21. Vita R, Saraceno G, Trimarchi F, et al. Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. J Clin Endocrinol Metab. 2014; 99(12): 4481–4486, doi: 10.1210/jc.2014-2684, indexed in Pubmed: 25259910.
22. Brancato D, Scorsone A, Saura G, et al. Comparison of TSH Levels with Liquid Formulation Versus Tablet Formulations of Levothyroxine in the Treatment of Adult Hypothyroidism. Endocr Pract. 2014; 20(7): 657–662, doi: 10.4158/EP13418.OR, indexed in Pubmed: 24449674.
23. Vita R, Di Bari F, Benvenga S. Oral liquid levothyroxine solves the problem of tablet levothyroxine malabsorption due to concomitant intake of multiple drugs. Expert Opin Drug Deliv. 2017; 14(4): 467–472, doi: 10.1080/17425247.2017.1290604, indexed in Pubmed: 28151692.
24. Virili C, Giovanella L, Fallahi P, et al. 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, doi: 10.3389/fendo.2018.00010, indexed in Pubmed: 29434573.
25. Laurent I, Tang S, Astère M, et al. Liquid L-thyroxine versus tablet L-thyroxine in patients on L- thyroxine replacement or suppressive therapy: a meta-analysis. Endocrine. 2018; 61(1): 28–35, doi: 10.1007/s12020-018-1574-8, indexed in Pubmed: 29572710.
26. Ruchała M, Szczepanek-Parulska E, Zybek A. The influence of lactose intolerance and other gastro-intestinal tract disorders on L-thyroxine absorption. Endokrynol Pol. 2012; 63(4): 318–323, indexed in Pubmed: 22933169.
27. Bellastella G, Caputo M, Maiorino MI, et al. EMPATHY: A New Tool for Identifying the Most Suitable Thyroxine Formulation in Hypothyroid Patients. Thyroid. 2019; 29(7): 928–933, doi: 10.1089/thy.2018.0493, indexed in Pubmed: 30963820.
28. Trimboli P, Scappaticcio L, De Bellis A, et al. Different Formulations of Levothyroxine for Treating Hypothyroidism: A Real-Life Study. Int J Endocrinol. 2020; 2020: 4524759, doi: 10.1155/2020/4524759, indexed in Pubmed: 32184819.
29. Virili C, Trimboli P, Romanelli F, et al. Liquid and softgel levothyroxine use in clinical practice: state of the art. Endocrine. 2016; 54(1): 3–14, doi: 10.1007/s12020-016-1035-1, indexed in Pubmed: 27473098.
30. Bednarczuk T, Attanasio R, Hegedüs L, et al. Use of thyroid hormones in hypothyroid and euthyroid patients: a THESIS* questionnaire survey of Polish physicians. *THESIS: Treatment of hypothyroidism in Europe by specialists: an international survey. Endokrynol Pol. 2021; 72(4): 357–365, doi: 10.5603/EP.a2021.0048, indexed in Pubmed: 34010443.
31. Sawicka-Gutaj N, Watt T, Sowiński J, et al. ThyPROpl — The Polish version of the thyroid-specific quality of life questionnaire ThyPRO. Endokrynol Pol. 2015; 66(4): 367–380, doi: 10.5603/EP.2015.0047, indexed in Pubmed: 26323475.
32. Cappelli C, Negro R, Pirola I, et al. Levothyroxine liquid solution versus tablet form for replacement treatment in pregnant women. Gynecol Endocrinol. 2016; 32(4): 290–292, doi: 10.3109/09513590.2015.1113518, indexed in Pubmed: 26585420.
33. Kucharska AM, Beń-Skowronek I, Walczak M, et al. Congenital hypothyroidism - Polish recommendations for therapy, treatment monitoring, and screening tests in special categories of neonates with increased risk of hypothyroidism. Endokrynol Pol. 2016; 67(5): 536–547, doi: 10.5603/EP.2016.0062, indexed in Pubmed: 27828692.
34. Meyer LM, Stephens K, Carter CA, et al. Stability and consistency of compounded oral liquid levothyroxine formulations. J Am Pharm Assoc (2003). 2020; 60(6): e168–e172, doi: 10.1016/j.japh.2020.05.014, indexed in Pubmed: 32591200.
35. Peroni E, Vigone MC, Mora S, et al. Congenital hypothyroidism treatment in infants: a comparative study between liquid and tablet formulations of levothyroxine. Horm Res Paediatr. 2014; 81(1): 50–54, doi: 10.1159/000356047, indexed in Pubmed: 24247169.
36. Cassio A, Monti S, Rizzello A, et al. Comparison between liquid and tablet formulations of levothyroxine in the initial treatment of congenital hypothyroidism. J Pediatr. 2013; 162(6): 1264–9, 1269.e1, doi: 10.1016/j.jpeds.2012.11.070, indexed in Pubmed: 23312689.
37. Feldt MM. Delayed Diagnosis of Congenital Hypothyroidism in a Child with Trisomy 21 and Biotinidase Deficiency and Successful Use of Levothyroxine Sodium Oral Solution. Case Rep Endocrinol. 2020; 2020: 8883969, doi: 10.1155/2020/8883969, indexed in Pubmed: 33425403.
38. Asamoah E. Levothyroxine sodium oral solution to control thyroid function in a patient with hypothyroidism and celiac disease. Clin Case Rep. 2021; 9(5): e04170, doi: 10.1002/ccr3.4170, indexed in Pubmed: 34094556.
39. Ruchała M. Increased efficacy of hypothyroidism control with liquid levothyroxine [Większa skuteczność lewotyroksyny w postaci płynnej w wyrównywaniu niedoczynności tarczycy]. Endokrynol Pol. 2021; 72(3): 271–275, doi: 10.5603/EP.a2021.0049, indexed in Pubmed: 34292578.
40. Bohinc Henderson B. Levothyroxine Sodium Oral Solution Normalizes Thyroid Function in a Patient with Hashimoto's Disease, Gastritis, Diabetic Gastroparesis, and Small Intestinal Bacterial Overgrowth (SIBO). Int Med Case Rep J. 2021; 14: 627–632, doi: 10.2147/IMCRJ.S326481, indexed in Pubmed: 34557042.