

---

# Reevaluation of Patients on Thyroxine Therapy

Peter J. Rizzolo, MD, MAJ Daryl Porr, MC, USA, and Paul C. Fisher, MD  
*Chapel Hill and Fort Bragg, North Carolina, and Augusta, Georgia*

*A 21-day withdrawal test was utilized at four primary care practice sites to reevaluate individuals on thyroxine therapy. Utilizing elevated thyroid stimulating hormone (TSH) concentrations as the standard for diagnosing hypothyroidism, 22 of 37 patients previously on thyroxine were found to be euthyroid. Of the 15 hypothyroid individuals identified, 13 had elevated serum TSH 21 days after withdrawal of thyroxine. Two individuals who had serum TSH concentrations in the normal range at 21 days became symptomatic at five and eight weeks, respectively, and were found to have elevated serum TSH.*

*Several factors may account for the high percentage of euthyroid individuals being treated with thyroid medication. These include unreliability of symptoms as a basis for diagnosis of hypothyroidism, laboratory tests that are often difficult to interpret, the commonly held misconception that all forms of primary hypothyroidism are irreversible, the routine use of thyroxine by many surgeons after subtotal thyroidectomy, and the use of thyroxine to suppress diffuse or nodular goiter.*

In selected individuals on thyroxine therapy, a trial withdrawal will identify many euthyroid individuals in whom the indication for continued treatment should be reexamined.

Hypothyroidism is a commonly encountered entity with a reported prevalence of 19 cases for every 1,000 adult women.<sup>1</sup> Furthermore, a great many patients are given thyroid medication for reasons other than a confirmed diagnosis of hypothyroidism. Physicians, therefore, often encounter patients new to their practice who had previously started on long-term thyroxine replacement therapy. Documentation as to why

these individuals are taking the medication or the tests utilized in establishing the diagnosis are often not available. Assessment of the underlying functional status of the thyroid by stopping the hormone and reevaluating thyroid secretory capacity is not commonly done because hypothyroidism, once diagnosed, is usually considered a lifelong condition. Furthermore, the commonly recommended six-week withdrawal period<sup>2</sup> is often associated with significant hypothyroid symptoms.

After long-term suppression of the thyroid pituitary axis by administration of exogenous thyroxine, there is evidence to suggest that a normal thyroid gland is capable of responding to endogenous thyroid-stimulating hormone (TSH) within two to three weeks of stopping the exogenous hormone.<sup>3</sup> This knowledge was the basis for a previous study in which a 21-day withdrawal test was utilized to evaluate ten patients who had been on long-term thyroxine replacement therapy.<sup>4</sup> Six of ten patients in that study were found to be

---

*From the Department of Family Practice, University of North Carolina, Chapel Hill, the Department of Family Medicine, Womach Army Community Hospital, Fort Bragg, North Carolina, and the Department of Family Medicine, Medical College of Georgia, Augusta, Georgia. Requests for reprints should be addressed to Dr. Peter J. Rizzolo, Department of Family Medicine 269H, University of North Carolina, Chapel Hill, NC 27514.*



euthyroid. This paper reports the result of an expanded study involving three additional independent primary care practice sites.

## **METHODS**

Patients receiving thyroid hormone were selected from four primary care practice sites in North Carolina. The patients were identified by computerized diagnostic records at two sites and by pharmacy records at two sites. To enter the study, subjects had to meet one or more of the following criteria:

1. A diagnosis of hypothyroidism based on clinical evidence without appropriate laboratory documentation
2. Thyroxine started following subtotal thyroidectomy for a benign tumor
3. Thyroxine started after administration of radioactive iodine for Graves' disease

Patients were excluded from the study in either of the following situations:

1. Evidence or suspicion of thyroid malignancy
2. Diagnosis made in the previous 12 months based on convincing laboratory evidence

Patients who entered the study had an initial visit, at which time the history was reviewed and a physical examination was performed. Baseline thyroid function studies included serum thyroxine by radioimmunoassay ( $T_4$ , RIA), resin triiodothyronine uptake ( $RT_3U$ ), calculated free thyroxine index (FTI), and serum thyroid-stimulating hormone (TSH). These studies were repeated at 21 days following withdrawal of medication. Patients found to have normal TSH were continued off thyroxine and retested at 12 weeks after withdrawal. Individuals with elevated serum TSH (as defined by the laboratory performing the assay) at 21 days were considered hypothyroid and were placed back on thyroxine, and thyroid function studies as described above were repeated at 12 weeks after withdrawal.

A questionnaire consisting of eight symptoms commonly associated with hypothyroidism was administered to all patients at the initial and three-week visit. Patients rated the symptoms as being present, "always, frequently, occasionally, or never." The symptom questionnaire was

administered by the same physician at both the initial and 21-day visits.

## **RESULTS**

More than 90 percent of the patients identified by the computerized diagnostic records or pharmacy records met the study criteria. Of the 75 patients considered suitable candidates, 37 entered the study. Of the 39 who did not enter the study, 27 could not be located, 10 were not interested, and in two instances the primary physician advised against participation.

Thirty-five of the 37 patients were female. Patient ages at the time they entered the study ranged from 18 to 87 years, with 75 percent aged over 50 years.

Years on thyroxine medication in the hypothyroid group ranged from 4 to 30 years with a mean of 14 years. In the euthyroid group, the range was 1 to 25 years with a mean of 9 years.

Of the 37 patients who entered the study, 15 were considered to be hypothyroid as defined by an elevated serum TSH after discontinuing thyroxine medication. Two individuals had normal serum TSH levels three weeks after thyroxine had been discontinued. They became hypothyroid at five and eight weeks, respectively, at which time each was found to have an elevated serum TSH concentration.

In the group of 22 individuals found to be euthyroid, five had low serum  $T_4$  levels three weeks after withdrawal. Since they remained clinically euthyroid, thyroxine was not restarted, and at 12 weeks their serum  $T_4$  and serum TSH levels were both normal.

One individual in the hypothyroid group experienced an increase in all eight symptoms between the initial and three-week administration of the symptom questionnaire. Among the remaining 36 patients, there was little change in symptoms and no consistent difference was found between the hypothyroid and euthyroid groups.

The study results are displayed in Table 1; patients were divided into five diagnostic categories. In each category the number found to be euthyroid and hypothyroid is shown. Twelve patients in group 1 were started on thyroxine after subtotal thyroidectomy for benign conditions. Of



this number, nine (75 percent) were euthyroid. Group 2 was composed of seven individuals whose conditions were diagnosed as hypothyroidism based on clinical findings without adequate laboratory documentation. In this group, six (84 percent) were found to be euthyroid. Three patients in group 3 were started on thyroxine after radioactive iodine therapy for Graves' disease. Two were found to be euthyroid. Group 4 was made up of seven patients whose conditions were diagnosed as hypothyroidism based on laboratory studies. In this group, only one (14 percent) was euthyroid. The fifth category consisted of individuals for whom the diagnosis was based on clinical findings and the presence of a goiter. Of the eight patients in this group, four were euthyroid (50 percent).

**DISCUSSION**

The high percentage of individuals found to be euthyroid (22 of 37) suggests the usefulness of reevaluation of selected patients on thyroxine therapy.

When diagnosis was based on reliable laboratory tests as in diagnostic group 4, the degree of misdiagnosis was relatively low (14 percent). On the other hand, when the diagnosis was made on clinical grounds as in diagnostic groups 2 and 5, the misdiagnosis rate was 67 percent.

It was not surprising that 75 percent of the patients started on thyroxine after subtotal thyroidectomy were found to be euthyroid. After subtotal thyroidectomy, it has been common surgical practice to start patients on thyroxine routinely, since it was believed that many of them would eventually become hypothyroid. In a study by Toft et al,<sup>7</sup> only four of 40 patients developed permanent hypothyroidism after subtotal thyroidectomy. However, 10 of 40 patients developed transient hypothyroidism during the first six months postoperatively. The wide variation in reported incidence of hypothyroidism after subtotal thyroidectomy may well reflect the inclusion of those individuals diagnosed in the postoperative period when transient hypothyroidism is known to develop. Additionally, if the surgery had been

**TABLE 1. RESULTS OF THYROXINE WITHDRAWAL TEST GROUPED BY DIAGNOSTIC CATEGORY**

Group	Diagnostic Category		Total by Category
	Euthyroid Number (%)	Hypothyroid Number (%)	
1. Therapy started after subtotal thyroidectomy for benign condition	9 (75)	3 (25)	12
2. Clinical diagnosis without adequate laboratory confirmation	6 (86)	1 (14)	7
3. After radioactive iodine for Graves' disease	2 (66)	1 (33)	3
4. Diagnosis based on laboratory tests	1 (14)	6 (86)	7
5. Diagnosis based on symptoms and the presence of goiter	4 (50)	4 (50)	8
Total (%) patients by thyroid status	22 (59)	15 (41)	37

done for multinodular goiter, the thyroxine was given to suppress serum TSH production to decrease the likelihood of recurrent thyroid nodules. Unless reliable laboratory tests were utilized to diagnose hypothyroidism, it would appear to be worthwhile to reassess these individuals. Those individuals found to be euthyroid should be maintained off thyroxine and followed clinically.

Two of three patients who had radioactive iodine therapy (diagnostic group 4) were found to be euthyroid. Although this group is obviously too small to permit sound conclusions, it would seem reasonable to reassess them unless the diagnosis of hypothyroidism was based on reliable laboratory evidence.

Although the medical literature describes transient hypothyroidism in several clinical situations,<sup>5-8</sup> medical educators have placed little emphasis on this phenomenon. Transient hypothyroidism has been described in postpartum thyroiditis, in subacute thyroiditis, following subtotal thyroidectomy, and following radioactive



iodine therapy. Additionally, when the diagnosis of hypothyroidism is based on a clinical impression or laboratory tests other than elevated serum TSH, misdiagnosis is common.<sup>9</sup> Many patients were diagnosed as having primary hypothyroidism before serum TSH measurement became available, and a variety of less reliable tests were utilized. Many factors can influence total serum T<sub>4</sub> and resin T<sub>3</sub> uptake, including drugs, chronic illness, and a variety of iodine-containing contrast media.<sup>10-13</sup>

In all but two individuals the serum TSH level at three weeks after withdrawal of thyroxine was a reliable index of thyroid status. Serum T<sub>4</sub> level at three weeks was low in five patients in the euthyroid group. It would seem therefore that at three weeks after withdrawal of exogenous thyroxine, either thyroid gland ability to produce thyroxine or pituitary synthesis of TSH or both may be impaired in some individuals. The reason the authors did not utilize a six-week withdrawal period was to avoid the development of hypothyroid symptoms. A reasonable compromise approach would be to withdraw thyroxine and obtain serum TSH levels at *four weeks*. Individuals found to be hypothyroid at four weeks could be placed back on their previous dose of thyroxine. Those euthyroid at four weeks should have a repeat serum TSH at twelve weeks after withdrawal.

Physicians are urged to exercise caution in initiating a trial withdrawal of thyroxine in patients with multiple medical or psychiatric problems. Borderline cardiac compensation and diabetes mellitus are two examples of situations in which the individual might not tolerate even a temporary hypometabolic state.

In the presence of coronary artery disease with angina, it has been shown<sup>14</sup> that exogenous thyroxine therapy may make it more difficult to

control the patient's angina. These patients may therefore benefit from a trial withdrawal.

References

1. Tunbridge WMG, Evered DC, Hall R, et al: The spectrum of thyroid disease in a community: The Whickham Survey. *Clin Endocrinol (Oxf)* 1977; 7:481-493
2. Braverman LE: Update on tests and treatment for thyroid disease. *Mod Med*, May 1982, pp 58-81
3. Krugman LG, Hershman JM, Chopra IF, et al: Patterns of recovery of the hypothalamic-pituitary-thyroid axis in patients taken off chronic thyroid therapy. *J Clin Endocrinol Metab* 1975; 41:70-80
4. Rizzolo PF, Fisher PM: Re-evaluation of thyroid hormone status after long-term hormone therapy. *J Fam Pract* 1982; 14:1917-1921
5. Amina N, Miyai K, Kuro R, et al: Transient postpartum hypothyroidism: Fourteen cases with autoimmune thyroiditis. *Ann Intern Med* 1977; 87:155-159
6. Sawers JSA, Toft AD, Irvine WJ, et al: Transient hypothyroidism after iodine-131 treatment of thyrotoxicosis. *J Clin Endocrinol Metab* 1980; 50:226-229
7. Toft AD, McIntosh D, Cameron EHD, et al: Temporary hypothyroidism after surgical treatment of thyrotoxicosis. *Lancet* 1976; 2:817-818
8. Yamamoto T, Sakamoto H: Spontaneous remission from primary hypothyroidism. *Ann Intern Med* 1978; 88:808-809
9. White GH, Walmsley RN: Can the initial clinical assessment of thyroid function be improved? *Lancet* 1978; 2:933-935
10. Braverman LE, Woeber KA, Ingbar SH: Induction of myxedema by iodide in patients euthyroid after radioiodine or surgical treatment of diffuse toxic goiter. *N Engl J Med* 1969; 281:816-821
11. Braverman LE, Ingbar SH, Vagenakis AG, et al: Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. *J Clin Endocrinol Metab* 1970; 32:515-521
12. Prager EM, Gardner RE: Iatrogenic hypothyroidism from topical iodine containing medications. *West J Med* 1979; 130:553-555
13. Bahn AK, Mills JL, Snyder RJ, et al: Hypothyroidism in workers exposed to polybrominated biphenyls. *N Engl J Med* 1980; 302:31-33
14. Levine HD: Compromise therapy in patients with angina pectoris and hypothyroidism. *Am J Med* 1980; 69:411-418