

# Medication-Nonadherent Hypothyroidism Requiring Frequent Primary Care Visits to Achieve Euthyroidism

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**Background:** Nonadherence to medications is a common clinical issue. We describe a case in which weekly visits to assess medication adherence achieved euthyroidism in a patient with persistent primary hypothyroidism and suspected nonadherence to levothyroxine. The patient, however, did not report nonadherence.

**Case Presentation:** A male aged 67 years with multinodular goiter underwent total thyroidectomy for abnormal thyroid nodule biopsy. Surgical pathology revealed papillary thyroid cancer with lymph node metastasis for which he received radioactive iodine treatment. His plasma thyrotropin (TSH) was noted to be 0.28 uIU/mL (reference range 0.35-4.00 uIU/mL) 7 months postsurgery while taking 224 mcg levothyroxine tablets daily. His plasma TSH remained elevated for about 5 years despite titrations of the levothyroxine dosage, counseling, and multiple follow-up visits. A home care nurse was involved in monitoring the patient taking levothyroxine daily and correctly but was unsuccessful. The patient and his son reported taking

levothyroxine daily and correctly. The patient was asked to visit the primary care clinic every week for 6 weeks with all his medications. Repeat plasma TSH normalized to 1.01 uIU/mL. The suspected etiology of previously high plasma TSH was nonadherence to levothyroxine, which was discussed in detail with the patient. The patient verbalized understanding, was willing to follow recommendations and ended the weekly clinic visits. Repeat plasma TSH was again high and the patient claimed adherence, but weekly visits to primary care clinic were resumed, and life-threatening consequences of hypothyroidism were discussed with the patient and his son. After 9 weeks of visits, he was noted to have low plasma TSH (0.23 uIU/mL).

**Conclusions:** Weekly visits seem impractical but may help in cases of persistent hypothyroidism in which the patient admits to being or is suspected to be nonadherent to levothyroxine. Knowing their medication use will be checked at weekly clinic visits may motivate the patient to be adherent.

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Nonadherence to medications is an issue across health care. In endocrinology, hypothyroidism, a deficiency of thyroid hormones, is most often treated with levothyroxine and if left untreated can lead to myxedema coma, which can lead to death due to multiorgan dysfunction.<sup>1</sup> Therefore, adherence to levothyroxine is very important in preventing fatal complications.

We present the case of a patient with persistent primary hypothyroidism who was suspected to be nonadherent to levothyroxine, although the patient consistently claimed adherence. The patient's plasma thyrotropin (TSH) level improved to reference range after 6 weeks of weekly primary care clinic visits. After stopping the visits, his plasma TSH level increased again, so 9 more weeks of visits resumed, which again helped bring down his plasma TSH levels.

## CASE PRESENTATION

A male patient aged 67 years presented to the Dayton Veterans Affairs Medical Center (VAMC) endocrinology clinic for evaluation

of thyroid nodules. The patient reported no history of neck irradiation and a physical examination was unremarkable. At that time, laboratory results showed a slightly elevated plasma TSH level of 4.35 uIU/mL (reference range, 0.35-4.00 uIU/mL) and normal free thyroxine (T4) of 1.00 ng/dL (reference range, 0.74-1.46 ng/dL). Later that year, the patient underwent a total thyroidectomy at the Cincinnati VAMC for Hurthle cell variant papillary thyroid carcinoma that was noted on biopsy at the Dayton VAMC. After surgical pathology results were available, the patient started levothyroxine 200 mcg daily, although 224 mcg would have been more appropriate based on his 142 kg weight. Due to a history of arrhythmia, the goal plasma TSH level was 0.10 to 0.50 uIU/mL. The patient subsequently underwent radioactive iodine ablation. After levothyroxine dose adjustments, the patient's plasma TSH level was noted to be within his target range at 0.28 uIU/mL 3 months postablation.

Over the next 5 years the patient had regular laboratory tests during which his plasma TSH level rose and were typically high despite adjusting levothyroxine doses between

**TABLE** Patient's Plasma Thyrotropin and Free T4 Over Time

Variables	Initial visit	3 mo before thyroid removal	3 mo after radioactive iodine ablation	8 mo before weekly visits	After 6 weekly visits	4 mo after weekly visits stopped	After 2 mo of resumed weekly visits
Plasma thyrotropin, uIU/mL	4.35 <sup>a</sup> (H)	4.93 <sup>a</sup> (H)	0.28 <sup>a</sup> (L)	108.14 <sup>c</sup> (H)	1.01 <sup>c</sup>	80.72 <sup>c</sup> (H)	0.23 <sup>c</sup> (L)
Plasma free T4, ng/dL	1.00 <sup>b</sup>	1.00 <sup>b</sup>	1.60 <sup>b</sup> (H)	0.45 <sup>d</sup> (L)	1.82 <sup>d</sup> (H)	Not obtained	3.51 <sup>d</sup> (H)
Levothyroxine dose, mcg	0	0	224	300	300	300	300

Abbreviations: H, high level compared to reference range; L, low level compared to reference range; T4, thyroxine.

<sup>a</sup>Plasma thyrotropin reference range used by the contracted laboratory at the time of the test: 0.35-4.00 uIU/mL.

<sup>b</sup>Plasma free T4 reference range used by the contracted laboratory at the time of the test: 0.74-1.46 ng/dL.

<sup>c</sup>Reference range for plasma thyrotropin used by the contracted laboratory at the time of the test: 0.55-4.78 uIU/mL.

<sup>d</sup>Plasma free T4 reference range used by the contracted laboratory at the time of the test: 0.89-1.76 ng/dL.

200 mcg and 325 mcg. The patient received counseling on taking the medication in the morning on an empty stomach and waiting at least 1 hour before consuming anything, and he went to many follow-up visits at the Dayton VAMC endocrinology clinic. He reported no vomiting or diarrhea but endorsed weight gain once. The patient also had high free T4 at times and did not take extra levothyroxine before undergoing laboratory tests.

Nonadherence to levothyroxine was suspected, but the patient insisted he was adherent. He received the medication in the mail regularly, generally had 90-day refills unless a dose change was made, used a pill box, and had social support from his son, but he did not use a phone alarm to remind him to take it. A home care nurse made weekly visits to make sure the remaining levothyroxine pill counts were correct; however, the patient continued to have difficulty maintaining daily adherence at home as indicated by the nurse's pill counts not aligning with the number of pills which should have been left if the patient was taking the pills daily.

The patient was asked to visit a local community-based outpatient clinic (CBOC) weekly (to avoid patient travel time to Dayton VAMC > 1 hour) to check pill counts and assess adherence. The patient went to the CBOC clinic for these visits, during which pill counts indicated much better but not 100% adherence. After 6 weeks of clinic visits, his plasma TSH decreased to 1.01 uIU/mL, which was within the reference range, and the patient stopped coming to the weekly clinic visits (Table). Four

months later, the patient's plasma TSH levels increased to 80.72 uIU/mL. Nonadherence to levothyroxine was suspected again. He was asked to resume weekly clinic visits, and the life-threatening effects of hypothyroidism and not taking levothyroxine were discussed with the patient and his son. The patient made CBOC clinic visits for 9 weeks, after which his plasma TSH level was low at 0.23 uIU/mL.

## DISCUSSION

There are multiple important causes to consider in patients with persistent hypothyroidism. One is medication nonadherence, which was most likely seen in the patient in this case. Missing even 1 day of levothyroxine can affect TSH and thyroid hormone levels for several days due to the long half-life of the medication.<sup>2</sup> Hepp and colleagues found that patients with hypothyroidism were significantly more likely to be nonadherent to levothyroxine if they had comorbid conditions such as type 2 diabetes or were obese.<sup>3</sup> Another study of levothyroxine adherence found that the most common reason for missing doses was forgetfulness.<sup>4</sup> However, memory and cognition impairments can also be symptoms of hypothyroidism itself; Haskard-Zolnierok and colleagues found a significant association between nonadherence to levothyroxine and self-reported brain fog in patients with hypothyroidism.<sup>5</sup>

Another cause of persistent hypothyroidism is malabsorption. Absorption of levothyroxine can be affected by intestinal malabsorption due to inflammatory

bowel disease, lactose intolerance, or gastrointestinal infection, as well as several foods, drinks (eg, coffee), medications, vitamins, and supplements (eg, proton-pump inhibitors and calcium).<sup>2,6</sup> Levothyroxine is absorbed mainly at the jejunum and upper ileum, so any pathologies or ingested items that would directly or indirectly affect absorption at those sites can affect levothyroxine absorption.<sup>2</sup>

A liquid levothyroxine formulation can help with malabsorption.<sup>2</sup> Alternatively, weight gain may lead to a need for increasing the dosage of levothyroxine.<sup>2,6</sup> Other factors that can affect TSH levels include Addison disease, dysregulation of the hypothalamic-pituitary-thyroid axis, and TSH heterophile antibodies.<sup>2</sup>

Research describes methods that have effectively treated hypothyroidism in patients struggling with levothyroxine adherence. Two case reports describe weekly visits for levothyroxine administration successfully treating uncontrolled hypothyroidism.<sup>7,8</sup> A meta-analysis found that while weekly levothyroxine tablets led to a higher mean TSH level than daily use, weekly use still led to reference-range TSH levels, suggesting that weekly levothyroxine may be a helpful alternative for non-adherent patients.<sup>9</sup> Alternatively, patients taking levothyroxine tablets have been shown to forget to take their medication more frequently compared to those taking the liquid formulation.<sup>10,11</sup> Additionally, a study by El Helou and colleagues found that adherence to levothyroxine was significantly improved when patients had endocrinology visits once a month and when the endocrinologist provided information about hypothyroidism.<sup>12</sup>

Another method that may improve adherence to levothyroxine is telehealth visits. This would be especially helpful for patients who live far from the clinic or do not have the time, transportation, or financial means to visit the clinic for weekly visits to assess medication adherence. Additionally, patients may be afraid of admitting to a health care professional that they are nonadherent. Clinicians must be tactful when asking about adherence to make the patient feel comfortable with admitting to nonadherence if their cognition is not impaired. Then, a patient-

led conversation can occur regarding realistic ways the patient feels they can work toward adherence.

To our knowledge, the patient in this case report had no symptoms of intestinal malabsorption, and weight gain was not thought to be the issue, as levothyroxine dosage was adjusted multiple times. His plasma TSH levels returned to reference range after weekly pill count visits for 6 weeks and after weekly pill count visits for 9 weeks. Therefore, non-adherence to levothyroxine was suspected to be the cause of frequently elevated plasma TSH levels despite the patient's insistence on adherence. While the patient did not report memory issues, cognitive impairments due to hypothyroidism may have been contributing to his probable nonadherence. Additionally, he had comorbidities, such as type 2 diabetes mellitus and obesity, which may have made adherence more difficult.

Levothyroxine was also only prescribed in daily tablet form, so the frequency and formulation may have also contributed to nonadherence. While the home nurse was originally sent to assess the patient's adherence, the care team could have had the nurse start giving the patient weekly levothyroxine once nonadherence was determined to be a likely issue. The patient's adherence only improved when he went to the clinic for pill counts but not when the home nurse came to his house weekly; this could be because the patient knew he had to invest the time to physically go to clinic visits for pill checks, motivating him to increase adherence.

## CONCLUSIONS

This case reports a patient with frequently high plasma TSH levels achieving normalization of plasma TSH levels after weekly medication adherence checks at a primary care clinic. Weekly visits to a clinic seem impractical compared to weekly dosing with a visiting nurse; however, after review of the literature, this may be an approach to consider in the future. This strategy may especially help in cases of persistent abnormal plasma TSH levels in which no etiology can be found other than suspected medication nonadherence. Knowing their medication use will be checked at weekly clinic visits may motivate patients to be adherent.

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### Ethics and consent

Written informed consent was obtained from the patient presented in this case report. Patient identifiers have been removed to protect the privacy of the patient.

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