

Re-evaluation of Thyroid Hormone Status After Long-Term Hormone Therapy

Peter J. Rizzolo, MD, and Paul M. Fischer, MD
Chapel Hill, North Carolina

Once thyroid hormone is prescribed, it is usually continued throughout a person's lifetime. It is therefore important that the diagnosis be based on the most definitive tests available.

In this study with a primary care population of 6,000 individuals, 24 patients were found to carry the diagnosis of hypothyroidism. A careful review of the records showed that the diagnosis was inadequately documented by current standards in 20 of these 24 individuals.

A 21-day hormone withdrawal test was done in ten of the patients in whom the diagnosis was suspected, and 60 percent were found to be euthyroid. Although the number of patients was small, this does encourage the speculation that many patients diagnosed in the past as hypothyroid may in fact be euthyroid. The medical as well as economic impact of this high rate of misdiagnosis becomes apparent when one contemplates the 15,000,000 prescriptions for thyroid hormone written annually in the United States.

Hypothyroidism is a common clinical problem, found in 1.5 percent of women.¹ These patients require long-term treatment with exogenous thyroid hormone. This treatment is generally continued for the patient's entire life. It is therefore critical to firmly establish any diagnosis of hypothyroidism. It is common, in clinical practice, however, to encounter patients on exogenous thyroid hormone who have no documented need for this medication. Presumably, some individuals began thyroid hormone therapy for diseases other than hypothyroidism. In others the diagnosis of hypothyroidism was made before the availability of sensitive tests such as the thyrotropin (TSH) assay. A third group of patients may only have had transient hypothyroidism following an episode of thyroiditis, subtotal thyroidectomy, or treatment with radioactive iodine.²⁻⁴ It appears that these patients are continued on their medication because of the unavaila-

bility of a simple, safe, and inexpensive method to assess thyroid function in the population of patients on thyroid hormone therapy.

In spite of the availability of the necessary laboratory tools, there has been little study of the response of the thyroid gland to the withdrawal of long-term therapy with exogenous thyroid hormone. Several procedures have been proposed to establish a patient's thyroid status after long-term thyroid hormone therapy. One test involves a four-week substitution of triiodothyronine for the previous hormone medication.^{5,6} The serum TSH is measured at the end of the four-week period and then again 10 days following the discontinuation of all hormone replacement. A second method calls for the withdrawal of hormone therapy for 35 days and then measuring the serum TSH.⁷ In both tests an elevated TSH indicates hypothyroidism and therefore the need for continued hormone therapy. A normal TSH value indicates euthyroidism and therefore no need for further hormone replacement.

There has been no previous study of patients on thyroid hormone therapy within a primary care setting. The prevalence of euthyroidism in the group of previously diagnosed "hypothyroid" pa-

From the Department of Family Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina. Requests for reprints should be addressed to Dr. Peter J. Rizzolo, Department of Family Medicine, Trailer 15, 269-H, University of North Carolina, Chapel Hill, NC 27514.

tients would allow an estimation of the number of patients who are unnecessarily continued on thyroid hormone therapy.

The symptoms most often associated with hypothyroidism are not by themselves a reliable means of establishing the diagnosis of hypothyroidism.⁸ Also, there has been no systematic study of hypothyroid symptoms during a trial period with patients off thyroid hormone therapy. Krugman et al⁷ reported the presence of signs and symptoms of hypothyroidism after hormone withdrawal in a small group of patients who had documented hypothyroidism by a 35-day withdrawal test, but similar signs and symptoms were found in patients who were determined to be euthyroid. It is therefore unclear whether these symptoms in the euthyroid group reflected a transient but chemically undetected hypothyroid phase or a "reverse placebo effect" due to stopping a patient's regular medication.

This study was designed to answer the following questions:

1. What is the prevalence of euthyroidism in a population of patients who carry the diagnosis of hypothyroidism?
2. Do symptoms during a period of hormone withdrawal reflect the patient's eventual thyroid status (ie, hypothyroid or euthyroid)?
3. Is a shortened 21-day hormone withdrawal test effective in identifying the euthyroid and hypothyroid patients in a group of patients on thyroid hormone therapy?

Methods

The patients enrolled in a family practice residency clinic were chosen as the primary care population group. A computer bank of all outpatient visits was used to construct a listing of patients who had been seen with the diagnosis of hypothyroidism. The medical records of these patients were reviewed, and candidates for the study were chosen by the following criteria:

1. Patients with long-term thyroid replacement therapy based on only a clinical diagnosis of hypothyroidism,
2. Patients with long-term thyroid therapy in whom the diagnosis was made on laboratory evidence other than an elevated TSH,
3. Patients who had been placed on thyroid therapy following a subtotal thyroidectomy.

All selected patients were sent a letter describing the study and were invited to an initial screening examination. At that visit the history of thyroid disease was reviewed as well as other chronic illnesses and medications. The final selection was based on the patient's consent and the consent of the patient's family physician.

The selected patients were advised to discontinue thyroid hormone therapy after the initial visit. All patients were then seen three weeks following the initial examination. At each visit a history was taken, including a hypothyroid symptom questionnaire, and an examination was performed including the skin, hair, blood pressure, weight, and deep tendon reflexes. The symptom questionnaire was designed to document the frequency of nine common symptoms of hypothyroidism: fatigue, constipation, cold intolerance, dry skin, nervousness, palpitations, muscle weakness, loss of appetite, and emotional depression. These symptoms are some of the most commonly found complaints in patients with untreated hypothyroidism.⁹ Each patient was asked to rate the frequency of these symptoms on a four-point scale (never, occasionally, frequently, always). Increasing values correspond to increasing symptoms of hypothyroidism, with a maximum score of 36 points. At each visit blood was drawn for determination of serum thyrotropin (TSH), serum thyroxine (T₄), and the free thyroxine index (FTI).

Patients who were found to be hypothyroid by laboratory testing at the three-week visit were restarted on their previous dosage of thyroid medication. The remaining euthyroid patients were seen at a three-month follow-up visit.

Results

The practice population used for this study has an estimated enrollment of 6,000 patients. The computer listing of these patients produced 24 individuals with the diagnosis of hypothyroidism. This represents an illness prevalence of .4 percent in the practice. Of these 24 patients, four did not meet the criteria, and ten could not be located or did not choose to participate in the study.

The remaining ten patients enrolled in the study were all female with an average age of 60 years (range of 40 to 75 years). All were on suppressive dosages of thyroid hormone. This group included four patients with the diagnosis of hypothyroidism

Table 1. Hypothyroid Group After Withdrawal of Exogenous Thyroid Hormone

Age (yr)	Diagnosis	Years on Thyroxine	Initial			Three Weeks		
			T ₄	TSH	FTI	T ₄	TSH	FTI
60	Partial thyroidectomy	23	6.3	1.7	2.4	1.6	40	.49
59	Radioactive iodine for Graves' disease	15	6.3	4.8	2.1	2.5	33	.72
54	Symptoms of hypothyroidism	20	8.9	0.3	3.7	0.5	35	.17
75	Low basal metabolism rate	20	8.8	5.0	2.6	2.8	26	.64

Note: Normal Values: T₄, 4.5-11.5 μg/100 mL; FTI, 1.58-5.18; TSH < 7.3 μIU/mL

Table 2. Euthyroid Group After Withdrawal of Exogenous Thyroid Hormone

Age (yr)	Diagnosis	Years on Thyroxine	Initial			Three Weeks			Three Months		
			T ₄	TSH	FTI	T ₄	TSH	FTI	T ₄	TSH	FTI
67	Partial thyroidectomy for multinodular goiter	20	7.6	2.0	3.0	6.8	3.5	2.6	6.2	2.7	2.5
66	Partial thyroidectomy for nodule	11	4.6	2.9	1.7	6.3	4.1	2.3	5.3	5.3	2.1
46	Radioactive iodine for Graves' disease	1	9.9	1.6	4.1	8.8	2.6	3.6	10.4	3.0	4.3
57	Hypothyroid symptoms	8	7.4	1.1	3.0	5.4	2.2	1.9	6.2	2.5	2.2
62	Partial thyroidectomy for Graves' disease	11	6.7	3.8	2.2	9.9	3.1	3.1	9.1	3.6	2.8
40	Symptoms of hypothyroidism	15	5.9	—	2.3	7.9	5.7	2.8	7.1	4.1	2.8

Note: Normal Values: T₄, 4.5-11.5 μg/100 mL; FTI, 1.58-5.18; TSH < 7.3 μIU/mL

secondary to subtotal thyroidectomy, four patients with the diagnosis of idiopathic hypothyroidism, and two with the diagnosis of hypothyroidism secondary to radioactive iodine treatment for Graves' disease.

The initial laboratory data obtained while the patients were on thyroid hormone therapy showed all ten patients to be chemically euthyroid by T₄ and TSH values. At the three-week examination, only four of the ten patients were documented as being hypothyroid by both an elevated TSH and a low T₄. This group of documented hypothyroid patients consisted of one patient who had undergone a subtotal thyroidectomy, one patient with radioactive iodine treatment, and two with idiopathic hypothyroidism (Table 1). The six patients who were documented as being euthyroid at three

weeks were also euthyroid by laboratory studies at the three-month follow-up examination (Table 2).

Both euthyroid and hypothyroid patient groups were found to be symptomatically similar at the initial examination. The hypothyroid group had an average symptom rating of 16.2 on the symptom frequency scale. The euthyroid patients had a symptom average of 15.5. During the three-week period off thyroid hormone therapy, the group that was found to be euthyroid showed no significant change in their symptom score. Their final symptom score was 14.4. The patients that were shown to be hypothyroid also showed no significant change, with a three-week score of 14.7.

Three of the four patients who were found to be hypothyroid at three weeks elected not to restart the hormone therapy at the time of the laboratory

evidence for hypothyroidism. Each felt well and was interested in seeing how they would feel with a longer time off hormone therapy. All three patients became symptomatic by the fifth week and were restarted on hormone therapy.

The examination of blood pressure, weight, thyroid gland, skin, and deep tendon reflexes showed no clinically detectable change in either patient group between the time of the initial visit and the three-week examination.

Discussion

Hypothyroidism is the third most common endocrine disease seen in the primary care setting.¹⁰ In the United States there are 15,000,000 estimated prescriptions for thyroid hormone preparations each year.¹¹

There are three groups of patients now on thyroid hormone therapy who could safely be withdrawn from this medication. The first group consists of those individuals who were begun on thyroid therapy for diseases in which the drug is now not indicated. Thyroid hormone in the past was used in the treatment of obesity, depression, infertility, and a variety of other illnesses.¹² It is now recommended only for the treatment of documented hypothyroidism and for the growth suppression of nodular thyroid disease. The patients in this first group are often continued on thyroid hormone either because the clinical history is unknown or because there is a fear of producing hypothyroidism in a patient whose thyroid gland has been chronically suppressed.

A second group of patients was begun on thyroid therapy for hypothyroidism diagnosed before TSH assays were available. Some patients were diagnosed solely on clinical criteria. Yet, there is evidence to suggest that when the diagnosis is based solely on clinical suspicion, the diagnosis will be incorrect 96 percent of the time.⁸ Other patients were diagnosed as having hypothyroidism on the basis of a thyroxine or protein-bound iodine (PBI) value. These tests are less reliable than is the measurement of TSH for documenting hypothyroidism.

A third group of patients had had documented hypothyroidism but had with time recovered normal thyroid function. This little-studied phenomenon has been described for hypothyroidism resulting from thyroiditis, radioactive iodine treatment, and subtotal thyroidectomy.²⁻⁴ Transient hypothyroid-

ism has been seen in 71 percent of patients who undergo a subtotal thyroidectomy for hyperthyroidism. Five of 18 patients who became hypothyroid after radioactive iodine treatment were shown to recover normal thyroid function by six months after treatment. It seems likely that patients who have recovered from transient hypothyroidism represent a significant percentage of individuals who can be successfully taken off hormone replacement therapy.

All three of these groups of patients could benefit from a re-evaluation of their need for thyroid hormone therapy. Withdrawal of exogenous thyroid hormone and subsequent laboratory evaluation of thyroid function would enable the physician to determine which of these patients could safely discontinue hormone therapy.

In this study, 24 patients were found to carry the diagnosis of hypothyroidism in a 6,000-patient primary care practice. Of these, 20 met the study criteria, ie, they were felt to have inadequate documentation of a need for thyroid hormone therapy. Ten of these 20 patients agreed to enter the clinical study and were taken off thyroid hormone for a three-week period. Six of these patients were shown to be euthyroid at that time, with normal thyroxine and thyrotropin values. All six patients were euthyroid at a three-month follow-up examination. These euthyroid patients represent 60 percent of the studied patients. This compares with 5 of 13 patients in one previous study in which "hypothyroid" patients were withdrawn from hormone therapy. This group of proven euthyroid patients will benefit from no longer requiring thyroid replacement medication or periodic thyroid function testing. Furthermore, these patients would no longer be exposed to a medication that, although generally safe, is not without side effects and which is relatively contraindicated in patients with cardiac diseases.

In this study, 83 percent (20 of 24) of patients who carried the diagnosis of hypothyroidism were considered to be candidates for a trial off of hormone therapy. Sixty percent of the tested patients were eventually shown to be euthyroid. If these figures hold true for the general population, then \$40 million per year can be saved in the United States for the medication alone.

Only four of the ten studied patients were found to be hypothyroid by laboratory testing at the three-week visit. There were neither symptoms

nor physical examination evidence for the hypothyroidism at that time. There is some evidence to suggest that a period of pituitary suppression follows the chronic use of thyroid hormone.^{7,13} This would result in a reduced release of thyrotropin. There appears to be no similar suppression of the thyroid gland itself.^{7,13} The patients who therefore show an elevated TSH and a low thyroxine at three weeks represent patients with a normal functioning pituitary but inadequate thyroid activity. Since the thyroid gland does not go through a suppressed period, these patients are not expected to recover normal thyroid function beyond the three-week period.

A 21-day withdrawal period was shown effective in this study for differentiating euthyroid from hypothyroid patients after long-term thyroid hormone use. Compared with previously described procedures, this technique is quicker and does not require changing to a special thyroid hormone preparation.⁵⁻⁷ The 35-day withdrawal period described by Krugman et al⁷ could result in hypothyroid patients becoming symptomatic, as did three of the four hypothyroid patients in this study who delayed hormone therapy until the fifth week of drug withdrawal. A larger study is needed to verify that no patient who is found to be euthyroid at three weeks will go on to later become hypothyroid, but all of the euthyroid patients in this study were euthyroid at a three-month follow-up examination.

Both the serum thyroxine and thyrotropin levels indicated hypothyroidism in the four patients in this study. For routine use, the TSH level alone would be adequate for the laboratory documentation of hypothyroidism. Both the thyroxine and thyrotropin levels are necessary for the unusual patient with secondary rather than primary hypothyroidism. In such a patient the thyroxine level would be low, but there would be no elevation in the thyrotropin value.

Patient symptoms and physical examination were shown to be of little help in differentiating hypothyroid from euthyroid patients during the withdrawal procedure. Thyroid preparations have half-lives of 7 to 10 days. It is therefore unlikely that patient symptoms during the first week of hormone withdrawal have a physiologic basis. Several patients in this study complained of increased fatigue during the withdrawal period and were found to be euthyroid at the three-week examination. The clinician is therefore advised to

encourage patients to withhold medication until the withdrawal period is completed. This study suggests that even those patients who become chemically hypothyroid by the third week will have no increased frequency of hypothyroid symptoms.

Although the numbers in this study were small, the results indicate that the histories of patients on thyroid therapy be reviewed. If this review suggests that the patient could possibly be taken off thyroid hormone, then a three-week trial withdrawal period should be tried. A thyrotropin and thyroxine level should be measured after this period, and if normal, the patient can be assumed to be euthyroid. An elevated TSH and a low thyroxine indicates hypothyroidism, and hormone therapy should be resumed. This procedure can safely identify truly hypothyroid patients without producing unwanted symptoms.

It is hoped that future experience with this thyroid hormone withdrawal procedure will further document its clinical efficacy.

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