

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE
FOR THE EVALUATION AND TREATMENT OF
HYPERTHYROIDISM AND HYPOTHYROIDISM**

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE EVALUATION AND TREATMENT OF HYPERTHYROIDISM AND HYPOTHYROIDISM

ABSTRACT

These clinical practice guidelines summarize the recommendations of the American Association of Clinical Endocrinologists for the diagnostic evaluation of hyperthyroidism and hypothyroidism and for treatment strategies in patients with these disorders. The sensitive thyroid-stimulating hormone (TSH or thyrotropin) assay has become the single best screening test for hyperthyroidism and hypothyroidism, and in most outpatient clinical situations, the serum TSH is the most sensitive test for detecting mild thyroid hormone excess or deficiency. Therapeutic options for patients with Graves' disease include thyroidectomy (rarely used now in the United States), antithyroid drugs (frequently associated with relapses), and radioactive iodine (currently the treatment of choice). In clinical hypothyroidism, the standard treatment is levothyroxine replacement, which must be tailored to the individual patient. Awareness of subclinical thyroid disease, which often remains undiagnosed, is emphasized, as is a system of care that incorporates regular follow-up surveillance by one physician as well as education and involvement of the patient. (**Endocr Pract. 2002;8:457-469**)

Abbreviations:

AACE = American Association of Clinical Endocrinologists; **RIA** = radioimmunoassay; **T₃** = triiodothyronine; **T₄** = thyroxine; **TRAb** = thyrotropin receptor antibodies; **TSH** = thyroid-stimulating hormone (thyrotropin); **TSI** = thyroid-stimulating immunoglobulins

MISSION STATEMENTS

Guidelines Mission Statement

The purpose of these guidelines is to present a framework for the diagnosis, treatment, and follow-up of patients with hyperthyroidism and hypothyroidism. These thyroid guidelines address the difficulties involved in diagnosing thyroid disease and offer a system of care that should improve outcomes and reduce costs. The American Association of Clinical Endocrinologists (AACE) advocates a continuum of care by one physician with expertise in the diagnosis and treatment of thyroid disease and

follow-up conducted at regular intervals throughout the course of the patient's disease.

Public Service Mission Statement

Since the original AACE Thyroid Guidelines were published in 1995 (1), the sensitive thyroid-stimulating hormone (TSH or thyrotropin) assay has become the primary test to diagnose and treat thyroid disease, and subclinical thyroid disease has been more precisely defined and diagnosed. Subclinical hyperthyroidism has been shown to affect the health of untreated patients adversely, and subclinical hypothyroidism may also have important health consequences.

Patients with subclinical hyperthyroidism are often those who have received excessive amounts of thyroid hormone, which may result in an accelerated rate of bone loss—a frequent problem in the postmenopausal population. In addition, cardiac hypertrophy and atrial fibrillation are possible consequences of subclinical hyperthyroidism. The cardiac and bone problems in these patients can be prevented by the timely identification and correction of thyroid overreplacement.

Subclinical hypothyroidism is also an important condition, affecting up to 20% of persons beyond 60 years of age. Clinical endocrinologists agree that most patients with subclinical hypothyroidism require therapy. Although patients with this disorder can be asymptomatic, some patients have subtle findings, including alterations in lipid metabolism, cardiac, gastrointestinal, neuropsychiatric, and reproductive abnormalities, and an increased likelihood of developing a goiter. For increased recognition of subclinical hypothyroidism, physician education and patient awareness are necessary.

HYPERTHYROIDISM

Hyperthyroidism is the consequence of excessive thyroid hormone action. The causes of hyperthyroidism include the following:

- Toxic diffuse goiter (Graves' disease)
- Toxic adenoma
- Toxic multinodular goiter (Plummer's disease)
- Painful subacute thyroiditis
- Silent thyroiditis, including lymphocytic and postpartum variations

- Iodine-induced hyperthyroidism (for example, related to amiodarone therapy)
- Excessive pituitary TSH or trophoblastic disease
- Excessive ingestion of thyroid hormone

Clinical Features

The signs and symptoms of hyperthyroidism are attributable to the effects of excess thyroid hormone in the circulation. The severity of signs and symptoms may be related to the duration of the illness, the magnitude of the hormone excess, and the age of the patient.

The following list illustrates the spectrum of possible signs and symptoms associated with the various causes of hyperthyroidism:

- Nervousness and irritability
- Palpitations and tachycardia
- Heat intolerance or increased sweating
- Tremor
- Weight loss or gain
- Alterations in appetite
- Frequent bowel movements or diarrhea
- Dependent lower-extremity edema
- Sudden paralysis
- Exertional intolerance and dyspnea
- Menstrual disturbance (decreased flow)
- Impaired fertility
- Mental disturbances
- Sleep disturbances (including insomnia)
- Changes in vision, photophobia, eye irritation, diplopia, or exophthalmos
- Fatigue and muscle weakness
- Thyroid enlargement (depending on cause)
- Pretibial myxedema (in patients with Graves' disease)

A patient with hyperthyroidism need not have all these symptoms (2-5).

Diagnosis

A comprehensive history should be elicited, and a thorough physical examination should be performed, including the following:

- Weight and blood pressure
- Pulse rate and cardiac rhythm
- Thyroid palpation and auscultation (to determine thyroid size, nodularity, and vascularity)
- Neuromuscular examination
- Eye examination (to detect evidence of exophthalmos or ophthalmopathy)
- Dermatologic examination
- Cardiovascular examination
- Lymphatic examination (nodes and spleen)

Laboratory Evaluation

The development of sensitive TSH assays has considerably facilitated the diagnosis of hyperthyroidism. The sensitive TSH test refers to a TSH assay with a functional sensitivity of 0.02 or less. Hyperthyroidism of any cause

(except excess TSH production) results in a lower-than-normal TSH level (suppressed TSH). The sensitive TSH assay is the single best screening test for hyperthyroidism, and in most outpatient clinical situations, the serum TSH is the most sensitive test for detecting mild (subclinical) thyroid hormone excess or deficiency.

In patients with unstable thyroid states, such as those recently treated for hyperthyroidism or those who have been receiving excess thyroid hormone replacement, serum thyroxine (T_4) measurement more accurately indicates the thyroid status than does serum TSH. Patients with chronic or recent severe hyperthyroidism or hypothyroidism will benefit from having both TSH and T_4 monitored for 1 year until their condition becomes stable. Elderly patients or those patients suspected of being non-compliant also should have both TSH and T_4 measurements monitored.

Other laboratory and isotope tests may include the following:

- T_4 or free T_4
 - Triiodothyronine (T_3) radioimmunoassay (RIA) or free T_3
- Abnormal results of T_4 or T_3 measurements are often due to binding protein abnormalities rather than abnormal thyroid function. Therefore, total T_4 or T_3 must be determined in conjunction with some measure of their thyroid hormone binding such as T_3 resin uptake or assay of thyroid-binding globulin to yield a "free thyroid hormone estimate." Commercial laboratories often call these methods free T_4 or free T_3 even though they do not measure free hormone directly.
- Thyroid autoantibodies, including TSH receptor antibodies (TRAb) or thyroid-stimulating immunoglobulins (TSI)
- These studies are not routinely necessary but may be helpful in selected cases, such as in patients with hyperthyroidism during pregnancy.
- Radioactive iodine uptake
 - Thyroid scan—with either ^{123}I (preferably) or $^{99\text{m}}\text{Tc}$
- Such a scan is not a thyroid function test but is done to help determine the cause of the hyperthyroidism. The scan may also be useful in assessing the functional status of any palpable thyroid irregularities or nodules associated with a toxic goiter (5).

Reverse T_3 testing is seldom, if ever, helpful in clinical practice.

Differential Diagnosis

The diagnosis of overt Graves' disease with ophthalmopathy is usually obvious. In elderly persons, however, Graves' disease may be more difficult to diagnose and may manifest only with cardiac findings or weight loss (apathetic or masked thyrotoxicosis). Some patients may have a normal-size thyroid gland. The free thyroid hormone (T_4 and T_3) estimates are usually high, although some patients may have increased values only for free T_3 estimate (T_3 toxicosis). In Graves' disease, the TSH level

measured with use of a sensitive assay is always suppressed, and the thyroid scan shows diffuse isotope uptake and sometimes a pyramidal lobe.

A toxic adenoma ("hot nodule") is associated with a low TSH level, with or without a high free T_4 or T_3 estimate. The thyroid scan reveals a functioning nodule and suppression of the extranodular thyroid tissue. Toxic multinodular goiter has the same characteristics and similar laboratory findings as those associated with a toxic nodule, but the thyroid gland is variably enlarged and composed of multiple nodules. In both cases, radioactive iodine uptake is usually increased but may be in the normal range.

A low radioiodine uptake in conjunction with poor thyroid gland imaging on the thyroid scan characterizes subacute thyroiditis, silent thyroiditis, iodine-induced hyperthyroidism, and factitious thyroxine-induced hyperthyroidism. All these conditions are associated with variably increased T_4 and T_3 levels on RIA during the hyperthyroid phase.

Classic subacute thyroiditis is usually painful, sometimes causes fever, and is self-limited. The hyperthyroidism is due to the release of stored thyroid hormone from the inflamed gland. Frequently, the early hyperthyroid phase leads to a hypothyroid phase during a 2- or 3-month period, before resolution. Silent thyroiditis (painless), thought to be an autoimmune disorder, has a similar course; it is particularly common in postpartum women. Iodine-induced hyperthyroidism occurs most often in the older population and is typically seen in the setting of a preexisting nontoxic nodular goiter. The iodine load, from orally administered medications or supplements or from intravenously administered contrast agents, induces the hyperthyroidism, which does not readily resolve and may necessitate specific treatment. Factitious thyrotoxicosis produces a similar clinical picture; if suspected, it can be confirmed by finding a very low or absent thyroglobulin level (the thyroglobulin level is very high in all types of thyroiditis).

Not all high values for T_4 and T_3 on RIA, and not all suppressed TSH levels, are associated with hyperthyroidism. Estrogen administration or pregnancy raises the thyroxine-binding globulin level and results in high total T_4 and T_3 levels on RIA but normal free T_4 and T_3 estimates and a normal result on sensitive TSH assay. Euthyroid hyperthyroxinemia may also be attributable to other abnormal binding proteins, including albumin and prealbumin. Similarly, thyroid hormone resistance states can cause increased serum T_4 levels without hyperthyroidism. Administration of corticosteroids, severe illness, and pituitary dysfunction can be associated with a suppressed TSH level in the absence of hyperthyroidism.

Treatment and Management

Three types of therapy are available for Graves' disease: (1) surgical intervention, (2) antithyroid drugs, and (3) radioactive iodine.

Surgical Intervention

Although thyroidectomy for Graves' disease was frequently used in the past, it is now uncommonly performed in the United States unless coexistent thyroid cancer is suspected. Pregnant patients with hyperthyroidism who are intolerant of antithyroid drugs or nonpregnant patients desiring definitive therapy but who refuse radioactive iodine treatment are candidates for surgical intervention. Some physicians prefer surgical treatment of pediatric patients with Graves' disease or patients with very large or nodular goiters. Potential complications associated with surgical management of Graves' disease include hypoparathyroidism and vocal cord paralysis in a small proportion of patients. Surgeons trained and experienced in thyroid surgical procedures should perform this operation (2,3,5).

Antithyroid Drugs

Antithyroid drugs, methimazole and propylthiouracil, have been used since the 1940s and are prescribed in an attempt to achieve a remission. The remission rates are variable, and relapses are frequent. The patients in whom remission is most likely to be achieved are those with mild hyperthyroidism and small goiters. Antithyroid drug treatment is not without the risk of adverse reactions, including minor rashes and, in rare instances, agranulocytosis and hepatitis. The success of this therapy depends on a high degree of patient adherence to recommendations. Hyperthyroidism during pregnancy is one clear indication for antithyroid drug treatment. Elderly or cardiac patients may require "pretreatment" with antithyroid drugs, before radioiodine therapy. Moreover, some endocrinologists prefer antithyroid drug therapy in childhood Graves' disease. Treatment of Graves' disease with antithyroid drugs alone is an alternative therapeutic strategy but is used in only a minority of patients in the United States (2,3,6,7).

Radioactive Iodine

In the United States, radioactive iodine is currently the treatment of choice for Graves' disease. Many clinical endocrinologists prefer an ablative dose of radioactive iodine, but some prefer use of a smaller dose in an attempt to render the patient euthyroid. Ablative therapy with radioactive iodine yields quicker resolution of the hyperthyroidism than does small-dose therapy and thereby minimizes potential hyperthyroid-related morbidity.

Radioactive iodine therapy is safe, but most treated patients become hypothyroid and require lifelong thyroid replacement therapy. Some clinical endocrinologists are hesitant to use radioactive iodine to treat patients of child-bearing age, but no evidence has suggested that such therapy has any adverse effects. Specifically, studies have found no effect on fertility, no increased incidence of congenital malformations, and no increased risk of cancer in patients treated with radioactive iodine or in their offspring. Elderly or cardiac patients with Graves' disease may require antithyroid drug therapy before treatment

with radioactive iodine, to deplete the thyroid gland of stored hormone and reduce the risk of excessive posttreatment hyperthyroidism as a result of ^{131}I -induced thyroiditis. Use of radioactive iodine is contraindicated during pregnancy because it may ablate the thyroid in the fetus. Before radioactive iodine treatment, a negative pregnancy test should be obtained in all women of childbearing age, and pregnancy should be postponed after such therapy. A waiting period of 6 months is frequently advised. Furthermore, radioactive iodine should not be given to women who are breast-feeding because it appears in the breast milk. The use of radioactive iodine in patients younger than 20 years has become commonplace.

After administration of a dose of radioactive iodine, thyroid replacement therapy should be carefully initiated during the time the patient's thyroid function passes through the normal range into the hypothyroid range. The final thyroid replacement dose must be individualized. This approach promptly resolves the hyperthyroidism with a minimum of hypothyroid morbidity (2,3,6,7).

System of Care

Once the diagnosis of Graves' disease with hyperthyroidism has been established, the patient should be given a complete explanation of the illness and options for treatment. The goal is to involve the patient as a partner in the medical decision-making process and care, rather than have the endocrinologist dictate the choice of therapy.

Patients who elect to receive radioactive iodine should be given an explanation of the treatment, and a consent form for such therapy should be signed (see example in Appendix A). After receiving radioactive iodine, patients should be given an instruction sheet that itemizes appropriate precautions and explains follow-up management (see example in Appendix B).

The radioactive iodine uptake should be assessed before treatment to ensure adequate uptake at the time of therapy, to rule out the presence of a variant of thyroiditis or iodine contamination, and to help determine the dose of radioactive iodine. A thyroid scan is also useful in distinguishing toxic nodular goiter and toxic adenoma from Graves' disease. Typically, toxic nodular goiter is more resistant to radioactive iodine and frequently necessitates use of a larger dose.

β -Adrenergic antagonists provide symptomatic relief and can be administered before radioactive iodine is given. Because patients with hyperthyroidism may be relatively resistant to the effects of β -adrenergic blocking agents, larger and more frequent doses may be necessary. The dose of these drugs can be tapered and discontinued once the patient no longer has hyperthyroidism. In addition, in severe thyrotoxic states, adjuvant treatment can include organic or inorganic iodides and antithyroid drugs after radioactive iodine therapy.

After treatment with radioactive iodine, patients should have follow-up examinations at frequent intervals (varying from 4 to 6 weeks, but individualized for each case) until they are euthyroid and their condition is stable. Most patients will require full thyroid hormone replace-

ment therapy. Patients usually become hypothyroid within 3 months and could begin receiving partial replacement doses of levothyroxine approximately 2 months after receiving radioactive iodine. This schedule is determined by laboratory testing and clinical evaluation. At this time, the patient's thyroid status is quickly changing from euthyroid to hypothyroid, and the TSH level may not be a good indicator of function because it fails to increase quickly. From 2 weeks to several months may elapse before TSH responsiveness is recovered, and free thyroid hormone estimate tests are more accurate than TSH values during this interval.

When the condition of patients has stabilized, the frequency of visits and reevaluations can be extended. A common schedule for follow-up consultations is at 3 months, at 6 months, and then annually, but this can be modified on the basis of the physician's judgment (2,3,6).

Hyperthyroidism During Pregnancy

Hyperthyroidism during pregnancy presents special concerns and is best managed collaboratively by an obstetrician and a clinical endocrinologist. Use of radioactive iodine is contraindicated during pregnancy because it crosses the placenta. Antithyroid drugs are the treatment of choice for hyperthyroidism during pregnancy, and propylthiouracil is clearly preferred over methimazole. Antithyroid drugs also cross the placenta, and overtreatment with them may adversely affect the fetus. Therefore, the lowest possible dose of antithyroid drug should be used to maintain the mother's thyroid function at the upper limit of normal. Because pregnancy itself has an ameliorative effect on Graves' disease, the dose of antithyroid drug required usually decreases as the pregnancy progresses. Often the antithyroid drug can be discontinued before delivery. If surgical treatment does become necessary, it is best done during the second trimester of pregnancy.

The patient's active participation in treatment is critical to the successful outcome of pregnancy in the presence of Graves' disease. Of importance, the patient must understand the risk of the disease, the pathophysiologic factors, and the mechanisms involved in therapy. Patient education will enhance adherence to recommended therapy as well as awareness of changes that may necessitate treatment alterations. With this background, the patient should become more aware of the problems that might occur and should alert her endocrinologist.

The patient should also be informed about changes that may occur in her health or her baby's health during the postpartum period. She should be advised to inform the pediatrician of her thyroid disease and of the possibility that neonatal hyperthyroidism or hypothyroidism might develop in the baby. The infant's thyroid function must be tested at birth.

The patient should also be aware that postpartum recurrence of the hyperthyroidism is likely. This finding can be related to the Graves' disease or postpartum thyroiditis. If overt hyperthyroidism due to Graves' disease develops after delivery, the patient may be offered the alternative of resuming antithyroid drug therapy or receiv-

ing radioactive iodine. Radioactive iodine therapy is contraindicated if the patient is breast-feeding or, of course, is pregnant again. Postpartum follow-up with appropriate assessment by a clinical endocrinologist should be continued until the patient is in a stable euthyroid state.

Euthyroid pregnant patients treated for Graves' disease before the pregnancy may still have stimulating thyroid autoantibodies in the circulation, which can cross the placenta. Measurement of maternal TSI (TRAb) may be useful for assessment of potential fetal risk; on the basis of clinical judgment, the endocrinologist can have this study done (2,3,7).

Graves' Ophthalmopathy

Exophthalmos and other eye signs are the hallmark of Graves' disease and may occasionally be seen in the absence of hyperthyroidism. Severe Graves' ophthalmopathy occurs in a minority of patients with Graves' diathesis who are clinically euthyroid. The presence of ophthalmopathy necessitates a thorough thyroid evaluation. Orbital ultrasonography, computed tomography (without a contrast agent), or magnetic resonance imaging may be necessary, particularly in cases of unilateral exophthalmos. The finding of characteristic extraocular muscle swelling helps exclude the presence of a retro-orbital tumor. Serial exophthalmometry can document progression of the exophthalmos; such measurements are easily obtained during office visits. The rationale for local mechanical therapies—such as sunglasses, artificial tears, elevation of the head of the bed, bedtime diuretics, and use of eye protectors during sleep—should be explained to the patient in an effort to enhance adherence to recommendations. More aggressive treatment with corticosteroids, retro-orbital irradiation, or surgical intervention can be considered for progressive and severe ophthalmopathy. Consultation with an ophthalmologist experienced in the treatment of orbital disease is recommended in the management of such cases.

The question of a deleterious effect of ^{131}I therapy on ophthalmopathy in some patients has been raised by some, but not all, studies. The only two randomized studies suggest that, in patients with Graves' disease, thyroid-associated ophthalmopathy is slightly more likely to develop or worsen if the hyperthyroidism is treated with ^{131}I rather than thyroidectomy or antithyroid drugs (8,9). Both of these studies, however, have been criticized (10,11). Investigators generally accept that most patients do not have progression of their ophthalmopathy after radioactive iodine therapy. Cigarette smoking, posttherapy hypothyroidism, and the duration and severity of the hyperthyroidism are other possible risk factors for the progression of the ophthalmopathy. In patients with established ophthalmopathy, a course of corticosteroid therapy begun at the same time as administration of ^{131}I decreases the possibility of worsening the ophthalmopathy (12). The potential side effects of corticosteroids should be considered in the decision about such preventive treatment.

Patients Taking Amiodarone

Amiodarone therapy causes thyroid dysfunction in 14 to 18% of the involved patients. Therefore, before initiation of such therapy, patients should have a baseline TSH measurement, and then they should be monitored at 6-month intervals during treatment. In patients receiving amiodarone, either hypothyroidism, which is treated with levothyroxine replacement, or hyperthyroidism may develop. Amiodarone-induced hyperthyroidism is of two types. Type 1 is similar to iodine-induced hyperthyroidism (Jod-basedow phenomenon) and manifests with a low TSH level, a high free T_4 or T_3 estimate, and a low radioiodine uptake. Doppler ultrasonography shows increased vascularity of thyroid tissue, similar to that in Graves' disease (13). Because of low radioiodine uptake, ^{131}I treatment cannot be used, and use of antithyroid drugs has yielded only varied success. Although mild cases have resolved even when amiodarone therapy has been continued, consideration of ceasing this drug treatment is recommended. Restoration of euthyroidism may take months after cessation of amiodarone therapy. Type 2 amiodarone-induced hyperthyroidism resembles a destructive thyroiditis. Laboratory values and radioiodine uptake are similar to the findings in type 1; however, Doppler ultrasonography shows decreased vascularity of the thyroid tissue. Corticosteroid treatment is recommended, and patients sometimes require surgical removal of the thyroid.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is characterized by a serum TSH level <0.1 $\mu\text{IU/mL}$ and normal free T_4 and T_3 estimates (14-17). The low TSH levels result from either exogenous TSH suppression or endogenous production of thyroid hormones that, presumably, is sufficient to keep free T_4 and free T_3 levels normal but suppress pituitary TSH production and secretion. Most studies report a prevalence of $<2\%$ in the adult or elderly population (17-22).

The clinical significance of subclinical hyperthyroidism relates to three risk factors: (1) progression to overt hyperthyroidism, (2) cardiac effects, and (3) skeletal effects (17,22-25). In patients who are receiving levothyroxine for replacement therapy, the dose should be adjusted so serum TSH values range from 0.3 to 3.0 $\mu\text{IU/mL}$. An exception is thyroid hormone replacement treatment after thyroidectomy for differentiated thyroid cancer, in which case a mildly to moderately suppressed TSH level is generally desirable. In addition, some physicians treat hypofunctional thyroid nodules with levothyroxine in doses sufficient for minimal suppression of the TSH level.

In patients with subclinical hyperthyroidism attributable to nodular thyroid disease, treatment seems warranted because of the high rate of conversion to clinical hyperthyroidism. Recent studies have suggested that prolonged subclinical hyperthyroidism may be associated with decreased bone mineral density (26). Accordingly, investigators have concluded that subclinical hyperthyroidism should be considered a risk factor for osteoporosis, particularly in postmenopausal women. In men and pre-

menopausal women, bone loss seems to be minimal and of unknown clinical significance. In elderly patients with subclinical hyperthyroidism, the relative risk for atrial fibrillation increases threefold (22). Other adverse cardiac effects include impaired left ventricular diastolic filling and impaired ventricular ejection fraction response to exercise (24,25).

No consensus exists about the management of subclinical hyperthyroidism. One recent review of the topic suggested that, in most patients, treatment is unnecessary, but thyroid function tests should be performed every 6 months (17). AACE recommends that all patients with subclinical hyperthyroidism should undergo periodic clinical and laboratory assessment to determine individual therapeutic options.

Clearly, once a suppressed TSH level has been detected in a specific patient, a reassessment is appropriate to ensure that the suppressed TSH level is persistent rather than transient. Therefore, our suggestion is to reassess the TSH level along with free T₄ and T₃ estimates in 2 to 4 months. If a sustained TSH suppression (<0.1 μIU/mL) is established, then management should be based on an individual program. For example, patients with symptoms of hyperthyroidism, atrial fibrillation, or unexplained weight loss would be appropriate candidates for treatment. Women with osteopenia or osteoporosis should undergo assessment for treatment. In patients with multinodular goiter, treatment should be considered. The treatment options include antithyroid drugs or radioactive iodine. Obviously, in elderly women with osteoporosis, the treatment protocol should include calcium, estrogen, bisphosphonates, or some combination of these agents (27).

HYPOTHYROIDISM

Hypothyroidism results from undersecretion of thyroid hormone from the thyroid gland. In the United States, the most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease). Other causes are surgical removal of the thyroid gland, thyroid gland ablation with radioactive iodine, external irradiation, a biosynthetic defect in iodine organification, replacement of the thyroid gland by tumor (lymphoma), and drugs such as lithium or interferon. Secondary causes of hypothyroidism include pituitary and hypothalamic disease. Patients should undergo assessment for the cause of their hypothyroidism.

Clinical Features

The symptoms are generally related to the duration and severity of hypothyroidism, the rapidity with which hypothyroidism occurs, and the psychologic characteristics of the patient. The signs and symptoms of hypothyroidism can include one or more of the following:

- Fatigue
- Weight gain from fluid retention
- Dry skin and cold intolerance

- Yellow skin
- Coarseness or loss of hair
- Hoarseness
- Goiter
- Reflex delay, relaxation phase
- Ataxia
- Constipation
- Memory and mental impairment
- Decreased concentration
- Depression
- Irregular or heavy menses and infertility
- Myalgias
- Hyperlipidemia
- Bradycardia and hypothermia
- Myxedema fluid infiltration of tissues

Although most physicians can diagnose and treat hypothyroidism, in certain situations a clinical endocrinologist experienced in the spectrum of thyroid disease would be most likely to recognize the more subtle manifestations of hypothyroidism and most skilled in the physical examination of the thyroid gland. Consultation with an endocrinologist is recommended in the following situations:

- Patients of age 18 years or less
- Patients unresponsive to therapy
- Pregnant patients
- Cardiac patients
- Presence of goiter, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine disease

Not all patients with chronic thyroiditis have hypothyroidism, and if it is present, it may not persist. Rarely, patients with chronic thyroiditis have a change from a hypothyroid to a nonsuppressible euthyroid state or even to a hyperthyroid state because of the development of stimulating TSH receptor autoantibodies (TSI or TRAb) of Graves' disease. If such patients had been receiving levothyroxine treatment, downward dose adjustments or even cessation of levothyroxine therapy might be required. Therefore, adequate follow-up evaluations are imperative. The patient should be informed that this treatment adjustment may be necessary. When a patient has a goiter, a complete assessment, including a comprehensive history and physical examination and appropriate laboratory evaluation, should be performed. Patients with chronic thyroiditis have a high incidence of other associated autoimmune diseases such as vitiligo, rheumatoid arthritis, Addison's disease, diabetes mellitus, and pernicious anemia (2,28).

Diagnosis

Laboratory Evaluation

Appropriate laboratory evaluation is critical to establish the diagnosis and cause of hypothyroidism in the most cost-effective way. The most valuable test is a sensitive

measurement of TSH level. A TSH assay should always be used as the primary test to establish the diagnosis of primary hypothyroidism.

Additional tests may include the following:

- Free T₄ estimate
- Thyroid autoantibodies—anti-thyroid peroxidase and antithyroglobulin autoantibodies
- Thyroid scan, ultrasonography, or both (if necessary to evaluate suspicious structural thyroid abnormalities)

Differential Diagnosis

A patient with chronic thyroiditis may have an atrophic or an enlarged thyroid gland, or it may be of normal size. Thyroid autoantibodies are positive in 95% of patients with autoimmune thyroiditis (Hashimoto's thyroiditis), and high titers are of considerable value in making this specific diagnosis. Thyroid nodules are not uncommon with chronic thyroiditis and are associated with a small risk (5%) of thyroid cancer. Sudden enlargement of the thyroid gland in a patient with chronic thyroiditis should raise concern about thyroid lymphoma.

Patients with chronic thyroiditis may have normal results of thyroid function tests, including the sensitive TSH. Patients with associated subclinical hypothyroidism have a high TSH level in conjunction with normal free thyroid hormone (T₄ and T₃) estimates. Patients with clinical or overt hypothyroidism exhibit reduced free T₄ estimates and increased TSH levels (28,29).

Treatment and Management

Chronic Thyroiditis and Clinical Hypothyroidism

The treatment and management of chronic thyroiditis and clinical hypothyroidism must be tailored to the individual patient. Many clinical endocrinologists treat the goiter of chronic thyroiditis with levothyroxine, even in patients with a normal level of TSH, and all physicians will treat clinical hypothyroidism with levothyroxine replacement therapy. The management of subclinical hypothyroidism is addressed in the subsequent section.

AACE advocates the use of a high-quality brand preparation of levothyroxine. Bioequivalence of levothyroxine preparations is based on total T₄ measurement and not TSH levels; therefore, bioequivalence is not the same as therapeutic equivalence. Furthermore, various brands of levothyroxine are not compared against a levothyroxine standard. Preferably, the patient should receive the same brand of levothyroxine throughout treatment. In general, desiccated thyroid hormone, combinations of thyroid hormones, or triiodothyronine should not be used as replacement therapy. The mean replacement dosage of levothyroxine is 1.6 µg/kg of body weight per day, although the appropriate dosage may vary among patients. The appropriate pace of treatment depends on the duration and severity of the hypothyroidism and on the presence of other associated medical disorders. The initial levothyroxine dosage may range from 12.5 µg daily to a full replacement dose based on the age, weight, and cardiac status of

the patient and the severity and duration of the hypothyroidism. Importantly, patients should undergo reassessment and therapy should be titrated after an interval of at least 6 weeks following any change in levothyroxine brand or dose. The serum TSH level is most important, and a free T₄ estimate may be included in the assessment as well. Once the TSH level is in the normal range, the frequency of visits can be decreased. Although each patient's care must be individualized, a follow-up visit in 6 months and then annually is a common schedule. During follow-up assessments, an appropriate interim history should be recorded, and physical examination should be performed in conjunction with pertinent laboratory tests. Involving the patient in the levothyroxine treatment by explaining the thyroid disease and potential consequences should result in improved adherence to recommendations.

Thyroid hormone absorption can be affected by malabsorptive states and patient age. In addition, commercially available levothyroxine products may not be bioequivalent. Because levothyroxine has a narrow therapeutic range, small differences in absorption can result in subclinical or clinical hypothyroidism or hyperthyroidism. Drug interactions also present a problem. Certain drugs—such as cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide—interfere with levothyroxine absorption. Other drugs such as anticonvulsants affect thyroid hormone binding, whereas others such as rifampin and sertraline hydrochloride may accelerate levothyroxine metabolism and necessitate a higher replacement dose. The physician must make the appropriate adjustments in levothyroxine dosage in the face of absorption variability and drug interactions. Inappropriate levothyroxine replacement can result in increased costs because of the need for additional patient visits and laboratory tests (28,30-35).

Recent studies have shown a resurgence of interest in the possible benefits of treatment of hypothyroidism with combinations of T₄ and T₃ or with natural thyroid preparations. The small-scale study that seems to have sparked this interest treated patients for only 5 weeks, focused on mood changes, used a T₄ plus T₃ combination that differs substantially from that found in natural thyroid products, may have found benefit in only a subset of patients, and has not been replicated (36,37). Insufficient evidence is available to know which patients with hypothyroidism, if any, would be better treated with a combination of T₄ plus T₃ rather than with T₄ alone.

Subclinical Hypothyroidism

Subclinical hypothyroidism refers to mildly increased serum TSH levels in the setting of normal free T₄ and T₃ estimates. Although subclinical hypothyroidism may represent "early" thyroid failure, it may occur in the presence or absence of symptoms. It is a common disorder, the prevalence ranging from 1 to 10% of the adult population with increasing frequency in women, in patients with advanced age, and in those with greater dietary iodine intake. Usually, subclinical hypothyroidism is asymptomatic and is discovered on routine, screening TSH deter-

mination. The most common cause of subclinical hypothyroidism is autoimmune thyroiditis (Hashimoto's disease). Progression to overt hypothyroidism is reported to vary from 3 to 20%, the risks being greater in those patients with goiter or thyroid antibodies (or both) (16,18).

Although subclinical hypothyroidism is often asymptomatic, potential risks associated with the condition include progression to overt hypothyroidism, cardiovascular effects, hyperlipidemia, and neuropsychiatric effects (16,19). Recent studies have suggested that treatment of subclinical hypothyroidism will reduce cardiovascular risk factors, improve the lipid profile, and minimize neurobehavioral abnormalities (19,20). Some of these data, however, were derived from studies that included patients with TSH levels well above 10 $\mu\text{IU/mL}$; for patients with mildly increased TSH levels (5 to 10 $\mu\text{IU/mL}$), the data are controversial.

Treatment of subclinical hypothyroidism remains controversial, and recent arguments for and against treatment have been proposed (19,21). We believe that treatment is indicated in patients with TSH levels $>10 \mu\text{IU/mL}$ or in patients with TSH levels between 5 and 10 $\mu\text{IU/mL}$ in conjunction with goiter or positive anti-thyroid peroxidase antibodies (or both). These patients have the highest rates of progression to overt hypothyroidism. An initial dosage of levothyroxine of 25 to 50 $\mu\text{g/day}$ can be used, the serum TSH level should be measured in 6 to 8 weeks, and the levothyroxine dose should be adjusted as necessary. The target TSH level should be between 0.3 and 3.0 $\mu\text{IU/mL}$. Once a stable TSH level is achieved, annual examination is appropriate.

Hypothyroidism During Pregnancy

Untreated overt hypothyroidism during pregnancy may increase the incidence of maternal hypertension, preeclampsia, anemia, postpartum hemorrhage, cardiac ventricular dysfunction, spontaneous abortion, fetal death or stillbirth, low birth weight, and, possibly, abnormal brain development (38). Evidence from a population-based study suggests that even mild, asymptomatic, untreated maternal hypothyroidism during pregnancy may have an adverse effect on cognitive function of the offspring and that this outcome can be prevented by thyroid hormone replacement therapy (39). Mildly increased serum TSH levels during pregnancy might also increase the risk of fetal death, but whether treatment prevents this complication is not yet known. In most of these women, thyroid antibodies develop—a finding that seems to be a risk factor for spontaneous abortion independent of thyroid hormone and TSH levels (38,40). Because levothyroxine therapy is safe during pregnancy, thyroid hormone replacement treatment seems advisable for all pregnant women with hypothyroidism, even if it is mild. As a further recommendation, TSH measurement should be routine before pregnancy or during first trimester screening for thyroid dysfunction.

When a woman with hypothyroidism or underlying chronic thyroiditis becomes pregnant, the thyroid function

may change—it can improve in some mild cases or deteriorate in others. In general, the dosage of thyroid hormone should be increased in patients with moderate to severe hypothyroidism. These patients should undergo assessment of their serum TSH level every 6 weeks during pregnancy to ensure that the requirement for levothyroxine has not changed (41-43).

Hypothyroidism and Concurrent Conditions

Diabetes Mellitus

In approximately 10% of patients with type 1 diabetes mellitus, chronic thyroiditis will develop during their lifetime, which may include the insidious onset of subclinical hypothyroidism. Of importance, patients with diabetes should be examined for the development of a goiter. Sensitive TSH measurements should be obtained at regular intervals in patients with diabetes, especially if a goiter develops or if evidence is found of other autoimmune disorders. In addition, postpartum thyroiditis will develop in up to 25% of women with type 1 diabetes (44,45).

Infertility

Some patients with infertility and menstrual irregularities have underlying chronic thyroiditis in conjunction with subclinical or clinical hypothyroidism. Typically, these patients seek medical attention because of infertility or a previous miscarriage, rather than hypothyroidism. Chronic thyroiditis can be identified by a careful, comprehensive history, physical examination, and appropriate laboratory evaluation. In some patients with high TSH levels, levothyroxine replacement therapy may normalize the menstrual cycle and restore normal fertility (2,28,46).

Depression

The diagnosis of subclinical or clinical hypothyroidism must be considered in every patient with depression. In fact, a small proportion of all patients with depression have primary hypothyroidism—either overt or subclinical. Moreover, all patients receiving lithium therapy require periodic thyroid evaluation because lithium may induce goiter and hypothyroidism.

The diagnosis of chronic thyroiditis or subclinical or clinical hypothyroidism is based on a high serum TSH level and positive thyroid autoantibodies. Appropriate levothyroxine replacement therapy should be instituted. Occasionally in psychiatric practice, some patients who have depression are treated not only with antidepressants but also with thyroid hormone replacement, even though they have normal thyroid function. No firm evidence has shown that thyroid hormone treatment alone does anything to alleviate depression in such patients (28,33).

Euthyroid Sick Syndrome

The evaluation of thyroid function in chronically ill patients may be confusing. Many medications, such as corticosteroids and dopamine, may interfere with the results of thyroid function tests. In addition, when a patient is ill or starving, the body tends to compensate by decreas-

ing metabolic rates, which may result in a low free T₄ or T₃ estimate and a normal or low TSH level. If the TSH value is less than 10 μ IU/mL, treatment should ideally be deferred until the patient's medical condition has resolved. Assessment of the patient by a clinical endocrinologist is appropriate before initiation of levothyroxine treatment.

CONCLUSION

These guidelines established by AACE present several approaches to the assessment and treatment of patients with hyperthyroidism and hypothyroidism. They highlight the complexity of thyroid diseases and describe diagnostic and therapeutic strategies in various settings. These guidelines are not intended to be a comprehensive outline of therapeutic options.

Subclinical thyroid disease often remains undiagnosed. Through sound judgment, timely intervention, initiation of appropriate treatment, and patient involvement, an optimal level of care is attainable.

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APPENDIX A

Sample Consent Form for Treatment With Radioactive Iodine

Patient _____ Age _____ Date _____

I hereby request and authorize Dr. _____ or a designated assistant to administer radioactive iodine to _____ (patient).

The effect and nature of this treatment and any potential adverse reactions have been explained to me. I understand that this treatment may eliminate part or all of my thyroid gland and that, as a consequence, I may require lifetime treatment with thyroid medication. Also, in a few instances, this treatment may not be entirely effective, and a second dose of radioactive iodine would then be necessary.

I voluntarily accept the risks involved in this treatment.

I have been informed that examinations by Dr. _____ will be necessary every 4 weeks for at least 3 months after the treatment, or as otherwise recommended. Subsequent periodic follow-up may be necessary.

Signature of patient

Signature of parent or guardian

Signature of witness

APPENDIX B

Instructions for Patient After Radioactive Iodine Treatment

1. Do not kiss, exchange saliva, or share food or eating utensils for 5 days. Your dishes should be washed in a dishwasher, if one is available.
2. Avoid *close* contact with infants, young children (under 8 years), and pregnant women for 5 days. (You can be in the same room with them.)
3. If you have an infant, no breast-feeding is allowed.
4. Flush the toilet twice after urinating, and wash your hands thoroughly.
5. If a sore throat or neck pain develops, take acetaminophen or aspirin.
6. If you note increased nervousness, tremulousness, or palpitations, call a physician.