

Update on the Diagnosis and Treatment of Hyperthyroidism

Case Study and Commentary, *Elias S. Siraj, MD*



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Program Audience

Primary care physicians.

Educational Needs Addressed

Signs and symptoms of hyperthyroidism are wide-ranging and the frequency and severity of symptoms can vary, which makes diagnosis a challenge. Primary care physicians are often the first to evaluate these patients. A detailed evaluation that includes questions about extent and duration of symptoms, past medical history, family history, physical examination (including thyroid examination), and appropriate laboratory tests can help guide the treating physician to the etiology. Proper management depends on properly identifying the cause of hyperthyroidism. Regular monitoring for changes in thyroid function is required, as prognosis can be adversely affected if a euthyroid state is not maintained.


Educational Objectives

After participating in this CME activity, primary care physicians should be able to

1. Differentiate between etiologies of hyperthyroidism
2. Describe management options for subclinical hyperthyroidism
3. Outline the typical course of and management strategies for subacute thyroiditis
4. Understand the approach to diagnosis and management of Graves' disease
5. Describe signs and symptoms of thyroid storm

CASE STUDY

Initial Presentation

 A 25-year-old woman presents to her physician with symptoms of fatigue, headaches, and fluctuating weight. On examination, vital signs are within normal range. Body mass index (BMI) is 28 kg/m². Thyroid examination is unremarkable. A thyroid-stimulating hormone (TSH) level is ordered and found to be low at 0.1 mIU/L (reference range, 0.5–5.0 mIU/L). Free levorotatory thyroxine (T₄) and free triiodothyronine (T₃) levels are subsequently checked and found to be normal.

- How should the results of the patient's thyroid function tests be interpreted?

A patient with low TSH and normal T₄ and T₃ is considered to have subclinical hyperthyroidism. Typically, these patients do not have clear signs and symptoms of hyperthyroidism. The prevalence of subclinical hyperthyroidism ranges from 0.7% to 12.4%. This variability is partly due to differences among studies in the definition of a low serum TSH value [1–4].

The causes of subclinical hyperthyroidism are similar to those of overt hyperthyroidism (Table 1). The most common causes of subclinical hyperthyroidism are

- Exogenous administration of levothyroxine for treating hypothyroidism. Among patients taking levothyroxine, as many as 25% may have low serum TSH values [5]
- Autonomously functioning thyroid adenomas and multinodular goiters
- Subacute thyroiditis
- Less commonly, Graves' disease

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• **What is the clinical significance of subclinical hyperthyroidism?**

The cardiovascular system and the skeletal system are the major organs affected by subclinical hyperthyroidism.

Skeletal System

Although some uncertainty remains, the majority of studies in both exogenous and endogenous subclinical hyperthyroidism showed that a prolonged hyperthyroid state may lead to lower bone mineral density [6,7]. This may be more pronounced in postmenopausal women. Whether decreased bone mineral density translates into increased risk of fractures is unclear.

Cardiovascular

As with overt hyperthyroidism, the frequency of atrial fibrillation is increased in patients with subclinical hyperthyroidism [8,9]. Increased occurrence of tachycardia and ectopic beats may also be present. Possible induction of reentrant atrioventricular nodal tachycardia may occur in predisposed patients. Increases in cardiac contractility and left ventricular mass index as well as diastolic dysfunction may be seen. Mortality studies are not conclusive as to whether risk of mortality is increased [10,11].

• **Should subclinical hyperthyroidism be treated?**

The decision to treat subclinical hyperthyroidism depends on several factors, including the age of the patient, degree of abnormalities seen on thyroid function testing, and presence or absence of risk factors for cardiovascular and skeletal complications. Observation is preferred if TSH level is greater than 0.1 mIU/L and if there is a low risk of bone or cardiac complications. Treatment should be considered if the patient is elderly, TSH level is less than 0.1 mIU/L, or if there is evidence of or high risk for cardiac and bone complications [12]. In cases of exogenous subclinical hyperthyroidism, an attempt should be made to reduce the dose of the levothyroxine whenever possible.

If the decision is made to treat, treatment options include the following:

- β Blockers may help to control some mild symptoms and also have protective effect on the heart
- Antithyroid drugs or thionamides can be used in cases where β blockers are not considered to be adequate. The goal of treatment should be to normalize

Table 1. Common Causes of Hyperthyroidism

Autoimmune thyroid disease
Graves' disease
Autonomous thyroid tissues
Toxic adenoma
Toxic multinodular goiter
Subacute thyroiditis
Subacute granulomatous thyroiditis (painful)
Subacute silent thyroiditis (painless)
Includes postpartum thyroiditis
Exogenous thyroid hormone intake
Excessive replacement dose
Factitious hyperthyroidism
Iodine-induced hyperthyroidism (including amiodarone)
Thyroiditis
Autonomous thyroid hormone production
Other rare causes
hCG-mediated hyperthyroidism
Struma ovarii
TSH-mediated (eg, TSH-secreting pituitary adenoma)


hCG = human chorionic gonadotropin; TSH = thyroid-stimulating hormone.

TSH and bring the T₄ and T₃ levels toward low-normal while at the same time avoiding hypothyroid symptoms

- Radioactive iodine treatment is an option if radioactive iodine uptake and scan has shown autonomous nodule or a low-grade Graves' disease
- In patients where there is evidence of osteopenia or osteoporosis, bisphosphonate treatment may have to be initiated to protect the bones

Details regarding treatment options are described in more detail in subsequent sections.

Case Follow-up

 Given the asymptomatic nature of the patient's subclinical hyperthyroidism, a decision is made not to start treatment. She is lost to follow-up for 3 years.

The patient then presents 2 months after delivering a healthy baby complaining of dramatic weight loss, palpitations, and heat intolerance. On examination, heart rate is 110 bpm. She also has tremor, lid lag, and a slightly enlarged, nontender thyroid. TSH is low at less than 0.002 mIU/L, and T₄ and T₃ levels are high.

• **What is the most likely diagnosis?**

Table 2. Clues to Causes of Hyperthyroidism

Feature	Likely Disorder
Diffuse goiter	Graves' disease
Exophthalmos	Graves' disease
Pain and tenderness on the thyroid area	Subacute thyroiditis
Nodular goiter	Toxic adenoma or toxic nodular goiter
Recent intravenous contrast exposure	Iodine-induced
Patient taking amiodarone for a cardiac condition	Amiodarone-induced
Hypothyroid patient taking levothyroxine	Exogenous

As this patient is presenting in the immediate postpartum period, the physician should have a high degree of suspicion for postpartum thyroiditis, whose presentation is similar to subacute thyroiditis. There are other clinical clues that can be helpful in identifying the cause of hyperthyroidism (Table 2).

- Which tests may be helpful in the workup of the patient with hyperthyroidism?

Laboratory tests may help in differentiating between the causes of hyperthyroidism. Presence of TSH receptor antibodies, in particular thyroid-stimulating immunoglobulin, indicates Graves' disease. Very high thyroglobulin levels are consistent with subacute thyroiditis.

The radioactive iodine uptake and scan can be helpful in determining the etiology of hyperthyroidism and can help in directing treatment. Radioactive iodine uptake measures how much of the radioactivity given orally has been taken up by the thyroid over a period of time and is typically reported as a percentage. The scan complements the uptake and shows how the activity is distributed in the thyroid. Table 3 shows the results of radioactive iodine uptake and scan in the most commonly seen causes of hyperthyroidism.

- What is subacute thyroiditis?

Subacute thyroiditis is characterized by transient hyperthyroidism, occasionally followed by hypothyroidism, and then recovery. Some patients have transient increases in serum antithyroid antibody concentrations during the hypothyroid phase, probably caused by release of thyroid antigens during the preceding period of inflammation [13]. After recovery, thyroid function is normal, as are ultrasonography and thyroid biopsy [14,15].


A variant of subacute thyroiditis, sometimes called subacute granulomatous thyroiditis, is characterized by neck pain and a tender, diffuse goiter in addition to the other characteristics. Postpartum thyroiditis is subacute thyroiditis that occurs in women within 1 year after parturition.

The typical course of subacute thyroiditis is initially characterized by hyperthyroidism followed by euthyroidism, hypothyroidism, and ultimately restoration of normal thyroid function in most cases (Figure).

Subacute thyroiditis may have some pathologic similarities with Hashimoto's disease, as many patients with painless thyroiditis have high serum concentrations of antithyroid microsomal (thyroid peroxidase) antibodies and some develop overt chronic autoimmune thyroiditis several years later [14].

Treatment of patients with subacute thyroiditis is directed at relieving thyroid pain and tenderness and ameliorating symptoms of hyperthyroidism, if present. The few patients who have significant symptoms of hyperthyroidism, such as palpitations, anxiety, or tremor, may benefit from treatment with β blockers for few weeks. Some patients require no treatment because their symptoms are mild or subside by the time they seek medical attention or when the diagnosis is established. In some patients, anti-inflammatory therapy with a nonsteroidal anti-inflammatory drug is indicated to control pain; in patients with severe pain, steroids may be needed [16].

Case Continued

 The patient is prescribed β blockers for her postpartum thyroiditis. She does not return to the office for follow-up.

The patient returns for evaluation 5 years later. She reports that 5 years ago her thyroid "had gotten back to normal" after a few months on β blockers, but she has now developed similar symptoms consisting of palpitations, heat intolerance, and weight loss. On examination, she has a diffuse goiter estimated at 2 to 3 times the normal size, lid lag, and exophthalmos. TSH is suppressed at less than 0.002 mIU/L, and her T_4 and T_3 levels are high. TSH receptor antibody level is elevated.

- What is the most likely diagnosis at this time?
- What are other possible diagnoses?
- What are the next steps in evaluation?

The combination of clinical and biochemical hyperthyroidism together with a diffuse goiter, exophthalmos, and positive TSH receptor antibody test suggests that Graves' disease is the most likely diagnosis. Graves' disease is the leading cause

Table 3. Radioactive Iodine Uptake and Scan in Various Forms of Hyperthyroidism

Disorder	Uptake	Scan	Other Helpful Investigations
Graves' disease	Very high	Diffuse activity in an enlarged gland	Positive thyroid-stimulating hormone receptor antibodies
Toxic adenoma	Slightly high or normal	Hot nodule + the rest of the gland suppressed	
Toxic nodular goiter	Slightly high or normal	Areas of intense activity interspersed with areas of no/reduced activity	
Subacute thyroiditis/postpartum thyroiditis	Reduced or no uptake	Faint diffuse activity or no activity at all	High thyroglobulin
Exogenous levothyroxine	Reduced or no uptake	Faint diffuse activity or no activity at all	Low thyroglobulin
Iodine-/amiodarone-induced	Reduced or no uptake	Faint diffuse activity or no activity at all	High iodine in urine

of hyperthyroidism. It is an autoimmune disorder resulting from production of TSH receptor antibodies, which stimulate thyroid gland growth and thyroid hormone synthesis and release. Ophthalmopathy and pretibial myxedema are additional autoimmune manifestations of Graves' disease.

Other diagnoses that should be considered include toxic adenoma/toxic multinodular goiter, iodine-induced hyperthyroidism, and subacute thyroiditis. Toxic adenoma and toxic multinodular goiter are the result of hyperplasia of thyroid follicular cells whose functional capacity is independent of regulation by TSH. Activating somatic mutations of the genes for the TSH receptor have been identified in both toxic adenomas and nodules of toxic multinodular goiters [17,18]. Although uncommon, iodine-induced hyperthyroidism can develop after an iodine load, for example, after administration of contrast agents used for angiography or computed tomography or iodine-rich drugs such as amiodarone [19–21].

- **How should this patient with Graves' disease be treated?**

The therapeutic approach to Graves' hyperthyroidism consists of rapid amelioration of symptoms with a β blocker and measures aimed at decreasing thyroid hormone synthesis: the administration of antithyroid drugs, radioactive iodine ablation, or surgery [22]. In a randomized prospective trial comparing these 3 therapies, each was equally effective in normalizing serum thyroid hormone concentrations within 6 weeks [23]. The risk of relapse was highest with antithyroid drugs and lowest with surgery.

In all types of treatment, initial monitoring should consist of periodic clinical assessment and measurements of serum T_4 and sometimes T_3 levels. Serum TSH concentration may remain low for several weeks or even months after the patient becomes euthyroid.

Medications

β Blockers. β Blockers ameliorate the symptoms of hyperthyroidism that are caused by increased β -adrenergic tone [24]. These include palpitations, tachycardia, tremor, anxiety, and heat intolerance. Thus, a β blocker should be started in most patients as soon as the diagnosis of hyperthyroidism is made.

Antithyroid drugs or thionamides. Antithyroid drugs or thionamides are often started in patients with Graves' hyperthyroidism to attain a euthyroid state rapidly in preparation for radioiodine therapy or thyroidectomy. However, patients who want to avoid or defer ablative therapy with radioiodine or surgery can continue thionamides for prolonged periods. Although hyperthyroidism can almost always be controlled as long as the drug is taken, there is only a modest hope of attaining a permanent remission, which is about 20% to 30% within 1 to 2 years. It is also important to note that thionamide therapy may have a negative effect on the efficacy of subsequent radioactive iodine therapy. Methimazole and propylthiouracil (PTU) are the thionamides used to treat Graves' hyperthyroidism. Methimazole is usually preferred because of its longer duration of action, allowing for once-daily dosing, more rapid efficacy, and lower incidence of side effects. PTU is preferred during pregnancy because of the potential teratogenic effects of methimazole. Patients should have their thyroid function assessed at 4- to 6-week intervals until stabilized on maintenance antithyroid drug therapy. Potential significant side effects of thionamides include skin rash, agranulocytosis, and hepatotoxicity.

Iodinated contrast agents and iodine. Patients with severe hyperthyroidism or those who are allergic to antithyroid drugs may benefit from alternative medical therapies. The oral radiocontrast agents sodium ipodate and iopanoic acid are potent inhibitors of the peripheral conversion of T_4 to T_3 . They are not used as primary therapy because of possible induction of resistant hyperthyroidism. However, when given

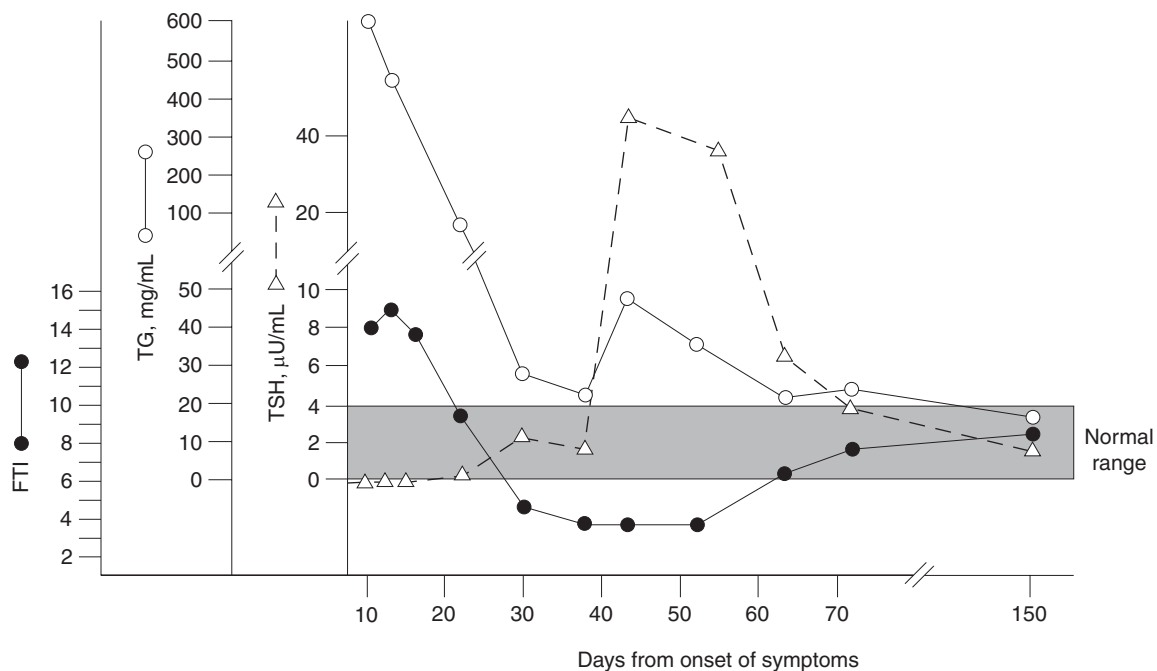


Figure. Course of subacute thyroiditis. FTI = free thyroxine index; TG = thyroglobulin; TSH = thyroid-stimulating hormone. (Reprinted with permission from DeGroot LJ, Larsen PR, Hennemann G. Acute and subacute thyroiditis. In: The thyroid and its diseases. 6th ed. New York: Churchill Livingstone; 1996:705.)

in combination with antithyroid drugs, they can rapidly ameliorate severe hyperthyroidism and can also be used to prepare a hyperthyroid patient for early surgery.

Other medications. A number of other medications have been used in the management of hyperthyroidism, including the following:

- Glucocorticoids inhibit peripheral T_4 to T_3 conversion and, in patients with Graves' hyperthyroidism, reduce thyroid hormone secretion. They have been used in patients with severe hyperthyroidism and thyroid storm
- Lithium blocks thyroid hormone release, but its use has been limited by its toxicity
- Cholestyramine, given in a dose of 4 g 4 times daily with methimazole, lowers serum T_4 and T_3 concentrations more rapidly than methimazole alone

Radioactive Iodine Ablation

Ablation with radioiodine is widely used for the treatment of Graves' hyperthyroidism. It is the therapy of choice in the United States, selected by approximately 70% of thyroid specialists [25]. It is considerably less popular in Europe (22%) and Japan (11%).

However, there are patients in whom it may be reasonable to delay radioiodine (or surgery), and therefore antithyroid drugs are the treatment of choice. Included in this group are patients with mild hyperthyroidism and patients with small goiters or with goiters that shrink during thioamide therapy. If radioiodine is chosen, the patient must be comfortable with the decision to ablate the thyroid, which in most cases will result in permanent hypothyroidism.

Physicians and patients must also be aware that radioiodine therapy may be associated with an increased risk of the development or worsening of Graves' ophthalmopathy [26]. However, ophthalmopathy did not progress in a study of patients with minimal ophthalmopathy who were carefully monitored to avoid hypothyroidism [27]. Some physicians advocate the use of glucocorticoids at the time of radioiodine treatment to prevent such effects [28].

Others suggest that radioactive iodine may not be the treatment of choice in patients with significant ophthalmopathy. However, careful control of thyroid function before and after therapy and cessation of smoking by the patient may minimize ocular changes.

Radioactive iodine may be given as primary therapy to patients with well-tolerated hyperthyroidism. In comparison, patients who are not tolerating hyperthyroidism well, are elderly, or have underlying heart disease are usually

Table 4. Comparison of Various Treatment Options for Graves' Hyperthyroidism

Treatment	Advantages	Disadvantages
Thionamides	Chance of permanent remission Avoids permanent hypothyroidism Lower cost	Minor side effects: rash, hives, arthralgias, fever, gastrointestinal symptoms Low risk of agranulocytosis Risk of fetal goiter and hypothyroidism if pregnant Frequent visits to the physician
Radioactive iodine therapy	Permanent resolution of hyperthyroidism	Permanent hypothyroidism Radiation precautions for several days after treatment; avoid contact with young children and pregnant women
Surgery	Rapid, permanent cure of hyperthyroidism	Permanent hypothyroidism Risk of hypoparathyroidism, recurrent laryngeal nerve damage, and general anesthesia

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pretreated with an antithyroid drug to ameliorate hyperthyroidism before radioactive iodine treatment.

The goal of radioactive iodine therapy is destruction of the gland, with the early development of hypothyroidism. This eliminates the risk of recurrent hyperthyroidism. On the other hand, some physicians prefer lower doses of radioactive iodine with the aim of achieving a euthyroid state while lowering the risk of early hypothyroidism [29]. However, many of these patients have persistent subclinical or overt hyperthyroidism. Furthermore, there is a risk of both recurrent overt hyperthyroidism and insidious-onset late hypothyroidism.

Approximately 20% of patients fail the first radioactive iodine treatment and require a subsequent dose. These patients usually have more severe hyperthyroidism or larger goiters.

Radioactive iodine therapy in toxic adenoma or toxic multinodular goiter. Depending upon patient preference, either radioactive iodine therapy or surgery is the treatment of choice for toxic adenoma or toxic multinodular goiter. An occasional patient can be managed, if preferred or necessary for other reasons, with antithyroid drugs.

Radioactive iodine therapy is less controversial in patients with a toxic adenoma or toxic multinodular goiter. Areas of focal autonomy take up radioiodine well, while uptake is limited in adjacent and contralateral thyroid tissue that has been suppressed by the hyperthyroid state. As a result, radioiodine tends to destroy only the autonomous areas, and most patients remain euthyroid after radioiodine administration [30].


Surgery

With the availability of other options, surgery is a less popular therapy for Graves' hyperthyroidism. It is primarily indicated

in patients who have an obstructive goiter or a very large goiter, in pregnant women who are allergic to antithyroid drugs, and in patients who have allergies or poor compliance on antithyroid drugs but refuse radioactive iodine. Surgery would also be indicated if there were a coexisting suspicious or malignant thyroid nodule. However, most thyroid nodules associated with Graves' disease are benign, in which case surgery would not be recommended [31]. Patients who want rapid restoration of euthyroidism, are concerned about radioactivity, or have had an adverse effect with thionamide drugs may also prefer surgery.

Thyroidectomy during pregnancy may be necessary in women who cannot tolerate antithyroid drugs because of allergy or agranulocytosis. The indications for surgery are similar to those in nonpregnant women and men. **Table 4** summarizes and compares treatment options for Graves' hyperthyroidism.

Case Continued

 The patient is started on methimazole, and her hyperthyroidism is well controlled with this treatment. One year later she presents to the emergency department with dyspnea, palpitations, fever, tremor, and agitation. Thyroid function tests show results consistent with severe hyperthyroidism. She also has atrial fibrillation with rapid ventricular response. Upon questioning, the patient reports that she has not taken her thyroid medication for a while, since she ran out.

- **What does the patient's presentation suggest?**

Patients with severe and life-threatening thyrotoxicosis

typically have an exaggeration of the usual symptoms of hyperthyroidism. This type of presentation is usually called thyroid storm.

Cardiovascular symptoms include severe tachycardia along with congestive heart failure in many patients. Hyperpyrexia to 104°F to 106°F is common. Agitation, delirium, psychosis, stupor, or coma are common and are considered by many to be essential to the diagnosis. Severe nausea, vomiting, or diarrhea, and hepatic failure with jaundice can also occur.

Although thyroid storm can develop in patients with long-standing untreated hyperthyroidism, it is more often precipitated by an acute event such as thyroid or nonthyroidal surgery, trauma, infection, or an acute iodine load. The advent of appropriate preoperative preparation of patients undergoing thyroidectomy for hyperthyroidism has led to a dramatic reduction in the prevalence of surgically induced thyroid storm.

• How is thyroid storm managed?

The therapeutic options for thyroid storm are the same as for uncomplicated hyperthyroidism, except that the drugs are given in higher doses and more frequently. In addition, full supportive therapy of the patient in an intensive care unit is essential, since the mortality rate of thyroid storm is high.

Supportive therapy should address various issues. Many patients require a substantial amount of fluid. Others may require diuresis because of congestive heart failure whereby digoxin requirements may be quite high. Infections need to be identified and treated. Hyperpyrexia should be aggressively corrected.

The therapeutic regimen typically consists of multiple medications, each of which has a different mechanism of action. β Blockers are used to control symptoms induced by increased adrenergic tone. A thionamide, such as methimazole, is needed to block new hormone synthesis. An iodinated radiocontrast agent can be used to inhibit the peripheral conversion of T_4 to T_3 . An iodine solution will help block the release of thyroid hormones. Glucocorticoids will help reduce T_4 -to- T_3 conversion and possibly treat the autoimmune process in Graves' disease.

• What should be recommended for long-term management of this patient's Graves' disease?

This patient has developed atrial fibrillation and admits to not adhering to her medication regimen. Antithyroid drugs

may not be her best long-term therapy option. Definitive therapy with radioactive iodine treatment may be a better choice for this patient.

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CME EVALUATION: Update on the Diagnosis and Treatment of Hyperthyroidism

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. In deciding whether to treat subclinical hyperthyroidism, all of the following factors are important EXCEPT
 - A. Presence of cardiac complications
 - B. Presence of osteopenia/osteoporosis
 - C. Presence of thyroid nodules
 - D. Age
 - E. Thyroid-stimulating hormone level
2. All of the following could be manifestations of subacute thyroiditis EXCEPT
 - A. Hyperthyroidism
 - B. Hypothyroidism
 - C. Pretibial myxedema
 - D. Thyroid pain and tenderness
3. All of the following regarding radioactive iodine therapy in Graves' disease are true EXCEPT
 - A. It is the most widely used therapy in the United States
 - B. It can lead to agranulocytosis
 - C. It may be associated with worsening ophthalmopathy
 - D. It results in permanent hypothyroidism in most patients
4. Thyroidectomy in hyperthyroidism is indicated in all of the following cases EXCEPT
 - A. Patients with thyroid storm
 - B. Patients with a coexisting suspicious or malignant nodule
 - C. Patients with obstructive goiter
 - D. Pregnant women allergic to antithyroid drugs
5. In regard to thyroid storm, all of the following are true EXCEPT
 - A. Patients may present with congestive heart failure
 - B. Usually there is an identifiable precipitating factor
 - C. Blocking the conversion of T_4 to T_3 is an important part of the treatment
 - D. The incidence of surgically induced thyroid storm has increased recently

EVALUATION FORM: Update on the Diagnosis and Treatment of Hyperthyroidism

Participants may earn 1 credit by reading the article named above and correctly answering at least 70% of the accompanying test questions. A certificate of credit and the correct answers will be mailed within 6 weeks of receipt of this page to those who successfully complete the test.

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- 1. A B C D E
- 2. A B C D
- 3. A B C D
- 4. A B C D
- 5. A B C D

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 Yes No
- 3. Please rate the clarity of the material presented in the article.
 Very clear Somewhat clear Not at all clear
- 4. How helpful to your clinical practice was this article?
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- 6. What topics would you like to see presented in the future?

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