

Hypothyroidism: Challenges in Optimal Patient Management

In this Medical Economics® “PrimaryView,” Todd Frieze, M.D., FACP, FACE, endocrinologist at the Thyroid Institute of Utah in Lehi, provides insights on hypothyroidism with an overview of the disease; an examination of the clinical manifestations, diagnosis and treatment guidelines; and a review of the importance of accurate dosing of a medication with a narrow therapeutic index (NTI) and its impact on switching therapies. This article summarizes the highlights of the presentation.

THYROID PHYSIOLOGY: DEFINING THYROID FUNCTION AND DYSFUNCTION

Hypothyroidism is the most common endocrine disease and can be defined as failure of the thyroid to produce sufficient thyroid hormone to meet the metabolic demands of the body.^{1,2} It is estimated that 20 million Americans have thyroid disease in some form, with over 12% of the population developing a thyroid condition in their lifetime.³ About 13 million Americans have hypothyroidism that is undiagnosed.^{2,3}

Overall, hypothyroidism disproportionately affects women and patients above 65 years of age. Women are five to eight times more likely to develop thyroid problems than men.³ According to one study, the estimated prevalence of

hypothyroidism in female patients is between 4% and 21%, whereas the prevalence in male patients is between 3% and 16%.⁴ Additionally, in evaluations of thyroid function by age, studies have shown progressively increasing thyroid-stimulating hormone (TSH) concentrations with aging.⁵ This is important to note as “hypothyroidism among patients aged 65 and older is associated with significant morbidity,” Dr. Frieze explained.⁶

THE ETIOLOGY OF HYPOTHYROIDISM

Two main categories of hypothyroidism exist: primary hypothyroidism and central hypothyroidism. Primary hypothyroidism, which presents as a deficiency in thyroid hormone, is far more common.^{2,7} Primary hypothyroidism is divided into two subcategories: overt hypothyroidism, which is characterized by elevated TSH with subnormal or low thyroxine (T_4) levels, and subclinical hypothyroidism, which presents with elevated TSH levels with normal T_4 levels.²

Central hypothyroidism, which is due to a reduction in the hormones that stimulate the thyroid gland to produce thyroid hormones, presents with low T_4 levels and low TSH levels. Dr. Frieze discussed how central hypothyroidism is also subdivided into two additional subtypes: secondary hypothyroidism, which is the failure of the pituitary gland to secrete TSH and occurs in roughly 5% of cases, and tertiary hypothyroidism, which is the failure of the hypothalamus to secrete thyrotropin-releasing hormone and occurs in 1% of cases or fewer.^{2,8}

CLINICAL MANIFESTATIONS AND PHYSIOLOGICAL IMPLICATIONS OF HYPOTHYROIDISM

Insufficient hormonal control can have “a profound effect on all physiological functions by impacting gene

expression, cellular function and growth,” Dr. Frieze noted.⁹ Hormonal imbalance due to hypothyroidism can adversely affect oxygen use and the body’s basal metabolic rate, the synthesis and mobilization of lipids in the blood, and thermogenic/metabolic homeostasis.⁹ The clinical presentation of hypothyroidism can be highly variable and includes a broad range of symptoms. Dr. Frieze added that “the most common symptoms that we typically see may be fatigue, weight gain, cold intolerance, dryness of the skin, loss of hair, depression and constipation.”^{8,10}

During pregnancy, the metabolic system plays a significant role in the development of the fetal central nervous system, muscle, bone and lungs, so the management of hypothyroidism is further complicated in patients of reproductive potential.^{3,11} Maternal hypothyroidism has been estimated to affect 2% to 4% of women of reproductive age.¹² If left untreated, hypothyroidism during pregnancy can increase the risk of adverse outcomes for the mother and fetus.^{10,13}

SCREENING AND DIAGNOSING HYPOTHYROIDISM

The American Academy of Family Physicians (AAFP), American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE), and American College of Physicians (ACP) all have provided recommendations for screening patients for hypothyroidism. Among these recommendations, it is typically suggested that physicians screen patients over 50 or 60 years of age and women, especially those who are of reproductive potential, are pregnant or have findings suggestive of symptomatic thyroid disease.⁷ Dr. Frieze also emphasized how “most professional societies recommend screening for thyroid dysfunction in patients (who) have new-onset cholesterol findings.”

Screening should be considered in asymptomatic patients with risk factors such as a history of autoimmune disease, a history of head or neck irradiation, previous radioactive iodine therapy, the presence of a goiter, a family history of thyroid disease, or a history of treatment with agents known to affect the function of the thyroid.²

Additionally, Dr. Frieze noted that the preferred laboratory assessment for diagnosing primary hypothyroidism is a serum TSH test and that if the TSH level is elevated, then it should be repeated with a serum free T₄ (FT₄) measurement.²

TREATING HYPOTHYROIDISM

The primary goal of treatment for hypothyroidism is the establishment of euthyroidism, or normal thyroid function, and physicians should consult published guidelines for therapeutic TSH ranges. In 2012, the AACE and ATA

clinical practice guidelines for hypothyroidism in adults set forth a TSH target range of 0.45 to 4.12 mIU/L to achieve euthyroidism.⁷ In 2014, the ATA established specific guidelines for the treatment of hypothyroidism, recommending a target range of 0.4 to 4.0 mIU/L.¹⁴ In 2017, the ATA revised the guidelines for the management of thyroid disease during pregnancy by recommending a therapeutic target of less than 2.5 mIU/L during the first trimester of pregnancy and less than 3.0 mIU/L during later trimesters.¹³ The AACE and ATA recommend measuring TSH levels within four to eight weeks of starting therapy or after adjusting dosage. It may take eight weeks or longer for levels to stabilize with small adjustments, Dr. Frieze pointed out. He added that after the adequate dose is determined and euthyroidism achieved, TSH should be measured after six months and at 12-month intervals thereafter, and possibly more frequently depending on clinical factors.⁷

THYROID HORMONE REPLACEMENT THERAPY

Most patients with hypothyroidism will require lifelong thyroid hormone therapy. Dr. Frieze stated that levothyroxine is available as brand-name and generic preparations. He added that levothyroxine has an NTI, meaning that even small differences in dosage or blood concentration may affect the efficacy and/or safety of treatment.¹⁵ In 2004, the Food and Drug Administration (FDA) approved the substitution of generic levothyroxine for brand-name levothyroxine. Endocrine medical organizations, including the AACE, the Endocrine Society and the ATA, disagreed with the FDA’s conclusion that generic preparations of levothyroxine were equivalent to brand-name levothyroxine. These organizations concluded that the “pharmacokinetic methods used, combined with the lack of TSH measurements to establish bioequivalence, could lead to significant over- or underestimation of generic equivalency compared with brand-name levothyroxine.”² According to Dr. Frieze, in the past decade, many publications have reviewed the bioequivalence data comparing generic and branded medications.¹⁶ He noted that “the FDA has recommended tighter quality and bioequivalence standards to ensure the safety and efficacy of generic [NTI] medications.”¹⁵



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LEVOTHYROXINE DOSING GUIDELINES

Once they have received a diagnosis of hypothyroidism, patients who are not pregnant can be started at a dose of 1.6 mcg/kg daily. For patients with subclinical hypothyroidism and a TSH of less than 10 mIU/L, Dr. Frieze specified that the starting dose may instead be 50 mcg daily, increasing by 25 mcg every six weeks until the level of TSH falls between the goal range of 0.35 and 5.5 mIU/L. With a TSH of 10 mIU/L or greater, a daily dose of 1.6 mcg/kg should be administered as “these patients may be more toward the overt hypothyroid phase,” Dr. Frieze noted.² When a patient finds out that she is pregnant, she should take an additional dose on two days each week, totaling nine doses per week, and the patient should be referred to an endocrinologist immediately.² In patients who are older or those who have or may have cardiac disease, the initial daily dose administered should be 25 mcg or 50 mcg, increasing by 25 mcg every three to four weeks until the patient has reached a full replacement dosage.²

PREVALENCE OF PATIENTS NOT TREATED ACCORDING TO GUIDELINES

Roughly half of pregnant patients are not treated according to established guidelines. A retrospective cohort study³ of data from the Optum Clinformatics database from 2013 through 2015 including 2,340 pregnant women aged 18 to 49 years with hypothyroidism who were treated with levothyroxine demonstrated that 23.9% of patients were undertreated, and 22.5% of patients were not monitored.¹² Another retrospective cohort study^b of data from the Optum Clinformatics database from 2007 through 2015 including 4,025 patients aged 65 years and older demonstrated that 17.4% of patients were undertreated, and 32.9% were not treated at all.⁶

CASE STUDY: A 66-YEAR-OLD WOMAN WITH A HISTORY OF HYPERTENSION AND TYPE 2 DIABETES^c

Dr. Frieze presented the patient case of a 66-year-old woman with a history of hypertension and Type 2 diabetes who has been experiencing symptoms that include fatigue, weight gain and constipation for several months. Her current medications include lisinopril 20 mg once

Table 1.
Patient Case Study Initial Laboratory Results

Lipid profile	
Total cholesterol (mg/dL) (normal: < 200 mg/dL)	340
Triglycerides (mg/dL) (normal: < 150 mg/dL)	250
HDL cholesterol (mg/dL) (normal: > 60 mg/dL)	50
LDL cholesterol (mg/dL) (normal: < 100 mg/dL)	250
Thyroid function tests	
TSH (mIU/L) (reference range: 0.4-4.0 mIU/L)	22.0
FT ₄ (ng/dL) (reference range: 0.8-1.7 ng/dL)	0.6
FT ₄ , serum free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.	

daily and metformin 500 mg twice daily. Upon physical examination, she is normotensive with a blood pressure of 120/75 mmHg and a normal pulse rate of 80 beats per minute.

INITIAL LABORATORY RESULTS

Her laboratory results indicate a lipid profile with above-normal levels with evidence of hypercholesterolemia. Her total cholesterol is 340 mg/dL, triglycerides are 250 mg/dL, high-density lipoprotein (HDL) cholesterol is 50 mg/dL, and low-density lipoprotein (LDL) cholesterol is 250 mg/dL. Initial thyroid function test results indicate that TSH is 22.0 mIU/L (reference range: 0.4-4.0 mIU/L) and FT₄ is 0.6 ng/dL (reference range: 0.8-1.7 ng/dL) (Table 1).

According to clinical and laboratory workup, this patient meets the diagnosis for primary hypothyroidism. Dr. Frieze explained that “the treatment plan that should be initiated is thyroid hormone replacement therapy.” Additionally, treatment of her underlying hypothyroidism has the potential to address secondary changes to her blood lipid levels, Dr. Frieze noted.

Table 2.
Patient Case Study Follow-up Laboratory Results at Two Months, Four Months, Six Months and Nine Months

	Two-month follow-up	Four-month follow-up	Six-month follow-up	Nine-month follow-up
TSH (mIU/L) (reference range: 0.4-4.0 mIU/L)	12	9	3.5	6.6
FT ₄ (ng/dL) (reference range: 0.8-1.7 ng/dL)	1.0	1.2	1.3	1.1
FT ₄ , serum free thyroxine; TSH, thyroid-stimulating hormone.				

FOLLOW-UP LABORATORY RESULTS AT TWO, FOUR, SIX AND NINE MONTHS

After two months of treatment, the patient's follow-up test results demonstrate improvement in TSH (12 mIU/L) and normalization in FT₄ (1.0 ng/dL) (Table 2). At this point, her medication is adjusted to further improve TSH levels. At the patient's four-month follow-up, however, the TSH is still high (9.0 mIU/L), but the FT₄ has continued to increase (1.2 ng/dL) (Table 2). A discrepancy in the change between TSH and FT₄ levels may occur when inconsistencies exist in medication adherence. Dr. Frieze commented, "This is where we have to look at things clinically and make determinations about patient [adherence]." Patients who may have been nonadherent to treatment may begin taking their medication more regularly as the follow-up testing time approaches. Therefore, FT₄ levels may appear normal because this hormone responds to treatment more quickly, but TSH levels may take longer. Additionally, there may be factors that affect medication absorption.

During the clinical visit, the physician prompts the patient to take her medication more consistently and routinely. The patient agrees to improve treatment adherence, and at the six-month follow-up, TSH has normalized to 3.5 mIU/L, and the FT₄ has remained normal at 1.3 ng/dL (Table 2). The TSH reference range of 0.4 mIU/L to 4.0 mIU/L is that for the entire population. This patient is a 66-year-old woman, so this reference range does not represent the age-adjusted population range. Therefore, a level of 3.5 mIU/L would be in the midrange of normal for a 66-year-old woman. The patient is maintained on the same medication dose and is instructed to return in three months. At nine months after initiation of treatment, the laboratory test results once again show an elevated TSH (6.6 mIU/L) (Table 2). Dr. Frieze explained that the cause of this rebound in TSH should be explored. The patient indicates 100% medication adherence in recent months; therefore, Dr. Frieze noted that the increase in TSH could instead be attributed to switching between generic and brand-name therapeutic formulations.

RECOMMENDATIONS AND TAKEAWAYS

Clinicians can take steps to address both adherence and pharmacy challenges in patients being treated for hypothyroidism. Patient adherence can be addressed by emphasizing that hypothyroidism is a chronic condition, requiring a lifelong commitment to hormone replacement therapy; educating the patient on their medical condition and the risks associated with untreated or undertreated disease; providing specific instruction to patients on how to take medication appropriately and consistently; and raising questions around nonadherence

in a problem-solving and nonjudgmental manner.

Because bioequivalence does not necessarily exist between all thyroid medication preparations, switching between different preparations could be a possible explanation for the loss of TSH normalization. In that setting, elevation of TSH can lead to levels that reach the thyrotoxic range, potentially causing patients to experience adverse outcomes. As such, Dr. Frieze added that clinicians can address pharmacy challenges in patients being treated for hypothyroidism by asking questions about the patient's experiences at their pharmacy and checking prescription refill data. "This becomes a very pertinent part of the discussion to have with the patient to determine whether or not (they) are getting the same prescribed medication each time (they have) gone to the pharmacy," he concluded.

DISCLOSURES

a This study also examined adherence to the 2012 American Association of Clinical Endocrinologists/American Thyroid Association guidelines, which recommend that pregnant women with hypothyroidism who receive treatment with levothyroxine consult with an endocrinologist and, when treated with levothyroxine, have their thyroid-stimulating hormone levels monitored.

b Key inclusion criteria consisted of patients who had two or more diagnoses of hypothyroidism or at least one diagnosis of hypothyroidism and at least one prescription for levothyroxine over the calendar year 2014, age 18 or older. Adequacy of treatment was assessed from diagnosis in 2014 to one year later.

c This patient case is arbitrary and does not reflect or represent any specific patient profile. This case was designed to engage the audience and provide education around older patients with hypothyroidism.

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