Thyroid Disorders in Elderly Adults, Part 1

Evaluation and Diagnosis

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The atypical presentation of thyroid dysfunction in elders challenges clinicians to detect these disorders before they cause significant morbidity or death.

The incidence and prevalence of thyroid dysfunction increases with age.[1] For this reason, thyroid disorders are very common among elderly adults.[1,2] Clinicians must maintain a high index of suspicion for such disorders within this population because their presentation is often subtle or atypical,[3] comorbidities and polypharmacy can complicate laboratory workups, and significant morbidity and mortality can occur with delayed diagnosis.[4]

In the first of this two-part series on thyroid disorders in elderly adults, we review the epidemiology, etiology, and pathophysiology of hypothyroidism and hyperthyroidism. We describe how thyroid disease presents in elderly adults and explain how to evaluate and diagnose it in this patient population. In part two of this series, we will discuss the various treatment options and how to manage both classic thyroid disease and the more challenging, less common variations of subclinical disease, myxedema coma, and thyroid storm.

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EPIDEMIOLOGY OF THYROID DYSFUNCTION

The reported prevalence of thyroid disease varies with geographic region, ethnic group, associated dietary iodine content, and diagnostic criteria, but these disorders are known to be more common among older adults than among the general population and to affect more women than men.[2,5–9] Highly sensitive laboratory assays for thyroid-stimulating hormone (TSH)—the pituitary hormone secreted to stimulate the production of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) when thyroid activity is deficient—have significantly increased diagnoses of both hypothyroidism and hyperthyroidism. These assays can detect subclinical disease, in which serum TSH levels are abnormal (high in patients with hypothyroidism and low in patients with hyperthyroidism) but patients generally are asymptomatic and exhibit no overt signs of thyroid dysfunction.[10,11]

Data obtained from the third National Health and Nutrition Examination Survey (NHANES III), show that the prevalence of both high serum TSH levels (defined in this survey as levels above 4.5 mU/L) and low serum TSH levels (defined in this survey as levels below 0.4 mU/L) increases dramatically with age (Figure).[9] The survey further found that antithyroid antibodies are more prevalent among those of advanced versus younger age, female versus male sex, and white or Mexican American versus black racial/ethnic identity.[9]

Various studies (using varying definitions of "elderly") have estimated the prevalence of overt hypothyroidism in the elderly population to range from 0.5% to 5%.[2,5,6,12] Subclinical hypothyroidism is estimated to affect 4% to 10% of all adults, 5% to 20% of elderly adults, and up to 20% of women older than 60 years.[1,9–11,13,14] Hypothyroidism occurs more frequently in iodine-sufficient than in iodine-deficient geographic regions.[15]

The prevalence of overt hyperthyroidism among the general population older than 60 years is estimated at between 0.5% and 2.3%,[2,12] and subclinical hyperthyroidism is estimated to affect an additional 0.8% to 5.8% of this age group.[16–19] Hyperthyroidism has been reported to be 10 times more common in women than in men.[1,2] It occurs more often in iodine-deficient than in iodine-sufficient geographic regions, most likely due to the thyroid enlargement and nodular development that often accompany iodine deficiency.

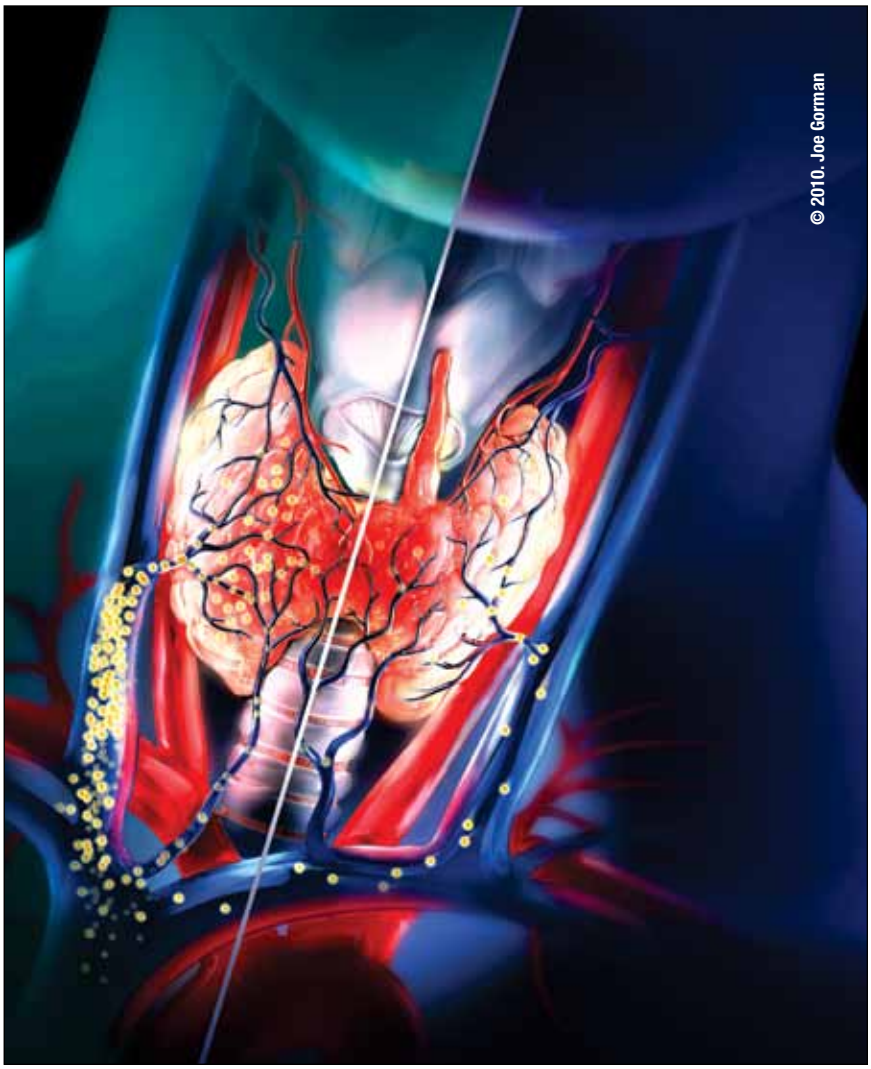
ETIOLOGY AND PATHOPHYSIOLOGY

Hypothyroidism

There are several potential causes of hypothyroidism in elders (Table 1). The most common, however, is autoimmune thyroiditis,[2,20] a condition in which the thyroid is gradu-

ally destroyed by autoantibodies to such thyroid enzymes as thyroid peroxidase (TPO) and thyroglobulin (Tg). Numerous studies, in addition to NHANES III,[9] have documented the high prevalence of such antibodies among elders.[21,22] In one cross-sectional study involving more than 4,000 participants, 30% of women and 10% of men aged 60 to 65 years were found to have TPO or Tg antibodies.[22]

After treatment for Graves' disease (a common form of hyperthyroidism among younger adults), patients are at elevated risk for hypothyroidism. About 76% of adults older than age 55 who are treated with radioactive iodine develop hypothyroidism after 11 years of observation.[23] Patients who undergo thyroid surgery are also at risk, with approximately 19% developing hypothyroidism within the first year of surgery and 27% having hypothyroidism after 11 years.[23,24] Pituitary and hypothalamic dysfunction are other common causes of hypothyroidism, as are many drugs, some of which are commonly used by older adults (Table 2).[6,8,11,25]



Hyperthyroidism

Although Graves' disease is the predominant cause of hyperthyroidism for the younger population, toxic multinodular goiter is the most common cause of hyperthyroidism among elderly patients.[26–28] A descriptive, observational, cross-sectional study of 313 patients older than age 55 who had hyperthyroidism confirmed that, in this population, toxic multinodular goiter was the most frequent cause of hyperthyroidism (43.1%), followed by Graves' disease (21.4%), iatrogenesis (16%), toxic adenoma (11.8%), thyroiditis (1.3%), iodine-induced thyrotoxicosis (1.2%), TSH-secreting pituitary adenoma (0.6%), factitious thyrotoxicosis (0.3%), and unknown etiology (3.8%).[28]

The pathogenic mechanism for toxic nodular hyperthyroidism is uncertain but is postulated to be caused by thyroid autonomy. Graves' disease develops when autoantibodies bind to TSH receptors, causing intracellular cyclic adenosine monophosphate (cAMP) levels to rise and increasing thyroid gland growth, as well as hormone synthesis and release. Toxic goiter is more common in geographic areas of iodine deficiency than in areas of iodine sufficiency, whereas Graves' disease is more prevalent in areas associated with high dietary iodine intake.[29]

Age-related changes in thyroid function

Historically, normal aging has been associated with few changes in thyroid function and, in general, was believed to exert very little effect on thyroid function tests.[2,8,30] Experts asserted that serum TSH and free T_4 levels typically were normal, whereas free T_3 levels would fluctuate[12] from low to normal, depending on the pa-

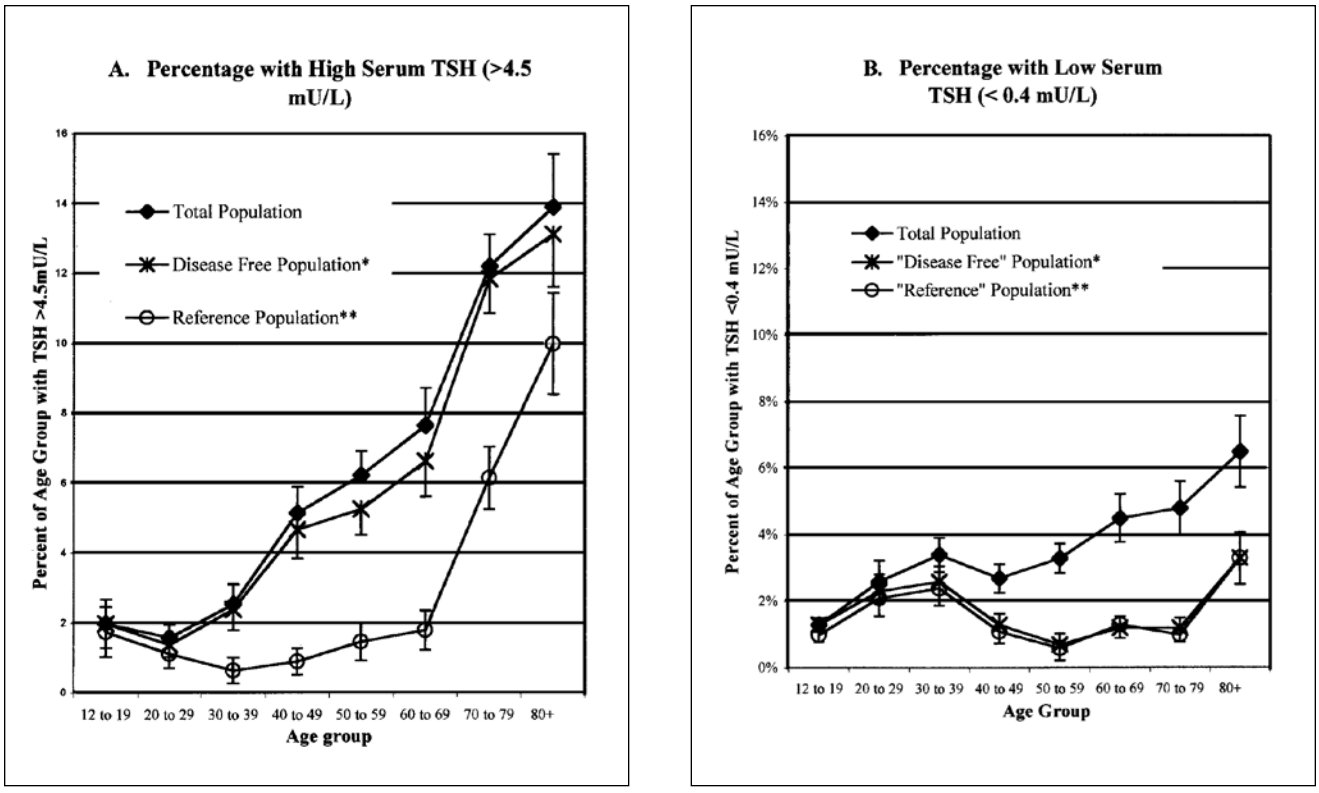


Figure. Prevalence of elevated (A) and diminished (B) serum thyroid-stimulating hormone (TSH) levels, by age, in the total, "disease-free,"[a] and "reference"[b] U.S. populations.[9] Reprinted with permission from: Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489–499. Copyright © 2002, The Endocrine Society. All rights reserved. [a]Disease-free excludes people who have reported having thyroid disease, goiter, or taking thyroid medications. [b]Reference population excludes people who reported having thyroid disease, goiter, or taking thyroid medications, who do not have such risk factors as pregnancy; use of estrogen, androgens, or lithium; and who have no thyroid antibodies or biochemical evidence of hypothyroidism or hyperthyroidism.

tient's nutritional status and comorbidities. Although aging has been associated with decreased T_4 production, this is balanced by reduced T_4 metabolism and clearance,[2,30] usually resulting in normal levels of free T_4. Nocturnal TSH secretion was found to be slightly diminished in elders in community-based studies,[1,13] but this wasn't observed to affect TSH concentration.[31]

More recently, some experts have argued for the development and application of race- and age-specific TSH reference ranges. This notion is supported by results from a recent cross-sectional study involving 22,116 outpatients who were free of clinical thyroid disease. The study found an increase in TSH values with age that occurred in all racial subpopulations studied (black, white, and Hispanic), although black patients tend to have lower TSH (and free T_4) values compared with white patients. After matching their study population to the TSH reference limits used in NHANES III, the authors concluded that 8% of black patients older than 80 years and 10.7% of white patients older than 80 years would have been misclassified as having hypothyroidism.[32]

This finding was affirmed by another study comparing TSH values of centenarian Ashkenazi Jews (median age, 98 years) with those of younger Ashkenazi Jews (median age, 72 years) and a U.S. population of individuals without thyroid disease (study population from NHANES [1998–2002]; median age, 68 years). Median TSH values and TSH value distribution in the centenarian study participants was shifted significantly to higher serum concentrations compared with the younger Ashkenazi and U.S. control participants.[33] The authors warned that applying normal TSH reference ranges to the aging

Table 1. Etiologies of thyroid dysfunction in elderly adults

Hypothyroidism	Hyperthyroidism
• Autoimmune thyroiditis —Hashimoto's thyroiditis —Chronic lymphocytic thyroiditis • Iatrogenic —Radioactive iodine ablation —Surgical intervention —Drugs • Iodine excess or deficiency • Pituitary or hypothalamic disorders • Transient hypothyroidism —Painless thyroiditis —Subacute thyroiditis	• Toxic multinodular goiter (Plummer disease) • Toxic adenoma • Graves' disease • Iatrogenic/factitious —Drugs • Iodine-induced hyperthyroidism • Transient hyperthyroidism —Painless thyroiditis —Subacute thyroiditis • Thyroid-stimulating hormone–producing pituitary adenoma

population might overestimate the incidence of hypothyroidism.[34]

The health impact of mildly elevated TSH levels in the older population is uncertain. Some experts have suggested that such elevations may be associated with extreme longevity[33] or may be necessary for healthy aging.[35,36] The exact protective mechanism is unknown, although genetic influences[37] and decreased metabolic rate with lower catabolism processes have been proposed as possible reasons. Currently, most experts agree that routine treatment of elderly patients with mildly elevated TSH (using current TSH reference ranges) is not necessary.[33,34,38] Nevertheless, for the present, it remains prudent to evaluate elders with abnormal TSH levels for possible thyroid disease.

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PRESENTATION AND EVALUATION

Hypothyroidism

In elders, hypothyroidism often presents atypically. One retrospective, observational study illustrated that patients older than 70 years have significantly fewer signs and symptoms of hypothyroidism compared to those younger than 55 years.[39]

Fatigue, weakness, and mental slowness are the three most common symptoms of hypothyroidism in elders. Unfortunately, such nonspecific symptoms can be viewed as part of normal aging,[5,6] and elders presenting with them often are ignored. Cold intolerance, slow reflexes (often considered the most reliable sign of hypothyroidism), weight gain, and paresthesia are four classic signs that occur significantly less frequently in elders than in younger patients ($P < .001$).[39]

Because undiagnosed hypothyroidism is associated with significant morbidity, especially in elders with comorbidities, clinicians should evaluate such patients for hypothyroidism in the presence of any classic sign or symptom (Table 3).[2,3,5–8,11] The two greatest risk factors for hypothyroidism in elders are family history of thyroid disease and a patient's personal history of thyroidectomy or radiation therapy.[20,23,24] The absence of goiters on physical examination does not exclude the possibility of hypothyroidism. Bradycardia, hypothermia, or diastolic hypertension are suggestive of hypothyroidism and require further evaluation, as do laboratory findings of hypercholesterolemia, hyponatremia, or high creatinine kinase or creatinine levels.[2]

Hyperthyroidism

Elderly patients with hyperthyroidism rarely present with the classic signs, symptoms, or laboratory results (Table 4).[29,40] Such sympathomimetic features as tachycardia, palpitations, hyperdefecation, and increased sweating usually are diminished and replaced by weakness, apathy, anorexia, or depression.[30] This so-called "apathetic hyperthyroidism" is believed to be caused by the down-regulation of catecholamine receptors that occurs as part of normal aging, and its prevalence among elders is estimated to be between 10% and 15%.[30,31]

One prospective study compared the frequency of 19 classic signs and symptoms of hyperthyroidism in 34 patients older than 70 years (mean age, 80.2 years) and in 50 patients younger than 50 years (mean age, 37.4 years) with chemically confirmed hyperthyroidism.[41] In general, the older patients had fewer signs and

Table 2. Common drugs that affect thyroid function in elderly adults[6,8,11,25]

Hypothyroidism

- Drugs that decrease absorption of exogenous thyroid hormone
  - Bile acid sequestrants
  - Products containing calcium or iron
  - Proton pump inhibitors
  - Raloxifene
- Drugs that increase thyroid hormone clearance
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifampin
- Drugs that inhibit thyroid hormone synthesis or release
  - Amiodarone
  - Products containing iodine
  - Expectorants
  - Radiographic dyes
  - Potassium iodide
  - Lithium
  - Methimazole
  - Propylthiouracil
- Drugs that inhibit expression of thyroid hormones through other mechanisms
  - Glucocorticoids
  - Dopamine
  - Interferon alfa

Hyperthyroidism

- Drugs that increase thyroid hormone synthesis or release
  - Amiodarone
  - Products containing iodine
  - Radiographic dyes
  - Potassium iodide
  - Expectorants
  - Levothyroxine
  - Armour thyroid
- Drugs that increase expression of thyroid hormones through other mechanisms
  - Interferon alfa
  - Lithium

symptoms, with the three most common being tachycardia, weight loss, and fatigue. By contrast, predominant features in the younger patients were tachycardia, hyperactive reflexes, heat intolerance, and excessive sweating.[41] A chart review of 922 patients treated for hyperthyroidism at an Asian hospital, 84 of whom were older than 60 years, yielded similar results: Older patients more frequently presented with atrial fibrillation, weakness, and anorexia; exophthalmos, goiter, heat intolerance, and hyperhidrosis were far less frequent.[42]

Because older patients with thyrotoxicosis are at increased risk for mortality,[4] the presence of any symptom or sign suggestive of hyperthyroidism should be evaluated thoroughly. Assessment should focus on apathetic as well as classic features. Symptoms seen frequently in younger patients, such as diarrhea or increased appetite, are the exception among elderly patients with hyperthyroidism.[2,31] Goiter, ocular signs (even in Graves' disease), and skin changes usually are absent in affected elders. Hyperactive reflexes seldom can be elicited, and tremors, if present, are coarse instead of fine.[2,7,26]Atrial fibrillation is very common, occurring in up to 27% of elderly patients with hyperthyroidism;[31] its presence should prompt immediate evaluation of thyroid function. Hyperthyroidism increases bone turnover and is an independent risk factor for the development of hip fracture.[43] Any elderly patient with osteoporosis (even if an obvious cause is known) should be thoroughly screened for thyrotoxicosis.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC STUDIES

Both hypothyroidism and hyperthyroidism have extensive differential diagnoses (Table 5). Because clinical presentations for these disorders are so varied and elusive in elders, laboratory testing is almost always necessary to confirm either diagnosis.

The sensitive TSH (sTSH) immunometric assay is considered the best screening test for thyroid dysfunction.[6,16,31,44] Since this test has a sensitivity and specificity greater than 98%,[31] normal results usual mean

Table 3. Classic clinical presentation of hypothyroidism[2,3,5–8,11]

Symptoms	Signs	Laboratory results
Cold intolerance; constipation; depression; dry skin; fatigue or lethargy; impaired cognition; memory loss; muscle cramps; psychosis; weakness; weight gain	Bradycardia; delayed relaxation of deep tendon reflexes; diastolic hypertension; dysarthria; goiter; hoarseness; hypothermia; illeus; mental status changes; nonpitting edema of face and limbs	Elevated TG[a]; elevated total cholesterol; elevated lipoproteins; hyponatremia; macrocytic anemia; elevated CPK[b]; elevated LDH[c]; elevated prolactin; elevated SCr[d]; elevated homocysteine

[a]TG = triglycerides. [b]CPK = creatinine phosphokinase. [c]LDH = lactate dehydrogenase. [d]SCr = serum creatinine.

that primary thyroid pathology can be excluded with no need for further testing.[18] There are a few circumstances under which sTSH should not be the first test performed: central hypothyroidism, sick euthyroid syndrome, recently treated hyperthyroidism, and central TSH excess.[45] Fortunately, the exceptions are rare, and sTSH remains the most cost effective screening tool for thyroid dysfunction.[46]

The American Thyroid Association currently recommends using the sTSH to screen for thyroid dysfunction in adults beginning at age 35 and repeated every five years. More frequent testing is appropriate in high risk populations, such as those older than 60 years.[47] Similarly, the American Association of Clinical Endocrinologists recommends using sTSH to screen all women older than 50 years for thyroid dysfunction.[44] The American College of Physicians recommends the test for all women aged 50 years and older who have at least one possible symptom of thyroid disease.[48] Although the Canadian Task Force on the Periodic Health Examination does not formally recommend general screening for thyroid dysfunction, they suggest that clinicians maintain a high index of suspicion for hypothyroidism in perimenopausal and postmenopausal women.[49] The United States Preventive Services Task Force[50] and the American Academy of Family Physicians[51] acknowledge that sTSH testing is appropriate for high risk populations, although they deem the evidence insufficient to recommend for or against routine screening for thyroid disease in adults.

Hypothyroidism

Elevated TSH levels on initial screening suggest hypothyroidism. A concomitant low level of free T_4 establishes the diagnosis of primary hypothyroidism, while a normal free T_4 suggests subclinical hypothyroidism, transient autoimmune thyroiditis, or sick euthyroid syndrome (recovery phase). The antithyroid antibody level may indicate the likelihood of progression from subclinical to overt hypothyroidism or help clinicians identify patients with autoimmune thyroiditis.[52] In the absence of other clinical signs, no further testing is needed. Serum free T_3 is a poor marker of thyroid hypofunction and is not indicated in evaluating suspected hypothyroidism.

A few caveats exist in the laboratory diagnosis of hypothyroidism. Some patients with central hypothyroidism (hypothalamic or pituitary disease) present with normal (or elevated) TSH levels but low free T_4 levels (a pattern similar to that of primary hypothyroidism). Although the TSH produced in these patients is biologically diminished, it remains immunoactive and, thus, detectable in laboratory assays.[53] Magnetic resonance imaging is required to evaluate such patients for hypothalamic or pituitary pathology.

Serum free T_3 is a poor marker of thyroid hypofunction and is not indicated in evaluating suspected hypothyroidism.

Sick euthyroid syndrome is another condition that can cause confusion during laboratory analysis. During the recovery phase, the TSH level may be above normal, mimicking the pattern typically seen in primary hypothyroidism (high TSH with low free T_4). These patients have normal thyroid function and do not

Table 4. Clinical presentation of hyperthyroidism[30,31]

Aspect of presentation	Classic features	Common features in elders
Symptoms	Nervousness; fatigue or weakness; palpitations; dyspnea; weight loss; heat intolerance; increased appetite; increased sweating; hyperdefecation; hyperactivity; irritability; restlessness	Fatigue or weakness; anorexia, decreased appetite, or weight loss; constipation; apathy; depression; confusion or dementia
Signs	Tachycardia; systolic hypertension; hyperactive reflexes; tremor; staring; goiter; eyelid retraction; excess perspiration	Tachycardia or atrial fibrillation; lack of eye, thyroid, or skin changes; congestive heart failure
Laboratory results	Elevated alkaline phosphatase; elevated hepatocellular enzymes	–

need therapy.[54] Clinical assessment and close follow-up are essential to prevent such patients from being treated unnecessarily.

Hyperthyroidism

A low TSH level with high free T_4 level is characteristic of primary hyperthyroidism. In cases in which the free T_4 level is normal, free T_3 levels must be measured to rule out T_3 toxicosis,[25] which is known to occur more frequently in the elderly population. A low TSH level with normal free T_4 and free T_3 levels suggest subclinical hyperthyroidism, although sick euthyroid syndrome and drugs can produce similar patterns.[2] Such findings warrant close monitoring. When Graves' disease is suspected, antibodies to the thyroid enzymes TPO and Tg or to TSH receptors should be measured.

In elderly patients, results of the medical history and physical examination often are inconclusive. For this reason, radioactive iodine uptake and scan may be needed to determine the etiology of hyperthyroidism. Normal or increased uptake is suggestive of Graves' disease or toxic (single or multinodular) goiter. Low uptake is indicative of transient thyroiditis or exogenous ingestion of thyroxine.[55]

In elderly patients, results of the medical history and physical examination often are inconclusive.

TIMELY DIAGNOSIS

Thyroid dysfunction is common among elders and can cause significant morbidity and mortality when untreated. Clinicians must maintain a high index of suspicion and a low threshold for laboratory testing to diagnose these disorders in a timely fashion.

Author disclosures

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Table 5. Differential diagnoses for thyroid dysfunction in elderly adults

Hypothyroidism	Hyperthyroidism
• Drug-induced • Infection/sepsis • Malnutrition • Malignancy • Sick euthyroid syndrome • Single or multiorgan dysfunction —Cardiac failure —Cerebrovascular event —Hepatic disease —Renal failure —Respiratory failure • Trauma/burns • Uncontrolled diabetes mellitus	• Anxiety/panic disorder • Congestive heart failure • Drug-induced • Heat exhaustion/heat stroke • Malignancy • Neuroleptic malignant syndrome • Pheochromocytoma • Psychosis • Pulmonary edema • Sepsis • Uncontrolled diabetes mellitus • Withdrawal symptoms/ delirium tremens

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