CLINICAL PRACTICE

Graves' Disease

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 23-year-old woman presents with palpitations. Over the past 6 months, she has reported loose stools, a 10-lb (4.5-kg) weight loss despite a good appetite and food intake, and increased irritability. She appears to be anxious and has a pulse of 119 beats per minute and a blood pressure of 137/80 mm Hg. Her thyroid gland is diffusely and symmetrically enlarged to twice the normal size, and it is firm and nontender; a thyroid bruit is audible. She has an eyelid lag, but no proptosis or periorbital edema. The serum thyrotropin level is 0.02 μU per milliliter (normal range, 0.35 to 4.50) and the level of free thyroxine is 4.10 ng per deciliter (normal range, 0.89 to 1.76). How should she be further evaluated and treated?

THE CLINICAL PROBLEM

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Graves' disease affects approximately 0.5% of the population and is the underlying cause of 50 to 80% of cases of hyperthyroidism.[1,2] The hyperthyroidism of Graves' disease is the result of circulating IgG antibodies that bind to and activate the G-protein–coupled thyrotropin receptor.[1] This activation stimulates follicular hypertrophy and hyperplasia, causing thyroid enlargement, as well as increases in thyroid hormone production and the fraction of triiodothyronine (T_3) relative to thyroxine (T_4) in thyroid secretion (from approximately 20% to as high as 30%).[3] Thyroid-function testing in Graves' disease typically reveals a suppressed serum thyrotropin level and elevated levels of serum T_4 and T_3. A suppressed serum thyrotropin level with normal serum levels of T_4 and T_3 is referred to as subclinical hyperthyroidism.[4] Graves' ophthalmopathy is clinically apparent in approximately 30 to 50% of patients with Graves' disease, but it is detected in more than 80% of patients who undergo assessment by means of orbital imaging.[1,5] Manifestations of ophthalmopathy, which vary in severity and have a course that is typically independent of the thyroid disease, can include proptosis, periorbital edema and inflammation, exposure keratitis, photophobia, extraocular muscle infiltration, and eyelid lag (which can also occur with augmented adrenergic stimulation).[1,5]

The female-to-male ratio among patients with Graves' disease is between 5:1 and 10:1. The peak incidence is between 40 and 60 years of age, although the disease can occur at any age.[1] The concordance rate for Graves' disease among monozygotic twins is 35%.[6] Triggers of Graves' disease in persons with genetic susceptibility to the disease include stressful life events, infection, and recent childbirth.[2] Several associated genetic loci have been identified, conferring susceptibility to Graves' disease alone or to both Hashimoto's thyroiditis and Graves' disease.[7] A family history of thyroid disease, especially in maternal relatives, is associated with an increased incidence of Graves' disease and a younger age at onset.[8]

This review focuses on the management of Graves' disease in adults. Most patients with Graves' disease are initially evaluated by and receive the diagnosis from

primary care practitioners, but in my opinion, when possible they should be referred to or cared for with input from an endocrinologist.

STRATEGIES AND EVIDENCE

EVALUATION

Clinical Manifestations

Overt hyperthyroidism due to Graves' disease is characterized by a variety of signs and symptoms (Table 1).[1,9,11] Symptoms include weight loss, heat intolerance, difficulty sleeping, tremor, increased frequency of defecation, proximal-muscle weakness, irritability, and menstrual irregularity. Signs include tachycardia, stare, eyelid lag, proptosis, goiter, resting tremor, hyperreflexia, and warm, moist, and smooth skin. Rare findings (in <1% of patients) include localized dermopathy (i.e., pretibial myxedema) and thyroid acropachy (i.e., clubbing).[12] Men with Graves' disease may have gynecomastia, reduced libido, and erectile dysfunction.[13] Women often have irregular menses. Weight loss (loss of both fat and lean body mass) is common, despite increased appetite and food intake.[14] Graves' disease is associated with a decreased quality of life[15] because of both the metabolic effects of elevated levels of thyroid hormone and thyrotropin-receptor antibodies (e.g., disturbed sleep and emotional lability) and the cosmetic effects[16] (e.g., goiter and ophthalmopathy).

As compared with younger patients, older patients are less likely to have tachycardia and tremor, and they present more often with weight loss or depression (referred to as apathetic hyperthyroidism).[2,17] Cardiovascular manifestations, especially atrial fibrillation, are common presenting symptoms in patients over 50 years of age.[11,18]

Laboratory Studies

The primary diagnostic considerations in a patient with a suppressed thyrotropin level and clinical hyperthyroidism are shown in Table 2.[2] Serum T_4 and T_3 levels vary among these conditions (Tables 2 and 3). Tests for Graves' disease–associated antibodies are useful in the evaluation of some conditions, but they are not usually required for diagnosis or to monitor disease activity (Tables 2 and 3).[19]

Table 1. Manifestations of Graves' Disease.*

System	Clinical Finding or Manifestation	Marker of Direct or Indirect Thyroid Hormone Action
Pituitary	Suppressed thyrotropin	Reduced expression of thyrotropin β subunit and common α subunit
Cardiac	Increased heart rate and contractility	Increased expression of HCN2, voltage-gated potassium channel (Kv1.5, Kv4.2, Kv4.3), and SERCA; increased α-MHC and decreased β-MHC expression; increased serum atrial natriuretic peptide
Hepatic	Increased peripheral T_3 production; reduced total and LDL cholesterol, lipoprotein(a)	Increased type 1 5′-deiodinase, LDL and VLDL receptor, lipase, SREBP-2, CYP7A, and CETP
Skeletal	Increased bone turnover, osteopenia, osteoporosis, and fractures	Increased osteocalcin, alkaline phosphatase, and urinary N-telopeptide
Reproductive		
Male	Erectile dysfunction, reduced libido	Increased sex hormone globulin, reduced free testosterone
Female	Irregular menses	Antagonism of estrogen action; impaired gonadotropin regulation
Metabolic	Increased thermogenesis and oxygen consumption	Increased fatty acid oxidation and sodium–potassium ATPase
White fat	Reduced fat mass	Augmented adrenergic-mediated lipolysis
Muscle	Proximal-muscle weakness, easy fatigability	Increased SERCA activity and serum creatine kinase
Thyroid	Increased thyroid secretion of T_3 and T_4	Increased type 1 and type 2 5′-deiodinase activity in thyroid

* Data are from Motomura and Brent,[9] Brenta et al.[10] and Klein and Ojamaa.[11] CETP denotes cholesterol ester transfer protein, CYP7A cholesterol 7 α-hydroxylase, HCN2 hyperpolarization-activated cyclic nucleotide-gated cation channel 2, LDL low-density lipoprotein, MHC myosin heavy chain, SERCA sarcoplasmic reticulum calcium-activated ATPase, SREBP-2 sterol regulatory element–binding protein 2, T_3 triiodothyronine, T_4 thyroxine, and VLDL very-low-density lipoprotein.

Table 2. Potential Diagnoses in Patients with Hyperthyroidism and Suppressed Serum Thyrotropin.*

Condition	Symptoms and Associated Features	Test Results		
		Thyroid-Function Tests	24-hr Radioiodine Uptake and Pattern	Additional Studies and Factors in Evaluation
Graves' disease	Usually symptoms for at least 2–3 mo; thyroid enlargement, thyroid bruit, Graves' ophthalmopathy	Elevated serum T_4 and T_3 (usually higher elevation of T_3 than T_4)	Elevated uptake with homogeneous symmetric distribution	Elevated TSI or thyrotropin-receptor antibodies
Painless thyroiditis	Usually modest symptoms of short duration (<3 mo); can occur in the postpartum period	Elevated serum T_4 and T_3 (usually equal elevation of T_4 and T_3)	Low uptake	Serum thyroid peroxidase antibodies usually positive
Painful subacute thyroiditis	Thyroid tenderness, modest symptoms of short duration; often occurs after a viral illness	Elevated serum T_4 and T_3 (usually equal elevation of T_4 and T_3)	Low uptake	Thyroid-related antibodies usually negative
Toxic multinodular goiter	Variable onset and range of severity; in iodine-sufficient locations, multinodular goiter more common in older persons (approximately >50 yr); in iodine-insufficient locations, may be common in younger persons	Elevated serum T_3; serum T_4 can be low, normal, or high	Increased uptake with patchy distribution	Thyroid-related antibodies usually negative
Solitary hyperfunctioning nodule	Variable onset and range of severity; incidence increases with increasing age; more common in women than in men; usually clinically significant hyperthyroidism when nodule >3 cm in diameter	Elevated serum T_3; serum T_4 can be low, normal, or high	Increased uptake with focal uptake in nodule and suppression in surrounding gland	Thyroid-related antibodies usually negative
Iodine-induced hyperthyroidism	Usually rapid onset of symptoms (hours to days) after exposure to excess iodine (e.g., from a contrast study or medications such as amiodarone)	Elevated serum T_3; serum T_4 can be low, normal, or high	Variable, depending on dose and form of iodine (and time required for excretion) and any underlying thyroid disease	Usually in the setting of an underlying multinodular goiter or in geographic areas of iodine deficiency
Exogenous ingestion of thyroid hormone	Variable, related to duration of ingestion	Reflects content of preparation of thyroid hormone; usually T_4 primarily elevated, although in some preparations both T_4 and T_3 or T_3 alone is elevated	Low uptake	Serum thyroglobulin concentration usually low

* T_3 denotes triiodothyronine, T_4 thyroxine, and TSI thyroid-stimulating immunoglobulin.

Imaging Studies

A scan obtained 24 hours after the administration of radioiodine provides a measure of iodine uptake as well as an image of functioning thyroid tissue (Fig. 1). A radioiodine-uptake study should be performed in patients in whom painless thyroiditis is considered to be a diagnostic possibility and in patients with an irregular or nodular thyroid gland (Table 3).[20] Increased blood flow detected by means of Doppler ultrasonography indicates Graves' disease, and low blood flow is characteristic of thyroiditis, although there is overlap between these two conditions, and the findings are likely to depend on the instrument and operator (Fig. 2).[21] Nonfunctioning nodules should be evaluated for the presence of thyroid cancer, usually by means of an ultrasound examination of the thyroid and fine-needle aspiration for cytology.[20] Some studies have shown that papillary thyroid cancer within a Graves' gland is more aggressive than it is in patients without Graves' disease,[22] although this is controversial.

Tests for Ophthalmopathy

A detailed discussion of ophthalmopathy is beyond the scope of this article, but it has been reviewed previously.[5,23,24] The measurement of eye prominence by means of an exophthalmometer in the clinician's office can be used to track changes over time. Formal visual-field testing, as well as orbital imaging, is needed in some patients (Table 3).[24] Patients with clinically significant symptoms or findings should be referred to an ophthalmologist.[23]

Other Diagnostic Studies

In a patient with an irregular heart rhythm, an electrocardiogram should be obtained to determine whether atrial fibrillation is present.[11] Postmenopausal women and other patients at risk for bone loss who have active or previously treated Graves' disease should have a bone-density test. Large goiters can be associated with airway or esophageal obstruction, causing shortness of breath or difficulty swallowing, and computed tomography of the neck (without the use of contrast material) or magnetic resonance imaging of the neck may be required.

THERAPY

The treatment options for Graves' disease include antithyroid drugs, radioiodine, and surgery.[1,2] A randomized trial comparing these treatments showed that all were similarly effective as initial treatment, although the relapse rate was highest among patients who received antithyroid drugs (approximately 40%) as compared with patients who received radioiodine (21%) and those who underwent surgery (5%).[25]

PHARMACOLOGIC THERAPY

Antithyroid drugs, specifically thionamides (either propylthiouracil or methimazole), are commonly used as initial therapy (Table 4) and primarily interfere with thyroid hormone synthesis.[26] The use of antithyroid drugs as initial treatment varies according to geographic location; they are used in the majority of patients in Europe and Asia, but radioiodine is used more often than medications in the United States.[27,28] The superiority of either propylthiouracil or methimazole is not clearly established; however, methimazole has a longer intrathyroidal half-life, often allowing for once-daily dosing (as compared with propylthiouracil, which is administered three times daily), and some studies have shown that it has greater efficacy and fewer side effects.[26,29]

Patients who receive either drug should be cautioned regarding the potential side effects of rash, joint pain, liver inflammation, and agranulocytosis[26]; agranulocytosis occurs in approximately 0.1 to 0.3% of patients treated with either of these drugs. Patients should be advised to discontinue antithyroid drugs if any potential signs of agranulocytosis develop; these signs include a fever, sore throat, or mouth ulcers. If these signs occur, a white-cell count should be obtained immediately. Prospective monitoring of the white-cell count on follow-up visits is not recommended, since the onset of agranulocytosis is typically acute and not detected by periodic surveillance. Agranulocytosis is slightly more likely in older patients and with larger doses of antithyroid drugs, and it can occur at any time in the course of therapy.[26] Elevations in aminotransferase levels may be due to the direct effects of thyroid hormone on the liver as well as to antithyroid drugs.[30] The treatment of Graves' disease often results in weight gain as the increased metabolic rate that is characteristic of Graves' disease normalizes; the average weight gain reported in several studies is approximately 10 lb (4.5 kg).[14]

Marked improvement in most symptoms generally occurs within 3 to 4 weeks after the initiation of antithyroid medication.[26] A short course

Table 3. Evaluation and Monitoring of Graves' Disease.*

Test	Description	Role in Evaluation	Role in Monitoring
Laboratory studies			
Thyrotropin	Direct serum measurement, highly sensitive for detecting abnormally suppressed levels when thyroid hormone levels are excessive	Suppressed thyrotropin required for diagnosis	Usually remains suppressed for ≥2 mo, even when serum T_4 and T_3 are normal or low; after suppression, thyrotropin testing is the standard for monitoring and adjusting therapy
T_4			
Free T_4 index	Product of total thyroxine measurement and estimate of thyroxine-binding globulin (e.g., resin uptake ratio)	Elevated levels in Graves' disease	Effective for monitoring response to therapy
Free T_4 by analogue method	Measures free T_4 indirectly; used in the automated platform instruments in most clinical laboratories	Elevated levels in Graves' disease; assay can be influenced by extremes of serum protein levels	Effective for monitoring response to therapy
Free T_4 by dialysis	Only direct measurement of free or unbound fraction of T_4; free T_4 is dialyzed from the bound T_4 and then measured	Elevated levels in Graves' disease	Effective for monitoring response to therapy; more expensive than the other approaches and available in only a few specialty laboratories
T_3			
Total T_3	Direct serum measurement of total hormone	Elevated levels in Graves' disease; measures bound and free, so total is influenced by levels of thyroid-binding globulin; can be corrected to index with binding estimate (e.g., resin uptake ratio)	Important early in treatment to assess level of active hormone; ratio of T_3 to T_4 increased in Graves' disease
Free T_3 by analogue method	Measures free T_3 indirectly; used in the automated platform instruments in most clinical laboratories	Elevated levels in Graves' disease; measurement can be influenced by extremes of serum protein levels	Effective for monitoring response to therapy
Free T_3 by dialysis	Only direct measurement of free or unbound fraction of T_3; free T_3 is dialyzed from the bound T_3 and then measured	Elevated levels in Graves' disease	Effective for monitoring response to therapy; more expensive than other approaches and available in only a few specialty laboratories

Thyroid antibodies			
Thyrotropin-receptor antibodies			
Thyrotropin-receptor–binding inhibition	Assay for serum immunoglobulins that inhibit binding of labeled thyrotropin to the thyrotropin receptor	Does not distinguish between blocking and stimulating thyrotropin receptor IgG, but provides support for diagnosis; used in some cases for diagnosis, for evaluating euthyroid Graves' ophthalmopathy, and during pregnancy (higher levels associated with increased risk of neonatal Graves' disease)	Persistent elevation correlates with disease activity, and remission is accompanied by a decrease in levels, but not usually necessary for monitoring
TSI	Bioassay measuring cyclic AMP production after patient's serum is applied to thyroid follicular cells or thyrotropin receptor–expressing engineered cells	Specific for thyrotropin-receptor–stimulating activity; more expensive and longer turnaround as compared with thyrotropin-receptor antibodies	Persistent elevation correlates with disease activity, remission usually accompanied by a decrease in activity
TPO antibodies	Measures antibody to enzyme thyroid peroxidase	TPO antibodies elevated in most patients with Hashimoto's disease, but also often elevated in Graves' disease; elevation not specific for diagnosis of Graves' disease	Not useful for monitoring
Imaging			
Thyroid ultrasonography	Provides high-resolution image of thyroid, can be used to determine blood flow by Doppler	Useful for detecting nodules; if a radioiodine-uptake study cannot be performed, increased blood flow by Doppler correlates with increased radioiodine uptake	Not routinely used but helpful for evaluation of nodules
Radioiodine-uptake scan	Capsule of iodine-123 given orally, thyroid uptake measured on scan obtained 24 hr later	Useful for distinguishing Graves' disease (high uptake) from subacute thyroiditis (low uptake); also useful for identifying multinodular toxic goiter (patchy uptake) or solitary toxic nodule	Usually only needed to measure uptake for planned radioiodine treatment
Neck CT or MRI	Imaging of thyroid in the context of trachea, esophagus, and chest	Used only if there are symptoms or signs of upper-airway or thoracic-inlet obstruction	Repeat only if worsening signs of obstruction
Orbital imaging	Techniques include CT, MRI, and ultrasonography	Useful in cases of unilateral proptosis, marked asymmetry of ophthalmopathy, or visual loss and in some cases of impairment of extraocular muscle movement	Repeat only if worsening ophthalmopathy

* CT denotes computed tomography, T_3 triiodothyronine, T_4 thyroxine, TPO thyroid peroxidase, and TSI thyroid-stimulating immunoglobulin.

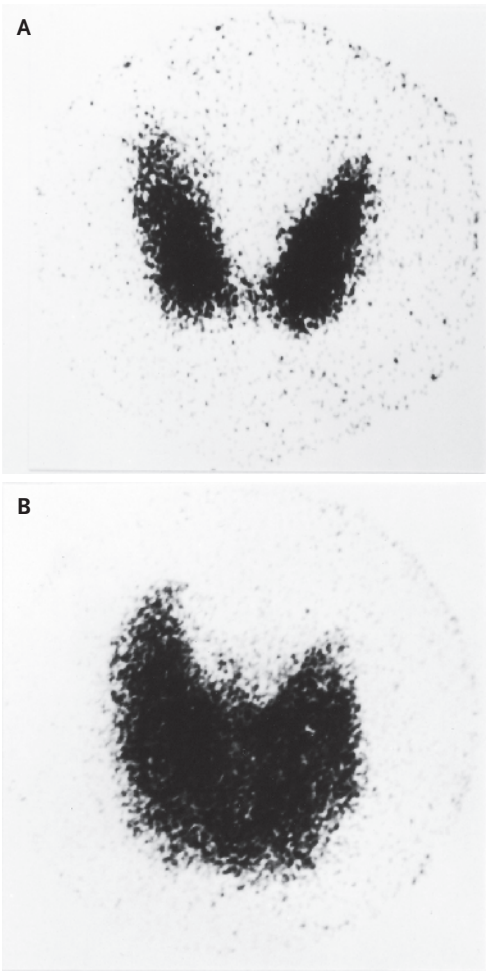

Figure 1. Radioiodine Scans of the Thyroid.
Images were obtained 24 hours after ingestion of iodine-123 by a patient with a normal thyroid (Panel A) and a patient with Graves' disease (Panel B). The thyroid of the patient with Graves' disease is larger and concentrates a higher fraction of radioiodine. (Images courtesy of Dr. Jerome Hershman, David Geffen School of Medicine at UCLA, Los Angeles.)

of therapy with a beta-adrenergic blocker may be used in the interim, since it provides rapid relief of such symptoms as tremor, palpitations, and sweating. The dose of the antithyroid drug should be adjusted to normalize the serum levels of T_4 and T_3 and eventually to maintain the serum level of thyrotropin in the normal range.

Among patients with Graves' disease who are treated with antithyroid drugs, the average rate of remission (defined as a serum level of thyrotropin in the normal range when the patient is not receiving medication) is 30 to 50%, but relapse occurs in more than 50% of patients.[26] Remission is less likely in men, older patients (over 40 years of age), and patients with more active disease (e.g., a large thyroid gland, higher serum T_4 and T_3 concentrations, and elevated levels of thyrotropin-receptor antibodies).[31] A longer duration of antithyroid drug therapy (1 year or more vs. 6 months) has been reported to improve remission rates, although a randomized trial showed no significant improvement in remission rates 2 years after discontinuation of therapy when treatment was continued well beyond 18 months as compared with discontinuation at 18 months.[32] Adjuvant treatment with T_4 (the so-called block-replace regimen) may improve remission rates as compared with the use of antithyroid drugs alone, but many trials[33] have shown no benefit, and this regimen is not currently recommended.

RADIOIODINE THERAPY

Radioiodine therapy may be used either as initial therapy or after treatment with medication.[34,35] Antithyroid drugs, when used, are generally discontinued for 3 to 7 days before radioiodine therapy, since the effectiveness of radioiodine may be diminished when antithyroid drugs are given concurrently.[36] A recent randomized trial showed that withdrawal of an antithyroid drug 3 days before treatment with radioiodine does not diminish the effectiveness of radioiodine, as compared with no antithyroid drug treatment, or result in exacerbation of symptoms, as compared with continuous antithyroid drug treatment.[37] Before the initiation of radioiodine therapy, a 24-hour radioiodine-uptake study is usually performed. When the diagnosis of Graves' disease is in question, the finding of diffuse radioiodine uptake throughout the thyroid is confirmatory. The percentage of uptake (either alone or in combination with the gland size) is also often used to calculate the dose of radioiodine,[38] although some clinicians deliver a fixed dose of radioiodine without measuring uptake.[39] The goal of radioiodine therapy is induced hypothyroidism in order to prevent a recurrence of Graves' disease. This goal is achieved in approximately 80% of patients,[39] regardless of the approach to dosing, although calculated dosing may have an efficacy similar to that of fixed dosing but with less radiation exposure.

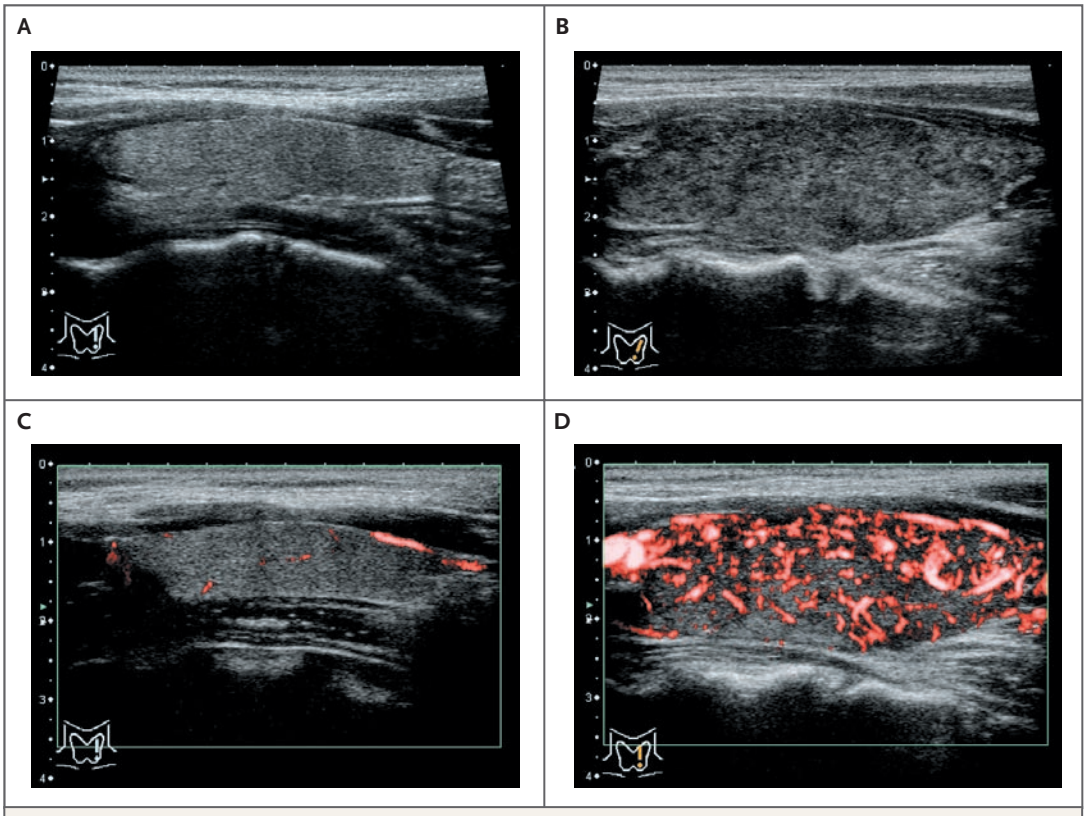

Figure 2. Ultrasonographic and Doppler Flow Images of the Thyroid.

Longitudinal ultrasonographic views of the left lobe of the thyroid are shown for a normal thyroid (Panel A) and the thyroid of a patient with Graves' disease (Panel B). Doppler flow is shown for the same images with a normal thyroid (Panel C) and the thyroid of a patient with Graves' disease (Panel D). Increased blood flow (red) is seen in the thyroid gland of the patient with Graves' disease as compared with the normal thyroid. (Images courtesy of Drs. Hisashi Ota and Shuji Fukata, Kuma Hospital, Kobe, Japan.)

All women of reproductive age should have a pregnancy test immediately before treatment. Unincorporated radioiodine is excreted in the urine, exposing the pelvic contents to radiation, and it crosses the placenta, where it can be taken up by the fetal thyroid gland late in the first trimester of pregnancy or thereafter. Although the half-life of iodine-131 is only about 1 week, it is generally recommended that women not attempt conception for 6 to 12 months after radioiodine treatment.

Acute side effects of radioactive iodine include a form of radiation thyroiditis that causes neck tenderness and in some cases a transient increase in thyroid hormone levels.[34,35] Although longitudinal studies have reported increased risks of cardiovascular disease and some cancers in patients who have received radioiodine for hyperthyroidism due to toxic multinodular goiter,[40,41] these risks have not been reported in patients with Graves' disease,[41] and they are thought likely to be attributable to hyperthyroidism rather than to the radioiodine treatment. Several studies have shown an association between radioiodine and worsening of Graves' ophthalmopathy,[42] although this association has not been shown in patients with mild ophthalmopathy.[43] In a randomized trial, prednisone therapy for 3 months after radioiodine treatment reduced the number of patients who had worsening of ophthalmopathy.[42] A transient reduction in the testosterone level has been reported in men after radioiodine treatment, but no effects on sperm concentration or permanent effects on testicular function have been shown.[44]

SURGERY

Surgical thyroidectomy is the treatment that is least often used, but it can be effective in selected

Table 4. Forms of Treatment for Graves' Disease.*

Treatment	Mechanisms	Indications	Expected Response	Adverse Effects
Medications				
Propylthiouracil (at a typical starting dose of 150–600 mg daily, usually split into 3–4 doses per day)	Inhibits thyroid hormone synthesis and T_4-to-T_3 conversion	For initial treatment; in severe hyperthyroidism, may be used for rapid lowering of serum T_3	Reduction in T_4 and T_3, and improvement in symptoms in approximately 3–4 wk	Minor: rash, urticaria, abnormal taste; major: agranulocytosis, hepatic necrosis, cholestasis
Methimazole (at a typical starting dose of 10–40 mg daily, usually given as a single daily dose or in a divided dose twice a day)	Inhibits thyroid hormone synthesis	For initial treatment	Reduction in T_4 and T_3, and improvement in symptoms in approximately 3–4 wk	Minor: rash, urticaria; major: agranulocytosis, hepatic necrosis, cholestasis; in pregnancy, rare complication of aplasia cutis and embryopathy (characterized by choanal or esophageal atresia)
Beta-adrenergic receptor blockers (at a typical dose of 50–200 mg of metoprolol daily and 25–100 mg of atenolol daily)	Blocks adrenergic signaling, which is potentiated in hyperthyroidism; tissues with augmented action of catecholamines include heart, skeletal muscle, bone, fat	For recently diagnosed disease in patients with significant sympathetic symptoms (e.g., tremor, tachycardia, sweating)	Rapid improvement of symptoms, usually within 1–2 days	Airway obstruction in patients with asthma or obstructive lung disease
Supersaturated potassium iodide and ipodate (Oragrafin), an iodinated radiographic contrast agent not currently available in the United States	Acute inhibition of thyroid hormone synthesis and release, reduced vascularity; ipodate reduces T_4-to-T_3 conversion	For rapid reduction of thyroid hormone levels, such as in patients with severe cardiac disease or thyroid storm,† or in preparation for surgery	Rapid reduction (in hours to days) in serum T_4 and T_3 for 5–7 days	Salivary-gland inflammation
Glucocorticoid agent (e.g., prednisone or dexamethasone)	Inhibits T_4-to-T_3 conversion	For rapid reduction in serum T_3, such as in patients with thyroid storm,† severe cardiac disease, or in preparation for surgery	Rapid reduction in serum T_3	Short-term minimal complications; long-term complications include glucose intolerance, bone loss, muscle breakdown
Radioiodine (iodine-131 given as an oral capsule or liquid)	Oral dose of iodine-131 results in radiation-induced thyroid destruction	For definitive initial treatment and for patients who do not go into remission after initial treatment with antithyroid drugs	Hypothyroidism develops in about 80% of patients within 2–6 mo, lifelong T_4 replacement then required	Acute radiation thyroiditis (i.e., thyroid pain and transiently increased thyroid hormone levels)
Thyroidectomy	Directly removes all or most hyperfunctioning thyroid tissue	For immediate, definitive treatment; indicated if significant side effects of antithyroid drugs, excessive antithyroid drug dose required in pregnancy, large goiter, or suspicious nodule, or if patient declines radioactive iodine	Usually complete response, will require lifelong T_4 replacement	Rare complication of hypoparathyroidism (<1% with experienced surgeons) and recurrent laryngeal-nerve damage

* T_3 denotes triiodothyronine, and T_4 thyroxine.

† In rare cases, severe thyrotoxicosis (referred to as thyroid storm) complicates Graves' disease when some or all of the following occur: fever, altered mental status, and hepatic, gastrointestinal, and cardiac dysfunction. Therapies that promote rapid inhibition of T_4-to-T_3 conversion are especially useful in such cases.

clinical situations,[45] such as in patients with complications of antithyroid drugs, pregnant women requiring high doses of antithyroid drugs, patients who decline treatment with radioiodine or who have large goiters or suspicious nodules, and patients wanting rapid and definitive treatment. Preoperative treatment with supersaturated potassium iodide, Lugol's iodine solution, or ipodate (Oragrafin), an iodinated radiographic contrast agent, for approximately 1 week is recommended, since these agents decrease the production and release of thyroid hormone and reduce thyroid vascularity.[46,47]

TREATMENT FOR OPHTHALMOPATHY

A discussion of treatments for ophthalmopathy is beyond the scope of this article, but they include systemic and intraocular glucocorticoid agents, antiinflammatory and immunosuppressive agents, radiation, and a range of corrective surgical procedures.[23]

GRAVES' DISEASE AND PREGNANCY

Both propylthiouracil and methimazole cross the placenta and can affect fetal thyroid function, especially at higher doses.[48,49] In the United States, propylthiouracil is the recommended antithyroid drug during pregnancy,[48,49] since in rare cases, methimazole has been associated with aplasia cutis and gastrointestinal defects in the fetus. Monitoring by means of ultrasonography is useful to assess fetal development and check for the presence of a fetal goiter, which indicates either excessive antithyroid drug treatment in the mother or fetal Graves' disease.[50] In women with Graves' disease who do not wish to become pregnant immediately, definitive treatment with radioiodine or surgery should be offered in order to minimize the potential need for antithyroid drugs during pregnancy. Most women with Graves' disease, however, can be treated medically during pregnancy, with a target T_4 level at or slightly higher than the upper limit of the reference range to ensure normal thyroid hormone levels in the fetus.[48] Maternal complications of Graves' disease in pregnancy include preeclampsia and preterm delivery. Graves' disease generally improves in the second and third trimesters of pregnancy, allowing reduction or discontinuation of antithyroid drug therapy, although the disease can flare during the postpartum period.[48]

AREAS OF UNCERTAINTY

Further study of genetic factors associated with susceptibility to Graves' disease and of factors that trigger the disease is needed.[7] The pathogenesis of Graves' orbitopathy and dermopathy also warrants further study.[5,12] The choice of treatment with antithyroid drugs versus radioiodine remains controversial, with varying practices in different areas of the world. The appropriate duration of treatment with antithyroid drugs in order to induce remission, the mechanism of remission, and the timing of drug treatment before and after radioiodine treatment are not established.[51] The optimal therapeutic targets in women with Graves' disease during pregnancy are uncertain, since both low and high serum levels of T_4 in the mother are associated with risks to the fetus.[48,52] In animal models, thyroid hormone–receptor antagonists rapidly block the action of thyroid hormone,[10] but these agents are not available for clinical use.

GUIDELINES FROM PROFESSIONAL SOCIETIES

Guidelines based on expert opinion for the management of hyperthyroidism have been published by both the American Thyroid Association[53] and the American Association of Clinical Endocrinologists,[54] and a joint evidence-based revision is in preparation. The Royal College of Physicians has issued treatment recommendations for the management of hyperthyroidism[55] and radioiodine therapy.[35] A multidisciplinary European group has developed guidelines for the evaluation and treatment of ophthalmopathy.[23] The recommendations provided here are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

In the patient described in the vignette, the duration of symptoms, elevated serum T_4 and T_3 levels and suppressed thyrotropin level, and characteristic clinical features strongly suggest Graves' disease. A radioiodine-uptake study is not necessary to make the diagnosis in this patient. Treatment options should be discussed with the patient. I often recommend that antithyroid therapy be tried first, since in many patients, this treat-

ment is followed by a sustained remission. Initial treatment with radioiodine is also an option, and it would eliminate the need for the use of an antithyroid drug during any future pregnancy. If treatment with an antithyroid drug is planned, I would first check the white-cell count and aminotransferase levels. In a nonpregnant patient, I generally recommend methimazole, which can often be given once daily. I explain to the patient the need to discontinue the medication and have a white-cell count checked if a fever or other evidence of infection develops, and I recommend the use of reliable contraception. A beta-adrenergic blocker should be considered initially, since it generally results in prompt symptomatic improvement. Thyroid-function tests should be repeated in approximately 3 weeks; the serum level of thyrotropin typically remains suppressed for up to several months. Treatment is recommended for up to 18 months in order to increase the likelihood of remission. If the patient's disease recurred after discontinuing medication, I would encourage consideration of radioiodine therapy, although surgery or further antithyroid drug therapy would also be options.

Resources for patients with Graves' disease include the National Graves' Disease Foundation (www.ngdf.org), the American Thyroid Association Alliance for Patient Education (www.thyroid.org/patients/patients.html), and the Thyroid Foundation of Canada (www.thyroid.ca).

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