Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association[1]

The American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults

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ABSTRACT

Background: 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 report. 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 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 TSH 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 (T4). The decision to treat subclinical hypothyroidism, when the serum TSH is less than 10 mIU/L, should be tailored to the individual patient.

INTRODUCTION

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

The ATA develops Clinical Practice Guidelines 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 circumstances. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients (See Supplement 1 for detailed information regarding ATA guidelines).

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 (See Supplement 1 for detailed information regarding AACE guidelines).

These guidelines are a document that reflects the current state of the field and are intended to provide a working document for guideline updates as 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.

A serum 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 T4 which must be tailored to the individual patient. The therapy and diagnosis of subclinical hypothyroidism, which often remains undetected, is discussed. The use of L-triiodothyronine (T3) in combination with T4 for treating hypothyroidism, thyroid hormone for conditions other than hypothyroidism, and nutraceuticals is only briefly considered.

METHODS

This Clinical Practice Guideline (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.

Objectives

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

Guidelines for Clinical Practice Guidelines (CPG)

Current guidelines for CPG 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 CPG to provide objectivity.

Levels of scientific substantiation and recommendation grades (Transparency)

All clinical data that are incorporated in these CPG have been evaluated in terms of levels of scientific substantiation. The detailed methodology for assigning evidence levels (EL) to the references used in these CPG has been reported by Mechanick et al. (7), from which Table 2 is taken. Supplement 2 summarizes the EL ratings of the authors for the references. The 4-step approach that the authors used to grade recommendations is summarized in tables 3 through 6, of

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the 2010 Standardized Production of Clinical Practice Guidelines (5), from which Table3 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. 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 CPG are that many recommendations are based on weak, scientific data (level 3) or consensus opinion (level 4), rather than strong scientific data (levels 1 and 2). There is also the problem 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, (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 been provided above (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 the recommendation it is explicitly stated after the recommendation.

TOPICS RELATING TO HYPOTHYROIDISM

Epidemiology (See Table 4)

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 T4. This designation is only applicable when thyroid function has been stable for weeks or more,

the hypothalamic pituitary thyroid axis is normal, and when there is no recent or ongoing severe illness. An elevated TSH, usually above 10 mIU/L in combination with a subnormal free T4, characterizes overt hypothyroidism. The National Health and Nutrition Examination Survey (NHANES III) studied an unselected US population over 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 had TSH values over 10 mIU/L, 39% of whom had subnormal T4 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 US, 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, for example, 5% of women and 1% of men had both positive antibody tests and a serum TSH value >6 (14). 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 thyroid antibody titers which include anti-thyroglobulin antibodies (TgAb), anti-microsomal/ thyroid peroxidase antibodies (TPOAb) and anti-TSH receptor antibodies (TSHRAb). Many patients with chronic autoimmune thyroiditis are biochemically euthyroid. However, approximately 75% have elevated 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 its measurement in those with subclinical hypothyroidism.

In patients with a diffuse, firm goiter, TPOAb should be measured to identify autoimmune thyroiditis. Since nonimmunologically 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 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 I 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 immunoglobulins (TSI) and/or thyrotropin binding inhibitory immunoglobulins (TBII) levels, employing sensitive assays, should be measured in euthyroid orT4 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 on 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 T4 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 T4 and T3 (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 of multiple autoimmune endocrinopathies (MAE). The three 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 (T4) Treatment of Hypothyroidism* in a later section).

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 non-specific therapeutic endpoints.

Measurement of L-Thyroxine (T4) and L-Triiodothyronine (T3)

T4 is bound to specific binding proteins in serum. These are T4-binding globulin (TBG) and, to a lesser extent, transthyretin or T4-binding prealbumin (TBPA) and albumin. As approximately 99.97% of T4 is protein bound, levels of serum total T4 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 T4, which is the metabolically available moiety (70), have been developed, and assessment of serum free T4 has now largely replaced measurement of serum total T4 as a measure of thyroid status. These methods include the serum free T4 index, which is derived as the product of total T4 and a thyroid hormone

binding ratio (THBR), and the direct immunoassay of free T4 after ultrafiltration or equilibrium dialysis of serum or after addition of anti-T4 antibody to serum (71).

A subnormal assessment of serum free T4 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 T4 (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 months.

In monitoring patients with hypothyroidism on T4 replacement, blood for assessment of serum free T4 should be collected before dosing as the level will be transiently increased by up to 20% after T4 administration (72). In one small study of athyreotic patients levels serum total T4 levels increased above baseline by 1 hour and peaked at 2.5 hours, while serum free T4 levels peaked at 3.5 hours and remained higher than baseline for 9 hours (72).

In pregnancy, measurement of serum total T4 is recommended over direct immunoassay of serum free T4. Because of alterations in serum proteins in pregnancy, direct immunoassay of free T4 may yield lower values using 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 T4 have not been generally established. By contrast, total T4 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 T4, T3 is also bound to serum proteins, principally TBG, but to a lesser extent than T4, ~99.7%. Methods for assessing free T3 concentration by direct immunoassay have been developed and are in current use (71). However, serum T3 measurement,

whether total or free, has limited utility in hypothyroidism as levels are often normal due to hyperstimulation of the remaining functioning thyroid tissue by elevated TSH and to upregulation of type 2 iodothyronine deiodinase (75). Moreover, levels of T3 are low in the absence of thyroid disease in patients with severe illness because of reduced peripheral conversion of T4 to T3 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 T4 and abnormal TSH levels occur during developing hypothyroidism and hyperthyroidism before free T4 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 comprised 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 twenty years (82, 83).

More recently (84) the NHANES III reference population was further analyzed and normal ranges based on age, United States Office of Management of Budget "Race and Ethnicity" categories, and gender were determined. These indicated the 97.5th percentile TSH values as low as 3.24 for African Americans between the ages of 30-39 and as high as 7.84 for Mexican Americans 80+ years of age. For every 10 year age increase after 30 to 39 years the 97.5th centile of serum TSH increases by 0.3 mIU/L. Body weight, antithyroid 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 sub-populations--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 non-thyroidal states. Serum TSH may be suppressed in hospitalized patients with acute illness, and levels below 0.1 mIU/L in combination with subnormal free T4 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 non-thyroidal 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 (HCG), 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 T4 (94), mimicking what may be seen in critically ill patients and in patients with central hypothyroidism, due to pituitary and hypothalamic disorders.

Patients with non-functioning 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).

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 (BMR) 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, LDL (99, 100) and the highly atherogenic subfraction Lp (a) (101).
- Delayed Achilles reflexes time (60)

- Increased creatine kinase due to an increase in MM fraction which can be marked and lead to an increase in 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 (See Table 8)

Criteria for population screening include (i) a condition that is prevalent and an important health problem, (ii) early diagnosis is not usually made, (iii) diagnosis is simple and accurate, and (iv) treatment is cost-effective and safe. Despite this seemingly straightforward guidance, expert panels have disagreed about TSH screening of the general population (See 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 (105). In contrast, a consensus panel (106), the Royal College of Physicians of London (107), and the U.S. Preventive Services Task Force (USPSTF) (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 (i) autoimmune disease, such as Type 1 diabetes (20, 21), (ii) pernicious anemia (109, 110), (iii) a first-degree relative with autoimmune thyroid disease (19) (iv) 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), (v) a prior history of thyroid surgery or dysfunction,

(vi) an abnormal thyroid examination, (vii) psychiatric disorders (114), (viii) patients taking amiodarone (37) or lithium (32-34) and (ix) patients with ICD-9 diagnoses as presented in Table 9.

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* (See below). 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, where the rate of pregnancy loss, including spontaneous miscarriage before 20 weeks gestation and stillbirth after 20 weeks, have been reported to be increased in thyroid antibody negative women with TSH values between 2.5 and 5.0 (127).

L-thyroxine (T4) Treatment of Hypothyroidism

Since the generation of biologically active T3 by the peripheral conversion of T4 to T3 was documented in 1970 (128) T4 monotherapy has become the mainstay of treating hypothyroidism, replacing desiccated thyroid and other forms of T4 and T3 combination therapy. Although a similar quality of life (129) and circulating T3 levels (130) have been reported in

patients treated with T4 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 T4 and T3 combination therapy (132) have re-addressed the benefits of synthetic T4 and T3 combination therapy, but have largely failed to confirm an advantage of this approach to improve cognitive or mood outcomes in hypothyroid individuals treated with T4 alone (133, 134).

Yet several matters remain uncertain. What should the ratios of T4 and T3 replacement be (133)? What is the pharmacodynamic equivalence of T4 and T3 (135)? It was previously believed to be 1:4, but in a recent small study indicated was approximately 1:3 (135)? Why do some patients prefer combination therapy to T4 monotherapy (133)? Some insight into the latter question may be gained from a large scale study of T4 and T3 combination therapy in which different responses were observed in those with different genetic subtypes of type 2 deiodinase (D2) (136), despite a prior smaller negative study (137). It is not known if those who responded positively to T4 and T3 combination therapy will prove to 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 T4 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 T4 preparation for individual patients to minimize variability from refill to refill (138, 139).

Some reports have indicated an apparent increased dosage requirement for T4 in some patients with diminished gastric acid secretion (140, 141). This has led to *in-vitro* work showing significant differences in dissolution among T4 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 findings remains unclear as 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 T4 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 T3 in desiccated thyroid is comparable to that of orally administered synthetic T3 (145). Therefore, the most commonly used form of desiccated thyroid, known as Armour® Thyroid, which is of porcine origin, may be viewed as a T4 and T3 combination with a ratio of approximately four to one by weight (145). The content of thyroid hormone and the ratio of T4 to T3 may vary in desiccated thyroid preparations depending on the brand employed and whether it is of porcine or bovine origin.

The daily dosage of T4 is dependent on age, gender and body size (146-151). Ideal body weight is best used for clinical dose calculations as 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 T4 dose per ideal body weight or

degree of overweight differed by gender --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 T4 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 to 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 T4 doses on the basis of the initial serum TSH values as follows: 25 μg for TSH 4.0 to 8.0 mIU/L, 50 μg for TSH 8 to 12 mIU/L, and 75 μg for TSH > 12 mIU/L. After two months only minimal further adjustments were required to achieve euthyroidism (162).

One recent study demonstrated that T4 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, T4 taken with water 60 minutes before breakfast or at bedtime 4 hours after the last meal on an empty stomach, is superior. Although T4 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.

T4 should be stored per product insert at 20 º25 ºCelsius, (range, 15 º30 º) or 68-77 degrees Fahrenheit (range, 59-86) 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 T4 is absorbed (167-169), individuals unable to ingest T4 should initially receive 70% or less of their usual dose intravenously. Crushed T4 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 one hour before resuming feeding. Administering intravenous T4 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 T4 preparation (139, 171). While TSH levels may decline within a month of initiating therapy with doses of T4 such as 50 or 75 ug, 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 T4 daily and assessment of free T4, 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 T4

in patients who are treated with T4 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 and then 12-month intervals are appropriate (172). Some authors think that more frequent testing is advisable to ensure and monitor compliance with therapy.

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 four to eight weeks of doing so, and tests performed at least every four to eight weeks until stable euthyroid indices have been documented while on the same dose of T4. Decreases in T4 requirements occur as patients age (151) and following significant weight loss. Moreover, although elderly patients absorb T4 less efficiently they often require 20-25% less per kg 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 micrograms 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 T4 to both reduce the serum TSH and maintain the patient angina-free. Emergency coronary artery bypass grafting (CABG) 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 T4 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 T4 (> 200 μg/d) with persistently or frequently elevated TSH levels may be non-compliant or have problems with T4 absorption (171). The former is much more common (184). Although daily dosing of T4 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 T4 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 T4. 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 T4, free T4 and T3 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 T4 will also be in the normal range. On the other hand, T3 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 to 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 Hypothyroidism - 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 USA 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 employed 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 T4. 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 non-endocrinologists for congenital, pediatric, and central hypothyroidism as well the uncommon, challenging clinical situations listed above, 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 T4 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 T4 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 T4 by 8 weeks of gestation had intellectual and psychomotor development comparable to controls (218). Finally, treatment with T4 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 T4 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 T4 transport (226-231). The offspring of mothers with serum T4 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 T4/T3 combinations, which cause lowering of serum T4 levels should not be used during pregnancy. Furthermore, patients being treated with these preparations should be switched to T4 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 T4 levels (232).

When a woman with hypothyroidism becomes pregnant, the dosage of T4 should be increased as soon as possible to ensure that serum TSH is <2.5 mIU/L and that serum total T4 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 T4 treatment should be initiated. Serum TSH and total T4 measurements should be monitored every four weeks during the first half of pregnancy (233), and at least once between 26 and 32 weeks gestation, to ensure that the requirement for T4 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. T4 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 T4 increases predictably during pregnancy and, as noted above the reference range is ~ 1.5 fold that of the non-pregnant range. Serum TSH levels decline in the first trimester when serum hCG 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 mIU/L 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 BMI (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 may have ultrasound findings suggestive of chronic thyroiditis without either elevated antithyroid antibody titers or decreased T4 and T3 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) weight loss (242) even in cases of profound hypothyroidism appears, at most, to be modest. This is despite the fact that resting energy expenditure (REE) 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, 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 T4 (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 (TCA) and selective serotonin re-uptake inhibitors (SSRI) to potential changes in brain thyroid hormone metabolism, which make the combination of T3 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-T3 combinations are inconsistent (114, 260, 261) and do not clearly support T3 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 T3 and normal or low serum T4 and TSH levels (262, 263). Since there is evidence that treatment with either T4 (264) or T3 (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 T3 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 T3 levels have been shown to benefit from intravenous T3 to restore serum T3 levels to normal (267). Evaluation of the patient by a clinical endocrinologist is appropriate before initiation of thyroid hormone treatment.

Dietary Supplements (DS) and Nutraceuticals (N) 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).

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

- "is 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 daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- 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.

- is labeled as a 'dietary supplement'.
- 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 4 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 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) where 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 to 300 ug/day, 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(T4) treatment of hypothyroidism*) contains T4 and T3. Since T3 levels vary substantially throughout the day in those taking desiccated thyroid T3 levels cannot be easily monitored. 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 is substantially more data on the use of synthetic T4 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 T4 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 T4 in the treatment of hypothyroidism or any other thyroid disease.

TRIAC

Another DS/N used for "thyroid health" is 3,5,3'-triiodothyroacetic acid (TRIAC; tiratricol), an active metabolite of T3, which has been sold over the counter for weight loss. TRIAC appears to have enhanced hepatic and skeletal thyromimetic effects compared with T4 (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 T4 alone appears to be inadequate, remains uncertain (279,

280). There are no data supporting its use in lieu of synthetic T4 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 T4 (> 91 mcg/day) and/or T3 (> 10 mcg/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 T4 or T3.

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 followup study of the study cohort, there was an increased risk of diabetes (287). In a well-designed, European, prospective, randomized controlled trial (PRCT) of 2143 euthyroid women, selenium (as 200 mcg/d selenomethionine) administration was associated with a reduction in autoimmune thyroid disease, post-partum 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 mcg/d) for 6 months were not associated with beneficial changes in T4 to T3 conversion (289). Most recently, (290) a meta-analysis was performed of blinded, PRCTs of patients with Hashimoto's thyroiditis receiving T4 therapy and found that selenium supplementation was associated with decreased anti-TPO titers and improved well-being or mood, but without significant changes in thyroid gland ultrasonographic morphology or T4 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[3]

When should antithyroid antibodies be measured?

Recommendation 1 - Thyroid peroxidase antibody (TPOAb) measurements should be considered when evaluating patients with subclinical hypothyroidism.

Grade B, BEL 1.

(See "*Epidemiology*" and "*Primary and Secondary Etiologies of Hypothyroidism*".)

Recommendation 1 was downgraded to B because the best evidence is only predictive in nature. If antibodies are positive, hypothyroidism occurs at a rate of 4.3% per year versus 2.6% per year when 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*.)

[3] Note: When referring to therapy in the recommendations, L-thyroxine and L-triiodothyronine and used instead of their respective abbreviations, T4 and T3.

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 TSH-receptor antibody (TSHRAb) 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 either be initially done 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 a strong one.

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* and *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* and *Other Diagnostic Tests for Hypothyroidism*.)

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

Recommendation 7 - Apart from pregnancy, assessment of serum free T4 should be done instead of total T4 in the evaluation of hypothyroidism. An assessment of serum free T4 includes a free T4 index (FTI) or free T4 estimate (FTE) and direct immunoassay of free T4 without physical separation using anti-T4 antibody.

Grade A, BEL 1.

(See *Measurement of L-Thyroxine (T4) and L-Triiodothyronine (T3)* and Table 6)

Recommendation 8 - Assessment of serum free T4, in addition to TSH, should be considered when monitoring L-thyroxine therapy.

Grade B, BEL 1.

(See *Measurement of L-Thyroxine (T4) and L-Triiodothyronine (T3)*)

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

Recommendation 9 - In pregnancy, the measurement of total T4 or a free thyroxine index (FTI), in addition to TSH, should be done to assess thyroid status. Because of the wide variation in the results of different free T4 assays, direct immunoassay measurement of free T4 should only be employed when method-specific and trimester-specific reference ranges for serum free T4 are available.

Grade B, BEL 2.

(See *Measurement of L-Thyroxine (T4) and L-Triiodothyronine (T3)*)

Recommendation 10 - Serum total T3 or assessment of serum free T3 should not be done to diagnose hypothyroidism.

Grade A, BEL 2.

(See *Measurement of L- Thyroxine (T4) and L-Triiodothyronine (T3)*)

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 L-Thyroxine (T4) and L-Triiodothyronine (T3), 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 T4 or FTI, not TSH, should be done to diagnose and guide treatment of hypothyroidism.

Grade A, BEL 1.

(See *Measurement of L-Thyroxine (T4) and L-Triiodothyronine (T3)* and *L-thyroxine (T4) 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 (T4) 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*, and 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*, and Table 7)

Which patients with TSH levels above a given laboratory's reference range should be considered for treatment with L-thyroxine (T4)?

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" and *When to treat Hypothyroidism - Cardiac Benefit from Treating Subclinical Hypothyroidism*.)

Recommendation 15 was downgraded to B because it is not generalizable and metaanalysis 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 they have symptoms suggestive of hypothyroidism, positive TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have 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*, and 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 (T4) what should the target TSH ranges 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*, and Table 7.)

In patients with hypothyroidism being treated with L-thyroxine (T4) 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; 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 Hypothyroidism - Hypothyroidism During Pregnancy, and Table 7.)

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

Which patients with normal serum TSH levels should be considered for treatment with L-thyroxine (T4)?

Recommendation 19.1 - Treatment with L-thyroxine *should be considered* in women of child bearing 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 and third 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. Grade B, BEL 2.

(See *When to Treat Hypothyroidism, Concurrent Conditions of Special Significance - Hypothyroidism During Pregnancy*, and Table 7)

Recommendation 19.2 - Treatment with L-thyroxine *should be considered* in women of child-bearing 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 - Hypothyroidism During Pregnancy*, and 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 - Hypothyroidism During Pregnancy*, and 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 four weeks in the first 20 weeks of pregnancy for the development of hypothyroidism.

Grade B, BEL 2.

(See *Concurrent Conditions of Special Significance - Hypothyroidism During Pregnancy*, and 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" for patients who are planning pregnancy should be considered.

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*, and 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*, and 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, BEL1.

(See *L-thyroxine (T4) Treatment of Hypothyroidism*.)

Recommendation 22.2 - The evidence does not support using L-thyroxine and L-Triiodothyronine combinations to treat hypothyroidism.

Grade B, BEL1.

(See *L-thyroxine (T4) Treatment of Hypothyroidism*, *Concurrent Conditions of Special Significance in Hypothyroid Patients*, *Dietary Supplements (DS) and Nutraceuticals (N) in the Treatment of*

Hypothyroidism, Desiccated Thyroid, AREAS FOR FUTURE RESEARCH - T4/T3 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 T4 and T3.

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 (T4) Treatment of Hypothyroidism*, *Dietary Supplements (DS) and Nutraceuticals (N) in the Treatment of Hypothyroidism* , and *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 (DS) and Nutraceuticals (N) in the Treatment of Hypothyroidism* , and *TRIAC*.)

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 (T4) Treatment of Hypothyroidism*.)

Recommendation 22.6 was a unanimous expert opinion.

Recommendation 22.7.1 - When initiating therapy in young healthy adults with hypothyroidism beginning treatment with full replacement doses should be considered.

Grade B, BEL 2.

(See *L-thyroxine (T4) Treatment of Hypothyroidism*.)

Recommendation 22.7.2 – 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 micrograms 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 (T4) Treatment of Hypothyroidism*.)

Recommendation 22.8 - When initiating therapy in patients older than 50-60 years, without evidence of coronary heart disease (CHD), an L-thyroxine dose of 50 micrograms daily should be considered. Grade D, BEL 4.

(See *L-thyroxine (T4) Treatment of Hypothyroidism*.)

Recommendation 22.8 was a unanimous expert opinion.

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,* and *L-Thyroxine (T4) Treatment of Hypothyroidism*.)

Recommendation 23 - L-thyroxine should be taken with water consistently 30 to 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 (T4) Treatment of Hypothyroidism and Table 10*.)

Recommendation 24 - In patients with central hypothyroidism, assessments of serum free T4 should guide therapy and targeted to exceed the mid-normal range value for the assay being used.

Grade B, BEL 3.

(See *Primary and Secondary Etiologies of Hypothyroidism, Measurement of Thyroxine and Triiodothyronine, Pitfalls Encountered when Interpreting Serum TSH Levels,* and *L-thyroxine (T4) 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 - Hypothyroidism During Pregnancy*, and *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 - Hypothyroidism During Pregnancy*, and *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 T4) should be monitored every four 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 - Hypothyroidism During Pregnancy*.)

Recommendation 26 – In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within four to eight 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 (T4) Treatment of Hypothyroidism, AREAS FOR FUTURE RESEARCH – Agents and Conditions having an Impact on L-Thyroxine (T4) 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, and (viii) unusual constellation of thyroid function test results.

Grade C, BEL 3.

(See *When to Consult an Endocrinologist*.)

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 (DS), and nutraceuticals (N) 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 (DS) and Nutraceuticals (N) in the Treatment of Hypothyroidism,* and *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 (DS) and Nutraceuticals (N) in the Treatment of Hypothyroidism,* and *Excess Iodine Intake and Hypothyroidism*.)

Recommendations 32.2 was an unanimous expert opinion

Recommendation 33 - Selenium should not be used to prevent or treat hypothyroidism.

Grade B, BEL 2.

(See *Dietary Supplements (DS) and Nutraceuticals (N) in the Treatment of Hypothyroidism,* and *Selenium*.)

Recommendation 34 - Patients taking Dietary Supplements (DS) and Nutraceuticals (N) 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 (DS) and Nutraceuticals (N) in the Treatment of Hypothyroidism, Thyroid Enhancing Preparations,* and *Thyromimetic Preparations*.)

Recommendation 34 was 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 (RR) of coronary heart disease 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 the risk was 1.51 compared to 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, 8 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, but not for those over 65 (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 and not treated with thyroid hormone had higher all-cause mortality (118). Most recently a United Kingdom general practitioner database was analyzed to assess the impact of T4 treatment on fatal and nonfatal cardiac events in over 3,000 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 T4 (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 3, 000 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 twenty 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 withT4 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 2,000 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 T4 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 T4 (295). However, other studies have not (296), (297).

L-Thyroxine (T4) / L-Triiodothyronine (T3) combination therapy

An important question is whether a recent study had sufficient data to warrant revisiting why some patients seem to feel better on T4/T3 combinations, and whether we can identify them and safely treat them (136) with this combination.

L-Triiodothyronine (T3) monotherapy

A potential role for T3 monotherapy in lieu of T4 monotherapy was recently raised by a small, randomized, double-blind, crossover intervention study done comparing T3 monotherapy with T4 monotherapy in patients with hypothyroidism (298). Thrice daily dosing was employed for each. Comparable TSH levels were achieved. Mild weight loss, decreases in total cholesterol,

LDL cholesterol, and apolipoprotein levels were seen without differences in cardiovascular function, insulin sensitivity, or quality of life with T3 monotherapy compared with T4 monotherapy. The small size and short duration of the study as well as thrice daily dosing presently precludes considering T3 monotherapy as an alternative to T4 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 DITPA (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 be of benefit in lowering 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 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 (CATS) in the United Kingdom and Italy examined the impact at three years of age of T4 treatment if FT4 is below the 2.5th percentile or if TSH is above the 97.5th percentile (219). Analyses failed to demonstrate a benefit when screening is 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 intelligence quotient (IQ) at 5 years of age following a universal screening versus case finding program.

Agents and Conditions having an impact on L-thyroxine (T4) 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 thyroxine binding globulin (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 T4.

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

    Non-organified
- Size of iodine pool
- Autoimmune Thyroid Disease
- Nodular Thyroid Disease
- Thyroid hormone status
- Genetic factors

The Principal mechanisms and reasons 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 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, are likely to do so, or 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. Some drugs, because of their potential importance, even though they are not generally available such as perchlorate, Iopanoic acid, and Ipodate, are also listed. 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).

DISCLOSURES

Dr. Jeffrey R. Garber reports that he does not have any relevant financial relationships with any commercial interests. Dr. Rhoda H. Cobin reports that she does not have any relevant financial relationships with any commercial interests. Dr. Hossein Gharib reports that he does not have any relevant financial relationships with any commercial interests. Dr. James V. Hennessey reports that he does not have any relevant financial relationships with any commercial interests. Dr. Irwin Klein reports that he does not have any relevant financial

relationships with any commercial interests. Dr. Jeffrey I. Mechanick reports that he has received speaker and program development honoraria from Abbott Nutrition. Dr. Rachel Pessah-Pollack reports that she does not have any relevant financial relationships with any commercial interests. Dr. Peter A. Singer reports that he does not have any relevant financial relationships with any commercial interests. Dr. Kenneth A. Woeber reports that he does not have any relevant financial relationships with any commercial interests.

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Table 1. Organization of Clinical Practice Guidelines for Hypothyroidism in Adults

	QUESTIONS AND GUIDELINE RECOMMENDATIONS			
Q1		*When should antithyroid antibodies be measured*?		
R1			TPO Ab measurements & subclinical hypothyroidism	
R2			TPO Ab measurements & nodular thyroid disease	
R3			TPO Ab measurements & recurrent miscarriage	
R4			TPO Ab measurements in women with Graves' disease who have had thyroidectomy or RAI Rx before pregnancy	
Q2		*What is the role of clinical scoring systems in the diagnosis of patients with hypothyroidism?*		
R5			Do not use CSS to diagnose hypothyroidism	
Q3		*What is the role of diagnostic tests apart from serum thyroid hormone levels and TSH in the evaluation of patients with hypothyroidism?*		
R6			Do not use indirect tests to diagnose hypothyroidism	
Q4		*What are the preferred thyroid hormone measurements in addition to TSH in the assessment of patients with hypothyroidism?*		
R7			When to use FT4 vs total T4	
R8			Using FT4 to monitor L-thyroxine Rx	
R9			Estimating serum FT4 in Pregnancy	
R10			Prohibition against using T3 to dx hypothyroidism	
R11			Measuring TSH in hospitalized patients	
R12			Serum T4 vs TSH for management of central hypothyroidism	
Q5		*When should TSH levels be measured in patients being treated for hypothyroidism?*		
R13			When to measure TSH in patients taking T4 for	

			hypothyroidism	
Q6		*What should be considered the upper limit of the normal range of TSH values?*		
R14.1			Reference ranges for TSH, age and lab variability	
R14.2			Reference ranges for TSH in pregnant women	
Q7		*Which patients with TSH levels above a given laboratory's reference range should be considered for treatment with L-thyroxine (T4)?*		
R15			Treating patients with TSH above 10mIU/L	
R16			Treating if TSH is elevated but below 10 mIU/L	
Q8		*In patients with hypothyroidism being treated with L-thyroxine what should the target TSH ranges be?*		
R17			Target TSH when treating hypothyroidism	
Q9		*In patients with hypothyroidism being treated with L-thyroxine who are pregnant, what should the target TSH ranges be?*		
R18			Target TSH when treating hypothyroid pregnant women	
Q10		*Which patients with normal serum TSH levels should be considered for Rx with L-thyroxine (T4)?*		
R19.1			L-thyroxine Rx in pregnant women with "normal" TSH	
R19.2			L-thyroxine Rx in women of child-bearing age or pregnant with "normal" TSH and have positive TPOAb or history of miscarriage or hypothyroidism	
R19.3			L-thyroxine Rx in pregnant women or those planning pregnancy with TPOAb and serum TSH is > 2.5 mIU/L	
R19.4			Monitoring of pregnant women with TPOAb or a or a "normal" TSH but > 2.5 mIU/L who are not taking L-thyroxine	

Q11		*Who, among patients who are pregnant, or planning pregnancy, or with other characteristics, should be screened for hypothyroidism?*		
R20.1.1			Universal screening of women planning pregnancy included assisted reproduction	
R20.1.2			Aggressive case finding for hypothyroidism for women planning pregnancy	
R20.2			Age and screening for hypothyroidism	
R21			Aggressive case finding for hypothyroidism – who to target	
Q12		*How should patients with hypothyroidism be treated and monitored?*		
R22.1			Form of thyroid hormone for treatment of hypothyroidism	
R22.2			L-thyroxine and L-triiodothyronine Combinations to treat hypothyroidism	
R22.3			Prohibition against using L- thyroxine and L-triiodothyronine combinations to treat pregnant women or those planning pregnancy	
R22.4			Prohibition against using desiccated thyroid hormone to treat hypothyroidism	
R22.5			Prohibition against using TRIAC (Tiratricol) to treat hypothyroidism	
R22.6			L- thyroxine Rx for hypothyroidism in patients with cardiac events	
R22.7.1			L- thyroxine Rx for hypothyroidism in young healthy adults	
R22.7.2			L- thyroxine Rx for subclinical hypothyroidism compared to overt hypothyroidism	
R22.8			L- thyroxine Rx for hypothyroidism in In patients older than 50 to 60	
R22.9			Order of L- thyroxine Rx & glucocorticoids in patients with adrenal insufficiency and hypothyroidism	

R23			L- thyroxine Rx for hypothyroidism – time to take, method of taking, and storage	
R24			FT4 as the target measurement when treating central hypothyroidism	
R25.1			Testing and treating women with hypothyroidism as soon as they become pregnant	
R25.2			Goal TSH in pregnant women with hypothyroidism	
R25.3			Monitoring pregnant women with hypothyroidism	
R26			Monitoring hypothyroid patients who start drugs affecting T4 bioavailability or metabolism	
R27			Prohibition against targeting specific TSH values in hypothyroid patients who are not pregnant	
Q13		*When should endocrinologists be involved in the care of patients with hypothyroidism?*		
R28			Type of hypothyroid patient who should be seen in consultation with an endocrinologist	
Q14		*Which patients should not be treated with thyroid hormone?*		
R29			Need for biochemical confirmation of the diagnosis before chronic treatment of hypothyroidism	
R30			Prohibition against using thyroid hormone to treat obesity	
R31			Thyroid hormone treatment and depression	
Q14		*What is the role of iodine supplementation, dietary supplements (DS), and nutraceuticals (N) in the treatment of hypothyroidism?*		
R32.1			Prohibition against using iodine supplementation to treat hypothyroidism in iodine sufficient areas	
R32.2			Inappropriate method for iodine supplementation in pregnant women	
R33			Prohibition against using selenium as treatment or preventive	

			measurement for hypothyroidism	
R34			Recommendation regarding dietary supplements, nutraceuticals, and products marked as “thyroid support” for hypothyroidism	
	AREAS FOR FUTURE RESEARCH			
		Cardiac benefit from treating subclinical hypothyroidism		
		Cognitive benefit from treating subclinical hypothyroidism		
		L-Thyroxine (T4) / L-Triiodothyronine (T3) Combination Therapy		
		L-Triiodothyronine (T3) Monotherapy		
		Thyroid Hormone analogues		
		Screening for hypothyroidism in pregnancy		
	Agents and Conditions having an impact on L-thyroxine (T4) therapy and interpretation of thyroid tests			
	DISCLOSURES			
	ACKNOWLEDGMENTS			
	REFERENCES			
	SUPPLEMENT 1 – Supplementary information regarding ATA and AACE guidelines)			See online version
	SUPPLEMENT 2 – Supplementary information regarding Evidence Levels (EL) for Reference Citations			See online version
	SUPPLEMENT 3 – Complete List of Guideline Recommendations			See online version

Table 2. Levels of Scientific Substantiation in Evidence-Based Medicine[a]

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 non-experimental, clinically obvious, evidence (for example, 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 non-experimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with 1 or more major or 3 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

[a]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.

Table 3: Grade-Recommendation Protocol Adopted by The American Association of Clinical Endocrinologists and The American Thyroid Association for the Hypothyroidism Clinical Practice Guideline

2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade[a]

Best evidence level	Subjective factor impact	Two – thirds consensus	Mapping	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

a Starting with the left column, best evidence levels (BEL), 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. NA = not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).

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: 5.9% women; 2.3% men; 39% of whom had subnormal T4
British Whickham			10.0	9.3% women; 1.2% men

See References 11-15 for sources of data.

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		

Table 6: Assessment of Free T4

Test	Method	Comments
free T4 index (FTI) or free T4 estimate (FTE)	product of total T4 and thyroid hormone binding ratio (THBR) or T3-resin uptake	normal values in pregnancy and with alterations in TBG binding;
direct immunoassay of free T4 (FT4)	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 T4 (FT4)	without physical separation using anti-T4 antibody	reduced values in pregnancy compared to nonpregnant reference ranges; normal values with alterations in TBG binding

Table 7: TSH 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 antithyroid antibodies Not pregnant Not on: estrogens, androgens, lithium
Hanford Thyroid Disease Study	4.10	No evidence of thyroid disease Negative antithyroid antibodies Not on thyroid medications Normal ultrasound (no nodules or thyroiditis)
Pregnancy 1st Trimester	2.0-2.5	See Sections L-Thyroxine Treatment of Hypothyroidism and Hypothyroidism during pregnancy
Pregnancy 2nd Trimester	3.0	See Sections L-Thyroxine Treatment of Hypothyroidism and Hypothyroidism during pregnancy
Pregnancy 3rd Trimester	3.5	See Sections L-

		Thyroxine Treatment of Hypothyroidism and Hypothyroidism during pregnancy

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

ORGANIZATION	SCREENING RECOMMENDATIONS
American Thyroid Association	Women and men >35 year of age should be screened every 5 years.
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened.
College of American Pathologists	Women >50 year of age should be screened "if they seek medical care;" all geriatric patients should be screened on admission to the hospital and at least every 5 years.
American Academy of Family Physicians	Patients > 60 years of age should be screened.
American College of Obstetrics and Gynecology	Women in "high-risk groups" (those with autoimmune disease or a strong family history of thyroid disease) should be screened starting at 19 years of age.
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.

Table 9: ICD 9 codes to support TSH 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

Table 10

10.1: Interference with absorption

Bile Acid Sequestrants (Cholestyramine, Colestipol, Colesevelam)
Sucralfate
Cation Exchange resins (Kayexelate)
Oral Bisphosphonates
Proton Pump Inhibitors
Raloxifene (*)
Multivitamins (containing Ferrous Sulfate or Calcium Carbonate)
Ferrous Sulfate
Phosphate Binders (Sevelamer, Aluminum Hydroxide)
Calcium salts (Carbonate, Citrate, Acetate)
Chromium Picolinate
Charcoal
Orlistat (**)
Ciprofloxacin
H2 Receptor Antagonists (*)

Malabsorption Syndromes
Celiac Disease
Jejunoileal Bypass Surgery
Cirrhosis (biliary)
Achlorhydria

Diet
Ingestion with a meal
Grapefruit juice (*)
Espresso coffee
High Fiber Diet
Infants Fed Soybean Formula
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***, Iopanoic Acid***)
    - Perchlorate (***)
  - Hormone Production
    - Iodine (including kelp supplements)
    - Amiodarone
    - Thionamides (carbimazole, methimazole, PTU)
    - Iodinated contrast (Ipodate***, Iopanoic Acid***)
    - Sulfonylureas
    - Sulfonamides
    - Ethionamide

- Secretion
  - Lithium
  - Iodine (including kelp supplements)
  - Amiodarone
  - Iodinated contrast (Ipodate***, Iopanoic Acid***)
- 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

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 (**)
    - St John's Wort (*)
- Hypophysitis
  - Ipilimumab

10.4: Increased Clearance

Phenobarbital
Primidone
Phenytoin

Carbamazepine Oxacarbazepine (**) Rifampin Growth Hormone Sertraline (**) Tyrosine Kinase Inhibitors (imatinib**, sunitinib) Quetiapine (**) Stavudine (**) Nevirapine (*, **)
10.5: Peripheral metabolism
Glucocorticoids Amiodarone Propylthiouracil Beta Blockers (e.g., propranolol, nadolol) Iodinated contrast (Ipodate***, Iopanoic Acid***) Interleukin-6 Clomipramine
*Impact uncertain **Mechanism uncertain *** Not presently available in the USA

INFORMATION PERTINENT TO THIS PUBLICATION REGARDING AMERICAN THYROID ASSOCIATION (ATA) CLINICAL PRACTICE GUIDELINES AND AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS (AACE) MEDICAL GUIDELINES FOR CLINICAL PRACTICE

Supplement 1, Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association, Garber *et al*. Thyroid, 2012

The ATA develops Clinical Practice Guidelines to provide guidance and recommendations for particular practice areas concerning thyroid disease and 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 circumstances. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients.

The ATA develops guidelines based on the evidence available in the literature and the expert opinion of the task force in the recent timeframe of the publication of the guidelines. Management issues have not been and cannot be comprehensively addressed in randomized trials; therefore, the evidence cannot be comprehensive. Guidelines cannot always account for individual variation among patients. Guidelines cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Therefore, the American Thyroid Association considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the treating physician and health care professionals with the full consideration of the individual patient’s clinical history and physical status. In addition, the guideline concerns the therapeutic

interventions used in clinical practice and do not pertain to clinical trials. Clinical trials are a separate matter, designed to research new and novel therapies, and the guidelines are not necessarily relevant to their purpose.

Guideline development includes an identification of areas for future study and research, indicating the focus for future investigational therapy; based on the findings reviewed and synthesized from the latest literature.

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. 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.

EVIDENCE LEVELS (EL) FOR REFERENCE CITATIONS
Supplement 2, Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association, Garber et al. Thyroid, 2012

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LIST OF HYPOTHYROIDISM GUIDELINE RECOMMENDATIONS

Supplement 3, Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association, Garber *et al*. Thyroid, 2012

Recommendation 1 - Thyroid peroxidase antibody (TPOAb) measurements should be considered when evaluating patients with subclinical hypothyroidism.

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.

Recommendation 3 - TPOAb measurement should be considered when evaluating patients with recurrent miscarriage, with or without infertility.

Recommendation 4 - Measurement of TSH-receptor antibody (TSHRAb) 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 either be initially done at 20-26 weeks of gestation or during the first trimester and if they are elevated again at 20-26 weeks of gestation.

Recommendation 5 - Clinical scoring systems should not be used to diagnose hypothyroidism.

Recommendation 6 - Tests such as clinical assessment of reflex relaxation time, cholesterol, and muscle enzymes should not be used to diagnose hypothyroidism.

Recommendation 7 - Apart from pregnancy, assessment of serum free T4 should be done instead of total T4 in the evaluation of hypothyroidism. An assessment of serum free T4 includes a free T4 index (FTI) or free T4 estimate (FTE) and direct immunoassay of free T4 without physical separation using anti-T4 antibody.

Recommendation 8 - Assessment of serum free T4, in addition to TSH, should be considered when monitoring L-thyroxine therapy.

Recommendation 9 - In pregnancy, the measurement of total T4 or a free thyroxine index (FTI), in addition to TSH, should be done to assess thyroid status. Because of the wide variation in the results of different free T4 assays, direct immunoassay measurement of free T4 should only be employed when method-specific and trimester-specific reference ranges for serum free T4 are available.

Recommendation 10 - Serum total T3 or assessment of serum free T3 should not be done to diagnose hypothyroidism.

Recommendation 11 - TSH measurements in hospitalized patients should be done only if there is an index of suspicion for thyroid dysfunction.

Recommendation 12 - In patients with central hypothyroidism, assessment of free T4 or FTI, not TSH, should be done to diagnose and guide treatment of 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.

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.

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.

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.

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 they have symptoms suggestive of hypothyroidism, positive TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have associated risk factors for these diseases.

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.

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

Recommendation 19.1 - Treatment with L-thyroxine *should be considered* in women of child bearing 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 and third 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.

Recommendation 19.2 - Treatment with L-thyroxine *should be considered* in women of child-bearing 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.

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.

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 four weeks in the first 20 weeks of pregnancy for the development of hypothyroidism.

Recommendation 20.1.1 - Universal screening is not recommended for patients who are pregnant or are planning pregnancy, including assisted reproduction.

Recommendation 20.1.2 – "Aggressive case finding" for patients who are planning pregnancy should be considered.

Recommendation 20.2 - Screening for hypothyroidism should be considered in patients over the age of 60.

Recommendation 21 - "Aggressive Case–Finding" should be considered in those at increased risk for hypothyroidism.

Recommendation 22.1 - Patients with hypothyroidism should be treated with L-thyroxine monotherapy.

Recommendation 22.2 - The evidence does not support using L-thyroxine and L-Triiodothyronine combinations to treat hypothyroidism.

Recommendation 22.3 - L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy.

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.

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.

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.

Recommendation 22.7.1 - When initiating therapy in young healthy adults with hypothyroidism beginning treatment with full replacement doses should be considered.

Recommendation 22.7.2 – 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 micrograms 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.

Recommendation 22.8 - When initiating therapy in patients older than 50-60 years, without evidence of coronary heart disease (CHD), an L-thyroxine dose of 50 micrograms daily should be considered.

Recommendation 22.9 - Treatment with glucocorticoids in patients with combined adrenal insufficiency and hypothyroidism should precede treatment with L-thyroxine.

Recommendation 23 - L-thyroxine should be taken with water consistently 30 to 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.

Recommendation 24 - In patients with central hypothyroidism, assessments of serum free T4 should guide therapy and targeted to exceed the mid-normal range value for the assay being used.

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.

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.

Recommendation 25.3 - Maternal serum TSH (and total T4) should be monitored every four weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation and L-thyroxine dosages adjusted as indicated.

Recommendation 26 – In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within four to eight weeks of initiation of treatment with drugs that decrease the bioavailability or alter the metabolic disposition of the L-thyroxine dose.

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.

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, and (viii) unusual constellation of thyroid function test results.

Recommendation 29 - Thyroid hormones should not be used to treat symptoms suggestive of hypothyroidism without biochemical confirmation of the diagnosis.

Recommendation 30 - Thyroid hormones should not be used to treat obesity in euthyroid patients.

Recommendation 31 - There is insufficient evidence to support using thyroid hormones to treat depression in euthyroid patients.

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.

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.

Recommendation 33 - Selenium should not be used to prevent or treat hypothyroidism.

Recommendation 34 - Patients taking Dietary Supplements (DS) and Nutraceuticals (N) 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.