

Effect of once weekly oral levothyroxine therapy

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Summary

Primary hypothyroidism is one of the most common endocrine disorders with widely available treatment. A minority of patients remain with uncontrolled hypothyroidism despite therapy. The objective of this case series was to demonstrate that medication non-adherence, rather than malabsorption, should be sought as the most common cause of unsuppressed TSH levels in patients receiving treatment for this condition. Non-adherence is often considered as a diagnosis of exclusion. Nonetheless, a diagnosis of malabsorption requires a more extensive workup, including imaging and invasive procedures, which increase healthcare costs and burden to the patient. The findings of this study allow for a cost-effective approach to uncontrolled hypothyroidism.

Learning points:

- Medication non-adherence is a common cause of insuppressible TSH levels.
- Once weekly levothyroxine is an alternative approach to non-compliant patients.
- Assessing compliance is more cost-effective and less burdensome than testing for malabsorption.

Background

Hypothyroidism is one of the most common endocrine disorders seen among Puerto Ricans, and levothyroxine (LT4) has been considered the gold-standard treatment for many years. A study by Gonzalez-Rodriguez *et al.* found a prevalence of hypothyroidism of 24.2% in a sample of 400 postmenopausal women in Puerto Rico (1).

Levothyroxine must be taken on an empty stomach for adequate absorption in the small intestine. This may compromise adherence to therapy in some patients who may not be willing to undergo fasting. The American Thyroid Association (ATA) guidelines on hypothyroidism suggest that taking levothyroxine at bedtime (3 or more h after the evening meal) may be the next best choice for those who not compliant with the fasting technique (2). A randomized crossover trial by Grebe *et al.* demonstrated that once weekly levothyroxine therapy was also a safe and effective method for treating hypothyroidism, without any associated toxicities (3).

Although it is agreed by many that non-compliance is the most common cause of TSH non-suppressibility in hypothyroid patients, this is a diagnosis of exclusion, and a careful review for possible medication interactions should be performed. For example, phenytoin, phenobarbital, carbamazepine, and rifampin are known to increase levothyroxine clearance. On the other hand, impaired absorption is seen with gastrointestinal disorders, such as *Helicobacter pylori*-related gastritis, Celiac disease, and Chron's disease, and certain medications, such as proton pump inhibitors, bile acid sequestrants, calcium carbonate, and ferrous sulfate (4). Despite the possible struggles in management, thyroid extracts are not recommended by the ATA for hypothyroid patients, due to potential safety concerns.

We present four cases of hypothyroid patients receiving high doses of either LT4 or LT4 plus liothyronine (LT3) and a non-suppressible TSH, despite reported



medication adherence. LT4 was administered at a dose of $1.6 \mu\text{g}/\text{kg} \times 7$, once weekly, as used by Jayakumari *et al.* (5) and Walker *et al.* (6). Currently, there are various protocols and no well-established standards for the levothyroxine absorption test, for which a 6-week weight-based approach was used. Data were collected using the same laboratory assay, technician, and facilities. Our patients were overweight or obese and denied weight loss, steatorrhea, nausea, or vomiting. Since no signs or symptoms of malabsorption were present, we believed that performing an extensive workup for this condition before testing for non-compliance would have been unnecessary and money- and time-consuming. Our study demonstrates the cost-effectiveness of testing for non-compliance before malabsorption. Nonetheless, this test may also be useful to identify concurrent malabsorptive problems.

Case presentation

Our first patient was a 52-year-old woman, weighing 62.5 kg, with persistently uncontrolled primary autoimmune hypothyroidism despite receiving Levoxyl 425 μg daily, for a total weekly dose of 2975 μg . This added up to a pre-study dose of 6.8 $\mu\text{g}/\text{kg}$. Hypothyroidism was diagnosed 5 years prior to the study. Her baseline TSH concentration was 56.33 mIU/L and FT4 was 0.04 ng/dL. She reported constipation, fatigue, cold intolerance, and a physical exam was remarkable for delayed deep tendon reflexes. She received a supervised total weekly dose of 700 μg of Synthroid, as calculated by weight, for a total of 6 weeks. At the end of the 6 weeks period, her TSH concentration was 0.75 mIU/L and FT4 was 1.47 ng/dL.

Our second patient was a 49-year-old obese male, weighing 122 kg, with uncontrolled primary autoimmune hypothyroidism, taking 375 μg daily, for a total weekly dose of 2625 μg . He had a pre-study dose of 3.1 $\mu\text{g}/\text{kg}$. Diagnosis was made approximately 10 years prior to the study. His baseline laboratories were remarkable for a TSH of 12.8 mIU/L and a FT4 of 0.66 ng/dL. Patient was asymptomatic. Our patient received a supervised total weekly dose of 1400 μg of Synthroid for 6 consecutive weeks. At the end of the study period, his TSH was 0.72 mIU/L and FT4 was 1.42 ng/dL.

Our third patient was a 46-year-old obese female, weighing 125 kg, with uncontrolled primary autoimmune hypothyroidism diagnosed 8 years ago, taking Synthroid 550 μg daily, for a total weekly dose of 3850 μg . She had a pre-study dose of 4.4 $\mu\text{g}/\text{kg}$ of LT4. Her baseline TSH was 4.92 mIU/L and FT4 was 1.19 mIU/L. Patient was asymptomatic. She received a supervised total weekly dose

of 1400 μg of Synthroid for 6 weeks. In week 3, laboratory results showed improvement in her thyroid function tests, with a TSH of 3.9 mIU/L and a FT4 of 2.27 ng/dL, which are above the reference range. Then, in week 6, an elevated TSH and normal FT4 were observed.

Our fourth patient was a 46-year-old obese female, weighing 103 kg, with uncontrolled primary autoimmune hypothyroidism diagnosed 7 years ago, despite taking Levoxyl 200 μg daily, for a total weekly dose of 1400 μg . She was receiving a pre-study dose of 2.0 $\mu\text{g}/\text{kg}$ of LT4. Her baseline TSH concentration was 17.42 mIU/L and FT4 was 0.78 ng/dL. At the moment of the study, she only reported fatigue and a physical exam was normal. She received a supervised total weekly dose of 1150 μg of Synthroid for the first 2 weeks. The dose was then reduced to 950 μg once weekly for the remainder of the study, due to the over suppression of TSH (0.23 mIU/L) and elevation of FT4 (2.77 ng/dL) with the initial calculated dose. At the end of the study, her TSH and FT4 levels were normal.

Treatment

Patients were treated with oral levothyroxine calculated as 1.6 $\mu\text{g}/\text{kg}$. The medication was provided as a single weekly dose, on Thursdays, for a total of 6 weeks.

Outcome and follow-up

The first and second patients in our case series demonstrated suppressibility of serum TSH values and normalization of FT4 levels with once weekly levothyroxine therapy by the end of the study period at week 6.

The third patient described in our case series was able to achieve suppressible serum TSH concentrations by week 3, together with increased levels of FT4, which demonstrated adequate levothyroxine absorption. Afterward, her serum TSH concentration increased and remained above the normal range. This is attributed to an interruption in the continuity of the study due to natural disasters (hurricanes Irma and Maria) in Puerto Rico during the time of the levothyroxine absorption test.

The fourth patient described in the case series exhibited over suppression of serum TSH by week 3, together with FT4 elevation, even though levothyroxine therapy was initially started at a dose calculated by weight. The dose was adjusted accordingly, and serum TSH and FT4 levels normalized by the end of the follow-up period at week 6.



Discussion

Medication non-adherence affects approximately 40–50% of patients with chronic diseases. Adherence to medical therapy is defined in most studies as taking 80% or more of the prescribed medication doses. Barriers to medication adherence include lack of patient motivation, depression, cognitive impairment, low educational level, drug or alcohol use, complexity, and costs of treatment, fear of side effects, poor physician-patient relationship, and asymptomatic disease (7).

Table 1 summarizes the baseline characteristics of our patients. As demonstrated in Figs 1 and 2, there is an overall trend toward suppressibility of serum TSH and an increase in FT4 after 6 consecutive weeks of once weekly levothyroxine bolus treatment, as determined by the patient's weight. All of the patients' calculated levothyroxine doses were less than the doses they had been receiving prior to the study and all patients had longstanding primary hypothyroidism, presumed to be of autoimmune etiology, given no history of thyroid surgery or radioiodine therapy. All patients tolerated the once weekly levothyroxine bolus without adverse effects. A workup for malabsorption was not performed in these patients in order to be cost-effective, given most patients were overweight or obese and they had no signs or symptoms suggesting this as a possible etiology.

The first and second patients in our case series demonstrated suppressibility of serum TSH values and normalization of FT4 levels with once weekly levothyroxine therapy. These results show that initial TSH non-suppressibility in these patients was clearly due to non-compliance with the medication regimen.

The third patient described in our case series was able to achieve suppressible serum TSH concentrations by week 3, together with increased levels of FT4, which demonstrated adequate levothyroxine absorption. Afterward, her serum TSH concentration increased and remained above the normal range. This is attributed to an interruption in the continuity of the study due to natural disasters (hurricanes Irma and Maria) in Puerto Rico during the time of the levothyroxine absorption test.

The fourth patient described in the case series exhibited over suppression of serum TSH by week 3, together with FT4 elevation, even though levothyroxine therapy was initially started at a dose calculated by weight. This strongly suggests that malabsorption is not present. The dose was adjusted accordingly, and serum TSH and FT4 levels were normalized by the end of the follow-up period. This demonstrates that when taken correctly and with adequate compliance, levothyroxine therapy is indeed capable of restoring euthyroidism.

We conclude that non-adherence to medical therapy was the most likely reason for non-suppressibility of serum TSH values in these patients who had been taking much larger doses of levothyroxine than merited by weight. In most cases, a thorough medical history and physical examination, including medication history and BMI, are enough to determine the cause for persistent uncontrolled hypothyroidism despite large doses of thyroxine replacement.

This condition in which the patient denies poor adherence is termed by some authors, pseudomalabsorption and often results in challenges in diagnosis and management. A complete malabsorption workup often includes a battery of blood tests and stool samples, together with radiologic imaging, endoscopy, and breath tests to determine a specific etiology. This process may be time-consuming, invasive, and results in higher costs and stress to the patient in the phase of an uncertain diagnosis. We believe that the evaluation of pseudomalabsorption with a supervised weekly levothyroxine bolus test is simple and cost-effective and should be done before a complete malabsorption workup unless the patient's symptoms clearly indicate otherwise. Gonzales *et al.* demonstrated the effectiveness of the levothyroxine absorption test in distinguishing malabsorption from pseudomalabsorption in patients with hypothyroidism, with 12 out of 13 patients proving to have non-adherence with therapy (8). Rangan *et al.* also demonstrated two case reports of patients who had uncontrolled hypothyroidism due to suspected non-compliance with treatment, but then achieved normal TSH levels after therapy was changed to weekly levothyroxine (4).

Table 1 Baseline characteristics of patients.

Patient	Age at diagnosis	Sex	Weight (kg)	Medication regimen pre-test	Baseline TSH (mIU/L)	Signs/symptoms
1	47	Female	62.5	Levoxyl at 6.8 µg/kg	56.33	Constipation, fatigue, cold intolerance, delayed deep tendon reflexes
2	39	Male	122	Synthroid at 3.1 µg/kg	12.8	Asymptomatic
3	38	Female	125	Synthroid at 4.4 µg/kg	4.92	Asymptomatic
4	39	Female	103	Levoxyl at 2 µg/kg	17.4	Fatigue

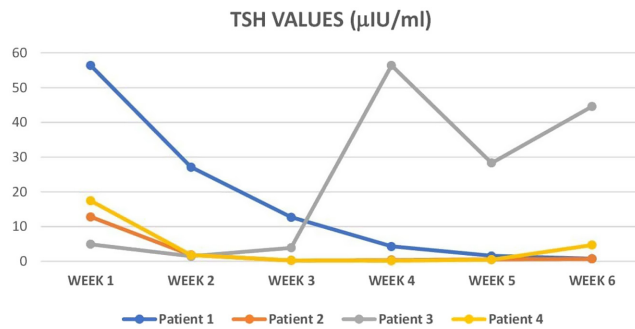


Figure 1
Weekly TSH values per patient.

Because the elimination half-life of thyroxine is approximately 7 days, it is plausible to administer once weekly thyroxine therapy in order to restore euthyroidism. Once weekly dosing helps maintain euthyroidism because intermittent administration of thyroxine may suppress antibody levels (9). Another mechanism is that at the end of the weekly treatment, when FT4 levels are considerably lower, there is more peripheral conversion of T4 to the metabolically active T3, whereas conversion of T4 to the metabolically inactive rT3, is decreased (3). Our results also aid us in avoiding the use of more complex replacement therapies that may result in higher costs and not necessarily control thyroid function tests. It has been demonstrated that the use of generic is as effective as brand-name levothyroxine in controlling thyroid dysfunction (10). Nonetheless, it is recommended that patients adhere to the same therapy throughout the treatment period, as the use of different formulations may impact the control of thyroid disease because they often have different bioavailability.

This case series demonstrates the cost-effectiveness of testing for pseudomalabsorption as an initial step. Using our first patient as a reference, before this study she was receiving 425 µg daily of LT4, resulting in a weekly cost of \$12.46 and a monthly cost of \$53.40, if calculated using one LT4 300 µg pill and a 125 µg pill. After the study, she needed 700 µg weekly of LT4, for a weekly cost of \$2.71 and a monthly cost of \$10.84. This was calculated using one 300 µg pill and two 200 µg pills. Medication compliance should be reinforced, and this will subsequently result in a significant reduction in cost with regards to pills, laboratory evaluation, and healthcare visits.

Potential limitations of our study are a small number of patients, one patient had an interruption in the continuity of treatment, and patients were not followed after the termination of the study to determine persistent compensation of thyroid function, as further follow-up was provided by Endocrinologists outside our clinics.

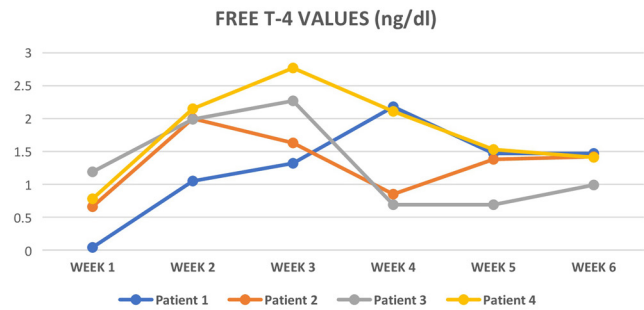


Figure 2
Weekly free T4 values per patient.

Strengths of the study include consistency of results and that the same laboratory assay, technician, and facilities were used for the duration of the study. Further studies could be performed to determine the effect of once weekly dosing on lipid homeostasis and quality of life.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written consent was obtained from patients.

Author contribution statement

Dr Del Toro-Diez was involved in the literature review, manuscript writing, and revision. Dr Ernesto Solá-Sánchez and Dr Michelle Mangual-García are Endocrinologists who were involved in patient care and manuscript revision.

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