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CLINICAL PRACTICE GUIDELINES FOR HYPOTHYROIDISM IN ADULTS: COSPONSORED BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN THYROID ASSOCIATION

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ABSTRACT

Objective: Hypothyroidism has multiple etiologies and manifestations. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions. This paper describes evidence-based clinical guidelines for the clinical management of hypothyroidism in ambulatory patients.

Methods: The development of these guidelines was commissioned by the American Association of Clinical Endocrinologists (AACE) in association with American Thyroid Association (ATA). AACE and the ATA assembled a task force of expert clinicians who authored this article. The authors examined relevant literature and took an evidence-based medicine approach that incorporated their knowledge and experience to develop a series of specific recommendations and the rationale for these recommendations. The strength of the recommendations and the quality of evidence supporting each was rated according to the approach outlined in the American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Guidelines—2010 update.

Results: Topics addressed include the etiology, epidemiology, clinical and laboratory evaluation, management, and consequences of hypothyroidism. Screening, treatment of subclinical hypothyroidism, pregnancy, and areas for future research are also covered.

Conclusions: Fifty-two evidence-based recommendations and subrecommendations were developed to aid in the care of patients with hypothyroidism and to share what the authors believe is current, rational, and optimal medical practice for the diagnosis and care of hypothyroidism. A serum thyrotropin is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinical situations. The standard treatment is replacement with L-thyroxine. The decision to treat subclinical hypothyroidism when the serum thyrotropin is less than 10 mIU/L should be tailored to the individual patient.

INTRODUCTION

These updated clinical practice guidelines (CPGs) (1–3) summarize the recommendations of the authors, acting as a joint American Association of Clinical Endocrinologists (AACE) and American Thyroid Association (ATA) task force for the diagnostic evaluation and treatment strategies for adults with hypothyroidism, as mandated by the Board of Directors of AACE and the ATA.

The ATA develops CPGs to provide guidance and recommendations for particular practice areas concerning thyroid disease, including thyroid cancer. The guidelines are not inclusive of all proper approaches or methods, or exclusive of others. the guidelines do not establish a standard of care, and specific outcomes are not guaranteed. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual

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circumstances. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients (for detailed information regarding ATA guidelines, see the Supplementary Data, available online at www.liebertpub.com/thy).

The AACE Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision making for specific clinical conditions. Most of their content is based on literature reviews. In areas of uncertainty, professional judgment is applied (for detailed information regarding AACE guidelines, see the Supplementary Data).

These guidelines are a document that reflects the current state of the field and are intended to provide a working document for guideline updates since rapid changes in this field are expected in the future. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

The guidelines presented here principally address the management of ambulatory patients with biochemically confirmed primary hypothyroidism whose thyroid status has been stable for at least several weeks. They do not deal with myxedema coma. The interested reader is directed to the other sources for this information (4). The organization of the guidelines is presented in Table 1.

Serum thyrotropin (TSH) is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinical situations, but it is not sufficient for assessing hospitalized patients or when central hypothyroidism is either present or suspected. The standard treatment is replacement with L-thyroxine which must be tailored to the individual patient. The therapy and diagnosis of subclinical hypothyroidism, which often remains undetected, is discussed. L-triiodothyronine in combination with L-thyroxine for treating hypothyroidism, thyroid hormone for conditions other than hypothyroidism, and nutraceuticals are considered.

METHODS

This CPG adheres to the 2010 AACE Protocol for Standardized Production of Clinical Practice Guidelines published in *Endocrine Practice* (5). This updated protocol describes a more transparent methodology of rating the clinical evidence and synthesizing recommendation grades. The protocol also stipulates a rigorous multilevel review process.

The process was begun by developing an outline for reviewing the principal clinical aspects of hypothyroidism. Computerized and manual searching of the medical literature and various databases, primarily including Medline®, was based on specific section titles, thereby avoiding inclusion of unnecessary detail and exclusion of important studies. Compilation of the bibliography was a continual and dynamic process. Once the principal clinical aspects of hypothyroidism were defined, questions were formulated with the intent to then develop recommendations that addressed these questions. The grading of recommendations was based on consensus among the authors.

The final document was approved by the American Association of Clinical Endocrinologists (AACE) and American Thyroid Association (ATA), and was officially endorsed by the American Association of Diabetes Educators (AADE), American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS), American College of Endocrinology (ACE), Italian Association of Clinical Endocrinologists (AME), American Society for Metabolic & Bariatric Surgery (ASMBS), The Endocrine Society of Australia (ESA), International Association of Endocrine Surgeons (IAES), Latin American Thyroid Society (LATS), and Ukranian Association of Endocrine Surgeons (UAES).

Objectives

The purpose of these guidelines is to present an updated evidence-based framework for the diagnosis, treatment, and follow-up of patients with hypothyroidism.

Guidelines for CPGs

Current guidelines for CPGs in clinical medicine emphasize an evidence-based approach rather than simply expert opinion (6). Even though a purely evidence-based approach is not applicable to all actual clinical scenarios, we have incorporated this into these CPGs to provide objectivity.

Levels of scientific substantiation and recommendation grades (transparency)

All clinical data that are incorporated in these CPGs have been evaluated in terms of levels of scientific substantiation. The detailed methodology for assigning evidence levels (ELs) to the references used in these CPGs has been reported by Mechanick *et al*. (7), from which Table 2 is taken. The authors' EL ratings of the references are included in the References section. The four-step approach that the authors used to grade recommendations is summarized in Tables 3, 4, 5, and 6 of the 2010 Standardized Production of Clinical Practice Guidelines (5), from which Table 3 is taken. By explicitly providing numerical and semantic descriptors of the clinical evidence as well as relevant subjective factors and study flaws, the updated protocol has greater transparency than the 2008 AACE protocol described by Mechanick *et al*. (7).

In these guidelines, the grading system used for the recommendations does not reflect the instruction of the recommendation, but the strength of the recommendation.

Table 1
Organization of Clinical Practice Guidelines for Hypothyroidism in Adults

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Table 1 ***(Continued)***

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Note: When referring to therapy and therapeutic preparations in the recommendations and elsewhere, L-thyroxine and L-triiodothyronine are generally used instead of their respective hormonal equivalents, T_4 and T_3.

Abbreviations: AACE = American Association of Clinical Endocrinologists; ATA = American Thyroid Association; CPG = Clinical Practice Guideline; RAI = radioactive iodine; T_3 = triiodothyronine; T_4 = thyroxine; TPOAb = anti-thyroid peroxidase antibodies; TRIAC = 3,5,3´-triiodothyroacetic acid; TSH = thyrotropin; TSHRAb, TSH receptor antibodies.

For example in some grading systems "should not" implies that there is substantial evidence to support a recommendation. However the grading method employed in this guideline enables authors to use this language even when the best evidence level available is "expert opinion." Although different grading systems were employed, an effort was made to make these recommendations consistent with related portions of "Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists" (8,9), as well as the "Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum" (10).

The shortcomings of this evidence-based methodology in these CPGs are that many recommendations are based on weak scientific data (Level 3) or consensus opinion (Level 4), rather than strong scientific data (Levels

Table 2
Levels of Scientific Substantiation in Evidence-Based Medicine*

Level	Description	Comments
1	Prospective, randomized, controlled trials—large	Data are derived from a substantial number of trials with adequate statistical power involving a substantial number of outcome data subjects.
		Large meta-analyses using raw or pooled data or incorporating quality ratings
		Well-controlled trial at one or more centers
		Consistent pattern of findings in the population for which the recommendation is made (generalizable data).
		Compelling nonexperimental, clinically obvious, evidence (e.g., thyroid hormone treatment for myxedema coma), "all-or-none" indication
2	Prospective controlled trials with or without randomization—limited body of outcome data	Limited number of trials, small population sites in trials
		Well-conducted single-arm prospective cohort study
		Limited but well-conducted meta-analyses
		Inconsistent findings or results not representative for the target population
		Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials
		Uncontrolled or poorly controlled trials
		Any randomized clinical trial with one or more major or three or more minor methodological flaws
		Retrospective or observational data
		Case reports or case series
		Conflicting data with weight of evidence unable to support a final recommendation
4	Expert opinion	Inadequate data for inclusion in level 1, 2, or 3; necessitates an expert panel's synthesis of the literature and a consensus
		Experience based
		Theory driven

*Levels 1, 2, and 3 represent a given level of scientific substantiation or proof. Level 4 or Grade D represents unproven claims. It is the "best evidence" based on the individual ratings of clinical reports that contributes to a final grade recommendation.
Source: Mechanick *et al*., 2008 (7).

1 and 2). There are also the problems of (i) subjectivity on the part of the authors when weighing positive and negative, or epidemiologic versus experimental, data in order to arrive at an evidence-based recommendation grade or consensus opinion, (ii) subjectivity on the part of the authors when weighing subjective attributes, such as cost effectiveness and risk-to-benefit ratios, in order to arrive at an evidence-based recommendation grade or consensus opinion, (iii) potentially incomplete review of the literature by the authors despite extensive diligence, and (iv) bias in the available publications, which originate predominantly from experienced clinicians and large academic medical centers and may, therefore, not reflect the experience at large. The authors, through an *a priori* methodology and multiple levels of review, have tried to address these shortcomings by discussions with three experts (see *Acknowledgments*).

Summary of recommendation grades

The recommendations are evidence-based (Grades A, B, and C) or based on expert opinion because of a lack of conclusive clinical evidence (Grade D). The "best evidence" rating level (BEL), which corresponds to the best conclusive evidence found, accompanies the recommendation grade. Details regarding the mapping of clinical evidence ratings to these recommendation grades have already been provided [see *Levels of scientific substantiation and recommendation grades (transparency)*]. In this CPG, a substantial number of recommendations are upgraded or downgraded because the conclusions may not apply in other situations (non-generalizability). For example, what applies to an elderly population with established cardiac disease may not apply to a younger population without cardiac risk factors. Whenever expert opinions resulted in upgrading or downgrading a recommendation, it is explicitly stated after the recommendation.

TOPICS RELATING TO HYPOTHYROIDISM

Epidemiology

Hypothyroidism may be either subclinical or overt. Subclinical hypothyroidism is characterized by a serum TSH above the upper reference limit in combination with a normal free thyroxine (T_4). This designation is only applicable when thyroid function has been stable for weeks or more, the hypothalamic-pituitary-thyroid axis is normal, and there is no recent or ongoing severe illness. An elevated TSH, usually above 10 mIU/L, in combination with a subnormal free T_4 characterizes overt hypothyroidism.

The results of four studies are summarized in Table 4. The National Health and Nutrition Examination Survey (NHANES III) studied an unselected U.S. population over

Table 3
Grade-Recommendation Protocol

2010 AACE Protocol for Production of Clinical Practice Guidelines—Step III: Grading of recommendations; How different evidence levels can be mapped to the same recommendation grade

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping[a]	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1,2,3,4	N/A	No	Adjust down	D

Adopted by the AACE and the ATA for the Hypothyroidism CPG.
[a]Starting with the left column, best evidence levels (BELs) subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D.
Source: Mechanick *et al.*, 2010 (5).
N/A, not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).

age 12 between 1988 and 1994, using the upper limit of normal for TSH as 4.5 mIU/mL (11). The prevalence of subclinical disease was 4.3% and overt disease 0.3%. The Colorado thyroid disease prevalence survey, in which self-selected individuals attending a health fair were tested and an upper normal TSH value of 5.0 mIU/L was used, reported a prevalence of 8.5% and 0.4% for subclinical and overt disease, respectively, in people not taking thyroid hormone (12). In the Framingham study, 5.9% of women and 2.3% of men over the age of 60 years had TSH values over 10 mIU/L, 39% of whom had subnormal T_4 levels (13). In the British Whickham survey 9.3% of women and 1.2% of men had serum TSH values over 10 mIU/L (14,15). The incidence of hypothyroidism in women was 3.5 per 1000 survivors per year and in men it was 0.6 per 1000 survivors per year. The risk of developing hypothyroidism in women with positive antibodies and elevated TSH was 4% per year versus 2%-3% per year in those with either alone (14,15). In men the relative risk rose even more in each category, but the rates remained well below those of women.

Primary and secondary etiologies of hypothyroidism

Environmental iodine deficiency is the most common cause of hypothyroidism on a worldwide basis (16). In areas of iodine sufficiency, such as the United States, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Autoimmune thyroid diseases (AITDs) have been estimated to be 5-10 times more common in women than in men. The ratio varies from series to series and is dependent on the definition of disease, whether it is clinically evident or not. In the Whickham survey (14), for example, 5% of women and 1% of men had both positive antibody tests and a serum TSH value >6. This form of AITD (i.e., Hashimoto's thyroiditis, chronic autoimmune thyroiditis) increases in frequency with age (11), and is more common in people with other autoimmune diseases and their families (17-25). Goiter may or may not be present.

AITDs are characterized pathologically by infiltration of the thyroid with sensitized T lymphocytes and serologically by circulating thyroid autoantibodies. Autoimmunity to the thyroid gland appears to be an inherited defect in immune surveillance, leading to abnormal regulation of immune responsiveness or alteration of presenting antigen in the thyroid (26,27).

One of the keys to diagnosing AITDs is determining the presence of elevated anti-thyroid antibody titers which include anti-thyroglobulin antibodies (TgAb), anti-microsomal/anti-thyroid peroxidase antibodies (TPOAb), and TSH receptor antibodies (TSHRAb). Many patients with chronic autoimmune thyroiditis are biochemically euthyroid. However, approximately 75% have elevated anti-thyroid antibody titers. Once present, these antibodies generally persist, with spontaneous disappearance occurring infrequently. Among the disease-free population in the NHANES survey, tests for TgAb were positive in 10.4% and TPOAb in 11.3%. These antibodies were more common in women than men and increased with age. Only positive TPOAb tests were significantly associated with hypothyroidism (11). The presence of elevated TPOAb titers in patients with subclinical hypothyroidism helps to predict progression to overt hypothyroidism—4.3% per year with TPOAb vs. 2.6% per year without elevated TPOAb titers (14,28). The higher risk of developing overt hypothyroidism in TPOAb-positive patients is the reason that several professional societies and many clinical endocrinologists endorse measurement of TPOAbs in those with subclinical hypothyroidism.

In patients with a diffuse, firm goiter, TPOAb should be measured to identify autoimmune thyroiditis. Since non-immunologically mediated multinodular goiter is rarely associated with destruction of functioning tissue and progression to hypothyroidism (29), it is important to identify those patients with the nodular variant of autoimmune thyroiditis in whom these risks are significant. In some cases, particularly in those with thyroid nodules, fine-needle

Table 4
Prevalence of Hypothyroidism

Study	Subclinical	Overt	TSH	Comment
NHANES III	4.3%	0.3%	4.5	
Colorado Thyroid Disease Prevalence	8.5%	0.4%	5.0	Not on thyroid hormone
Framingham			10.0	Over age 60 years: 5.9% women; 2.3% men; 39% of whom had subnormal T_4
British Whickham			10.0	9.3% women; 1.2% men

Sources: Hollowell *et al.*, 2002 (11); Canaris *et al.*, 2000 (12); Sawin *et al.*, 1985 (13); Vanderpump *et al.*, 1995 (14); Vanderpump and Tunbridge, 2002 (15).
Abbreviations: NHANES = National Health and Nutrition Examination Survey.

aspiration (FNA) biopsy helps confirm the diagnosis and to exclude malignancy. Also, in patients with documented hypothyroidism, measurement of TPOAb identifies the cause.

In the presence of other autoimmune disease such as type 1 diabetes (20,21) or Addison's disease (17,18), chromosomal disorders such as Down's (30) or Turner's syndrome (31), and therapy with drugs such as lithium (32-34), interferon alpha (35,36), and amiodarone (37) or excess iodine ingestion (e.g., kelp) (38-40), TPOAb measurement may provide prognostic information on the risk of developing hypothyroidism.

TSHRAb may act as a TSH agonist or antagonist (41). Thyroid stimulating immunoglobulin (TSI) and/or thyrotropin binding inhibitory immunoglobulin (TBII) levels, employing sensitive assays, should be measured in euthyroid or L-thyroxine-treated hypothyroid pregnant women with a history of Graves' disease because they are predictors of fetal and neonatal thyrotoxicosis (42). Since the risk for thyrotoxicosis correlates with the magnitude of elevation of TSI, and since TSI levels tend to fall during the second trimester, TSI measurements are most informative when done in the early third trimester. The argument for measurement earlier in pregnancy is also based, in part, on determining whether establishing a surveillance program for ongoing fetal and subsequent neonatal thyroid dysfunction is necessary (43).

Hypothyroidism may occur as a result of radioiodine or surgical treatment for hyperthyroidism, thyroid cancer, or benign nodular thyroid disease and after external beam radiation for non-thyroid-related head and neck malignancies, including lymphoma. A relatively new pharmacologic cause of iatrogenic hypothyroidism is the tyrosine kinase inhibitors, most notably sunitinib (44,45), which may induce hypothyroidism through reduction of glandular vascularity and induction of type 3 deiodinase activity.

Central hypothyroidism occurs when there is insufficient production of bioactive TSH (46,47) due to pituitary or hypothalamic tumors (including craniopharyngiomas), inflammatory (lymphocytic or granulomatous hypophysitis) or infiltrative diseases, hemorrhagic necrosis (Sheehan's syndrome), or surgical and radiation treatment for pituitary or hypothalamic disease. In central hypothyroidism, serum TSH may be mildly elevated, but assessment of serum free T_4 is usually low, differentiating it from subclinical primary hypothyroidism.

Consumptive hypothyroidism is a rare condition that may occur in patients with hemangiomata and other tumors in which type 3 iodothyronine deiodinase is expressed, resulting in accelerated degradation of T_4 and triiodothyronine (T_3) (48,49).

Disorders associated with hypothyroidism

The most common form of thyroid failure has an autoimmune etiology. Not surprisingly, there is also an increased frequency of other autoimmune disorders in this population such as type 1 diabetes, pernicious anemia, primary adrenal failure (Addison's disease), myasthenia gravis, celiac disease, rheumatoid arthritis, systemic lupus erythematosis (17-25), and rarely thyroid lymphoma (50).

Distinct genetic syndromes with multiple autoimmune endocrinopathies have been described, with some overlapping clinical features. The presence of two of the three major characteristics is required to diagnose the syndrome

Table 5
Factors that Alter Thyroxine and Triiodothyronine Binding in Serum

Increased TBG	Decreased TBG	Binding inhibitors
Inherited	Inherited	Salicylates
Pregnancy	Androgens	Furosemide
Neonatal state	Anabolic steroids	Free fatty acids
Estrogens	Glucocorticoids	Phenytoin
Hepatitis	Severe illness	Carbamazepine
Porphyria	Hepatic failure	NSAIDs (variable, transient)
Heroin	Nephrosis	Heparin
Methadone	Nicotinic acid	
Mitotane	L-Asparaginase	
5-Fluorouracil		
SERMS (e.g., tamoxifen, raloxifene)		
Perphanazine		

Abbreviations: TBG = T_4-binding globulin; SERMS = selective estrogen receptor modulators; NSAIDs = nonsteroidal anti-inflammatory drugs.

of multiple autoimmune endocrinopathies (MAEs). The defining major characteristics for type 1 MAE and type 2 MAE are as follows:

- Type 1 MAE: Hypoparathyroidism, Addison's disease, and mucocutaneous candidiasis caused by mutations in the autoimmune regulator gene (AIRE), resulting in defective AIRE protein (51). Autoimmune thyroiditis is present in about 10%-15% (52).
- Type 2 MAE: Addison's disease, autoimmune thyroiditis, and type 1 diabetes known as Schmidt's syndrome (53).

When adrenal insufficiency is present, the diagnosis of subclinical hypothyroidism should be deferred until after glucocorticoid therapy has been instituted because TSH levels may be elevated in the presence of untreated adrenal insufficiency and may normalize with glucocorticoid therapy (54,55) (see *L-thyroxine treatment of hypothyroidism*).

Signs and symptoms of hypothyroidism

The well-known signs and symptoms of hypothyroidism tend to be more subtle than those of hyperthyroidism. Dry skin, cold sensitivity, fatigue, muscle cramps, voice changes, and constipation are among the most common. Less commonly appreciated and typically associated with severe hypothyroidism are carpal tunnel syndrome, sleep apnea, pituitary hyperplasia that can occur with or without hyperprolactinemia and galactorrhea, and hyponatremia that can occur within several weeks of the onset of profound hypothyroidism. Although, for example, in the case of some symptoms such as voice changes subjective (12,56) and objective (57) measures differ. Several rating scales (56,58,59) have been used to assess the presence and, in some cases, the severity of hypothyroidism, but have low sensitivity and specificity. While the exercise of calculating clinical scores has been largely superseded by sensitive thyroid function tests, it is useful to have objective clinical measures to gauge the severity of hypothyroidism. Early as well as recent studies strongly correlate the degree of hypothyroidism with ankle reflex relaxation time, a measure rarely used in current clinical practice today (60).

Normalization of a variety of clinical and metabolic end points including resting heart rate, serum cholesterol, anxiety level, sleep pattern, and menstrual cycle abnormalities including menometrorrhagia are further confirmatory findings that patients have been restored to a euthyroid state (61-65). Normalization of elevated serum creatine kinase or other muscle (66) or hepatic enzymes following treatment of hypothyroidism (67) are additional, less well-appreciated and also nonspecific therapeutic endpoints.

Measurement of T_4 and T_3

T_4 is bound to specific binding proteins in serum. These are T_4-binding globulin (TBG) and, to a lesser extent, transthyretin or T_4-binding prealbumin and albumin. Since approximately 99.97% of T_4 is protein-bound, levels of serum total T_4 will be affected by factors that alter binding independent of thyroid disease (Table 5) (68,69). Accordingly, methods for assessing (including estimating and measuring) serum free T_4, which is the metabolically available moiety (70), have been developed, and assessment of serum free T_4 has now largely replaced measurement of serum total T_4 as a measure of thyroid status. These methods include the serum free T_4 index, which is derived as the product of total T_4 and a thyroid hormone binding ratio, and the direct immunoassay of free T_4 after ultrafiltration or equilibrium dialysis of serum or after addition of anti-T_4 antibody to serum (71).

Table 6
Assessment of Free Thyroxine

Test	Method	Comments
Free T_4 index or free T_4 estimate	Product of total T_4 and thyroid hormone binding ratio or T_3-resin uptake	Normal values in pregnancy and with alterations in TBG binding;
Direct immunoassay of free T_4	With physical separation using equilibrium dialysis or ultrafiltration	Reduced values in pregnancy compared to nonpregnant reference ranges; normal values with alterations in TBG binding
Direct immunoassay of free T_4	Without physical separation using anti-T_4 antibody	Reduced values in pregnancy compared to nonpregnant reference ranges; normal values with alterations in TBG binding

Abbreviations: TBG = T_4-binding globulin

A subnormal assessment of serum free T_4 serves to establish a diagnosis of hypothyroidism, whether primary, in which serum TSH is elevated, or central, in which serum TSH is normal or low (46,47). An assessment of serum free T_4 (Table 6) is the primary test for detecting hypothyroidism in antithyroid drug-treated or surgical or radioiodine-ablated patients with previous hyperthyroidism in whom serum TSH may remain low for many weeks to months.

In monitoring patients with hypothyroidism on L-thyroxine replacement, blood for assessment of serum free T_4 should be collected before dosing because the level will be transiently increased by up to 20% after L-thyroxine administration (72). In one small study of athyreotic patients, serum total T_4 levels increased above baseline by 1 hour and peaked at 2.5 hours, while serum free T_4 levels peaked at 3.5 hours and remained higher than baseline for 9 hours (72).

In pregnancy, measurement of serum total T_4 is recommended over direct immunoassay of serum free T_4. Because of alterations in serum proteins in pregnancy, direct immunoassay of free T_4 may yield lower values based on reference ranges established with normal nonpregnant sera. Moreover, many patients will have values below the nonpregnant reference range in the third trimester, including values obtained with equilibrium dialysis (73). Finally, method-specific and trimester-specific reference ranges for direct immunoassay of free T_4 have not been generally established. By contrast, total T_4 increases during the first trimester and the reference range is ~1.5-fold that of the nonpregnant range throughout pregnancy (73,74).

As is the case with T_4, T_3 is also bound to serum proteins, principally TBG, but to a lesser extent than T_4, ~99.7%. Methods for assessing free T_3 concentration by direct immunoassay have been developed and are in current use (71). However, serum T_3 measurement, whether total or free, has limited utility in hypothyroidism because levels are often normal due to hyperstimulation of the remaining functioning thyroid tissue by elevated TSH and to up-regulation of type 2 iodothyronine deiodinase (75). Moreover, levels of T_3 are low in the absence of thyroid disease in patients with severe illness because of reduced peripheral conversion of T_4 to T_3 and increased inactivation of thyroid hormone (76,77).

Pitfalls encountered when interpreting serum TSH levels

Measurement of serum TSH is the primary screening test for thyroid dysfunction, for evaluation of thyroid hormone replacement in patients with primary hypothyroidism, and for assessment of suppressive therapy in patients with follicular cell-derived thyroid cancer. TSH levels vary diurnally by up to approximately 50% of mean values (78), with more recent reports indicating up to 40% variation on specimens performed serially during the same time of day (79). Values tend to be lowest in the late afternoon and highest around the hour of sleep. In light of this, variations of serum TSH values within the normal range of up to 40%-50% do not necessarily reflect a change in thyroid status.

TSH secretion is exquisitely sensitive to both minor increases and decreases in serum free T_4, and abnormal TSH levels occur during developing hypothyroidism and hyperthyroidism before free T_4 abnormalities are detectable (80). According to NHANES III (11), a disease-free population, which excludes those who self-reported thyroid disease or goiter or who were taking thyroid medications, the upper normal of serum TSH levels is 4.5 mIU/L. A "reference population" taken from the disease-free population composed of those who were not pregnant, did not have laboratory evidence of hyperthyroidism or hypothyroidism, did not have detectable TgAb or TPOAb, and were not taking estrogens, androgens, or lithium had an upper normal TSH value of 4.12 mIU/L. This was further supported by the Hanford Thyroid Disease Study, which analyzed a cohort without evidence of thyroid disease, were seronegative for thyroid autoantibodies, were not on thyroid medications, and had normal thyroid ultrasound examinations (which did not disclose nodularity or evidence of thyroiditis) (81). This upper normal value, however, may not apply to iodine insufficient regions even after becoming iodine sufficient for 20 years (82,83).

More recently (84) the NHANES III reference population was further analyzed and normal ranges based on age, U.S. Office of Management of Budget "Race and Ethnicity" categories, and sex were determined. These indicated the 97.5th percentile TSH values as low as 3.24 for African Americans between the ages of 30 and 39 years and as high as 7.84 for Mexican Americans ≥80 years of age. For every 10-year age increase after 30-39 years, the 97.5th percentile of serum TSH increases by 0.3 mIU/L. Body weight, anti-thyroid antibody status, and urinary iodine had no significant impact on these ranges.

The National Academy of Clinical Biochemists, however, indicated that 95% of individuals without evidence of thyroid disease have TSH concentrations below 2.5 mIU/L (85), and it has been suggested that the upper limit of the TSH reference range be lowered to 2.5 mIU/L (86). While many patients with TSH concentrations in this range do not develop hypothyroidism, those patients with AITD are much more likely to develop hypothyroidism, either subclinical or overt (87) (see *Therapeutic endpoints in the treatment of hypothyroidism* for further discussion).

In individuals without serologic evidence of AITD, TSH values above 3.0 mIU/L occur with increasing frequency with age, with elderly (>80 years of age) individuals having a 23.9% prevalence of TSH values between 2.5 and 4.5 mIU/L, and a 12% prevalence of TSH concentrations above 4.5 mIU/L (88). Thus, very mild TSH elevations in older individuals may not reflect subclinical

thyroid dysfunction, but rather be a normal manifestation of aging. The caveat is that while the normal TSH reference range—particularly for some subpopulations—may need to be narrowed (85,86), the normal reference range may widen with increasing age (84). Thus, not all patients who have mild TSH elevations are hypothyroid and therefore would not require thyroid hormone therapy.

There are other pitfalls in the interpretation of the serum TSH because abnormal levels are observed in various nonthyroidal states. Serum TSH may be suppressed in hospitalized patients with acute illness, and levels below 0.1 mIU/L in combination with subnormal free T_4 estimates may be seen in critically ill patients, especially in those receiving dopamine infusions (89) or pharmacologic doses of glucocorticoids (90). In addition, TSH levels may increase to levels above normal, but generally below 20 mIU/L during the recovery phase from nonthyroidal illness (91). Thus, there are limitations to TSH measurements in hospitalized patients and, therefore, they should be only performed if there is an index of suspicion for thyroid dysfunction (76).

Serum TSH typically falls, but infrequently to below 0.1 mU/L, during the first trimester of pregnancy due to the thyroid stimulatory effects of human chorionic gonadotropin and returns to normal in the second trimester (10) (see Table 7).

TSH secretion may be inhibited by administration of subcutaneous octreotide, which does not cause persistent central hypothyroidism (92), and by oral bexarotene, which almost always does (93). In addition, patients with anorexia nervosa may have low TSH levels in combination with low levels of free T_4 (94), mimicking what may be seen in critically ill patients and in patients with central hypothyroidism due to pituitary and hypothalamic disorders.

Patients with nonfunctioning pituitary adenomas, with central hypothyroidism, may have mildly elevated serum TSH levels, generally not above 6 or 7 mIU/L, due to secretion of bioinactive isoforms of TSH (47). TSH levels may also be elevated in association with elevated serum thyroid hormone levels in patients with resistance to thyroid hormone (95). Heterophilic or interfering antibodies, including human antianimal (most commonly mouse) antibodies, rheumatoid factor, and autoimmune anti-TSH antibodies may cause falsely elevated serum TSH values (96). Lastly, adrenal insufficiency, as previously noted in *Disorders associated with hypothyroidism*, may be associated with TSH elevations that are reversed with glucocorticoid replacement (54,55).

Table 7
Thyrotropin Upper Normal

Group, study, society	TSH upper normal	Comments
NACB	2.5	When there is no evidence of thyroid disease
NHANES III, disease free	4.5	No self-reported thyroid disease Not on thyroid medications
NHANES III, reference population	4.12	No self-reported thyroid disease Not on thyroid medications Negative anti-thyroid antibodies Not pregnant Not on estrogens, androgens, lithium
Hanford Thyroid Disease Study	4.10	No evidence of thyroid disease Negative anti-thyroid antibodies Not on thyroid medications Normal ultrasound (no nodules or thyroiditis)
Pregnancy, first trimester	2.0-2.5	See sections *L-thyroxine treatment of hypothyroidism* and *Hypothyroidism during pregnancy*
Pregnancy, second trimester	3.0	See sections *L-thyroxine treatment of hypothyroidism* and *Hypothyroidism during pregnancy*
Pregnancy, third trimester	3.5	See sections *L-thyroxine treatment of hypothyroidism* and *Hypothyroidism during pregnancy*

Sources: Stagnaro-Green et al., 2011 (10); Hollowell et al., 2002 (11); Hamilton et al., 2008 (81); Baloch et al., 2003 (85).
NACB, National Academy of Clinical Biochemists; NHANES, National Health and Nutrition Examination Survey

Other diagnostic tests for hypothyroidism

Prior to the advent of routine validated chemical measurements of serum thyroid hormones and TSH, tests that correlated with thyroid status, but not sufficiently specific to diagnose hypothyroidism, were used to diagnose hypothyroidism and to gauge the response to thyroid hormone therapy. The following are previous notable and more recent examples:

- Basal metabolic rate was the "gold standard" for diagnosis. Extremely high and low values correlate well with marked hyperthyroidism and hypothyroidism, respectively, but are affected by many unrelated, diverse conditions, such as fever, pregnancy, cancer, acromegaly, hypogonadism, and starvation (97,98).
- Decrease in sleeping heart rate (61)
- Elevated total cholesterol (62,99) as well as low-density lipoprotein (LDL) (99,100) and the highly atherogenic subfraction Lp (a) (101)
- Delayed Achilles reflex time (60)
- Increased creatine kinase due to an increase in the MM fraction, which can be marked and lead to an increase in the MB fraction. There is a less marked increase in myoglobin (66) and no change in troponin levels even in the presence of an increased MB fraction (102).
-

Screening and aggressive case finding for hypothyroidism

Criteria for population screening include:

- A condition that is prevalent and an important health problem
- Early diagnosis is not usually made
- Diagnosis is simple and accurate
- Treatment is cost effective and safe

Despite this seemingly straightforward guidance, expert panels have disagreed about TSH screening of the general population (Table 8). The ATA recommends screening in all adults beginning at age 35 years and every 5 years thereafter (103). AACE recommends routine TSH measurement in older patients—age not specified—especially women (2). The American Academy of Family Physicians recommends routine screening in asymptomatic patients older than age 60 years (104), and the American College of Physicians recommends case finding in women older than 50 years (105). In contrast, a consensus panel (106), the Royal College of Physicians of London (107), and the U.S. Preventive Services Task Force (108) do not recommend routine screening for thyroid disease in adults. For recommendations in pregnancy, see **Recommendations 20.1.1** and **20.1.2**.

While there is no consensus about population screening for hypothyroidism there is compelling evidence to support case finding for hypothyroidism in:

- Those with autoimmune disease, such as type 1 diabetes (20,21)
- Those with pernicious anemia (109,110)
- Those with a first-degree relative with autoimmune thyroid disease (19)
- Those with a history of neck radiation to the thyroid gland including radioactive iodine therapy for hyperthyroidism and external beam radiotherapy for head and neck malignancies (111-113)
- Those with a prior history of thyroid surgery or dysfunction
- Those with an abnormal thyroid examination
- Those with psychiatric disorders (114)
- Patients taking amiodarone (37) or lithium (32-34)
- Patients with ICD-9 diagnoses as presented in Table 9

Table 8
Recommendations of Six Organizations Regarding Screening of Asymptomatic Adults for Thyroid Dysfunction

Organization	Screening recommendations
American Thyroid Association	Women and men >35 years of age should be screened every 5 years.
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened.
American Academy of Family Physicians	Patients ≥60 years of age should be screened.
American College of Physicians	Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated.
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified

When to treat hypothyroidism

Although there is general agreement that patients with primary hypothyroidism with TSH levels above 10 mIU/L should be treated (106,115-117), which patients with TSH levels of 4.5-10 mIU/L will benefit is less certain (118,119). A substantial number of studies have been done on patients with TSH levels between 2.5 and 4.5, indicating beneficial response in atherosclerosis risk factors such as atherogenic lipids (120-123), impaired endothelial function (124,125), and intima media thickness (126). This topic is further discussed in the section *Cardiac benefit from treating subclinical hypothyroidism*. However, there are virtually no clinical outcome data to support treating patients with subclinical hypothyroidism with TSH levels between 2.5 and 4.5 mIU/L. The possible exception to this statement is pregnancy because the rate of pregnancy loss, including spontaneous miscarriage before 20 weeks gestation and stillbirth after 20 weeks, have been reported to be increased in anti-thyroid antibody-negative women with TSH values between 2.5 and 5.0 (127).

L-thyroxine treatment of hypothyroidism

Since the generation of biologically active T_3 by the peripheral conversion of T_4 to T_3 was documented in 1970 (128), L-thyroxine monotherapy has become the mainstay of treating hypothyroidism, replacing desiccated thyroid and other forms of L-thyroxine and L-triiodothyronine combination therapy. Although a similar quality of life (129) and circulating T_3 levels (130) have been reported in patients treated with L-thyroxine compared with individuals without thyroid disease, other studies have not shown levels of satisfaction comparable to euthyroid controls (131). A number of studies, following a 1999 report citing the benefit of L-thyroxine and L-triiodothyronine combination therapy (132), have re-addressed the benefits of synthetic L-thyroxine and L-triiodothyronine combination therapy but have largely failed to confirm an advantage of this approach to improve cognitive or mood outcomes in hypothyroid individuals treated with L-thyroxine alone (133,134).

Yet several matters remain uncertain. What should the ratios of L-thyroxine and L-triiodothyronine replacement be (133)? What is the pharmacodynamic equivalence of L-thyroxine and L-triiodothyronine (135)? It was previously believed to be 1:4, but a recent small study indicated that it was approximately 1:3 (135). Why do some patients prefer combination therapy to L-thyroxine monotherapy (133)? Some insight into the latter question may be gained from a large-scale study of L-thyroxine and L-triiodothyronine combination therapy in which different responses were observed in patients with different genetic subtypes of type 2 deiodinase (136), despite a prior, smaller negative study (137). It is not known if those who responded positively to L-thyroxine and L-triiodothyronine combination therapy will have long-term benefit and whether genotyping patients with hypothyroidism who are clinically and biochemically euthyroid will ultimately reliably identify patients with hypothyroidism who are most likely to benefit from combination therapy.

Treatment of hypothyroidism is best accomplished using synthetic L-thyroxine sodium preparations. Because of the uniqueness of the various tablet formulations and a recently introduced preparation of liquid-containing capsules with the inactive ingredients gelatin, glycerin, and water, and because of uncertainty about the sensitivity of current bioequivalence assessment procedures to assure true interchangability among the tablets, current recommendations encourage the use of a consistent L-thyroxine preparation for individual patients to minimize variability from refill to refill (138,139).

Some reports have indicated an apparent increased dosage requirement for L-thyroxine in some patients with diminished gastric acid secretion (140,141). This has led to *in vitro* work showing significant differences in dissolution among L-thyroxine preparations (142), profiles of which appear to be dependent on the pH of the solution in which the preparations were dissolved. The liquicap preparation (Tirosint®) (143) dissolution profile was the least affected by changes in pH (142). The clinical significance of these

Table 9
ICD-9-CM Codes to Support Thyrotropin Testing

Adrenal insufficiency	255.41
Alopecia	704.00
Anemia, unspecified deficiency	281.9
Cardiac dysrhythmia, unspecified	427.9
Changes in skin texture	782.8
Congestive heart failure	428.0
Constipation	564.00
Dementia	294.8BA
Diabetes mellitus, type 1	250.01
Dysmenorrhea	625.3
Hypercholesterolemia	272.0
Hypertension	401.9
Mixed hyperlipidemia	272.2
Malaise and fatigue	780.79
Myopathy, unspecified	359.9
Prolonged QT interval	794.31
Vitiligo	709.01
Weight gain	783.9M

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification (www.cdc.gov/nchs/icd/cd9cm.htm).

findings remains unclear. In more recent, though short-term studies, the use of histamine H2 receptor blockers and proton pump inhibitors does not appear to influence clinical measures in L-thyroxine tablet-treated patients (144).

Desiccated thyroid has not been systematically studied (see *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*). Absorption studies indicate that the bioavailability of T_3 in desiccated thyroid is comparable to that of orally administered synthetic L-triiodothyronine (145). Therefore, the most commonly used form of desiccated thyroid, known as Armour® Thyroid, which is of porcine origin, may be viewed as a L-thyroxine and L-triiodothyronine combination with a ratio of approximately 4:1 by weight (145). The content of thyroid hormone and the ratio of T_4 to T_3 may vary in desiccated thyroid preparations depending on the brand employed and whether it is of porcine or bovine origin.

The daily dosage of L-thyroxine is dependent on age, sex, and body size (146-151). Ideal body weight is best used for clinical dose calculations because lean body mass is the best predictor of daily requirements (152,153). A recent study, however, which did not subclassify patients on the basis of their initial degree of hypothyroidism, found that while the L-thyroxine dose per ideal body weight or degree of overweight differed by sex—with females having a higher dose requirement than men—it did not confirm that age was an independent predictor of dosage (154).

With little residual thyroid function, replacement therapy requires approximately 1.6 μg/kg of L-thyroxine daily (155,156). Patients who are athyreotic (after total thyroidectomy and/or radioiodine therapy) (157) and those with central hypothyroidism may require higher doses (158), while patients with subclinical hypothyroidism (159-162) or after treatment for Graves' disease (163) may require less. Young healthy adults may be started on full replacement dosage, which is also preferred after planned (in preparation for thyroid cancer imaging and therapy) or short-term inadvertent lapses in therapy. Starting with full replacement versus low dosages leads to more rapid normalization of serum TSH but similar time to symptom resolution (164). However, patients with subclinical hypothyroidism do not require full replacement doses (159). Doses of 25-75 μg daily are usually sufficient for achieving euthyroid levels (160), with larger doses usually required for those presenting with higher TSH values (161). One randomized control trial assigned L-thyroxine doses on the basis of the initial serum TSH values as follows: 25 μg for TSH 4.0-8.0 mIU/L, 50 μg for TSH 8-12 mIU/L, and 75 μg for TSH >12 mIU/L. After 2 months only minimal further adjustments were required to achieve euthyroidism (162).

One recent study demonstrated that L-thyroxine absorption within 30 minutes of breakfast is not as effective as when it is taken 4 hours after the last meal (165). Another study showed that taking it 60 minutes before breakfast on an empty stomach was better than taking it within 2 hours of the last meal of the day, which in turn was better than taking it within 20 minutes of breakfast (166). However, these two studies do not establish which of the two methods, L-thyroxine taken with water 60 minutes before breakfast or at bedtime 4 hours after the last meal on an empty stomach, is superior. Although L-thyroxine is better absorbed when taken 60 minutes before a meal compared to 30 minutes before a meal, compliance may be enhanced by instructing patients to consistently take it with water between 30 and 60 minutes prior to eating breakfast.

L-thyroxine should be stored per product insert at 20°C-25°C, (range, 15°C-30°C) or 68°F-77°F (range, 59°F-86°F) and protected from light and moisture. It should not be taken with substances or medications (see Table 10) that interfere with its absorption or metabolism. Because approximately 70% of an orally administered dose of L-thyroxine is absorbed (167-169), individuals unable to ingest L-thyroxine should initially receive 70% or less of their usual dose intravenously. Crushed L-thyroxine suspended in water should be given to patients receiving enteral feeding through nasogastric and other tubes. For optimal absorption feeding should be interrupted with doses given as long as possible after feeding and at least 1 hour before resuming feeding. Administering intravenous thyroxine solution, which is not universally available, should be considered when feeding may not be interrupted.

Dose adjustments are guided by serum TSH determinations 4-8 weeks (156,170) following initiation of therapy, dosage adjustments, or change in the L-thyroxine preparation (139,171). While TSH levels may decline within a month of initiating therapy with doses of L-thyroxine such as 50 or 75 μg, making adjustments with smaller doses may require 8 weeks or longer before TSH levels begin to plateau (170,172). Increment changes of 12.5-25 μg/d are initially made, but even smaller changes may be necessary to achieve goal TSH levels.

In the case of central hypothyroidism estimates of dosage based on 1.6 μg/kg L-thyroxine daily and assessment of free T_4, not TSH should guide therapy. Determinations are best done prior to taking thyroid hormone. The goal of therapy is generally to attain values above the mean for assays being employed, in keeping with observations that mean values for estimates of free T_4 in patients who are treated with L-thyroxine tend to be higher than mean values observed in untreated controls (150,173-175).

Some clinical manifestations of hypothyroidism, such as chronic skin changes, may take up to 3-6 months to resolve after serum TSH has returned to normal (176).

Once an adequate replacement dosage has been determined most, but not all of us, are of the opinion that periodic follow-up evaluations with repeat TSH testing at 6-month and then 12-month intervals are appropriate (172). Some authors think that more frequent testing is advisable to ensure and monitor compliance with therapy.

Table 10
Agents and Conditions Having an Impact on
L-thyroxine Therapy and Interpretation of Thyroid Tests

10.1. Interference with absorption

Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
Sucralfate
Cation exchange resins (Kayexelate)
Oral bisphosphonates
Proton pump inhibitors
Raloxifene[a]
Multivitamins (containing ferrous sulfate or calcium carbonate)
Ferrous sulfate
Phosphate binders (sevelamer, aluminum hydroxide)
Calcium salts (carbonate, citrate, acetate)
Chromium picolinate
Charcoal
Orlistat[b]
Ciprofloxacin
H2 receptor antagonists[a]
Malabsorption syndromes
- Celiac disease
- Jejunoileal bypass surgery
- Cirrhosis (biliary)
- Achlorhydria

Diet
- Ingestion with a meal
- Grapefruit juice[a]
- Espresso coffee
- High fiber diet
- Soybean formula (infants)
- Soy

10.2. Thyroid gland hormone production and secretion

Direct and indirect effects on the thyroid gland
- Iodine uptake
  - Iodine (including kelp supplements)
  - Amiodarone
  - Ethionamide
  - Iodinated contrast (ipodate,[c] iopanoic acid[c])
  - Perchlorate[c]
- Hormone production
  - Iodine (including kelp supplements)
  - Amiodarone
  - Thionamides (carbimazole, methimazole, propylthiouracil)
  - Iodinated contrast (ipodate,[c] iopanoic acid[c])
  - Sulfonylureas
  - Sulfonamides
  - Ethionamide
- Secretion
  - Lithium
  - Iodine (including kelp supplements)
  - Amiodarone
  - Iodinated contrast (ipodate,[c] iopanoic acid[c])
- Thyroiditis
  - Induces
    - Amiodarone
    - Tyrosine kinase inhibitors (sunitinib, sorafenib)
    - Interferon alpha
    - Interleukins
    - Antiangiogenic (lenalidomide, thalidomide)
    - Lithium
    - Alemtuzumab
    - Denileukin diftitoxin
  - Ameliorates (if autoimmune)
    - Glucocorticoids
- Development of Graves'
  - Interferon alpha
  - HAART (highly active antiretroviral therapy)
  - Alemtuzumab
- Amelioration of Graves'
  - Glucocorticoids

Table 10 ***(Continued)***

10.3. Direct and indirect effects on the hypothalamic-pituitary axis

TSH secretion
- Decrease
  - Bexarotene
  - Dopamine
  - Dopaminergic agonists (bromocriptine, cabergoline)
  - Glucorticoids
  - Thyroid hormone analogues
  - Somatostatin analogues (octreotide, lanreotide)
  - Metformin
  - Opiates (e.g., heroin)
  - Interleukin-6
- Increase
  - Dopamine receptor blockers (metoclopramide)
  - Hypoadrenalism
  - Interleukin 2
  - Amphetamine
  - Ritonavir[b]
  - St. John's Wort[a]

Hypophysitis
- Ipilimumab

10.4. Increased clearance

Phenobarbital
Primidone
Phenytoin
Carbamazepine
Oxacarbazepine[b]
Rifampin
Growth hormone
Sertraline[b]
Tyrosine kinase inhibitors (imatinib,[b] sunitinib)
Quetiapine[b]
Stavudine[b]
Nevirapine[a,b]

10.5. Peripheral metabolism

Glucocorticoids
Amiodarone
Propylthiouracil
Beta blockers (e.g., propranolol, nadolol)
Iodinated contrast (ipodate,[c] iopanoic acid[c])
Interleukin-6
Clomipramine

[a]Impact uncertain
[b]Mechanism uncertain
[c]Not presently available in the United States

Dosage adjustments may be necessary as underlying function wanes. In pregnancy thyroid hormone requirements are increased, then revert back to baseline after delivery (177). Dosage adjustments are also necessary, generally when medications influencing absorption, plasma binding, or metabolism are added or discontinued. When such medications are introduced or discontinued thyroid hormone levels should initially be checked within 4-8 weeks of doing so, and tests performed at least every 4-8 weeks until stable euthyroid indices have been documented while on the same dose of L-thyroxine. Decreases in L-thyroxine requirements occur as patients age (151) and following significant weight loss. Moreover, although elderly patients absorb L-thyroxine less efficiently they often require 20-25% less per kilogram daily than younger patients, due to decreased lean body mass (152,153). Regardless of the degree of hypothyroidism, patients older than 50-60 years, without evidence of coronary heart disease (CHD) may be started on doses of 50 μg daily. Among those with known CHD, the usual starting dose is reduced to 12.5-25 μg/day. Clinical monitoring for the onset of anginal symptoms is essential (178). Anginal symptoms may limit the attainment of euthyroidism. However, optimal medical management of arteriosclerotic cardiovascular disease (ASCVD) should generally allow for sufficient treatment with L-thyroxine to both reduce the serum TSH and maintain the patient angina-free. Emergency coronary artery bypass grafting in patients with unstable angina or left main coronary artery occlusion may be safely performed while the patient is still moderately to severely hypothyroid (179,180) but elective cases should be performed after the patient has become euthyroid.

The exacerbation of adrenal insufficiency was first described in cases of central hypothyroidism over 70 years ago (181). Although it rarely occurs, those with adrenal insufficiency, either primary or central, or at risk for it, should be treated with clinically appropriate doses of hydrocortisone until adrenal insufficiency is ruled out (182,183). In the absence of central hypothyroidism, elevated TSH levels may be seen in conjunction with normal T_4 levels, making it initially indistinguishable from subclinical hypothyroidism. However, when due to adrenal insufficiency elevated TSH levels fall with glucorticoid therapy alone (54,55).

Patients on high doses of L-thyroxine (>200 μg/d) with persistently or frequently elevated TSH levels may be noncompliant or have problems with L-thyroxine absorption (171). The former is much more common (184). Although daily dosing of L-thyroxine is ideal, missed doses should be made up when the omission is recognized, even on the same or subsequent days. In those with significant compliance problems, weekly dosing with L-thyroxine results in similar clinical safety, outcomes, and acceptable TSH values (185). Absorption is diminished by meals (165,166,168,186) and competing medications (see Table 10).

Steps should be taken to avoid overtreatment with L-thyroxine. This has been reported in 20% of those treated with thyroid hormone (12). The principal adverse consequences of subtle or frank overtreatment are cardiovascular (187-190), skeletal (191-194), and possibly affective disturbances (195-197). The elderly are particularly susceptible to atrial fibrillation, while postmenopausal women, who constitute a substantial portion of those on thyroid hormone, are prone to accelerated bone loss.

Therapeutic endpoints in the treatment of hypothyroidism

The most reliable therapeutic endpoint for the treatment of primary hypothyroidism is the serum TSH value. Confirmatory total T_4, free T_4, and T_3 levels do not have sufficient specificity to serve as therapeutic endpoints by themselves, nor do clinical criteria. Moreover, when serum TSH is within the normal range, free T_4 will also be in the normal range. On the other hand, T_3 levels may be in the lower reference range and occasionally mildly subnormal (150).

The normal range for TSH values, with an upper limit of 4.12 mIU/L is largely based on NHANES III (11) data, but it has not been universally accepted. Some have proposed that the upper normal should be either 2.5 or 3.0 mIU/L (86) for a number of reasons:

- The distribution of TSH values used to establish the normal reference range is skewed to the right by values between 3.1 and 4.12 mIU/L.
- The mean and median values of approximately 1.5 mIU/L are much closer to the lower limit of the reported normal reference range than the upper limit.
- When risk factors for thyroid disease are excluded, the upper reference limit is somewhat lower.

The counter arguments are that while many with TSH values between 2.5-3.0 and 4.12 mIU/L may have early hypothyroidism, many do not. Data to support treating patients in this range are lacking, with the exception of data in pregnancy (see *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy). Though patients without thyroid disease have stable mean TSH values, measurements vary up to 50% above (78) and below the mean on a given day. Thus, if the upper normal of TSH were considered to be 2.5 mIU/L, patients with mean values just above the mean NHANES III value of 1.5 mIU/L would frequently be classified as hypothyroid when they are not (78,87). This would lead to more than 10 million additional diagnoses of hypothyroidism in the United States per year—without clear-cut benefit. The controversy has not only contributed to the debate about what TSH values should prompt treatment, but also what the target

TSH should be for patients being treated for hypothyroidism. Data concerning clinical benefit are lacking to support targeting to reach low normal or subnormal TSH levels in the treatment of hypothyroidism (198,199). As a result, in patients who are not pregnant, the target range should be within the normal range. If upper and lower normal values for a third generation TSH assay are not available, the range used should be based on the NHANES III reference population range of 0.45-4.12. Although there are substantial normative data establishing what trimester specific normal ranges are for pregnancy (200-207) (see Table 7, TSH upper range of normal), there are no prospective trials establishing optimal target TSH ranges for patients with hypothyroidism who are pregnant and are being treated with L-thyroxine. The lower range of normal for serum TSH in pregnancy is generally 0.1-0.2 mIU/L lower than the normal range for those who are not pregnant (10).

The appropriate target TSH values treatment for treating patients with differentiated thyroid cancer, goiter, and nodular thyroid disease are beyond the scope of these guidelines.

When to consult an endocrinologist

Although most physicians can diagnose and treat hypothyroidism, consultation with an endocrinologist is recommended in the following situations:

- Children and infants
- Patients in whom it is difficult to render and maintain a euthyroid state
- Pregnancy
- Women planning conception
- Cardiac disease
- Presence of goiter, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine disease such as adrenal and pituitary disorders
- Unusual constellation of thyroid function test results
- Unusual causes of hypothyroidism such as those induced by agents listed in Table 10.

The basis for these recommendations stems from observations that cost-effective diagnostic evaluations and improved outcomes in the medical and surgical evaluation and management of thyroid disorders such as nodular thyroid disease and thyroid cancer are positively correlated with the volume of experience a surgeon has or whether or not the patient was evaluated by an endocrinologist (208-210). In addition, endocrinologists were more knowledgeable about thyroid disease and pregnancy than obstetrician-gynecologists, internists, and family physicians (211). Observational studies comparing care provided by endocrinologists with nonendocrinologists for congenital, pediatric, and central hypothyroidism as well the uncommon, challenging clinical situations just listed, which are regularly addressed by clinical endocrinologists, are lacking, and controlled studies would be unethical.

Concurrent conditions of special significance in hypothyroid patients

Hypothyroidism during pregnancy. Overt untreated hypothyroidism during pregnancy may adversely affect maternal and fetal outcomes. These adverse outcomes include increased incidences of spontaneous miscarriage, preterm delivery, preeclampsia, maternal hypertension, postpartum hemorrhage, low birth weight and stillbirth, and impaired intellectual and psychomotor development of the fetus (212-214). While there is evidence to suggest that subclinical hypothyroidism in early pregnancy may also be associated with impaired intellectual and psychomotor development (215-218), and that this impairment may be prevented with L-thyroxine treatment (217,218), this is not supported by a recent randomized control trial (219). Finally, women with positive TPOAb may have an increased risk for first trimester miscarriage (220), preterm delivery (221), and for offspring with impaired cognitive development (218,222). This risk may be due to reduced thyroid functional reserve from chronic autoimmune thyroiditis leading to subtle hypothyroidism (223). One European study has shown that treatment with L-thyroxine reduced the risk of miscarriage to that of TPOAb-negative euthyroid controls (224). A recent prospective study done in China showed that intellectual and psychomotor development of offspring born to women with positive TPOAb and normal thyroid function who were treated with L-thyroxine by 8 weeks of gestation had intellectual and psychomotor development comparable to controls (218). Finally, treatment with L-thyroxine before conception has been shown to reduce the miscarriage rate and to increase live birth rate in women with subclinical hypothyroidism undergoing assisted reproduction (225).

A sustained rise in serum total T_4 and a drop in serum TSH characterize the early stage of normal pregnancy. Studies of fetal development and at least one outcome study done in Europe suggest that early central nervous system development requires adequate transplacental T_4 transport (226-231). The offspring of mothers with serum T_4 levels in the lowest 10th percentile of the reference range at the end of the first trimester have been reported to have subnormal intellectual development even if TSH levels are normal (228-231). Based on these findings, desiccated thyroid and L-thyroxine/L-triiodothyronine combinations, which cause lowering of serum T_4 levels, should not be used during pregnancy. Furthermore, patients being treated with these preparations should be switched to L-thyroxine when planning to conceive and at the very latest when found to be pregnant. At this time TSH should also be measured. A more recent study done in Greater Boston, which is iodine sufficient, however, did not demonstrate a relationship

between fetal intellectual development and maternal serum T_4 levels (232).

When a woman with hypothyroidism becomes pregnant, the dosage of L-thyroxine should be increased as soon as possible to ensure that serum TSH is <2.5 mIU/L and that serum total T_4 is in the normal reference range for pregnancy. Moreover, when a patient with a positive TPOAb test becomes pregnant, serum TSH should be measured as soon as possible and if >2.5 mIU/L, T_4 treatment should be initiated. Serum TSH and total T_4 measurements should be monitored every 4 weeks during the first half of pregnancy (233) and at least once between 26 and 32 weeks gestation to ensure that the requirement for L-thyroxine has not changed. Some of us would continue to monitor thyroid indices after 32 weeks in order to confirm that thyroid indices are in the normal range. L-thyroxine dosages should be adjusted as indicated, aiming for TSH levels that are within the normal range for that phase of pregnancy (177,200-207,234-238). Some advocate doing so more frequently in order to ensure compliance and the efficacy of dose adjustments, as reflected by dropping TSH levels. Total T_4 increases predictably during pregnancy and, as already noted, the reference range is ~1.5 fold that of the nonpregnant range. Serum TSH levels decline in the first trimester when serum human chorionic gonadotropin levels are high and rise after 10-12 weeks gestation. While the upper limit of normal for the first trimester is generally <2.5 mIU/L respective upper normal values for the second and third trimesters are approximately 3.0 and 3.5 mIU/L.

Diabetes Mellitus. Approximately 10% of patients with type 1 diabetes mellitus will develop chronic thyroiditis (53) during their lifetime, which may lead to the insidious onset of subclinical hypothyroidism. Patients with diabetes should be examined for the presence and development of a goiter. Sensitive TSH measurements should be obtained at regular intervals in patients with type 1 diabetes, especially if a goiter develops or if evidence is found of other autoimmune disorders. In addition, postpartum thyroiditis will develop in up to 25% of women with type 1 diabetes (239).

Infertility. Some patients with infertility and menstrual irregularities have underlying chronic thyroiditis in conjunction with subclinical or overt hypothyroidism. Moreover, TPOAb-positive patients, even when euthyroid, have an excess miscarriage rate (220,224). Typically, these patients seek medical attention because of infertility or a previous miscarriage, rather than hypothyroidism.

A careful, comprehensive history, physical examination, and appropriate laboratory evaluation can identify chronic thyroiditis. It has long been recognized that in some with patients with overt hypothyroidism, thyroid hormone replacement therapy may normalize the menstrual cycle and restore normal fertility (63-65).

Obesity. Hypothyroidism and obesity are often linked at least in the consciousness of the lay public. However, appetite in those with marked hypothyroidism is often suppressed offsetting the impact of a decrease in metabolic rate, myxedema may present with weight loss, and overt hypothyroidism does not appear to be more common in the obese population than in the general population (240). Nonetheless this impression dates back to early observations of significant weight loss following the resolution of myxedema, an effect that was principally the result of fluid mobilization (241). This was recently confirmed in a prospective year-long study of newly diagnosed patients with overt hypothyroidism whose mean TSH levels at the onset of the study was 102 (242). Some observational studies correlate TSH levels with body mass index (243-245) while others do not (246). However, obesity may have an impact on the hypothalamic-pituitary-thyroid axis as evidenced by relatively elevated TSH levels in morbidly obese adults (247) and children (248) who have ultrasound findings suggestive of chronic thyroiditis without either elevated anti-thyroid antibody titers or decreased T_4 and T_3 levels. Caution must therefore be exercised when diagnosing subclinical hypothyroidism in the setting of marked obesity (249).

Apart from the mobilization of fluid and the ensuing diuresis in myxedematous states, however, the impact of thyroid hormone therapy on waist-hip ratio (250) and weight loss (242), even in cases of profound hypothyroidism, appears at most to be modest. This is despite the fact that resting energy expenditure increases significantly in individuals who are rendered subclinically hyperthyroid after being subclinically hypothyroid (251). Clearly behavioral and other physiological factors apart from thyroid status have an impact on weight status. Because of the negative impact on nitrogen balance, cardiovascular factors, bone, and affective status, supraphysiological doses of thyroid hormone as used in the past (252,253) should not be employed as an adjunct to weight loss programs in patients with or without hypothyroidism (254). However, it is advisable to counsel patients about the effect any change in thyroid status may have on weight control. This includes thyroidectomy although recent studies concerning its effect are contradictory (255,256).

Patients with normal thyroid tests. Patients with symptoms of hypothyroidism, but normal thyroid hormone levels do not benefit from treatment with L-thyroxine (257). Moreover, treatment confers a substantial risk of subclinical or overt hyperthyroidism, which in one large-scale study was approximately 20% (12).

Depression. The diagnosis of subclinical or overt hypothyroidism must be considered in every patient with depression. In fact, a small proportion of all patients with depression have primary hypothyroidism—either overt or subclinical. Those with autoimmune disease are more likely to have depression (258) as are those with postpartum thyroiditis regardless of whether the hypothyroidism is treated or not (259).

All patients receiving lithium therapy require periodic thyroid evaluation because lithium may induce goiter and hypothyroidism (32-34). Occasionally in psychiatric practice, some patients who have depression are treated not only with antidepressants but also with thyroid hormone, even though they have normal thyroid function. No firm evidence has shown that thyroid hormone treatment alone does anything to alleviate depression in such patients.

Substantial evidence supports the use of thyroid hormone to treat the mood disturbances associated with hypothyroidism (114). Interesting animal data link the use of both tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) to potential changes in brain thyroid hormone metabolism, which make the combination of L-triiodothyronine with these an appealing therapeutic hypothesis (114). However, the clinical data from randomized controlled trials evaluating the acceleration and augmentation of response with TCA as well as SSRI/L-triiodothyronine combinations are inconsistent (114,260,261) and do not clearly support L-triiodothyronine use in euthyroid depressed subjects.

Nonthyroidal illness. The evaluation of thyroid function in chronically or markedly acutely ill patients may be confusing. Medications, such as glucocorticoids (90), amiodarone (37), and dopamine (89) may have an impact on thyroid hormone levels and in the case of amiodarone, a marked effect on thyroid status. In addition, major illness and starvation may be accompanied by a change in thyroid hormone economy, resulting in a low serum T_3 and normal or low serum T_4 and TSH levels (262,263). Since there is evidence that treatment with either L-thyroxine (264) or L-triiodothyronine (265) is of no benefit, patients who are not clearly hypothyroid should not be treated until their acute medical condition has resolved. A 2010 study showed that infants under 5 months of age undergoing cardiac surgery for complex congenital heart disease benefited from intravenous L-triiodothyronine treatment (266), raising the possibility that under certain circumstances treating nonthyroidal illness with thyroid hormone may be beneficial. In addition, patients with NYHA class III or IV heart failure with low serum T_3 levels have been shown to benefit from intravenous L-triiodothyronine to restore serum T_3 levels to normal (267). Evaluation of the patient by a clinical endocrinologist is appropriate before initiation of thyroid hormone treatment.

Dietary supplements and nutraceuticals in the treatment of hypothyroidism

The majority of dietary supplements (DS) fail to meet a level of scientific substantiation deemed necessary for the treatment of disease (268,269). In the case of hypothyroidism, this is the case for over-the-counter products marketed for "thyroid support" or as a "thyroid supplement" or to promote "thyroid health," among others. The authors do not recommend the use of these or any unproven therapies (269).

DS are generally thought of as various vitamins, minerals, and other "natural" substances, such as proteins, herbs, and botanicals. The U.S. Food and Drug Administration (FDA) 1994 Dietary Supplement Health and Education Act expanded the definition of DS as follows (270):

DSHEA 1994 §3(a). "(ff) The term 'dietary supplement':

1. means a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any [of these ingredients].
2. means a product that is intended for ingestion in [pill, capsule, tablet, or liquid form]; is not represented for use as a conventional food or as the sole item of a meal or diet; and is labeled as a dietary supplement."
3. [*paraphrased*] includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

Nutraceuticals (N), a term coined to reflect its "nutrition" origin and "pharmaceutical" action, do not have a "regulatory definition." They are dietary supplements that "contain a concentrated form of a presumed bioactive substance originally derived from a food, but now present in a non-food matrix, and used to enhance health in dosages exceeding those obtainable from normal foods" (268). Guidelines for the use of DS/N in endocrinology have been previously published by AACE (269). Functional foods are those foods containing substances having physiological actions beyond their simple nutritional value.

Overlap of symptoms in euthyroid and hypothyroid persons

The symptoms of hypothyroidism are nonspecific and mimic symptoms that can be associated with variations in lifestyle, in the absence of disease, or those of many other conditions. This is well illustrated in the Colorado thyroid disease prevalence study (12). That study found that four or more symptoms of hypothyroidism were present in approximately 25% of those with overt hypothyroidism, 20% of those with subclinical hypothyroidism, and in 17% of euthyroid patients. Although the differences were statistically significant since 88% of the population studied was euthyroid, 9% had subclinical hypothyroidism, and

only 0.4% were overtly hypothyroid, it is clear that there are many more euthyroid patients with symptoms suggestive of hypothyroidism than those who are subclinically or overtly hypothyroid.

A recent study compared symptoms in euthyroid patients who underwent surgery for benign thyroid disease. Those with Hashimoto's thyroiditis, the commonest cause of hypothyroidism in iodine sufficient regions, were more likely to complain of chronic fatigue, chronic irritability, chronic nervousness, and lower quality-of life than those without evidence of chronic thyroiditis (271). Nonetheless, the promulgation of claims that substances other than thyroid hormone may reverse these symptoms or influence thyroid status has contributed to the widespread use of alternative therapies for hypothyroidism.

Excess iodine intake and hypothyroidism

Iodine is used as a pharmaceutical in the management of hyperthyroidism and thyroid cancer (as radioiodine). Kelp supplements contain at least 150-250 μg of iodine per capsule compared with the recommended daily intake of iodine of 150 μg for adults who are not pregnant or nursing. In euthyroid patients, especially those with chronic thyroiditis, substantial kelp use may be associated with significant increases in TSH levels (38). No clinical data exist to support the preferential use of stable iodine, kelp, or other iodine-containing functional foods in the management of hypothyroidism in iodine-sufficient regions unless iodine deficiency is strongly suspected and confirmed.

Adverse metabolic effects of iodine supplementation are primarily reported in patients with organification defects (e.g., Hashimoto's thyroiditis) in which severe hypothyroidism ensues and is referred to as "iodide myxedema" (39,40). Even though pregnant women may be iodine deficient and require supplementation to achieve a total iodine intake of 200-300 μg/d, ingesting kelp or other seaweed-based products is not recommended owing to the variability in iodine content (16,272,273).

Desiccated thyroid

Animal-derived desiccated thyroid (see *L-thyroxine treatment of hypothyroidism*) contains T_4 and T_3. Since T_3 levels vary substantially throughout the day in those taking desiccated thyroid, T_3 levels cannot be easily monitored. Being viewed by some as a natural source of thyroid hormone has made it attractive to some patients who may not even have biochemically confirmed hypothyroidism and wish to lose weight or increase their sense of well-being (274). There are substantially more data on the use of synthetic L-thyroxine in the management of well-documented hypothyroidism, goiter, and thyroid cancer than for desiccated thyroid hormone. A PubMed computer search of the literature in January 2012 yielded 35 prospective randomized clinical trials (PRCTs) involving synthetic L-thyroxine published in 2007-2011, compared with no PRCTs involving desiccated thyroid extract for all years in the database. Thus, there are no controlled trials supporting the preferred use of desiccated thyroid hormone over synthetic L-thyroxine in the treatment of hypothyroidism or any other thyroid disease.

3,5,3´-Triiodothyroacetic acid

Another DS/N used for thyroid health is 3,5,3´-triiodothyroacetic acid (TRIAC; tiratricol), an active metabolite of T_3, which has been sold over the counter for weight loss. TRIAC appears to have enhanced hepatic and skeletal thyromimetic effects compared with L-thyroxine (275). The FDA scrutinized its use because of its lack of proven benefit as well as thyrotoxic and hypothyroid side effects (276-278). It is difficult to titrate or monitor clinically and biochemically. Its role in the treatment of hypothyroidism in syndromes of generalized resistance to thyroid hormone, particularly when L-thyroxine alone appears to be inadequate, remains uncertain (279,280). There are no data supporting its use in lieu of synthetic L-thyroxine in the treatment of hypothyroidism.

Thyroid-enhancing preparations

L-tyrosine has been touted as a treatment for hypothyroidism by virtue of its role in thyroid hormone synthesis. There are no preclinical or clinical studies demonstrating that L-tyrosine has thyromimetic properties. B vitamins, garlic, ginger, gingko, licorice, magnesium, manganese, meadowsweet, oats, pineapple, potassium, saw palmetto, and valerian are included in various commercially available "thyroid-enhancing preparations." There are no preclinical or clinical studies demonstrating any thyromimetic properties of any of these DS/N. In a recent study (281), 9 out of 10 thyroid health supplements (marketed as "thyroid support") studied contained clinically significant amounts of L-thyroxine (>91 μg/d) and/or L-triiodothyronine (>10 μg/day). Physicians should specifically engage patients regarding all forms of DS/N, specifically those marketed as thyroid support, and consider the possibility that any DS/N could be adulterated with L-thyroxine or L-triiodothyronine.

Thyromimetic preparations

Some DS/N with thyromimetic properties that have been studied but are of unproven clinical benefit include Asian ginseng (282), bladderwrack (283), capsaicin (284), echinacea (285), and forskolin (286).

Selenium

Selenium is an essential dietary mineral that is part of various selenoenzymes. These compounds are in many antioxidant, oxidation-reduction, and thyroid hormone deiodination pathways. It is not surprising that by virtue of these biochemical effects, selenium has been investigated as a modulator of autoimmune thyroid disease and thyroid

hormone economy. In one study, selenium administration was found to reduce the risk for cancer, but in a follow-up study of the study cohort, there was an increased risk of diabetes (287). In a well-designed, European PRCT of 2143 euthyroid women, selenium administration (as 200 μg/d selenomethionine) was associated with a reduction in autoimmune thyroid disease, postpartum thyroiditis, and hypothyroidism (288). Since dietary selenium intake varies worldwide, these results may not be generalizable to all populations. In another PRCT involving 501 patients in the United Kingdom who were over age 60 years, varying doses of selenium (100, 200, or 300 μg/d) for 6 months were not associated with beneficial changes in T_4 to T_3 conversion (289). Most recently, a meta-analysis was performed of blinded PRCTs of patients with Hashimoto's thyroiditis receiving L-thyroxine therapy (290). The analysis found that selenium supplementation was associated with decreased anti-TPO titers and improved well-being or mood, but there were no significant changes in thyroid gland ultrasonographic morphology or L-thyroxine dosing. Taken together, what do these limited clinical data suggest? Selenium has notable theoretical potential for salutary effects on hypothyroidism and thyroid autoimmunity including Graves' eye disease (291), both as a preventive measure and as a treatment. However, there are simply not enough outcome data to suggest a role at the present time for routine selenium use to prevent or treat hypothyroidism in any population.

QUESTIONS AND GUIDELINE RECOMMENDATIONS*

*When referring to therapy and therapeutic preparations in the recommendations and elsewhere, L-thyroxine and L-triiodothyronine are generally used instead of their respective hormonal equivalents, T_4 and T_3.

When should anti-thyroid antibodies be measured?

- **RECOMMENDATION 1** Anti-thyroid peroxidase antibody (TPOAb) measurements should be considered when evaluating patients with subclinical hypothyroidism. **Grade B, BEL 1**

SEE: *Epidemiology*; *Primary and secondary etiologies of hypothyroidism*

Recommendation 1 was downgraded to B because the best evidence is only predictive in nature. If anti-thyroid antibodies are positive, hypothyroidism occurs at a rate of 4.3% per year versus 2.6% per year when anti-thyroid antibodies are negative. Therefore, the presence of positive TPOAb may or may not influence the decision to treat.

- **RECOMMENDATION 2** TPOAb measurement should be considered in order to identify autoimmune thyroiditis when nodular thyroid disease is suspected to be due to autoimmune thyroid disease. **Grade D, BEL 4**

SEE: *Primary and secondary etiologies of hypothyroidism*

- **RECOMMENDATION 3** TPOAb measurement should be considered when evaluating patients with recurrent miscarriage, with or without infertility. **Grade A, BEL 2**

SEE: *Concurrent conditions of special significance* — Infertility

Recommendation 3 was upgraded to A because of favorable risk-benefit potential.

- **RECOMMENDATION 4** Measurement of TSHRAbs using a sensitive assay should be considered in hypothyroid pregnant patients with a history of Graves' disease who were treated with radioactive iodine or thyroidectomy prior to pregnancy. This should be initially done either at 20-26 weeks of gestation or during the first trimester and if they are elevated again at 20-26 weeks of gestation. **Grade A, BEL 2**

SEE: *Primary and secondary etiologies of hypothyroidism*

Recommendation 4 was upgraded to A because the correlation between a high titer of TSHRAb and the development of fetal or neonatal Graves' disease is strong.

What is the role of clinical scoring systems in the diagnosis of patients with hypothyroidism?

- **RECOMMENDATION 5** Clinical scoring systems should not be used to diagnose hypothyroidism. **Grade A, BEL 1**

SEE: *Signs and symptoms of hypothyroidism*; *Other diagnostic tests for hypothyroidism*

What is the role of diagnostic tests apart from serum thyroid hormone levels and TSH in the evaluation of patients with hypothyroidism?

- **RECOMMENDATION 6** Tests such as clinical assessment of reflex relaxation time, cholesterol, and muscle enzymes should not be used to diagnose hypothyroidism. **Grade B, BEL 2**

SEE: *Signs and symptoms of hypothyroidism*; *Other diagnostic tests for hypothyroidism*

What are the preferred thyroid hormone measurements in addition to TSH in the assessment of patient with hypothyroidism?

- **RECOMMENDATION 7** Apart from pregnancy, assessment of serum free T_4 should be done instead of total T_4 in the evaluation of

hypothyroidism. An assessment of serum free T_4 includes a free T_4 index or free T_4 estimate and direct immunoassay of free T_4 without physical separation using anti-T_4 antibody. **Grade A, BELL 1**

SEE: *Measurement of T_4 and T_3*; Table 6

- **RECOMMENDATION 8** Assessment of serum free T_4, in addition to TSH, should be considered when monitoring L-thyroxine therapy. **Grade B, BEL 1**

SEE: *Measurement of T_4 and T_3*

Recommendation 8 was downgraded to B since it should only be used selectively.

- **RECOMMENDATION 9** In pregnancy, the measurement of total T_4 or a free T_4 index, in addition to TSH, should be done to assess thyroid status. Because of the wide variation in the results of different free T_4 assays, direct immunoassay measurement of free T_4 should only be employed when method-specific and trimester-specific reference ranges for serum free T_4 are available. **Grade B, BEL 2**

SEE: *Measurement of T_4 and T_3*

- **RECOMMENDATION 10** Serum total T_3 or assessment of serum free T_3 should not be done to diagnose hypothyroidism. **Grade A, BEL 2**

SEE: *Measurement of T_4 and T_3*

Recommendation 10 was upgraded to A because of many independent lines of evidence and expert opinion.

- **RECOMMENDATION 11** TSH measurements in hospitalized patients should be done only if there is an index of suspicion for thyroid dysfunction. **Grade A, BEL 2**

SEE: *Measurement of T_4 and T_3*; *Pitfalls encountered when interpreting serum TSH levels*; *Concurrent conditions of special significance in hypothyroid patients*—Nonthyroidal illness

Recommendation 11 was upgraded to A because of cost considerations and potential for inappropriate intervention.

- **RECOMMENDATION 12** In patients with central hypothyroidism, assessment of free T_4 or free T_4 index, not TSH, should be done to diagnose and guide treatment of hypothyroidism. **Grade A, BEL 1**

SEE: *Measurement of T_4 and T_3*; *L-thyroxine treatment of hypothyroidism*

When should TSH levels be measured in patients being treated for hypothyroidism?

- **RECOMMENDATION 13** Patients being treated for established hypothyroidism should have serum TSH measurements done at 4-8 weeks after initiating treatment or after a change in dose. Once an adequate replacement dose has been determined, periodic TSH measurements should be done after 6 months and then at 12-month intervals, or more frequently if the clinical situation dictates otherwise. **Grade B, BEL 2**

SEE: *L-thyroxine treatment of hypothyroidism*

What should be considered the upper limit of the normal range of TSH values?

- **RECOMMENDATION 14.1** The reference range of a given laboratory should determine the upper limit of normal for a third generation TSH assay. The normal TSH reference range changes with age. If an age-based upper limit of normal for a third generation TSH assay is not available in an iodine sufficient area, an upper limit of normal of 4.12 should be considered. **Grade A, BEL 1**

SEE: *Pitfalls encountered when interpreting serum TSH levels*; *Therapeutic endpoints in the treatment of hypothyroidism*; Table 7

- **RECOMMENDATION 14.2** In pregnancy, the upper limit of the normal range should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges for TSH are not available in the laboratory, the following upper normal reference ranges are recommended: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; third trimester, 3.5 mIU/L. **Grade B, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

Which patients with TSH levels above a given laboratory's reference range should be considered for treatment with L-thyroxine?

- **RECOMMENDATION 15** Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine. **Grade B, BEL 1**

SEE: **Areas for Future Research**; *When to treat hypothyroidism*—Cardiac benefit from treating subclinical hypothyroidism

Recommendation 15 was downgraded to B because it is not generalizable and meta-analysis does not include prospective interventional studies.

- **RECOMMENDATION 16** Treatment based on individual factors for patients with TSH levels between the upper limit of a given laboratory's reference range and 10 mIU/L should be considered particularly if patients have symptoms suggestive of hypothyroidism, positive TPOAb or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases. **Grade B, BEL 1**

SEE: *Epidemiology*; *Primary and secondary etiologies of hypothyroidism*; *Screening and aggressive case finding for hypothyroidism*; *When to treat hypothyroidism*; **Areas for Future Research—** *Cardiac benefit from treating subclinical hypothyroidism*; Table 9

Recommendation 16 was downgraded to B because the evidence is not fully generalizable to the stated recommendation and there are no prospective, interventional studies.

In patients with hypothyroidism being treated with L-thyroxine, what should the target TSH range be?

- **RECOMMENDATION 17** In patients with hypothyroidism who are not pregnant, the target range should be the normal range of a third generation TSH assay. If an upper limit of normal for a third generation TSH assay is not available, in iodine-sufficient areas an upper limit of normal of 4.12 mIU/L should be considered and if a lower limit of normal is not available, 0.45 mIU/L should be considered. **Grade B, BEL 2**

SEE: *Pitfalls encountered when interpreting serum TSH levels*; *When to treat hypothyroidism*; *Therapeutic endpoints in the treatment of hypothyroidism*; Table 7

In patients with hypothyroidism being treated with L-thyroxine who are pregnant, what should the target TSH ranges be?

- **RECOMMENDATION 18** In patients with hypothyroidism who are pregnant, the target range for TSH should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges are not available in the laboratory, the following upper-normal reference ranges are recommended: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; and third trimester, 3.5 mIU/L. **Grade C, BEL 2**

SEE: *Pitfalls encountered when interpreting serum TSH levels*; *When to treat hypothyroidism*; *Therapeutic endpoints in the treatment of hypothyroidism*; *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

Recommendation 18 was downgraded to C due to lack of prospective studies establishing benefit.

Which patients with normal serum TSH levels should be considered for treatment with L-thyroxine?

- **RECOMMENDATION 19.1** Treatment with L-thyroxine *should be considered* in women of childbearing age with serum TSH levels between 2.5 mIU/L and the upper limit of normal for a given laboratory's reference range if they are in the first trimester of pregnancy or planning a pregnancy including assisted reproduction in the immediate future. Treatment with L-thyroxine should be considered in women in the second trimester of pregnancy with serum TSH levels between 3.0 mIU/L and the upper limit of normal for a given laboratory's reference range and in women in the third trimester of pregnancy with serum TSH levels between 3.5 mIU/L and the upper limit of normal for a given laboratory's reference range. **Grade B, BEL 2**

SEE: *When to treat hypothyroidism*; *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

- **RECOMMENDATION 19.2** Treatment with L-thyroxine *should be considered* in women of childbearing age with normal serum TSH levels when they are pregnant or planning a pregnancy, including assisted reproduction in the immediate future, if they have or have had positive levels of serum TPOAb, particularly when there is a history of miscarriage or past history of hypothyroidism. **Grade B, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

- **RECOMMENDATION 19.3** Women of childbearing age who are pregnant or planning a pregnancy, including assisted reproduction in the immediate future, *should be treated* with L-thyroxine if they have or have had positive levels of serum TPOAb and their TSH is greater than 2.5 mIU/L. **Grade B, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

- **RECOMMENDATION 19.4** Women with positive levels of serum TPOAb or with a TSH greater than 2.5 mIU/L who are not being treated with L-thyroxine should be monitored every 4 weeks in the first 20 weeks of pregnancy for the development of hypothyroidism. **Grade B, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

Who, among patients who are pregnant, or planning pregnancy, or with other characteristics, should be screened for hypothyroidism?

- **RECOMMENDATION 20.1.1** Universal screening is not recommended for patients who are pregnant or are planning pregnancy, including assisted reproduction. **Grade B, BEL 1**

SEE: **Areas for Future Research—***Screening for hypothyroidism in pregnancy*

Recommendation 20.1.1 was downgraded to B because there are limitations to the evidence and therefore insufficient evidence for lack of benefit.

- **RECOMMENDATION 20.1.2** "Aggressive case finding," rather than universal screening, should be considered for patients who are planning pregnancy. **Grade C, BEL 2**

SEE: **Areas for Future Research—***Screening for hypothyroidism in pregnancy*

Recommendation 20.1.2 was downgraded to C because even when a diagnosis of hypothyroidism is made, impact on outcomes has not been demonstrated.

- **RECOMMENDATION 20.2** Screening for hypothyroidism should be considered in patients over the age of 60. **Grade B, BEL 1**

SEE: *Epidemiology*; *Primary and secondary etiologies of hypothyroidism*; *Screening and aggressive case finding for hypothyroidism*; Table 8

Recommendation 20.2 was downgraded to B because there is strong evidence that hypothyroidism is common in this group but insufficient evidence of benefit or cost effectiveness.

- **RECOMMENDATION 21** "Aggressive case finding" should be considered in those at increased risk for hypothyroidism. **Grade B, BEL 2**

SEE: *Epidemiology*; *Primary and secondary etiologies of hypothyroidism*; *Screening and aggressive case finding for hypothyroidism*; Table 8

How should patients with hypothyroidism be treated and monitored?

- **RECOMMENDATION 22.1** Patients with hypothyroidism should be treated with L-thyroxine monotherapy. **Grade A, BEL 1**

SEE: *L-thyroxine treatment of hypothyroidism*

- **RECOMMENDATION 22.2** The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism. **Grade B, BEL 1**

SEE: *L-thyroxine treatment of hypothyroidism*; *Concurrent conditions of special significance in hypothyroid patients*; *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Desiccated thyroid*; **Areas for Future Research—** *L-thyroxine /L-triiodothyronine combination therapy*

Recommendation 22.2 was downgraded to Grade B because of still unresolved issues raised by studies that report that some patients prefer and some patient subgroups may benefit from a combination of L-thyroxine and L-triiodothyronine.

- **RECOMMENDATION 22.3.** L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy. **Grade B, BEL 3**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy

Recommendation 22.3 was upgraded to B because of potential for harm.

- **RECOMMENDATION 22.4** There is no evidence to support using desiccated thyroid hormone in preference to L-thyroxine monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism. **Grade D, BEL 4**

SEE: *L-thyroxine treatment of hypothyroidism*; *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Desiccated thyroid*

Recommendation 22.4 was a unanimous expert opinion.

- **RECOMMENDATION 22.5** 3,5,3´-triiodothyroacetic acid (TRIAC; tiratricol) should not be used to treat primary and central hypothyroidism

due to suggestions of harm in the literature. **Grade C, BEL 3**

See: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *3,5,3´-Triiodothyroacetic acid*

- **RECOMMENDATION 22.6** Patients resuming L-thyroxine therapy after interruption (less than 6 weeks) and without an intercurrent cardiac event or marked weight loss may resume their previously employed full replacement doses. **Grade D, BEL 4**

See: *L-thyroxine treatment of hypothyroidism*

Recommendation 22.6 was a unanimous expert opinion.

- **RECOMMENDATION 22.7.1** When initiating therapy in young healthy adults with overt hypothyroidism, beginning treatment with full replacement doses should be considered. **Grade B, BEL 2)**

See: *L-thyroxine treatment of hypothyroidism*

- **RECOMMENDATION 22.7.2** When initiating therapy in patients older than 50-60 years with over hypothyroidism, without evidence of coronary heart disease, an L-thyroxine dose of 50 μg daily should be considered. **Grade D, BEL 4**

See: *L-thyroxine treatment of hypothyroidism*

Recommendation 22.7 was a unanimous expert opinion.

- **RECOMMENDATION 22.8** In patients with subclinical hypothyroidism initial L-thyroxine dosing is generally lower than what is required in the treatment of overt hypothyroidism. A daily dose of 25 to 75 μg should be considered, depending on the degree of TSH elevation. Further adjustments should be guided by clinical response and follow up laboratory determinations including TSH values. **Grade B, BEL 2**

See: *L-thyroxine treatment of hypothyroidism*

- **RECOMMENDATION 22.9** Treatment with glucocorticoids in patients with combined adrenal insufficiency and hypothyroidism should precede treatment with L-thyroxine. **Grade B, BEL 2**

See: *Disorders associated with hypothyroidism*; *Pitfalls encountered when trying to interpret serum TSH levels*; *L-thyroxine treatment of hypothyroidism*

- **RECOMMENDATION 23** L-thyroxine should be taken with water consistently 30-60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption. **Grade B, BEL 2**

See: *L-thyroxine treatment of hypothyroidism*; Table 10

- **RECOMMENDATION 24** In patients with central hypothyroidism, assessments of serum free T_4 should guide therapy and targeted to exceed the midnormal range value for the assay being used. **Grade B, BEL 3**

See: *Primary and secondary etiologies of hypothyroidism*; *Measurement of T_4 and T_3*; *Pitfalls encountered when interpreting serum TSH levels*; *L-thyroxine treatment of hypothyroidism*

Recommendation 24 was upgraded to B because more than 50% of patients with central hypothyroidism adequately treated with L-thyroxine have values in this range.

- **RECOMMENDATION 25.1** In patients with hypothyroidism being treated with L-thyroxine who are pregnant, serum TSH should be promptly measured after conception and L-thyroxine dosage adjusted, with a goal TSH of less than 2.5 mIU/L during the first trimester. **Grade B, BEL 2**

See: *Therapeutic endpoints in the treatment of hypothyroidism*; *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7

- **RECOMMENDATION 25.2** In patients with hypothyroidism being treated with L-thyroxine who are pregnant, the goal TSH during the second trimester should be less than 3 mIU/L and during the third trimester should be less than 3.5 mIU/L. **Grade C, BEL 2**

See: *Therapeutic endpoints in the treatment of hypothyroidism*; *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy; Table 7.

Recommendation 25.2 was downgraded to C due to lack of prospective studies establishing benefit.

- **RECOMMENDATION 25.3** Maternal serum TSH (and total T_4) should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation and L-thyroxine dosages adjusted as indicated. **Grade B, BEL 2**

See: *Concurrent conditions of special significance in hypothyroid patients*—Hypothyroidism during pregnancy

- **RECOMMENDATION 26** In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within 4-8 weeks of initiation of treatment with drugs that decrease the bioavailability or alter the metabolic disposition of the L-thyroxine dose. **Grade A, BEL 1**

SEE: *L-thyroxine treatment of hypothyroidism*; **Areas for Future Research—***Agents and conditions having an impact on L-thyroxine therapy and interpretation of thyroid tests*; Tables 5 and 10.

- **RECOMMENDATION 27** Apart from pregnant patients being treated with L-thyroxine for hypothyroidism, the evidence does not support targeting specific TSH values within the normal reference range. **Grade B, BEL 2**

SEE: *Therapeutic endpoints in the treatment of hypothyroidism*

When should endocrinologists be involved in the care of patients with hypothyroidism?

- **RECOMMENDATION 28** Physicians who are not endocrinologists, but who are familiar with the diagnosis and treatment of hypothyroidism *should be able* to care for most patients with primary hypothyroidism. However, patients with hypothyroidism who fall into the following categories should be seen in consultation with an endocrinologist. These categories are (i) children and infants, (ii) patients in whom it is difficult to render and maintain a euthyroid state, (iii) pregnancy, (iv) women planning conception, (v) cardiac disease, (vi) presence of goiter, nodule, or other structural changes in the thyroid gland, (vii) presence of other endocrine disease such as adrenal and pituitary disorders, (viii) unusual constellation of thyroid function test results and (ix) unusual causes of hypothyroidism such as those induced by agents that interfere with absorption of L-thyroxine impact thyroid gland hormone production or secretion, affect the hypothalamic-pituitary-thyroid axis (directly or indirectly), increase clearance, or peripherally impact metabolism. **Grade C, BEL 3**

SEE: *When to consult an endocrinologist; Table 10*

Which patients should not be treated with thyroid hormone?

- **RECOMMENDATION 29** Thyroid hormones should not be used to treat symptoms suggestive of hypothyroidism without biochemical confirmation of the diagnosis. **Grade B, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Patients with normal thyroid tests

- **RECOMMENDATION 30** Thyroid hormones should not be used to treat obesity in euthyroid patients. **Grade A, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Obesity

Recommendation 30 was upgraded to Grade A because of potential harm.

- **RECOMMENDATION 31** There is insufficient evidence to support using thyroid hormones to treat depression in euthyroid patients. **Grade B, BEL 2**

SEE: *Concurrent conditions of special significance in hypothyroid patients*—Depression

What is the role of iodine supplementation, dietary supplements, and nutraceuticals in the treatment of hypothyroidism?

- **RECOMMENDATION 32.1** Iodine supplementation, including kelp or other iodine-containing functional foods, should not be used in the management of hypothyroidism in iodine-sufficient areas. **Grade C, BEL 3**

SEE: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Excess iodine intake and hypothyroidism*

- **RECOMMENDATION 32.2** Iodine supplementation in the form of kelp or other seaweed-based products should not be used to treat iodine deficiency in pregnant women. **Grade D, BEL 4**

SEE: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Excess iodine intake and hypothyroidism*

Recommendation 32.2 was a unanimous expert opinion

- **RECOMMENDATION 33** Selenium should not be used to prevent or treat hypothyroidism. **Grade B, BEL 2**

SEE: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Selenium*.

- **RECOMMENDATION 34** Patients taking dietary supplements and nutraceuticals for hypothyroidism should be advised that commercially available thyroid-enhancing products are not a remedy for hypothyroidism and should be counseled about the potential side effects

of various preparations particularly those containing iodine or sympathomimetic amines as well as those marked as "thyroid support" since they could be adulterated with L-thyroxine or L-triiodothyronine. **Grade D, BEL 4**

SEE: *Dietary supplements and nutraceuticals in the treatment of hypothyroidism*; *Thyroid enhancing preparations*; *Thyromimetic preparations*

Recommendation 34 was a unanimous expert opinion.

AREAS FOR FUTURE RESEARCH

Cardiac benefit from treating subclinical hypothyroidism

Overt hypothyroidism produces reversible changes in cardiovascular hemodynamics and in many of the modifiable cardiovascular risk factors for ASCVD and heart failure. Some prospective studies also indicate that treatment of subclinical hypothyroidism, including groups with minimally elevated TSH levels, results in improvement in surrogate markers for ASCVD such as atherogenic lipids (120-123) and carotid intima media thickness (126).

A meta-analysis of 10 longitudinal studies of subclinical hypothyroidism (119), which excluded patients with ASCVD at baseline, showed a relative risk of CHD of 1.2 when all studies were combined. When only higher quality studies were analyzed, the risk dropped to 1.02-1.08 depending on whether the study design allowed for adjudicated outcomes with or without knowledge of thyroid status. However, in studies with mean age younger than 65 years, the risk was 1.51 compared with 1.05 in studies with a mean age of 65 and over. Another meta-analysis, also done in 2008, of 15 studies with over 2500 participants with subclinical hypothyroidism, eight of which were also used in the aforementioned meta-analysis, showed elevated odds ratios for the incidence of ASCVD and cardiovascular all-cause mortality of 1.57 and 1.37 for those under 65 years, but not for those over 65 years (292).

A study from the Cleveland Clinic Preventive Cardiology Clinic of patients at high risk for ASCVD showed that those with TSH levels of 6.1-10 mIU/L as well as greater than 10 mIU/L who were under 65 years and not treated with thyroid hormone had higher all-cause mortality (118). Most recently a U.K. general practitioner database was analyzed to assess the impact of L-thyroxine treatment on fatal and nonfatal cardiac events in over 3000 individuals with subclinical hypothyroidism (TSH between 5.01 and 10 mIU/L) aged between 40 and 70 years and over 1500 individuals older than 70 years who were followed up for a median of ~8 years. In the ~50% of individuals between 40 and 70 years of age who were treated with L-thyroxine (87.4% women) the hazard ratio for ischemic heart disease events was reduced compared to the ~50% of untreated individuals (82.5% women) (0.61, CI 0.49-0.92). This reduction was not evident in those older than 70 years, of whom 84.6% in the treatment group and 75.6% in the untreated group were women (293).

Yet other studies fail to show that an increased risk of cardiac disease in those with subclinical hypothyroidism is age dependent. The Cardiovascular Health Study followed 3000 patients 65 years or older with subclinical hypothyroidism who were initially free of heart failure. Those with TSH levels of 10 mIU/L or greater had an increased risk of heart failure (294). During the 20 years of follow-up in the Whickham Survey, an association was found between ASCVD and ASCVD-related mortality in those with subclinical hypothyroidism whose TSH values were between 6 and 15 mIU/L independent of age. When those treated with L-thyroxine were excluded, ASCVD-related morbidity and mortality were no longer evident (116). Additional large-scale studies in those with serum TSH values of 10 mIU/L or greater including a study of 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan demonstrated an increase in ASCVD that was independent of age (115) while a study of six prospective cohorts with over 2000 patients had an increased incidence of heart failure in those up to 80 years of age (117).

The absence of randomized prospective controlled trials leaves us with several unresolved key issues pertaining to subclinical hypothyroidism, including whether or not L-thyroxine treatment will prevent the development of ASCVD or decrease the frequency of hospital admissions for heart failure and whether age is a critical determinant of risk for cardiac morbidity. A prospective study to assess both of these parameters is currently being planned.

Cognitive benefit from treating subclinical hypothyroidism

Some reports on mood, cognitive, and other objective brain function studies in subclinical hypothyroidism demonstrate the presence and reversal of deficits after treatment with L-thyroxine (295). However, other studies have not (296,297).

L-thyroxine and L-triiodothyronine combination therapy

An important question is whether a recent study had sufficient data to warrant revisiting why some patients seem to feel better on L-thyroxine/L-triiodothyronine combinations and whether we can identify them and safely treat them (136) with this combination.

L-triiodothyronine monotherapy

A potential role for L-triiodothyronine monotherapy in lieu of L-thyroxine monotherapy was recently raised by a small randomized, double-blind crossover intervention study done comparing L-triiodothyronine monotherapy with L-thyroxine monotherapy in patients with hypothyroidism (298). Thrice daily dosing was employed for each.

Comparable TSH levels were achieved. Mild weight loss and decreases in total cholesterol, LDL cholesterol, and apolipoprotein levels were seen without differences in cardiovascular function, insulin sensitivity, or quality of life with L-triiodothyronine monotherapy compared with L-thyroxine monotherapy. The small size and short duration of the study as well as thrice daily dosing presently precludes considering L-triiodothyronine monotherapy as an alternative to L-thyroxine monotherapy (298).

Thyroid hormone analogues

Thyroid hormone's effects are protean, affecting virtually every organ system. Efforts are underway to develop and study analogues that have selective beneficial effects on weight control, lipoproteins, and TSH suppression without inducing hypothyroidism or the most important negative consequences of hyperthyroidism on the heart and skeleton. Compounds studied to date include D-thyroxine (299), tiratricol (275), eprotiromone (KB 2115) (300,301), and diodothyropropionic acid (302). A recent prospective Phase II clinical trial of the thyroid hormone analogue eprotirome, designed to be a selective beta II receptor agonist, has been shown to lower both total cholesterol and Lp(a) without any change in thyroid hormone levels or untoward cardiovascular or bone effects (300). However, the development program for eprotirome has been discontinued due to adverse findings in preclinical studies. Further studies will be needed to confirm the benefit and lack of side effects of these agents.

Screening for hypothyroidism in pregnancy

It remains unclear if screening for hypothyroidism in pregnancy is beneficial. A consensus statement in 2004 (106) and clinical practice guidelines in 2007 (303) and 2011 (10) found insufficient data to support a 1999 (304) and restated 2005 recommendation (305) for universal screening for thyroid dysfunction during pregnancy, but rather recommended aggressive case finding.

Arguments for screening include the following:

- Limiting evaluation to women in high-risk groups misses 30% of pregnant women with overt or subclinical hypothyroidism (306).
- A study comparing universal screening to case finding found that there was a statistically significant difference in a composite endpoint of adverse obstetric and neonatal outcomes associated with treatment of thyroid dysfunction in low-risk women who were screened compared to those who were not (307).
- A cost-effectiveness model to evaluate universal screening, which was predicated on the effectiveness of thyroid hormone treatment in lowering the incidence of offspring with intelligence quotient (IQ) <85, concluded that a random TSH done during the first trimester of pregnancy would ultimately save $84 per pregnancy (308). However, this has not been confirmed by a recent randomized controlled trial (219).

However, questions remain about the utility of screening those at low risk for developing hypothyroidism (307) and whether screening and intervention earlier on in the first trimester (219) may be cost effective.

The Controlled Antenatal Thyroid Study in the United Kingdom and Italy examined the impact at 3 years of age of L-thyroxine treatment if free T_4 is below the 2.5th percentile or if TSH is above the 97.5th percentile (219). Analyses failed to demonstrate a benefit when screening was performed around the end of the first trimester. Whether earlier intervention, different cognitive testing, or the same testing performed at age greater than 3 years would yield different results is uncertain. "A Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy", done under the auspices of the National Institute of Child Health and Human Development, is presently studying the IQ at 5 years of age following a universal screening versus case finding program.

Agents and conditions having an impact on L-thyroxine therapy and interpretation of thyroid tests

Conditions such as pregnancy and malabsorption, drugs, diagnostic agents, dietary substances, and supplements can have an impact on thyroid hormone economy, which may or may not result in a change in thyroid status. For example, orally administered estrogens increase TBG levels. While this does not alter thyroid status in euthyroid individuals with normal thyroid reserve, it may do so when there is either marginal thyroid reserve or established hypothyroidism. Drugs may have multiple effects on thyroid hormone metabolism. Notable examples include glucocorticoids and amiodarone. In a number of cases, the mechanisms by which agents alter thyroid status are not known. The impact that an agent or condition has on thyroid status may require clinicians to increase monitoring, adjust dosages, or instruct patients to change how and when they take L-thyroxine.

Major determinants of whether or not drugs and other substances will have an impact on thyroid status include the following:

- Dosage
- Duration of action
- Proximity to when thyroid hormone is taken
- Duration of treatment
- Iodine content
- Organified
- Nonorganified
- Size of iodine pool
- Autoimmune thyroid disease
- Nodular thyroid disease
- Thyroid hormone status
- Genetic factors

The principal mechanisms and reasons that conditions, drugs, and other substances have an impact on thyroid status are the following:

- Effects on thyroid hormone metabolism:
  - Absorption
  - Binding
  - Peripheral metabolism
  - Clearance
- Direct and indirect effects on the hypothalamic-pituitary-thyroid axis
  - TSH secretion
  - Hypophysitis
- Direct and indirect effects on the thyroid gland
  - Iodine uptake
  - Hormone production
  - Hormone secretion
- Thyroiditis (amelioration or development)
  - Destructive
  - Autoimmune
- Amelioration or development of Graves' disease

Table 10 lists agents and some conditions that affect thyroid status—particularly if they are commonly used—and are likely to do so or to have a profound impact on it. However, some very commonly used drugs such as sulfonylureas or sulfonamides or foodstuffs such as grapefruit juice that may only have a minor impact have been included. Because of their potential importance, some drugs such as perchlorate, iopanoic acid, and ipodate, are also listed even though they are not generally available.. On the other hand, some drugs that are rarely used have been omitted. Agents may appear more than once if there is more than one known mechanism of action. A comprehensive review of this subject and references for each drug or condition is beyond the scope of these guidelines. The interested reader is encouraged to consult other sources for more information (309-311).

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