

CASE STUDIES

T3, The Other Thyroid Hormone

Jeff Grabenstein, MD, FAAFP

Oak Ridge, TN

INTRODUCTION**Normal Thyroid Function**

A negative-feedback mechanism links the hypothalamic–pituitary–thyroid axis. Once low levels of thyroid hormones (THs) have been detected by osmoreceptors in the hypothalamus, thyroid-releasing hormone (TRH) is secreted into circulation.¹ TRH stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH) targeting the thyroid gland. The thyroid gland is made up of colloid-filled follicles, reservoirs for the building blocks for the THs iodine and thyroglobulin. Stimulated by TSH, iodine and thyroglobulin synthesize to form tyrosine amino acids or TH consisting of thyroxine (T_4), which is bound to 4 iodine atoms, and liothyronine (synthetic triiodothyronine) (T_3), bound to 3. The superior and inferior thyroid arteries provide the blood supply for transport of T_4 and significantly less T_3 to the target tissues via the hepatic-derived transport proteins— T_4 -binding globulins. T_3 is produced mainly at the nuclear receptor sites in response to enzymatic activity; however, when T_3 is available in circulation, it is more active in binding to cell receptors than T_4 .² THs affect nearly every part and function of the body except the adult brain, spleen, and maintenance of testes or ovaries.¹ THs also affect oxygen consumption, basal metabolic rate, and body heat production, as well as playing a role in maintaining blood pressure (ie, stimulation of adrenergic receptors in blood vessels) and aiding regulation of tissue growth (ie, ossification, nervous system development, and maturation of reproductive systems). Both overproduction (hyperthyroidism) and underproduction (hypothyroidism) of TH can result in severe metabolic disturbances.¹

Hyperthyroidism

Patients with hyperthyroidism typically present with nervousness, palpitations, heat intolerance, and weight loss.

Graves' disease (toxic diffuse goiter), the most common form of hyperthyroidism, is estimated to have a prevalence of ~1 million patients in the United States, and 15% of these cases are in patients over the age of 60.^{3,4}

Hypothyroidism

Patients with Hashimoto's disease (chronic autoimmune thyroiditis), the most common cause of underactive thyroid in the United States, experience fatigue, weight gain, difficulty concentrating, and depression.^{3,4} At least 10% of women in the United States will have signs of a failing thyroid by the age of 50 and, by the age of 60, 17% of women and 8% of men experience hypothyroidism.³

Clinical Features and Treatment of Hypothyroidism

Symptoms of hypothyroidism are usually related to the duration and severity of the undersecretion of TH and may vary from patient to patient. The symptoms/signs include⁴:

- fatigue,
- weight gain and fluid retention,
- dry and/or yellow skin,
- cold intolerance,
- coarse or thinning hair,
- hoarse voice,
- goiter,
- reflex delay,
- ataxia,
- constipation,
- memory or mental impairment,
- depression,
- reproductive irregularities (women),
- myalgias,
- hyperlipidemia,
- bradycardia and hypothermia, and
- myxedema.

The diagnosis of hypothyroidism is confirmed through laboratory evaluation of the TSH level (normal serum TSH range by immunoassay, 0.05–4.70 μ IU/mL).⁵ Secondary tests may include free T₄ (normal range, 0.8–1.8 ng/dL), free T₃ (230–420 pg/dL), or a thyroid scan (to evaluate structural abnormalities).^{4,5}

The first-line therapy for hypothyroidism is levothyroxine, with emphasis on high-quality formulations.⁴ The recommended dosage is 1.7 μ g/kg daily to be taken preferably 1/2 to 1 hour before breakfast⁶; however, therapeutic doses may vary. Due to the long half-life of levothyroxine, a therapeutic effect may not be evident for up to 4 to 6 weeks after treatment initiation.⁶ Follow-up laboratory examinations include TSH and free T₄, with follow-up office evaluations recommended every 6 months or annually as needed.⁴

PRESENTATION AND HISTORY

Presentation

A 39-year-old married white female with 2 children, who is employed as an elementary school teacher, presents for a hypothyroidism follow-up. She was first diagnosed with hypothyroidism 6 years ago by a different physician. Blood tests showed a TSH level of 1.5 mIU/mL. She was started on levothyroxine and titrated to 125 μ g QD at the time of her first visit. Her most recent retest was 1 year ago, showing a TSH of 1.92 mIU/mL. At this follow-up visit, the patient confirmed that she had been compliant with the medication dosing instructions—QD 1/2 to 1 hour before eating breakfast—but she still complained of a constellation of symptoms, including constipation, depression, dry skin, fatigue, hair loss, menstrual irregularities, poor appetite, and weight gain. The patient reported no symptoms suggestive of adverse events from the medication, including arthralgias, cold intolerance, myalgias, thick-tongued speech, or generalized weakness.

Medical History

The patient had experienced irritable bowel syndrome (IBS) for 6 years, was prescribed a low dose of paroxetine, and had felt significantly better.⁷ In 1997, colonoscopy results were positive for polyps, which were removed at the time. Subsequent colonoscopy the following year was normal. Hypothyroidism was diagnosed in 1998. The patient's obstetric/gynecologic history includes 1 miscarriage and 2 viable births. She complained of menstrual irregularities relating to the amount of bleeding each month before beginning treatment with birth

control pills. Also, the patient experienced premenstrual symptoms of moodiness and irritability. Her current method of contraception was norethindrone acetate/ethinyl estradiol (1 mg/20 μ g) and her last Pap test was negative in 2000. The patient reports sensitivity to sulfa medications that results in nausea.

Family History

The patient's father is 59 years old and suffers from rheumatoid arthritis. Her mother, also 59, has a medical history of a cervical spine fracture from a motor vehicle accident and experiences residual problems.

Social History

The patient exercises 4 days a week. Reading books and running are her main sources of recreation. She has never smoked, uses alcohol socially, and drinks 3 caffeinated beverages a day.

Medication List

She is currently taking levothyroxine sodium 125 μ g daily.^{4,6} The patient is also taking paroxetine (20 mg QD) for IBS.⁷

REVIEW OF SYSTEMS

The review of systems (ROS) revealed specific positive aspects related to her history of IBS. Gastrointestinal review was positive for abdominal pain and bloating, with alternating constipation and diarrhea; however, it was negative for epigastric pain, melena, or change in stool caliber. Constitutional aspects were positive for weight gain and fatigue. Genitourinary system revealed moodiness and irritability before her periods began and irregular timing of her periods before she was placed on birth control pills. The amount of blood lost each month also varied before the birth control pills were started. The ROS was negative for musculoskeletal disorders (back pain and joint stiffness), neurological disorders (dizziness, memory loss, and weakness), endocrine disorders (polydipsia and polyphagia), and psychiatric disorders (anxiety, depression, and sleep disturbances). She noted that she had experienced more colds than usual and that the lymph glands in her neck were swollen more often than they had been in the past. All other systems were negative.

PHYSICAL EXAMINATION

A general physical examination revealed a patient who was well developed and well nourished, appropriately

groomed, and in no apparent distress, although appearing tired. Vital signs were normal (Table).

TABLE. VITAL SIGNS ON FEBRUARY 2004 OFFICE VISIT.

Weight	Temperature	Blood Pressure	Pulse
130 lb (58.96 kg)	97.4°F oral	115/78 in right arm, sitting	68 bpm, sitting

DIAGNOSIS AND TREATMENT PLAN

The preliminary diagnosis of acquired hypothyroidism was not resolved by the present dosage of levothyroxine sodium. Additional therapeutic options, such as liothyronine, may be considered for management of the patient's chronic symptoms. Laboratory examinations were scheduled and results will be called to the patient. Laboratory studies ordered during the February 2004 office visit included TSH assay (2.41 mIU/mL), free T₃ (279 pg/dL), and free T₄ (1.1 ng/dL).

The patient was instructed to call the office if new or worsening symptoms developed, including swelling, tremulousness, sweats, or tachycardia. A follow-up appointment was scheduled for 6 weeks.

The patient was informed about normal thyroid physiology and the existence of thyroid disease that may be related to other nonthyroid causes, such as the failure of cells to convert T₄ to T₃. In this condition, there is a relative lack of T₃ and the patient may experience symptoms of hypothyroidism. Because this problem is intracellular, the circulatory osmoreceptors in the hypothalamus would sense that the proper amount of T₄ was being produced. Hypothyroid symptoms due to the relative lack of intracellular T₃ is controversial and research is ongoing. Investigators would have to check T₄ and T₃ levels at the cellular receptor sites, which cannot be done at this time. Referred to as nonthyroidal thyroid disease, this condition is not a dysfunction of the thyroid gland; rather, it is theorized that the target cells are the dysfunctional mechanism. Nonthyroidal thyroid disease would be conceptually similar to type 2 diabetes; that is, the production of the involved hormone is initially normal and, subsequently, problems begin with the insulin receptor sites in the target cells.⁸ The dysfunctional intracellular mechanism of nonthyroidal thyroid disease would explain the fact that the patient complained of symptoms consistent with hypothyroidism while the TSH laboratory value was in the normal range.

After reviewing the lab results, the patient was contacted and prescribed 1 tablet of liothyronine (5 µg) by mouth each morning. As a starting dose, the patient was instructed to take half the prescribed dose for the first 4 days. This new prescription was to be taken with her current prescription of 1 tablet of levothyroxine 125 µg QD. A 6-week follow-up visit was confirmed.

6-WEEK FOLLOW-UP OFFICE VISIT FOLLOWING PRESCRIBING LEVOTHYROXINE AND LIOTHYRONINE COMBINATION THERAPY

The patient presented at this routine follow-up visit for acquired hypothyroidism showing signs of some resolution of her symptoms. However, the patient still reported experiencing hair loss and fatigue, although she stated that overall she has been feeling better since beginning combination therapy with levothyroxine and liothyronine. Vital signs and weight have remained in the normal range since her initial follow-up exam in February. To treat the residual symptoms, liothyronine was increased to 5 µg BID to be taken along with the maintenance dose of levothyroxine 125 µg daily. Clinical studies have found that normal diurnal variation affects the biologic effectiveness of liothyronine dosing in healthy subjects suggesting the BID dosing.¹

Scattered acne lesions were seen on the patient's face. Her birth control pill had been recently changed to desogestrel/ethinyl estradiol (0.15 mg/30 mg tablet) by her gynecologist and this was refilled as requested. A prescription for Retin-A topical gel was prescribed for current acne.

The patient was instructed to call if she developed new or worsening symptoms, including behavior changes, tenderness, swelling, fever, increasing tremulousness, sweats, tachycardia, or weakness. A follow-up appointment was scheduled for 8 weeks. Laboratory studies were ordered to be done 1 week before the next office visit and included TSH assay, free T₃, and free T₄.

DISCUSSION

Current understanding of thyroid functioning identifies that under the influence of TSH from the anterior pituitary, the thyroid gland releases T₄ and some T₃. These hormones are then transported to and taken up by the cells, where they make their way to the TH receptors in the nucleus. It is estimated that ~80% of the biological activity of TH comes from T₃, which is produced by

removing 1 iodine molecule from T₄ in the cytoplasm of target cells. This intracellular process is difficult to measure but very powerful. Each molecule of T₃ is about 3 or more times more potent than a molecule of T₄.¹

Based on these data, it is clear to see that there is a dramatic amplification of effectiveness of TH when both T₄ and T₃ are present in the proper concentrations in the TH receptors of the target cells. Although most current textbooks on thyroid physiology make a clear point regarding the amplification of TH by this intracellular conversion of T₄ to T₃ in the body, there is no proof that this system always functions properly.

When patients have normal TSH levels but still complain of symptoms of hypothyroidism, the addition of T₃ in a patient's treatment regimen can help normalize the amount of TH in target cell receptors and improve the overall metabolic functioning.⁹ Following this regimen, many patients report that their symptoms improve. However, with no laboratory tests to quantify the intracellular levels of T₄ and T₃, it is difficult to evaluate.

Because of the more potent activity of T₃ compared with T₄, it is important to increase the T₃ dose slowly to prevent overstimulation of target receptors, which may lead to symptoms of hyperthyroidism. In some patients, the clinical need for orally administered T₃ is reduced over time because it is speculated that, as a patient continues to take T₃, target cells may be better able to convert T₄ to T₃.

Since 1999, when a *New England Journal of Medicine* article by Bunevicius et al¹⁰ was published, there has been continued interest in the effect of coadministration of levothyroxine and liothyronine. Subsequent to that study, other clinical trials have not shown the same positive physiologic result of using levothyroxine and liothyronine compared with administration of levothyroxine alone; however, a Dutch study by Appelhof et al¹¹ showed patient preference for combined therapy, causing the investigators to conclude that patients who lost weight on the combina-

tion therapy were most satisfied with the study medication. However, it should be noted that with overdosage, subclinical thyrotoxicosis is a risk factor for serious adverse events, such as atrial fibrillation and osteoporosis.¹¹ More research is needed to investigate these well-documented and improved clinical experiences of patients on combination T₃ and T₄ therapy for hypothyroidism.

REFERENCES

1. Marieb EN. The endocrine system. In: *Human Anatomy & Physiology*. 6th ed. San Francisco, Calif: Pearson Education; 2004.
2. Sawin CT, Hershman JM, Chopra IJ. The comparative effect of T₄ and T₃ on the TSH response to TRH in young adult men. *J Clin Endocrinol Metab*. 1977;44:273-278.
3. New York Thyroid Center. Available at: <http://cpmnet.columbia.edu/dept/thyroid/disorders.html>. Accessed August 18, 2005.
4. American Association of Clinical Endocrinologists Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8:457-469.
5. *The Merck Manual of Diagnosis and Therapy*. Available at: <http://www.merck.com/mrkshared/mmanual/tables/296tb2g.jsp>. Accessed August 18, 2005.
6. Synthroid [package insert]. Abbott Park, Ill: Abbott Laboratories; 2002.
7. Tabas G, Beaves M, Wang J, et al. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: A double-blind, placebo-controlled trial. *Am J Gastroenterol*. 2004;99:914-920.
8. Buren J, Eriksson JW. Is insulin resistance caused by defects in insulin's target cells or by a stressed mind? *Diabetes Metab Res Rev*. In press.
9. Cytomel [package insert]. St. Louis, Mo: King Pharmaceuticals; 2001.
10. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med*. 1999;340:424-429.
11. Appelhof BC, Fliers E, Wekking EM, et al. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: A double-blind, randomized, controlled clinical trial. *J Clin Endocrinol Metab*. 2005;90:2666-2674.