American Thyroid Association Guidelines for Detection of Thyroid Dysfunction

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Objective: To define the optimal approach to identify patients with thyroid dysfunction.

Participants: The 8-member Standards of Care Committee of the American Thyroid Association prepared a draft, which was reviewed by the association's 780 members, 50 of whom responded with suggested revisions.

Evidence: Relevant published studies were identified through MEDLINE and the association membership's personal resources.

Consensus Process: Consensus was reached at group meetings. The first draft was prepared by a single author (P.W.L.) after group discussion. Suggested revisions were incorporated after consideration by the committee.

Conclusions: The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter. The indication for screening is particularly compelling in women, but it can also be justified in men as a relatively cost-effective measure in the context of the periodic health examination. Individuals with symptoms and signs potentially attributable to thyroid dysfunction and those with risk factors for its development may require more frequent serum thyrotropin testing.

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THYROID dysfunction is common in adults[1-5] (**Table 1**) and frequently has significant clinical consequences. Hypothyroidism and hyperthyroidism can be accurately diagnosed with laboratory tests[6,7] and are readily treatable. (Although *hyperthyroidism* can be narrowly construed as those causes of thyrotoxicosis that result from glandular hyperactivity, the term here refers to all conditions causing thyroid hormone excess, including certain forms of thyroiditis and exogenous thyroid hormone administration.)

Clinical manifestations of thyroid dysfunction vary considerably among patients in their character and severity. Associated symptoms and signs are often nonspecific and progress slowly. Consequently, the accuracy of clinical diagnosis is limited. Physicians must consider and exclude thyroid dysfunction much more often than they will establish a diagnosis. If only patients presenting with clearly suggestive symptoms and signs are evaluated, many affected individuals will remain undiagnosed. For these persons, appropriate treatment for thyroid dysfunction or conservative monitoring to anticipate its potential future consequences can only be implemented when routine laboratory screening identifies them (see the "Screening for Thyroid Dysfunction" section below).

CASE FINDING FOR THYROID DYSFUNCTION

A number of symptoms and signs are well-established manifestations of thyroid dysfunction (**Table 2**). Additional findings in patients' personal and family histories indicate increased risk of developing thyroid dysfunction. Risk factors identifiable in personal history include (1) previous thyroid dysfunction; (2) goiter; (3) surgery or radiotherapy affecting the thyroid gland; (4) diabetes mellitus; (5) vitiligo; (6) pernicious anemia; (7) leukotrichia (prematurely gray hair); and (8) medications and other compounds, such as lithium carbonate and iodine-containing compounds (eg, amiodarone hydrochloride, radiocontrast agents, expectorants containing potassium iodide, and

Table 1. Prevalence of Thyroid Dysfunction*

Condition	Reported Prevalences in Adult Populations, %
Hypothyroidism	2
Mild (subclinical) hypothyroidism†	5-17
Hyperthyroidism	0.2
Mild (subclinical) hyperthyroidism‡	0.1-6.0

*Vanderpump and Tunbridge.[1]
†Elevated serum thyrotropin concentration with a normal serum free thyroxine concentration.
‡Serum thyrotropin concentration less than 0.1 mIU/L with normal serum free thyroxine and triidothyronine concentrations.

Table 2. Common Symptoms and Signs of Thyroid Dysfunction

Hypothyroidism	Hyperthyroidism
Fatigue	Fatigue
Weight gain	Weight loss
Cold intolerance	Heat intolerance
Skin dryness	Hyperhydrosis
Hair dryness or loss	
Depression	Nervousness
Dementia	Insomnia
	Tremor
Muscle cramps and myalgias	Muscle weakness
Edema	Dyspnea
Bradycardia	Palpitations
	Tachycardia and atrial tachyarrhythmias
Constipation	Hyperdefecation
Menstrual irregularity (especially menorrhagia)	Menstrual irregularity (especially hypomenorrhea)
Infertility	

kelp). Risk factors identifiable in the family history include (1) thyroid disease, (2) pernicious anemia, (3) diabetes mellitus, and (4) primary adrenal insufficiency.

Abnormal results in certain commonly obtained laboratory tests also suggest hypothyroidism or hyperthyroidism. Findings of these tests for hypothyroidism may include (1) hypercholesterolemia, (2) hyponatremia, (3) anemia, (4) creatine phosphokinase and lactate dehydrogenase elevations, and (5) hyperprolactinemia; and for hyperthyroidism, (1) hypercalcemia, (2) alkaline phosphatase elevation, and (3) hepatocellular enzyme elevation. Any of these clinical and laboratory findings justify thyroid function testing, particularly if they are sustained for 2 weeks or more, occur in combination, have not been present previously during documented euthyroidism, or occur in individuals with increased risk of thyroid disease.

SCREENING FOR THYROID DYSFUNCTION

Thyroid dysfunction meets many criteria for a condition justifying population screening:

1. The prevalences of various forms of thyroid dysfunction are substantial.

2. Overt hypothyroidism and hyperthyroidism have well-established clinical consequences. Even mild hypothyroidism can progress to overt hypothyroidism,[1,8] particularly in patients with antithyroid antibodies or previous thyroid irradiation. (*Mild hypothyroidism* refers to patients in whom there is elevation of the serum thyrotropin [thyroid-stimulating hormone (TSH)] concentration in association with a normal serum free thyroxine [(FT$_4$)] concentration. This state is also termed *subclinical hypothyroidism*, *compensated hypothyroidism*, *decreased thyroid reserve*, and *prehypothyroidism*.) Mild

hypothyroidism can also be associated with reversible hypercholesterolemia,[9-12] particularly when the serum TSH concentration is greater than 10 mIU/L, and, in some patients, with reversible symptoms[13,14] and cognitive dysfunction.[15,16] Mild (subclinical) hyperthyroidism has been associated with a higher incidence of atrial fibrillation in older persons[17]; reduced bone mineral density,[18,19] particularly in postmenopausal women; and symptoms (eg, palpitations) in some patients.[20]

3. The serum TSH assay is an accurate, widely available, safe, and relatively inexpensive diagnostic test for all common forms of hypothyroidism and hyperthyroidism.[21]

4. There are effective therapies for both hypothyroidism and hyperthyroidism for patients in whom treatment is indicated.

Screening of all newborn children for hypothyroidism is already a widely accepted and legislatively mandated practice. In addition, serum TSH measurement in adults every 5 years has been shown by decision analysis to have equivalent or more favorable cost-effectiveness in comparison with other widely accepted disease detection strategies,[22] for example, for hypertension, breast cancer, and hypercholesterolemia. The cost-effectiveness of screening is more favorable in women and older persons and is strongly influenced by the cost of TSH measurement. Consequently, it is recommended that all adults have their serum TSH concentration measured beginning at age 35 years and every 5 years thereafter, the interval at which a periodic health examination has been advocated by the US Preventive Services Task Force.[23] More frequent screening may be appropriate in individuals at higher risk of developing thyroid dysfunction.

LABORATORY TESTING STRATEGIES

Serum TSH measurement is the single most reliable test to diagnose all common forms of hypothyroidism and hyperthyroidism, particularly in the ambulatory setting. An elevated serum TSH concentration is present in both overt and mild hypothyroidism. In the latter, the se-

rum FT_4 concentration is, by definition, normal. While serum TSH measurement confirms or excludes the diagnosis in all patients with primary hypothyroidism, it will not reliably identify patients with central (secondary) hypothyroidism, in whom serum TSH concentrations may be low, normal, or mildly elevated. When there is suspicion of pituitary or hypothalamic disease, the serum FT_4 concentration should be measured in addition to the serum TSH concentration.

Virtually all types of hyperthyroidism encountered in clinical practice are accompanied by suppressed serum TSH concentrations, typically less than 0.1 mIU/L. These include Graves disease, toxic adenoma and nodular goiter, subacute and lymphocytic (silent, postpartum) thyroiditis, iodine-induced hyperthyroidism, and exogenous thyroid hormone excess. Serum FT_4 measurement and serum triiodothyronine (T_3) assay in patients with a normal serum FT_4 level are indicated to further assess patients with a serum TSH level less than 0.1 mIU/L.

To diagnose hyperthyroidism accurately, TSH assay sensitivity, the lowest reliably measured TSH concentration, must be 0.02 mIU/L or less. Some less sensitive TSH assays cannot reliably distinguish patients with hyperthyroidism from those with euthyroidism. When such less sensitive TSH assays are the only ones available, a serum FT_4 assay or estimate and a total or free T_3 (FT_3) assay should be employed in addition to measurement of the serum TSH concentration. There are 2 rare types of TSH-mediated hyperthyroidism, TSH-secreting pituitary adenomas and selective pituitary resistance to thyroid hormone, that will be overlooked by serum TSH measurement alone; serum FT_4 and FT_3 concentrations should also be measured when these conditions are suspected. Finally, it is important to recognize that isolated abnormalities of the serum TSH concentration do not always connote sustained thyroid dysfunction and may be caused by other conditions and medications.

The causes of isolated TSH elevation include (1) mild (subclinical) hypothyroidism, (2) recovery from hypothyroxinemia of nonthyroid illnesses, and (3) medications such as lithium carbonate and amiodarone. (Inhibition of thyroid hormone production by these drugs may cause both transient reversible elevation of the serum TSH level and true hypothyroidism.) The causes of isolated TSH suppression include (1) mild (subclinical) hyperthyroidism, (2) recovery from overt hyperthyroidism, (3) nonthyroidal illnesses (which can cause a low serum FT_4 concentration), (4) pregnancy during the first trimester, and (5) medications, such as dopamine and glucocorticoids.

CONCLUDING RECOMMENDATIONS

The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum TSH concentration, beginning at age 35 years and every 5 years thereafter. The indication for screening is particularly compelling in women, but it may also be justified in men as a relatively cost-effective measure in the context of the periodic health examination. Individuals with clinical manifestations potentially attributable to thyroid dysfunction and those with risk factors for its development may require more frequent serum TSH testing.

REFERENCES

1. Vanderpump MPJ, Tunbridge WMG. The epidemiology of thyroid diseases. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. 7th ed. Philadelphia, Pa: Lippincott-Raven; 1996.
2. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham Survey. *Clin Endocrinol (Oxf)*. 1977;7:481-493.
3. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;43:55-68.
4. Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid: thyroid deficiency in the Framingham Study. *Arch Intern Med*. 1985;145:1386-1388.
5. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years: a study in an urban US community. *Arch Intern Med*. 1990;150:785-787.
6. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. *JAMA*. 1995;273:808-812.
7. Klee GG, Hay ID. Biochemical testing of thyroid function. *Endocrinol Metab Clin North Am*. 1997;26:763-775.
8. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly: microsomal antibodies as discriminant for therapy. *JAMA*. 1987;258:209-213.
9. Tanis BC, Westendorp GJ, Smelt HM. Effect of thyroid substitution on hypercholesterolaemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. *Clin Endocrinol (Oxf)*. 1996;44:643-649.
10. Arem R, Patsch W. Lipoprotein and apolipoprotein levels in subclinical hypothyroidism: effect of levothyroxine therapy. *Arch Intern Med*. 1990;150:2097-2100.
11. Staub JJ, Althaus BU, Engler H, et al. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *Am J Med*. 1992;92:631-642.
12. Franklyn JA, Daykin J, Betteridge J, et al. Thyroxine replacement therapy and circulating lipid concentrations. *Clin Endocrinol (Oxf)*. 1993;38:453-459.
13. Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. L-Thyroxine therapy in subclinical hypothyroidism: a double-blind, placebo-controlled trial. *Ann Intern Med*. 1984;101:18-24.
14. Nystrom E, Caidahl K, Fager G, Wikkelso C, Lundberg PA, Lindstedt G. A double-blind crossover 12-month study of L-thyroxine treatment of women with "subclinical" hypothyroidism. *Clin Endocrinol (Oxf)*. 1988;29:63-76.
15. Jaeschke R, Guyatt G, Gerstein H, et al. Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med*. 1996;11:744-749.
16. Baldini IM, Vita A, Mauri MC, et al. Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1997;21:925-935.
17. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994;331:1249-1252.
18. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. *J Clin Endocrinol Metab*. 1996;81:4278-4289.
19. Faber J, Galloe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. *Eur J Endocrinol*. 1994;130:350-356.
20. Biondi B, Fazio S, Carella C, et al. Control of adrenergic overactivity by beta-blockade improves the quality of life in patients receiving long term suppressive therapy with levothyroxine. *J Clin Endocrinol Metab*. 1994;78:1028-1033.
21. Spencer CA, Takeuchi M, Kazarosyan M. Current status and performance goals for serum thyrotropin (TSH) assays. *Clin Chem*. 1996;42:140-145.
22. Danese MD, Powe NR, Sawin CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. *JAMA*. 1996;276:285-292.
23. *Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1995.

REFERENCES

1. Maudsley G, Williams EMI. Inaccuracy in death certification: where are we now? *J Public Health Med*. 1996;18:59-66.
2. National Committee on Vital and Health Statistics. Report of the second workshop on improving cause-of-death statistics. Presented at: National Center for Health Statistics; April 21-23, 1991; Virginia Beach, Va.
3. Hanzlick R, ed. *The Medical Cause of Death Manual*: *Instructions For Writing Cause of Death Statements For Deaths Due to Natural Causes*. Northfield, Ill: College of American Pathologists; 1994.
4. Cameron HM, McGoogan E. A prospective study of 1152 hospital autopsies, I: inaccuracies in death certification. *J Pathol*. 1981;133:273-283.
5. Cameron HM, McGoogan E. A prospective study of 1152 hospital autopsies, II: analysis of inaccuracies in clinical diagnoses and their significance. *J Pathol*. 1981; 133:285-300.
6. Hanzlick R. Improving accuracy of death certificates [letter]. *JAMA*. 1993;269:2850.
7. Jordan JM, Bass MJ. Errors in death certificate completion in a teaching hospital. *Clin Invest Med*. 1993;16:249-255.
8. Kaplan J, Hanzlick R. Improving the accuracy of death certificates [letter]. *JAMA*. 1993;270:1426.
9. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. *N Engl J Med*. 1985;313:1263-1269.
10. Maclaine GDH, Macarthur EB, Heathcote CR. A comparison of death certificates and autopsies in the Australian Capital Territory. *Med J Aust*. 1992;156:462-468.
11. McKelvie PA. Medical certification of causes of death in an Australian metropolitan hospital: comparison with autopsy findings and a critical review. *Med J Aust*. 1993;158:816-821.
12. Moussa MAA, Shafie MZ, Khogali MM, et al. Reliability of death certificate diagnoses. *J Clin Epidemiol*. 1990;43:1285-1295.
13. Nielsen GP, Bjornsson J, Jonasson JG. The accuracy of death certificates: implications for health statistics. *Virchows Arch A Pathol Anat Histopathol*. 1991; 419:143-146.
14. Hanzlick R. Protocol for writing cause-of-death statements for deaths due to natural causes. *Arch Intern Med*. 1996;156:25-26.
15. Hanzlick R. Principle for including or excluding "mechanisms" of death when writing cause-of-death statements. *Arch Pathol Lab Med*. 1997;121:377-380.
16. Kircher T, Anderson RE. Cause of death: proper completion of the death certificate. *JAMA*. 1987;258:349-352.
17. Barber JB. Improving accuracy of death certificates. *J Natl Med Assoc*. 1990; 84:1007-1008.
18. Hanzlick R. Death certificates: the need for further guidance. *Am J Forensic Med Pathol*. 1993;14:249-252.
19. Feinstein AR. Epidemiologic and clinical challenges in reviving the necropsy. *Arch Pathol Lab Med*. 1996;120:749-752.
20. AMA Council on Scientific Affairs. Autopsy: a comprehensive review of current issues. *Arch Pathol Lab Med*. 1996;120:721-726.
21. Smith AE, Hutchins GM. Case of the month: making amends. *Arch Intern Med*. 1998;158:1739-1740.

Correction

Error in Byline and Affiliation Footnote. In the Special Article by Ladenson et al titled "American Thyroid Association Guidelines for Detection of Thyroid Dysfunction" published in the June 12 issue of the ARCHIVES (2000;160:1573-1575), an error occurred in the byline and in the affiliation footnote on page 1573. Harvey D. Cohen, MD, should have been added to the author byline, and Harvey D. Cohen, MD, Rancho Cuchamonga, Calif, should have been added to the affiliation footnote.