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Managing the Challenges of Hypothyroidism

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Thyroid dysfunction is the one of the most commonly encountered endocrine abnormalities in primary care, with mild hypothyroidism occurring in about 4% to 10% of the US population and in up to 18% of those over age 60; for women in this age group, the prevalence of hypothyroidism may be as high as 20%.^{1,2} Primary hypothyroidism is a graded disorder, with a wide spectrum of severity between mild and overt disease.³ Because hypothyroidism is associated with several other comorbid disorders and many vague symptoms, the diagnostic workup may include screening tools for a variety of other diseases, such as depression and anxiety, to rule these out as a primary diagnosis. Although hypothyroidism has significant clinical consequences, it is also readily treatable. As in diagnosis, nuances in treatment can present important clinical challenges.

This supplement focuses on the clinical consequences and diagnosis of hypothyroidism, including identification of special populations. It also discusses management of hypothyroidism and use of thyroid hormone replacement therapy, particularly levothyroxine (synthetic T4) (Levo-T, Levolet, Levotheroid, Levoxyl, Novothyrox, Synthroid,

Practice recommendations

- Hypothyroidism is a commonly encountered endocrine disorder with serious clinical consequences, but it is readily treatable. (SOR: A)
- Screening of thyroid function is clearly indicated in persons with signs/symptoms of hypothyroidism. Other possible groups include those with subclinical hypothyroidism, diabetes mellitus, previous thyroid surgery or neck irradiation, the elderly, and others. (SOR: C)
- Underdosing thyroid replacement puts patients at risk for clinical sequelae of continued hypothyroidism, such as hypercholesterolemia or depression. (SOR: A)
- Oversedosing thyroid replacement puts patients at risk for clinical sequelae of hyperthyroidism, such as osteoporosis or atrial fibrillation. (SOR: A)
- Although the FDA has recognized bioequivalent levothyroxine products, the current standards potentially allow for significant differences in the bioavailability of products rated as bioequivalent. (SOR: B)



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TABLE 1

Recommendations for thyroid testing among professional organizations

Professional association	Summary of TSH screening recommendation
American Thyroid Association	Age 35 years and every 5 years thereafter (2000)
American Association of Clinical Endocrinologists	Older, especially women (2002), pregnancy (1999)
American College of Physicians	Women >50 years with 1 or more symptoms possibly caused by thyroid disease (1998)
US Preventive Services Task Force	Insufficient evidence for or against adult routine screening
American Academy of Family Physicians	Routine screening for patients >60 years (2002)

Unithroid, and generics) and briefly addresses hyperthyroidism resulting from overtreatment of hypothyroidism. Central hypothyroidism, caused by pituitary-based deficiencies of thyrotropin-stimulating hormone or thyrotropin-releasing hormone, will not be discussed.

BACKGROUND

The pituitary hormone thyrotropin (thyroid-stimulating hormone [TSH]) is responsible for maintaining normal thyroid morphology and for providing the primary stimulus for synthesis and secretion of the thyroid hormones thyroxine (T4) and triiodothyronine (T3).⁴ An inverse relationship exists between TSH levels and circulating T4 and T3, where high TSH levels typically indicate hypothyroidism and too little thyroid secretion. Thyroid hormone has many critical roles for both homeostasis and growth and development; therefore, an imbalance of thyroid hormone may severely impact patient functioning.

The most common cause of permanent hypothyroidism in North America is a chronic autoimmune condition, Hashimoto's thyroiditis.⁵ High titers of antithyroid peroxidase autoantibodies may be present in up to 95% of those with Hashimoto's thyroiditis and are helpful in diagnosis.⁶ Other permanent causes of hypothyroidism include thyroidectomy, radioactive iodine therapy, head or neck irradiation, and congenital defects. Hypothyroidism may temporarily arise from an inflammation of the thyroid gland, from some medications, or from too much or too little iodine.⁶

SCREENING

Screening in asymptomatic patients is controversial even among expert groups (TABLE 1). The American Academy of Family Physicians recommends routine screening for persons beginning at age 60 years, while some groups recommend beginning screening at an earlier age. Thyroid function tests are clearly indicated for patients who have signs

and symptoms indicative of hypothyroidism and are also appropriate for those with subclinical hypothyroidism, since they are at increased risk for progression to overt hypothyroidism; patients with diabetes, previous thyroid surgery or neck radiation, premature gray hair, or pernicious anemia; and the elderly, especially women and those with dementia. Women in the second trimester of pregnancy should be screened for antimicrosomal antibodies since at least 5% of women develop postpartum thyroiditis, 25% of whom develop chronic hypothyroidism requiring lifelong therapy.⁷ Additionally, any patient with an unexplained laboratory abnormality (eg, hypercholesterolemia, hyponatremia, anemia, hypercalcemia, elevated creatine phosphokinase) likely warrants a serum TSH test. The incremental cost of adding a TSH determination to quintennial cholesterol screening starting at age 35 years has been estimated to be \$9200 per quality-adjusted life year for women and \$22,600 for men; these figures are comparable to those for screening for breast cancer and hypertension.⁷

Routine thyroid function screening is not recommended for patients who are hospitalized with acute illness but have no evidence of thyroid dysfunction, since these patients have a high frequency of transient thyroid function abnormalities.⁷

DIAGNOSIS

Signs and symptoms. The presentation and clinical manifestation of hypothyroidism vary widely. Classic clinical signs of hypothyroidism are often subtle and insidious in onset and include fatigue, cold skin, and a general slowing of activity⁸ (TABLE 2). In addition, comorbid disorders or serum abnormalities are often present and may make accurate diagnosis more difficult. One of the most common is hypercholesterolemia, but others include carpal tunnel-like symptoms of tingling in the hands, menstrual changes, infertility, or arthritis-like aches in and around the joints.⁶ Patients with subclinical hypothyroidism may be asymptomatic or have nonspecific signs and symptoms such as

TABLE 2

Signs and symptoms of hypothyroidism

Fatigue	Facial puffiness
Slow speech	Macroglossia
Depression	Reflex delay in the relaxation phase
Weight gain	Ataxia
Dry skin, yellow skin	Irregular or heavy menses and infertility
Cold intolerance	Myalgias
Hair loss or coarse hair	Hyperlipidemia
Hoarse voice	Bradycardia and hypothermia
Constipation	Myxedema or nonpitting edema
Fluid retention	Anemia
Decreased concentration, forgetfulness, and other evidence of intellectual impairment	

depression, cognitive dysfunction, and weight gain. Use of available screening tools for depression and anxiety may help narrow the diagnosis or identify other underlying causes of the symptoms. Other symptoms may also include abnormalities in cardiac, gastrointestinal, or reproductive function.^{5,8} The effects of subclinical disease on the cardiovascular system and mental health and its impact during pregnancy are less established than for overt hypothyroidism.

Thyroid physical exam. The normal isthmus is several millimeters thick, with a felt-like consistency. Extending from the isthmus upward and either left or right of midline, a pyramidal lobe may be palpable in the presence of generalized thyroid enlargement as seen in Hashimoto's thyroiditis or Graves' disease and may be mistaken for an isthmus nodule or a pretracheal, "delphian" lymph node.

The physician should examine the patient's thyroid lobes for size, texture, consistency, and the presence of nodules or tenderness. The right lobe may be somewhat larger than the left, and each is expected to be about 4 to 5 cm long and 2 to 3 cm wide, approximately the size of the distal phalanx of the patient's thumb. The volume of the thyroid gland varies directly with body size, gender, and, to a lesser degree, age.

The consistency of normal thyroid tissue is described as rubbery. A spectrum of increasing firmness of thyroid tissue has been described, ranging from the softness associated with Graves' disease to the firmness of colloid goiter and early Hashimoto's thyroiditis.

The physician should note the size, location, and consistency of nodular lesions palpated in the course of the thyroid exam. When an apparent solitary nodule is palpated,

multiple occult nodules are likely to be present in about half of patients. Only about 6% of nodules <0.5 cm in diameter are palpable, while about half of the nodules >2 cm are reliably detected by experienced examiners. Pain in the thyroid may indicate the presence of thyroiditis.

TSH values. An appropriate laboratory evaluation is critical to establish the diagnosis and etiology of hypothyroidism, and to do so most cost-effectively.⁵ The sensitive TSH assay has become the single best screening test for hypothyroidism (and hyperthyroidism),⁵ but establishment of a single TSH reference range to diagnose and monitor thyroid disease continues to be controversial. In the NHANES III study, serum TSH levels fell in the range of 0.45 to 4.12 mU/L,¹ while The National Academy of Clinical Biochemistry proposed a normal TSH range of 0.4 to 4.0 mU/L;⁹ other organizations propose 0.3 to 3.0 mU/L. Complicating matters, each laboratory may use a different TSH reference range. For the purposes of this supplement, a normal TSH is considered to be 0.45 to 4.12 mU/L; although physicians should be aware that there is some flexibility in interpretation.

Other assays. Free-T4 level testing is important to determine thyroid gland function and, in conjunction with TSH testing, the cause of the hypothyroidism. A high TSH level and low free-T4 level indicate primary hypothyroidism, while a low TSH level and low free-T4 level indicate secondary hypothyroidism. A high TSH level and normal free-T4 level indicate subclinical hypothyroidism.⁶ Free-T3 level testing is not useful in diagnosing hypothyroidism.

Measurement of antithyroid antibodies is useful for determining if the etiology of primary hypothyroidism is an

autoimmune disorder. Antithyroid peroxidase antibodies are especially helpful in predicting progress from subclinical to overt hypothyroidism¹⁰ and in screening for preclinical hypothyroidism in children whose parents both have autoimmune thyroid disease.¹¹

Referral. Although most primary care physicians can diagnose and treat hypothyroidism, referral to an endocrinologist may be warranted for children and adolescents, patients unresponsive to therapy, pregnant or postpartum women, severely ill and cardiac patients, those taking amiodarone or phenytoin, patients with sodium levels <130 mEq/L, and in the presence of goiter, nodule, or other structural changes in the thyroid gland or other endocrine disease.^{5,6}

Even small changes in the dose of levothyroxine can shift a patient from a euthyroid to a hyperthyroid or hypothyroid state.

TREATMENT

Symptomatic individuals with lesser degrees of subclinical hypothyroidism may benefit from thyroid replacement, but this has not been proved. The American Association of Clinical Endocrinologists suggests treatment for patients with a TSH level ≥ 10 mU/mL, as well as close follow-up of patients with subclinical hypothyroidism to monitor for conversion to overt hypothyroidism.^{2,5}

Treatment goals for patients with hypothyroidism are to

- Restore normal thyroid hormone concentrations in the tissue
- Provide symptomatic relief
- Prevent neurologic deficits in newborns and children
- Reverse the biochemical abnormalities of hypothyroidism.

Product types available for thyroid replacement therapy include synthetic and natural combinations of T3 (liothyronine) and T4 (levothyroxine), and desiccated natural thyroid, with levothyroxine alone considered the drug of choice for thyroid replacement therapy.

Liothyronine (Cytomel) produces fluctuating levels of T3, has a shorter elimination half-life than T4, and often requires twice-daily dosing. Liothyronine is 4 times more potent than levothyroxine and may, therefore, cause palpitations and other cardiac side effects. Additionally, liothyronine produces high T3 but low T4 levels, which is the opposite of a normal physiologic condition and is potentially hazardous to fetal welfare during pregnancy. In general, combining levothyroxine with liothyronine has not been

definitively shown to provide superior results to levothyroxine alone;¹²⁻¹⁴ however, there may be an occasional patient who benefits from combined therapy.¹⁵

Desiccated thyroid is derived from thyroids of slaughtered pigs (Armour Thyroid, Thyrolar) or cows, and may contain a variable T3:T4 ratio that also may provide a higher ratio of T3 than physiologically required. The T3 in desiccated thyroid is available shortly after ingestion.

Levothyroxine (synthetic T4) is the drug of choice for thyroid replacement therapy because it is dosed once daily, produces reliable results, is chemically stable, has a long elimination half-life (~7 days), and is relatively inexpensive. About 85% of the T4 dose is converted to T3 in vivo, at an expected consistent rate. The US Food and Drug Administration (FDA) recently approved generic levothyroxine preparations based on standardized bioequivalency testing. However, professional endocrine organizations have argued that the method by which products are determined to be bioequivalent allows too much variability in tablet strength to ensure consistent levothyroxine dosing across products and puts patients at risk for over- or undertreatment of their thyroid disorder.

How to start replacement therapy. Physicians must tailor treatment and management of hypothyroidism to individual patients.⁵ Individualized doses are important because even small changes in the administered dose of levothyroxine can shift a patient from a euthyroid to a hyperthyroid or hypothyroid state. A small study comparing fixed-dose to individually titrated levothyroxine in hypothyroid patients showed that fixed-dose levothyroxine therapy can cause hyperthyroid symptoms, modifications in myocardial structure, and altered cardiopulmonary function, primarily during physical activity.¹⁶ However, careful adjustment of the levothyroxine dose reversed and almost completely normalized cardiopulmonary function parameters in study participants.

An initial levothyroxine dosage may range from 12.5 μg to a full replacement dose (average of 1.6 $\mu\text{g}/\text{kg}$) based on age, weight, presence of associated disorders, cardiac status of the patient, and severity and duration of hypothyroidism.^{5,6} Titration with 12.5 to 25 $\mu\text{g}/\text{day}$ should occur slowly every 6 to 8 weeks until the TSH level reaches about 0.3 to 3.0 mU/mL; smaller levothyroxine doses should be used as the TSH nears the desired range.⁵ An even more gradual dosing schedule should be instituted for patients who have congestive heart failure, angina, or anxiety. In older adults, dosage should be titrated carefully in increments of 12.5 μg to 25 μg until the TSH normalizes. The higher the pretreatment TSH level, the longer the expected titration period.

After a patient's TSH level has normalized, the maintenance dosage should be continued with an annual or semi-annual TSH test or when the patient demonstrates a change

in symptoms.⁵ Requirements may change with patient age, severe illness, and pregnancy. If a patient shows no appreciable benefit after 3 months, the need for treatment should be reassessed and referral to an endocrinologist considered.

Thyroid overreplacement. Some evidence indicates that up to 20% of patients receiving levothyroxine are overtreated.² This may result in overt or subclinical hyperthyroidism, which may cause cardiac hypertrophy, atrial fibrillation, and accelerated bone turnover.^{17,18} The risk of atrial fibrillation is increased up to 3-fold in elderly patients who receive thyroid overreplacement with a TSH <0.1 mU/mL compared with patients who are euthyroid.¹⁹

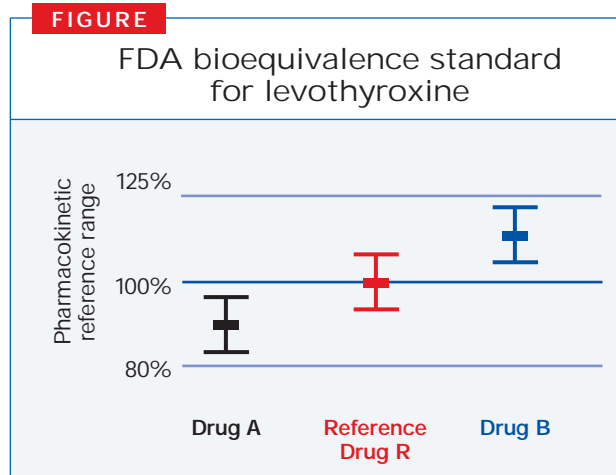
Hyperthyroidism is considered a risk factor for osteoporosis, which may be compounded in the postmenopausal population.⁵ One meta-analysis demonstrated a clear relationship between hyperthyroidism and decreased bone mineral density, with normalization of bone mineral density upon normalization of the thyroid state.¹⁷ However, timely identification and correction can prevent the cardiac and bone problems of thyroid overreplacement. In patients suspected of exposure to higher-than-needed doses of thyroid hormone, a T4 test more accurately assesses thyroid status since it may take weeks or months for the TSH to reach steady state.⁵

Hypothyroidism is often accompanied by weight gain, so it is no surprise that treatment of hypothyroidism often results in weight loss. One study showed that small changes in the levothyroxine dose can have a significant impact on the resting energy expenditure.²⁰ However, it is not advisable to increase the levothyroxine dose beyond that necessary to achieve a euthyroid state. Although additional weight loss may occur, it is likely to be short-lived, since it is thought that the body will adapt by increasing appetite and decreasing physical activity, thereby negating effects on the metabolic rate.⁶

Interacting conditions and drugs. Dosing requirements may be affected by malabsorptive states or drug interactions. Many medications are known to cause drug-induced hypothyroidism or hyperthyroidism⁵ (TABLE 3). Other medications may alter thyroid function tests without inducing thyroid dysfunction; for example, estrogen, even at low doses, increases serum levels of thyroxine-binding globulin. Therefore, euthyroid patients receiving any form of estrogen generally show elevated total T3 and T4 values, while serum TSH, free T3, and free T4 levels remain unchanged.

BIOEQUIVALENCE AND ITS CLINICAL IMPORTANCE

Twelve strengths of levothyroxine are available (25 µg, 50 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg, 175 µg, 200 µg, 300 µg), with some strengths differing by as lit-



tle as 9% to 12.5%. The wide range of tablet strengths is offered to accommodate once-daily dosing of a variety of individual patient requirements and to avoid both over- and underreplacement. As is the case with warfarin, phenytoin, and digoxin, to name a few, levothyroxine is a drug with a narrow therapeutic index (NTI) since the difference between subtherapeutic and toxic blood levels is small. In fact, Carr and colleagues showed that a 25-µg increase in dose was generally sufficient to make a clinically and biochemically euthyroid patient subclinically hyperthyroid.²¹ The converse was observed for a 25-µg decrease in dose. Several professional organizations have proposed that the FDA reassess its bioequivalence standards for NTI drugs because these standards may classify 2 generic brands of an NTI drug as bioequivalent, yet produce therapeutically different results.

In determining if 2 drugs are bioequivalent (rated as A or AB), the FDA compares the pharmacokinetics of the drugs, specifically, differences in the area under the time-concentration curve (AUC) and the maximum drug concentration (C_{max}). For drug A to be rated as bioequivalent to drug R (the reference standard), both the mean and the standard deviation (90% confidence interval [CI]) of the AUC and the C_{max} of drug A must fall between 80% and 125% of the reference standard R.

For levothyroxine, this approach is problematic. First, bioequivalence studies are conducted in healthy subjects and assess surrogate endpoints (AUC and C_{max}) that have not been shown to correlate with thyroid function. Also, the FDA has not identified a single reference levothyroxine standard against which other levothyroxine products must be compared; rather, the FDA recognizes multiple levothyroxine reference standards yielding 3 distinct groups of levothyroxine products with an AB rating.²² Consequently, it can be difficult to remember which products are

TABLE 3

Interactions with levothyroxine

Other drugs			
Amiodarone	Ferrous sulfate	Phenytoin	Sucralfate
Antacids containing aluminum hydroxide	Furosemide	Rifampin	Tamoxifen
Calcium	Glucocorticoids	Salicylates	
Carbamazepine	Methadone	Sertraline	
Cholestyramine	Phenobarbital	Soy	
Conditions			
<ul style="list-style-type: none"> • Hypothyroidism can cause higher serum digoxin levels and increased sensitivity to anesthetic and sedative agents. 			
<ul style="list-style-type: none"> • Higher phenytoin levels have been reported with hypothyroidism. 			
<ul style="list-style-type: none"> • Treatment with thyroid hormone may affect the INR of patients being treated with warfarin. 			
<ul style="list-style-type: none"> • Higher estrogen levels (higher estrogen levels and other factors in pregnancy usually lead to a significant increase in T4 dose requirement, while estrogen replacement may lead to an increase in dose requirement). 			
<ul style="list-style-type: none"> • Requirement for insulin or antidiabetic agents may be reduced in hypothyroid patients and subsequently increase after initiation of thyroid replacement. 			
Magnitude and relative importance are likely to be patient-specific.			

bioequivalent. Finally, 2 levothyroxine products within the same group can be rated as bioequivalent, yet differ significantly in the amount of drug delivered.

As shown in the FIGURE, drug A is classified as bioequivalent to drug R since the mean and the 90% CI of drug A fall within the 80% to 125% range;²² this is similar for drug B. Note, however, that the mean for drug A is approximately 90%, while the mean for drug B is 115%. Should a patient stabilized on drug B be switched to drug A, that patient would receive 78% of the previous levothyroxine dose ($90\% \div 115\%$) when taking drug A than when taking drug B. This is analogous to taking a patient stabilized on a daily dose of 112 μg and decreasing the dose by 2 tablet strengths to 88 μg . This patient's thyroid classification would likely change to hypothyroidism, as shown by Carr and colleagues²¹ and illustrated by the following published case study²³ (TABLE 4). A patient stabilized on one levothyroxine product was changed to the same dose of another levothyroxine product. Three months later, she exhibited signs and symptoms of hypothyroidism. She was switched back to her original levothyroxine product and subsequently became euthyroid.

Using current standards, bioequivalent levothyroxine products used interchangeably may put patients at risk of hypothyroidism or hyperthyroidism. It is, therefore, essential that patients remain on the same levothyroxine product.

Pharmacists can substitute levothyroxine products classified by the FDA as bioequivalent without physician consultation. In fact, substitution to a generic drug is legally required in some states. Physicians should ensure that patients receive and remain on the same levothyroxine product.²⁴ Steps physicians may take to manage levothyroxine product substitution include the following:²⁴

- Restrict substitution by writing on the prescription: "Do not substitute," "Dispense as written," or whatever is necessary in your state.
- Alert patients that their levothyroxine brand may be switched at the pharmacy, and encourage them to ask to remain on the same brand at every pharmacy refill.
- Make sure patients understand the need to have their TSH levels retested and dosing readjusted every time their levothyroxine brand is switched.
- Obtain serum TSH levels 8 to 12 weeks after dose or brand changes. If TSH levels deviate from the therapeutic goal range, consider brand substitution as a possible explanation.

SPECIAL SUBGROUPS

Older adults. Thyroid dysfunction occurs frequently in the elderly population, yet often goes unnoticed.²⁵ Because older adults are at increased risk of many other co-presenting disorders, including depression, dry skin,

and cardiac abnormalities, overt hypothyroidism should always be a diagnostic consideration. However physicians do not have clear guidance on how to treat subclinical hypothyroidism in elderly patients. A study from the Netherlands demonstrated that people over 85 years of age with high levels of TSH may have a prolonged life span. Interestingly, this population did not experience adverse effects of hypothyroidism.²⁵ Therefore, the clinical benefit of treating subclinical hypothyroidism in individuals older than 85 may be limited.

Depressed patients. A high incidence of comorbidity exists between depression and both clinical and subclinical hypothyroidism.²⁶ A small study of 31 subjects highlighted that the lifetime frequency of depression was significantly higher in those who met the criteria for subclinical hypothyroidism (56%) than in those who did not (20%).²⁷ The authors speculated that subclinical hypothyroidism might lower the threshold for the development of depression in response to other factors. Accordingly, the American Association of Clinical Endocrinologists and the American College of Endocrinology recommend that overt or subclinical hypothyroidism should be considered in every person with depression.⁵ Case reports and small studies also have indicated that thyroid replacement in depressed patients may improve the signs and symptoms of depression when used alone or as adjunctive therapy.^{28,29}

Patients with hypercholesterolemia. Elevated cholesterol levels are often present in patients with hypothyroidism. In overt hypothyroidism, adequate thyroid substitution therapy can often reverse hypercholesterolemia.^{30,31} One analysis demonstrated that adequate thyroid replacement and subsequent normalization of TSH significantly reduced an abnormally high serum total cholesterol level.³¹ However, in patients with subclinical hypothyroidism and hypercholesterolemia, the benefits may be more modest, with one retrospective analysis observing a 6% reduction in total cholesterol with thyroid replacement therapy. Presently, the total cholesterol threshold above which screening for hypothyroidism is cost-effective is unknown.

Pregnant and postpartum patients. Hypothyroidism during pregnancy and the postpartum period may present significant risk to the mother, fetus, and neonate due to possible unrecognized thyroid pathology.³² One large retrospective study showed that pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption and preterm delivery.³³ Also, women with pre-existing hypothyroidism frequently require increased doses of levothyroxine, particularly during the first trimester of pregnancy, to maintain serum TSH in the low-normal range and serum free T4 in the high-normal range.^{5,34} Consequently, primary care physicians should

TABLE 4

Case study

- 37-year-old woman with a history of hypothyroidism for 18 years was being treated with levothyroxine preparation A 200 µg/d and doing well with no symptoms.
- Her physician changed her therapy to levothyroxine preparation B 200 µg/d.
- After 3 months, she reported feeling puffy. Her thyroid function test results were:
 - TSH 15.15 mU/L (0.5 to 6.5 mU/L)
 - T4 83.7 nmol/L (58 to 154 nmol/L)
- She was switched back to levothyroxine preparation A 200 µg/d. One year later her thyroid function test results were:
 - TSH 4.9 mU/L
 - T4 117.1 nmol/L

consider referral to an endocrinologist for such patients.

Transient thyroiditis occurs postpartum in 5% to 8% of women in the general population and in up to 25% of women with type 1 diabetes mellitus.³⁵ Most of these women return to a euthyroid state within 1 year, but about 25% develop permanent primary hypothyroidism.³⁵ The risk increases with previous postpartum hypothyroidism, diabetes mellitus, or a family history of autoimmune thyroid disease. Postpartum thyroiditis is an autoimmune thyroid disorder, characterized by elevated levels of antithyroid antibodies, that may or may not cause symptoms. Thyroperoxidase antibody and TSH testing are used in its diagnosis. Free-T4 levels are used adjunctively to confirm that patients are either hypothyroid or hyperthyroid.

ENCOURAGING PATIENT ADHERENCE

Patient nonadherence is thought to be the principal reason for lack of expected response to therapy or high TSH levels, despite high doses of levothyroxine. An elevated serum thyrotropin concentration with serum free thyroxine at the upper end of the normal range suggests improved adherence immediately before testing due to a lag in the thyrotropin response.³⁶

Physicians may increase patients' adherence to treatment for hypothyroidism if, during the initial treatment and as needed throughout therapy, they educate and engage their patients in dialogue:

- Explain the risks associated with hypothyroidism and hyperthyroidism.
- Inform patients that clinic visits will become less frequent once a euthyroid state has been established.
- Alert patients to the need to take levothyroxine on an empty stomach.

- Describe interactions of thyroid replacement therapy with drugs such as iron, calcium, and multivitamins and explain how to manage those interactions.
- Encourage patients to ask questions and seek answers.
- Provide advice on how and where to obtain reliable information.

CONCLUSION

Although hypothyroidism is a readily treatable disease, challenges remain regarding diagnosis, screening, and treatment. Among the diagnostic challenges is the absence of a universally accepted reference range. Familiarity with the normal range for the local laboratory is essential. Hypothyroidism is typically treated with levothyroxine, which is slowly titrated to achieve a normal TSH level. Overdosing is to be avoided as this puts patients at risk for clinical sequelae of hyperthyroidism, such as osteoporosis or atrial fibrillation. Although the FDA has established groups of bioequivalent levothyroxine products, the wide range of these standards and the therapeutic substitution possible can subject patients to potential clinically important differences in the amount of levothyroxine actually taken. Therefore, switching the patient from one levothyroxine product to another at any point during therapy is discouraged. Primary care physicians can help their patients with hypothyroidism manage their disease through education and ongoing dialogue.

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