

GUIDELINES FOR THE TREATMENT OF HYPOTHYROIDISM

Prepared by the American Thyroid Association Task Force

on Thyroid Hormone Replacement

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ABSTRACT

Background

A number of recent advances in our understanding of thyroid physiology may shed light on why some patients feel unwell while taking levothyroxine monotherapy. The purpose of this task force was to review the goals of levothyroxine therapy, the optimal prescription of conventional levothyroxine therapy, the sources of dissatisfaction with levothyroxine therapy, the evidence on treatment alternatives, and the relevant knowledge gaps. We wished to determine whether there are sufficient new data generated by well-designed studies to provide reason to pursue such therapies and change the current standard of care. This document is intended to inform clinical decision-making on thyroid hormone replacement therapy, and is not a replacement for individualized clinical judgment.

Methods

Task force members identified 24 questions relevant to the treatment of hypothyroidism. The clinical literature relating to each question was then reviewed. Clinical reviews were supplemented, when relevant, with related mechanistic and bench research literature reviews, performed by our team of translational scientists. Ethics reviews were provided, when relevant, by a bioethicist. The responses to questions were formatted, when possible, in the form of a formal clinical recommendation statement. When responses were not suitable for a formal clinical recommendation, a summary response statement without a formal clinical recommendation was developed. For clinical recommendations, the supporting evidence was appraised, and the strength of the clinical recommendations was assessed, using the American College of Physicians (ACP) system. The final document was organized so that each topic is introduced with a question, followed by a formal clinical recommendation. Stakeholder input was received at a national meeting, with some subsequent refinement of the clinical questions addressed in the document. Consensus was achieved for all recommendations by the task force.

Results

We reviewed the following therapeutic categories: i) levothyroxine therapy, ii) non-levothyroxine based thyroid hormone therapies, and iii) use of thyroid hormone analogs. The

second category included thyroid extracts, synthetic combination therapy, triiodothyronine therapy, and compounded thyroid hormones.

Conclusions

We concluded that levothyroxine should remain the standard of care for treating hypothyroidism. We found no consistently strong evidence for the superiority of alternative preparations (e.g. levothyroxine-liothyronine combination therapy, or thyroid extract therapy, or others) over monotherapy with levothyroxine, in improving health outcomes. Some examples of future research needs include: development of superior biomarkers of euthyroidism to supplement TSH measurements, mechanistic research on serum triiodothyronine levels (including effects of age and disease status, relationship with tissue concentrations, as well as potential therapeutic targeting), and long-term outcome clinical trials testing combination therapy or thyroid extracts (including sub-group effects) Additional research is also needed to develop thyroid hormone analogs with a favorable benefit to risk profile.

INTRODUCTION

Background, Objectives and Rationale

Levothyroxine (L-T4) has been considered the standard of care for treatment of hypothyroidism for many years. This treatment is efficacious when administered orally, has a long serum half-life that permits daily administration, and results in resolution of the signs and symptoms of hypothyroidism in the majority of patients. However, a small proportion of patients being treated for hypothyroidism does not feel that L-T4 therapy is efficacious in restoring optimum health.

A number of recent advances in our understanding of thyroid physiology may shed light on why some patients feel unwell while taking L-T4 monotherapy. For example, much has been learned about the sources and regulation of triiodothyronine (T3) in the plasma and within specific tissues, as well as about the regulation of thyroid stimulating hormone (TSH). In addition, new data have emerged concerning associations of dissatisfaction with L-T4 therapy with genetic variation in deiodinases, and fatigue and depression in treated hypothyroid patients with genetic variations in thyroid hormone transporters. The mandate of this task force was to review the goals of L-T4 therapy, examine sources of dissatisfaction with L-T4 therapy, examine the evidence concerning treatment alternatives, discuss gaps in our current knowledge of these therapies, and determine whether new data provide reason to pursue such therapies.

In this document the latest data regarding combination therapy, L-T3 monotherapy, compounded thyroid hormones, and nutraceuticals are presented. As a secondary objective, we also review the literature on thyroid hormone analogs. Pharmacology and regulatory aspects of the therapies that we reviewed is discussed. The potential for genetic variations to influence the ability to optimize thyroid hormone therapy is explored. The challenges of titrating thyroid hormone therapy in specific groups such as the pediatric, pregnant, and elderly populations are considered. However, the topic of subclinical hypothyroidism (SCH) is not addressed, other than in the pediatric population, because of prior extensive reviews of this topic in adults (1-4). Thyroid hormone therapy in patients with thyroid cancer is only mentioned when it was considered germane to the topic being discussed. Our goal is to promote discussion to improve our understanding of these issues, provide recommendations where possible, and to identify areas where further research is needed.

A recent comprehensive document, the “Clinical Practice Guidelines for Hypothyroidism in Adults Co-sponsored by the American Association of Clinical Endocrinologists (AACE) and

the American Thyroid Association (ATA)”, covers broader aspects of the management of hypothyroidism (3). In addition, two recent consensus documents published by the ATA and the Endocrine Society address the management of hypothyroidism during pregnancy (1, 2). While this document was in preparation, guidelines from the European Thyroid Association (ETA) specifically addressing the issue of combined treatment with L-T4 and L-T3 were published (5). We acknowledge these guidelines, and our document was prepared with a goal of minimizing redundancy. It was intended that the features that would distinguish this document from these guidelines would be 1) attention to the basic science and translational underpinning for the various thyroid hormone therapies, 2) extensive consideration of ethical issues, 3) focus on treatment itself, as opposed to other aspects of diagnosis and management, and, most importantly, 4) focus on evaluation of treatment alternatives. We also wished to explore promising pre-clinical data for potential future therapies. For each topic, we evaluated the scientific validity of the studies cited.

The target audience for these guidelines includes clinicians providing care to patients with hypothyroidism. We outline what we believe is rational and optimal medical practice based on our evaluation of the evidence at the time of publication. However, areas of uncertainty and difference of opinion among experts remain, and it is not the intent of these guidelines to replace clinical judgment or individual decision-making. Rather, these recommendations are intended to inform the clinical decision-making process.

Approach Utilized in Conducting this Review

Our task force was commissioned and approved by officers of the American Thyroid Association (ATA). We formed in the summer of 2011 and our composition included members with particular expertise in mechanistic and translational science (4 members), members with particular expertise in clinical thyroidology (6 members), a member with a background in pediatric endocrinology, a member with expertise in design and evaluation of health research, and a bioethicist. As of October 2011, we were re-directed and specifically asked to develop clinical practice guidelines. Our task force met face to face in October 2011, June 2012, September 2012, June 2013, October 2013, and June 2014 with 7 interim discussions using conference calls. A spring meeting of the ATA that was open to all potential stakeholders (e.g. healthcare providers, patients, public) was held on April 25th and 26th, 2013 in order to highlight

and promote broad discussion regarding relevant and topical issues (6). Information needs identified by stakeholders at this meeting were incorporated in task force group decisions in considering topics for review.

Task force members identified 24 questions relevant to the management of hypothyroidism, which were divided among the members. The clinical literature relating to each question was then reviewed by a primary reviewer, who summarized the findings, and compiled a response to the question in the form of a recommendation. The summary of the literature and response to each question were next revised by a secondary reviewer. Clinical reviews were supplemented, when relevant, with related mechanistic and bench research literature reviews, performed by a translational scientist, and reviewed by a panel subgroup of basic scientists. These sections served as the mechanistic background for the clinical reviews and are indicated in italicized font. Task force members also reviewed published guidelines from other groups (and related cross-references) when available. For some topics, such as compounding of thyroid hormones, nutraceuticals, and Wilson's syndrome, when sparse published medical literature was available, we consulted the Internet using Google search. Ethics reviews were provided, when relevant, by a bioethicist, with a second review by one or more task force members with clinical expertise.

The development of each recommendation was as follows: the first reviewer developed the recommendation, reached consensus with the second reviewer, then presented to the group for input, with revisions until the entire group reached consensus. There was opportunity for revision at all steps of the review process. Formal consensus was obtained among group members for all recommendations. There was also agreement regarding the interpretation of areas of uncertainty discussed in the text, except in two instances where the differences in interpretation are noted. Each recommendation, along with the associated literature review was assembled into a document. The responses to questions were formatted, when possible, in the form of a formal clinical recommendation statement. However, given the broad nature of questions posed by the task force and the broad nature of reviewed literature (including basic science and ethics literature), not all responses were amenable to a formal clinical recommendation, and in such circumstances, a summary response statement without a formal clinical recommendation was developed. For clinical recommendations, the supporting evidence was appraised, and the strength of the clinical recommendations was described, using the

American College of Physicians (ACP) system (7). The quality of basic science and ethics papers was not appraised, due to lack of availability of appropriate grading systems for this purpose. The final document is organized so that each topic is introduced with a question, which is followed by a formal clinical recommendation, and completed with a literature review. When a formal clinical recommendation was not feasible because of sparse evidence an ungraded summary statement without a formal recommendation is provided.

In searching for relevant citations for review, task force members conducted electronic database searches of PubMed, using relevant search terms. Databases searches were generally updated once or more. A language restriction was not imposed on studies considered for review. Only published studies were eligible for inclusion for review for the purpose of formulating clinical recommendations. Electronic searches were supplemented with hand searches, including cross-referencing of included papers and reviews, as well as papers suggested by other task force members. For the clinical topic reviews, the authors preferentially selected papers of the highest methodologic quality for inclusion (e.g. randomized controlled trials and meta-analyses/systematic reviews of randomized controlled trials), but when these were not available, articles with lower quality of evidence were reviewed. Greater credence was afforded to such articles when the findings were consistent or congruent

Clinical recommendations were graded according to the ACP grading system for evidence and recommendations (7) (see table 1). Using this system as a foundation, the strength of each clinical recommendation was reported according to the following categories: Strong, Weak, or No Recommendation due to Insufficient Evidence. The quality of evidence upon which the recommendation was based was graded as strong, moderate, low, or insufficient. The interpretation of this grading system is explained in detail in table 2, which is a reproduction of table 2 from the original article (7). It should be noted that in this grading system strong recommendations can be made based on low quality evidence if it is nevertheless assessed that benefits clearly outweigh the risks and burden. Such strong recommendations may change when higher-quality evidence becomes available.

Our final guidelines document was approved by the board of directors of the ATA, underwent a one month period of open comment by the ATA membership, and was peer-reviewed by reviewers for the journal *Thyroid*. Revisions were made in response to each of these reviews. As with other ATA-sponsored guidelines, we anticipate that this document will be

revised and updated on a 5-year cycle.

Management of potential competing interests

Special attention was paid to potential conflicts of interest. Possible conflicts of interest of potential task force members were reviewed by the officers of the ATA. No confirmed task force member was considered to have a serious conflict that precluded inclusion on the task force. As per ATA policy, potential competing interests of task force members were recorded at baseline and updated on a yearly basis. The competing interests of members of this task force were shared with the entire group and are listed separately. The task force members volunteered their time and expertise and did not receive funds from the ATA. No funds were received from commercial sources for the development of this document. Task force members did not receive any funding or gifts for their participation, and paid for their own travel expenses and registration related to face-to-face meetings. Task force members were encouraged to share any questions or concerns about potential competing interests (or the appearance of any competing interests) with the co-chairs of the task force, and, where appropriate, any such questions or concerns were formally reviewed by the ATA Ethics committee. As per ATA policy, the results of any reviews by the Ethics Committee were shared with the entire group, with an opportunity to voice any additional potential questions or concerns relating to the review.

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SECTION I. LEVOTHYROXINE THERAPY

Levothyroxine therapy and endpoints during therapy

1a. Why is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?

Recommendation

Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost.

Strong recommendation. Moderate quality evidence.

Mechanistic background

Thyroid hormone action is an important determinant of development and growth, and in adults plays a critical role in the regulation of the function and metabolism of virtually every organ system (8, 9). Tissue-specific modulation of the thyroid hormone action is achieved by a complex and redundant control system that includes thyroid hormone secretion, plasma transport, transmembrane transport, activation/inactivation, and interaction with nuclear receptor isoforms and their co-regulators.

Hypothyroid patients are deficient in endogenously produced thyroid hormone. The rationale for the therapeutic use of L-T₄ in the treatment of hypothyroidism lies in the peripheral conversion of the exogenously administered pro-hormone T₄ into its active metabolite T₃ (10). This activating conversion is accomplished by two enzymes, the type 1 (D1) and type 2 (D2) deiodinases. A third deiodinase, type 3 deiodinase (D3) participates in the clearance of both serum T₄ and T₃ (11). Understanding the impact of the deiodinases on thyroid hormone action requires knowledge of their kinetics, tissue distribution, sub-cellular localization, and regulation (see table 3). Currently, no clinical assays measure the deiodinase activities directly, thus their contributions to thyroid hormone homeostasis in humans have been established in the research setting in which thyroid hormone levels, kinetic studies with radioactive iodothyronines, mathematical modeling, and tissue biopsies can be utilized.

D1 is expressed predominantly in liver and kidney, with lesser expression in the thyroid (12). D1 has a dual role, both producing a small amount of circulating T3 (D1 is estimated to contribute approximately 24% of circulating T3 in healthy individuals), and also preserving iodide by removing iodine from inactive metabolites of T3 and T4 in the liver and kidney (conjugated iodothyronines) (13). Of note, the D1 gene is upregulated by T3, and thus in hyperthyroidism the proportion of circulating T3 arising from the D1 pathway is significantly increased (11). Propylthiouracil inhibits D1, explaining some of its therapeutic benefit in this setting (14).

D2 activity in humans has been detected in various tissues, predominantly in the central nervous system, pituitary gland, thyroid, heart, brown adipose tissue and skeletal muscle (15-17). The role of D2 is to convert T4 to T3; approximately 60% of circulating T3 is estimated to originate from the D2 pathway (18-20). Expressed in the endoplasmic reticulum (21, 22), D2 generated T3 first accumulates in the cell long enough to contribute to the nuclear T3 pool (23); thus changes in D2 activity can cause intracrine tissue-specific changes in thyroid signaling. Intracrine refers to the conversion of T4 into T3 within the cell resulting in a cell-specific modulation of the hormonal signaling. Subsequently, D2-generated T3 exits the cells, thus contributing thyroid signaling in surrounding tissues (paracrine effects) and to the plasma pool of T3 affecting thyroid signaling in other tissues. D1 on the other hand resides in the plasma membrane and does not seem to alter the intracellular T3 concentration.

In healthy adults, D3 expression is found predominantly in the brain and skin (24, 25). In contrast to D1 and D2, D3 is an inactivating deiodinase, catalyzing the conversion of T3 to T2 (3',5'-T2), and T4 to reverse T3 (rT3: 3,3',5'-T3). Thus, the role of D3 is to clear T3. Like D2, D3 is thought to have tissue-specific effects, preventing circulating T3 from entering the nucleus. In disease states, and in particular in hypoxic states, D3 expression can be found ectopically in a wide range of tissues (26); the resultant increase in T3 clearance promotes both tissue-specific and systemic lowering of T3, and has been implicated in the pathogenesis of the "non-thyroidal illness syndrome" (27). Whether this is true tissue hypothyroidism or adaptation to illness is unclear (28, 29).

Thyroid hormone was long thought to cross the plasma membrane via simple diffusion, but recent studies have identified a number of thyroid hormone transporters including members of the monocarboxylate transporter family (MCT) and the organic anion transporting

polypeptides (OATP), which are important for maintaining the intracellular concentrations of thyroid hormones (30). Thus, the particular circulating levels of thyroid hormones achieved during monotherapy, with higher serum T4 and lower serum T3 levels than the naturally euthyroid state (see section 7b) are available to the thyroid hormone transporters, which are then responsible for modulating intracellular levels of T3. MCT and OATP transporters are expressed in liver, kidney, brain, and heart, with MCT8 and OATP1C1 being most important in the brain. Mutations identified in the thyroid hormone transporters constitute a clinically relevant group of mutations in the thyroid hormone signaling pathway (see section 13a).

Discussion of the clinical literature

Until the 1970's, the mainstay of thyroid hormone replacement therapy was performed with desiccated thyroid extracts. Three factors were likely responsible for L-T4's rise to the predominant therapy in the latter half of the 20th century: first, the isolation of T4 in 1927 by Kendall (31); second, the synthesis of T4 (32) and its better-absorbed sodium salt by Chalmers et al. (33); and third, the demonstration that the biologically active T3 was generated from T4 in humans (10).

Approximately 85 micrograms (mcg) of T4 are secreted by the thyroid gland daily. Of the total daily T3 production of about 33 mcg in normal man, approximately 80% (about 26 mcg) arises from peripheral conversion from T4, and only about 20% (approximately 6.5 mcg) derives from direct thyroidal secretion (34). It is now well established that while T4 is the major secretory product of the thyroid gland, thyroid hormone action in peripheral tissues is due to the effects of T3 binding to its nuclear receptor, defining T4 as a pro-hormone for T3.

Gastrointestinal absorption of the tablet formulation of L-T4 is in the 70-80% range in healthy fasting adults (35). The long (approximately 7 day) half-life allows once-a-day dosing, and stable serum levels of both T4 and T3 (36). With such therapy, there will be a transient peak in serum T4 and FT4 levels of about 15% magnitude about 4 hours after L-T4 administration (37). Moreover, in athyreotic individuals treated with L-T4 to achieve a normal serum TSH, the serum FT4 is usually higher and the serum T3 is either normal (38, 39) or lower than the values seen in normal individuals (39-43). Steady state levels of T4 and TSH are generally achieved in 6 weeks (approximately 5-6 half-lives) after initiation of therapy (38). Although there are no

randomized clinical trials comparing L-T4 to placebo to treat hypothyroidism, it has clearly been demonstrated that L-T4 or L-T3 withdrawal leads to a recurrence of hypothyroidism in patients who have undergone thyroid surgery for thyroid cancer or who were diagnosed with profound hypothyroidism (44-46).

1b. What are the clinical and biochemical goals for levothyroxine replacement in primary hypothyroidism?

Recommendation

Levothyroxine replacement therapy has three main goals. These are (i) to provide resolution of the patients' symptoms and hypothyroid signs, including biological and physiologic markers of hypothyroidism, (ii) to achieve normalization of serum TSH with improvement in thyroid hormone concentrations, and (iii) to avoid overtreatment (iatrogenic thyrotoxicosis), especially in the elderly.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

The goals of L-T4 replacement in primary hypothyroidism are to achieve a state of euthyroidism and normalization of the circulating levels of TSH and thyroid hormones (47, 48). A state of euthyroidism is defined as the normalization of indices of thyroid hormone action and the absence or the regression of symptoms and clinical signs associated with hypothyroidism. The lack of specificity of hypothyroid symptoms and signs (49) and, particularly in case of autoimmune thyroid disease (AITD), the slow development of the pathologic state, renders difficult the assessment of the adequacy of the replacement therapy on a purely clinical basis. A randomized controlled trial demonstrated that patients are unable to detect difference in the symptoms associated with hypothyroidism when the L-T4 dose is changed by approximately 20%. Of note, the change in dosage was sufficient to modify cholesterol levels (50). Similarly, patients may have no alteration in their hypothyroid symptom profile with changes in the L-T4 dose that affect TSH and resting energy expenditure (51). TSH is the most reliable marker of adequacy of replacement treatment, and a value within the reference range (0.4-4.0 mIU/L) should be considered the therapeutic target.

Although no randomized controlled trials are currently available, a recent meta-analysis showed that significantly increased risk of cardiovascular mortality and morbidity was primarily

observed in individuals with TSH levels >10 mIU/L, with potential effects of TSH values > 7 mIU/L (52). In an additional retrospective study, fewer ischemic heart disease events were associated with treatment of SCH in those under age 70 years (53). Thus, based on expectation of cardiovascular and other benefits, a target TSH in the age-specific reference range is generally recommended (see section 6a for a discussion of age-specific reference ranges). However, randomized trials are certainly needed before firm conclusions can be drawn. For example, it is certainly plausible that patients with worse cardiovascular disease might be less likely to be treated for subclinical hypothyroidism (for fear of exacerbating the cardiovascular disease) and have a worse overall clinical outcome. A target TSH in the lower tertile of the laboratory reference range, encompassing the median distribution of the values in the normal population (54), has also been proposed (55) and may, in general, be reasonable. However, this is not a universally endorsed approach (56). Moreover, a randomized crossover study of 8 weeks duration did not show changes in well-being or quality of life with TSH titration within the normal and subnormal range (50).

L-T4 alone may, in some cases, fail to restore the T3 levels to within the reference range in patients who have undergone total thyroidectomy and thus are devoid of residual endogenous production of thyroid hormone (39, 41, 42). In euthyroid patients undergoing thyroidectomy and not requiring suppressive therapy, if T3 levels are chosen as one of the therapeutic targets, it is reasonable to titrate the therapy to achieve circulating levels of T3 similar to the pre-surgery values while maintaining the TSH value within the range of normality. Levels of free T4 (FT4) above the reference range are often observed during replacement therapy with L-T4 (39); no evidence yet exists indicating that this condition is associated with adverse events or poor outcome.

1c. Are clinical parameters such as cold sensitivity and dry skin useful by themselves for assessing adequacy of levothyroxine replacement in primary hypothyroidism?

Recommendation

Although it may be helpful to follow changes in clinical symptoms longitudinally in patients treated for hypothyroidism, symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment. Therefore, symptoms should be followed, but considered in the context of serum TSH values, relevant co-morbidities, and other potential causes.

Weak recommendation. Low quality evidence.**Discussion of the clinical literature**

The signs and symptoms associated with hypothyroidism are well known, and include, but are not limited to, dry skin, cold intolerance, constipation, slowed thinking, weight gain, coarse skin, puffiness, slowed heart rate and delayed relaxation of ankle reflexes. The symptoms are often insidious in onset and have significant overlap between patients with and without thyroid disease. Many signs and symptoms of thyroid dysfunction are neither sensitive nor specific (57). For example, signs and symptoms associated with hypothyroidism such as dry skin, fatigue, and constipation may not reveal themselves with modest degrees of hypothyroidism and could have other causes. Several studies report a correlation between signs and symptoms of hypothyroidism and biochemical disease either based on an increasing cumulative number of symptoms (57) or on an abnormal clinical score (58). Unfortunately, while several signs or symptoms show relatively high specificity, such as puffiness and slowed movements, the sensitivity is relatively low. Physiological, psychological, and biochemical biomarkers of thyroid status, in addition to thyroid hormone levels, are available. Physiological parameters include heart rate, pulse wave arrival time (59, 60), echocardiographic parameters of left ventricular function, Achilles reflex time (58), voice fundamental frequency, and basal metabolic rate (61-63). To illustrate lack of specificity, basal metabolic rate, although profoundly affected by extreme hypothyroidism, is also affected by other conditions such as fever, malignancy, and nutritional status (64, 65). Pulse wave arrival time can also be affected by atherosclerosis and systemic sclerosis. Achilles reflex time seems to have a reasonable sensitivity of 77% and a good specificity of 93% to confirm or exclude hypothyroidism (58), but has is limited by the fact that a small percentage of euthyroid individuals have an abnormal reflex time. Other clinical indices used to assess thyroid function include psychiatric and neuropsychological measures. Various rating scales have been used to assess the degree of hypothyroidism (57, 58, 66-68). However, such clinical scores may not be sufficiently sensitive to signal subtle changes in thyroid status (69).

In summary, there are clearly signs and symptoms that are manifestations of untreated hypothyroidism, as documented in cross-sectional analyses. Resolution of symptoms can be documented even with treatment of mild hypothyroidism (70), but few studies document longitudinal monitoring of both symptoms and biochemical parameters within individual treated

patients. Symptoms, therefore, are probably best followed within a framework of biochemical parameters, particularly serum TSH. Future research could follow symptoms longitudinally in treated patients in order to examine specificity and reliability of such symptoms in reflecting thyroid status. Another potential area for additional research is whether it is helpful to modify the L-T4 dose because of residual signs and symptoms in a patient with a normal TSH, as long as the TSH remains within the goal reference range.

1d. Are tissue markers of thyroid hormone action helpful in determining the adequacy of levothyroxine replacement in primary hypothyroidism?

Recommendation

Tissue biomarkers of thyroid hormone action are not recommended for routine clinical use, outside of the research setting, since these parameters are not sensitive, specific, readily available, or standardized.

Weak recommendation. Low quality evidence.

Mechanistic Background

Thyroid hormone action affects a wide range of biological pathways, and virtually all organ systems have a measurable response to the administration of replacement or supraphysiologic doses of L-T4 (8, 9). Measurement of thyroid hormone-responsive gene expression is a means of assessing the impact of thyroid hormone on various tissues. The impact of the thyroidal secretion in a specific tissue depends on the amount of T3 bound to the thyroid hormone receptor (TR) over time, with increasing amounts of T3 establishing a greater thyroid hormone transcriptional “foot-print” in any given tissue. This is because T3 binding to TR modulates the expression of specific sets of T3-responsive genes, constituting the basis of most biological effects of thyroid hormone. Multiple cell types, including hepatocytes, cardiac myocytes, skeletal myocytes, kidney cells, lung endothelial cells, and brain cells express genes that are exquisitely sensitive to regulation by thyroid hormone. This regulation may be positive or negative, depending on the particular gene and tissue. Thyroid hormone effects on rodent and cell models (71), in particular the rat hepatocyte (72) and cardiac myocyte (73), have been extensively studied. Measurement of gene expression in these tissues is not routinely used for clinical assessment of thyroid hormone status, as it would require invasive procedures such as tissue biopsy, as was accomplished in a study of human skeletal muscle (74).

Discussion of the clinical literature

End-organ markers of response to thyroid hormone include SHBG, osteocalcin, urinary n-telopeptides (NTX), total cholesterol, LDL cholesterol, lipoprotein(a), creatine kinase, ferritin, myoglobin, and enzymes such as tissue plasminogen activator, ACE, and glucose 6-phosphate dehydrogenase (61, 75-81). The results of randomized controlled trials have indicated that cholesterol (50, 82-86), and SHBG levels (50) are particularly affected by the administration of L-T4. Similarly, randomized controlled trials have demonstrated that L-T4 replacement therapy affects myocardial function (87) and particularly diastolic function (88-92), and, over time, the brachial artery intimal thickness (89, 93). Of note, the changes observed in these tissue markers of thyroid hormone action are often within the range of variance of the normal population, so these tests may be considered as an additional tool to allow a further optimization of the replacement therapy, once the TSH is already within target range. While resting energy metabolism and accurate millisecond timing of the Achilles' tendon relaxation phase have been historically used to assess the adequacy of replacement therapy, these methods are neither readily available nor well standardized. However, one study did suggest that resting energy expenditure was specifically altered by changes in L-T4 dose, correlated well with TSH, and was more sensitive to dose alterations than either lipid profile, sex hormone binding globulin (SHBG) concentrations, or angiotensin converting enzyme (ACE) levels (51).

Choice of levothyroxine product

2a. Is there a clinical rationale for prescribing brand name levothyroxine preparations in preference to generic levothyroxine?

Recommendation

Prescription of brand name levothyroxine, or alternatively maintenance of the same generic preparation (i.e. maintenance of an identifiable formulation of levothyroxine), is advised. Switches between levothyroxine products could potentially result in variations in the administered dose and should generally be avoided for that reason (*see also recommendation 3d*).

Weak recommendation. Low quality evidence (for general populations)

Strong recommendation. Low quality evidence (frail patients, high-risk thyroid cancer patients, pregnant patients)

Strong recommendation, Moderate quality evidence (early childhood hypothyroidism)

Discussion of the clinical literature

A number of different brand name products and generic products are currently available. This literature review excluded studies on L-T4 products available only outside of the United States. There is a long history of regulatory and clinical discussion regarding L-T4 products (94, 95). The Food and Drug Administration (FDA) defines a L-T4 formulation as equivalent if the 90% confidence interval of the difference of the pharmacokinetically derived areas under the curve (AUC) and difference of maximum concentrations of serum T4 concentrations (Cmax) fall within 80-125% of a reference product when a comparable dose is administered to healthy volunteers. In this analysis, the L-T4 dose is only tested at a single oral dose of 600 mcg, and these results are extrapolated for all available dose strengths. There has been active discussion and controversy regarding this definition. This definition is problematic in that it does not require assessment of serum TSH, the commonly accepted marker of peripheral thyroid hormone action. Moreover, the dose of L-T4 administered (i.e., 600 mcg) is pharmacologic and it cannot be assumed that similar kinetics apply to lower, more physiologic doses. Correction for the endogenous thyroid hormone serum levels seen in euthyroid individuals has only been recommended by the FDA since 2003 (96). The ATA, The Endocrine Society, and AACE issued a combined statement in 2004 expressing their concerns about the FDA's definition and its application to establishing bioequivalence of L-T4 preparations (97).

Blakesley et al. (98), in a study funded by Abbott Laboratories, studied the FDA-recommended pharmacokinetic process of comparing L-T4 products. Even when correction was made for endogenous serum T4 levels in healthy individuals, enabling the detection of differences in the administered dose of 25% and 33%, they could not distinguish acute L-T4 doses that differed by 12.5%, leaving open the precise sensitivity of this method to exclude clinically meaningful differences in bioavailability between products considered equivalent.

It would seem more appropriate to determine bioequivalence of different L-T4 preparations by assessing for comparable serum T4, T3 and TSH levels after daily administration of the individual preparation for at least 4-6 weeks in athyreotic individuals. There are several

studies of historical interest that have used a similar clinical protocol. Escalante et al. (99) studied two well known, popular brands of L-T4 (one of which has been reformulated twice since this evaluation) and found them to be both bioequivalent and therapeutically equivalent. Dong et al. (100), in a study sponsored by Knoll Pharmaceuticals, studied the pharmacokinetics profiles of 2 proprietary L-T4 products (one of which has been re-formulated since this evaluation) and two generic L-T4 products (neither of which is currently available) and also concluded that they were bioequivalent and therapeutically equivalent. In contrast, Mayor et al. of Knoll pharmaceuticals re-analyzed the data by Dong et al. using correction for baseline T4 levels and the TSH data obtained during the trial (101), and found that the L-T4 products that seemed to be pharmacokinetically bioequivalent were, in fact, not equivalent therapeutically. There are no prospective studies assessing this question that have focused on bioequivalence as well as clinically therapeutic effectiveness in currently available products. However, there is likely an important difference between bioequivalence, which indicates meeting the FDA regulation, and clinical equivalence, which indicates comparability of FT4, T3, and TSH concentrations, as well as clinical parameters. Simulation studies also support the use of TSH-based protocols for judging bioequivalence, rather than using pharmacokinetic studies (102).

Since 2007 the FDA has required that L-T4 preparations maintain 95-105% of their stated potency, revised from a prior requirement of 90-110%, throughout their shelf life (103, 104). Furthermore, the FDA has required that all L-T4 products needed to be reassessed as if they were new drugs (105). When a generic or branded L-T4 preparation meets the criteria noted above for bioequivalence and potency, the FDA has determined that L-T4 preparations can be substituted for one another by the pharmacy, unless specifically designated to dispense as written by the prescriber. In their joint statement, referred to previously, the three different endocrine societies recommend repeat thyroid function testing when a patient is switched from one L-T4 preparation to another to ensure the goal TSH (and FT4 and T3) concentrations are achieved (97). Although, not based on specific studies of the utility of this approach, this would appear to be a clinically appropriate, “common sense” recommendation. It is recommended that once the therapeutic target is reached that the patient should remain on the same dose and preparation of medication to the extent possible.

In light of this discussion, the clinical question remains “Is there a clinical rationale for prescribing brand name L-T4 preparations in preference to generic L-T4?” This issue would not

arise if a patient could be maintained on an identifiable formulation of L-T4 (whether brand or generic). In other words, if a patient could be prescribed the same generic formulation from refill to refill, there would be no reason to be concerned about distinction between branded and generic products. However, if prescribing a generic product exposes the patient to the vagaries of the pharmacy and insurance system that permits switches between generic products, then a potential concern remains. Any recommendation is inherently based, at least to some extent, on expert opinion. It seems reasonable for a patient to remain on a given L-T4 product as long as possible, and if a change in product is made then thyroid function tests should be rechecked. In patients with thyroid cancer, especially when a desired goal TSH is relevant for curtailing possible disease recurrence or progression, it is important to maintain L-T4 product stability. A recent retrospective study of children treated for congenital hypothyroidism (CH) exclusively with either brand name or generic L-T4 noted no difference in clinical outcomes (106). However, a prospective, randomized trial, also conducted in the pediatric population being treated for hypothyroidism, showed that similar doses of a branded product and a generic considered by the FDA to be interchangeable did not result in the comparable TSH values (107). In this study, 30 children with primary hypothyroidism (20 with congenital hypothyroidism; 11 with autoimmune thyroiditis) and an initial TSH greater than 100 mIU/L were studied. Following 8 weeks of brand name L-T4, the serum TSH was statistically significantly lower ($p=.002$) as compared to 8 weeks of generic L-T4. This difference was still observed following adjustment for age. Thyroid hormone levels were not statistically different. In further analysis, the TSH difference was restricted to the patients with congenital hypothyroidism. The authors concluded that branded L-T4 was not bioequivalent to an AB-rated generic L-T4 preparation. The authors stated “It would therefore seem prudent not to substitute L-T4 formulations in patients with severe CH, particularly in those <3 years of age. Our results may have important implications for other severely hypothyroid patients in whom precise titration of L-T4 is necessary.” In general, aspects of the study design, including its prospective nature, give credence to the results of the latter study (108).

The recommendation for maintaining a particular identifiable formulation of L-T4 is not based on an anticipated inherent superiority of one particular L-T4 product, but is instead based on the concern that even products judged to be bioequivalent do not have therapeutic equivalence, and that switching of products could lead to perturbations in serum TSH. This is a

particular concern in frail patients, those with thyroid cancer, and the pediatric age group. This issue of bioequivalence is controversial and requires further study. Clinical trials should include comparisons of branded L-T4 products not only to various generic formulations, but also should compare brand L-T4 and generic formulations to themselves over time.

2b. Are there situations in which therapy with levothyroxine dissolved in glycerin and supplied in gelatin capsules may have advantages over standard levothyroxine?

Recommendation

Although there are preliminary small studies suggesting that levothyroxine dissolved in glycerin and supplied in gelatin capsules may be better absorbed than standard levothyroxine in selected circumstances such as concomitant use of proton pump inhibitors or concomitant coffee consumption, the present lack of controlled long term outcome studies does not support a recommendation for the use of such preparations in these circumstances. Switch to a gel capsule might be considered in the rare case of putative allergies to excipients.

Weak recommendation. Low quality of evidence.

Discussion of the clinical literature

An oral gel preparation that contains only L-T4, glycerin, gelatin and water has been developed. The gelatin capsule contains L-T4 as a liquid (109). This formulation is in contrast to standard solid L-T4 tablets that contain excipients and dyes. Pabla et al. (110) studied *in vitro* dissolution of gel capsules and noted rapid and efficient dissolution at low pH concentrations. Colucci et al. (111) observed that gel capsules met the revised FDA potency guidelines of 95-105% (103, 104) and also met equivalence criteria. At present, there are no prospective, randomized clinical trials in hypothyroid individuals comparing gel capsules to other commercial L-T4 preparations in terms of the serum FT4, T3 and TSH concentrations achieved during chronic therapy.

There is some evidence that gel capsules are absorbed preferentially in selected circumstances, such as during consumption with coffee and during use of proton pump inhibitors (PPIs). However, four of the studies that have examined this issue are published only in abstract form, and therefore this discussion and recommendation is based on three peer-reviewed publications only. Use of gel capsules, instead of standard L-T4, allowed suppression of serum TSH during chronic therapy in patients with thyroid disease that could not be achieved by ingestion of standard L-T4 with Italian style coffee (112). An uncontrolled retrospective study

noted lower serum TSH concentrations in patients who were switched from L-T4 tablets to the same dose of L-T4 as a soft gel capsule (113). A case report describes a patient taking a PPI whose serum TSH was higher during treatment with L-T4 tablets than with the same dose given as a gel capsule. An absorption study showed better absorption of the L-T4 form the gel capsule (114). Although no specific definitive recommendation can be made with regard to the use of gel capsules in patients with hypothyroidism because of the lack of peer-reviewed publications, preliminary evidence from retrospective studies suggests that it may have a more favorable absorption profile compared with standard L-T4 tablets. An alternative approach to switching to a soft gel capsule, in situations of suspected poor absorption, is to increase the dose of the L-T4 tablet with periodic monitoring of thyroid function tests.

A liquid formulation of L-T4 that is packaged in polyethylene ampoules, and that is not available within the United States, has been suggested, based on case reports or uncontrolled studies only, to be better absorbed than tablets if there is malabsorption following bariatric surgery or if L-T4 is consumed with breakfast (115, 116). When the liquid L-T4 preparation contained in these ampoules is added to breakfast beverages the T4 content is stable for at least 20 minutes (117).

There is the theoretical possibility that gel capsules or liquid LT-4 would be useful in patients with allergies to any of the excipients in solid L-T4 tablets.

Levothyroxine absorption and metabolism

3a. How should levothyroxine administration be timed with respect to meals and beverages in order to maintain maximum, consistent absorption?

Recommendation

Because co-administration of food and levothyroxine is likely to impair levothyroxine absorption, we recommend that, if possible, levothyroxine be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal), for optimal, consistent absorption.

Weak recommendation. Moderate quality of evidence.

Discussion of the clinical literature

Food, dietary fiber, and beverages. Absorption of L-T4 occurs in the jejunum and ileum (118). An acidic pH in the stomach, as occurs during fasting conditions, appears to be important for subsequent intestinal absorption. The absorption of an orally administered dose of L-T4 is about 70-80% under optimum, fasting, conditions (38, 119, 120). Therefore, if a patient is unable to take oral medications, the appropriate intravenous dose is approximately 75% of the oral dose.

Seven studies regarding co-administration with foods and beverages in adults were identified based on literature review (120-126). It should be noted that only one of these is a randomized study (125), thus limiting the ability to draw firm conclusions from the data. When L-T4 is co-administered with food, there is reduced absorption compared with absorption in the fasting state. In one study using double isotope methods in healthy volunteers, which is limited by the participants not serving as their own controls, the documented L-T4 absorption with food was determined to be 64% compared with 80% in the fasting state (120). In another case report, four patients who had failure to suppress their TSH values while consuming their breakfast within 20 minutes of their L-T4 ingestion underwent absorption testing (121). The ingestion of food and L-T4 in close proximity to each other was associated with a L-T4 absorption curve that was characterized by delayed absorption. After a one-month period of delaying breakfast by 60 minutes, the patients were seen to achieve suppression of their TSH values, suggesting correction of the impaired absorption, although absorption testing was not repeated to confirm this.

Case reports also show that fiber (123) and soy products (124) appear to be associated with impaired L-T4 absorption. However, fiber did not appear to affect absorption in a study of L-T4 in healthy volunteers (127). A summary of several case studies of increased TSH values in hypothyroid patients ingesting their L-T4 with espresso coffee has been reported (122). Absorption studies performed in these patients and in volunteers support the role of coffee in reducing L-T4 absorption. Compared with water, coffee reduced both the maximum concentration (C_{max}) and the AUC documented during these absorption studies. *In vitro* binding studies performed by the same investigators (122) suggested, as has been previously reported with fiber (123), that espresso coffee acts to sequester L-T4, and so it may have this action within the intestine. Grapefruit juice, which increases the plasma concentrations of several drugs that are substrates for CYP3A4 and possibly inhibits intestinal uptake transporters, was not found to substantially affect L-T4 absorption in a randomized cross-over study of 10 healthy subjects (125).

Timing of levothyroxine administration. Four studies (121, 126, 128, 129), out of the six studies examining this issue (121, 128-131), have shown that the timing of L-T4 administration influences the serum TSH values of hypothyroid patients receiving treatment. Three of these had a crossover design and thus are the most rigorous studies. The previously mentioned case study from 1995 examined 4 patients in whom TSH suppression therapy was difficult to achieve while they were eating breakfast 15-20 minutes after L-T4 ingestion (121). Consuming breakfast within 20 minutes after taking L-T4 resulted in a higher TSH, compared with when these same patients had breakfast 60 minutes after taking their L-T4, suggesting impaired absorption with a separation of less than 60 minutes. A retrospective study of elderly nursing home residents, on the other hand, showed that serum TSH values were unaffected when the timing of L-T4 administration was changed from 9 am (1-2 hours after breakfast) compared with midnight (3 hours after a snack) (130). Presumably, both these conditions qualified as post-prandial. Another parallel design study, in which patients newly diagnosed with hypothyroidism were prescribed L-T4 either 30 minutes before breakfast or in the evening, showed that at 12 weeks the achieved TSH was 5.13 mIU/L (standard deviation 9.36) with morning dosing versus 3.27 mIU/L (standard deviation 4.19 mIU/L) with evening dosing (131). These two results were not statistically different. However, the study utilized two separate groups of patients who were hypothyroid with serum TSH values of approximately 80 mIU/L at the start of the study, and thus not at steady state.

Two recent crossover studies had different findings with the lowest serum TSH values being seen either one hour before breakfast or at bedtime (128, 129). In one of these studies, patients took their L-T4 either at least 1 hour before breakfast, with breakfast, or at bedtime for 8 weeks. The mean TSH values seen with these different conditions were 1.06, 2.93, and 2.19 mIU/L respectively (128). In the other study, which incorporated a double blind design, patients took either L-T4 or placebo capsules 30 minutes before breakfast and at bedtime for 12 weeks of each regimen. TSH values were 0.9-1.6 mIU/L higher with the morning compared with the bedtime L-T4 ingestion (129). A third crossover study found higher, more variable TSH values when L-T4 was consumed with breakfast, compared with when it was taken 60 minutes before breakfast (126), although TSH values remained within the reference range even with the non-fasting regimen. If the results of these studies are consolidated, with lower TSH values being equated with better absorption, the conditions associated with better absorption (ordered from

best to most impaired) are 60 minutes before breakfast, bedtime, 30 minutes before breakfast, and with breakfast. The fasting regimen has the additional advantage of producing more consistent TSH values compared with the bedtime regimen.

In order to try and put the summarized data in context, it is important to not only consider when L-T4 absorption is optimal, but also to be aware of what timing promotes adherence. For example, although a fasting regimen may promote absorption, it may have the disadvantage of being maximally inconvenient for patients. Thus, a patient's schedule and preference should be taken into account and if consumption of L-T4 one hour before breakfast is not feasible, a bedtime regimen may be the next best choice. Another regimen that is consistently maintained, such as 30 minutes before breakfast, may also be reasonable. For this latter regimen to maintain a stable serum TSH, it would probably also be important to consume a breakfast with similar daily food choices, and avoid foods that are most noted for interfering with L-T4 absorption. It is important to remember that no long-term studies have examined adherence with the various timing regimens, the consequences of variability in serum TSH values, or outcomes with different timing of L-T4 ingestion.

3b. Are there medications and supplements that should not be co-administered with levothyroxine in order to avoid impaired absorption?

Recommendation

We recommend that where feasible, levothyroxine should be separated from other potentially interfering medications and supplements (e.g. calcium carbonate and ferrous sulfate). A 4-hour separation is traditional, but untested. Other medications (e.g. aluminum hydroxide and sucralfate) may have similar effects, but have been insufficiently studied.

Weak recommendation. Weak quality evidence.

Discussion of the clinical literature

Literature review revealed 20 relevant articles. Studies documenting altered L-T4 absorption in animals were not included. The list of medications that can alter the absorption of L-T4 is extensive and includes calcium carbonate (132-134), proton pump inhibitors (135), bile acid sequestrants (cholestyramine and colesevelam) (136, 137), phosphate binders (138, 139), ferrous sulfate (140, 141), aluminum-containing antacids (142, 143), and sucralfate (144, 145). Only two of these medications have been studied in a crossover study design of chronic therapy (132, 145), with two other studies also conducted prospectively (140, 143). The effects of calcium carbonate

and ferrous sulfate were shown in prospective, but non-randomized, non-controlled trials. The prospective study of aluminum hydroxide was performed only in 5 patients. The study of sucralfate was randomized and controlled, but was carried out in only nine patients. Moreover, many of these effects have been documented in individual case reports only.

Hypothyroid patients with normal TSH concentrations were asked to take their L-T4 with calcium carbonate for several months. Their serum TSH values increased from a mean of 1.6 mIU/L to 2.7 mIU/L, and returned to 1.4 mIU/L after discontinuation of the calcium (132). *In vitro* binding studies suggested adsorption of L-T4 to calcium at acidic pH levels. A subsequent absorption study showed that both the C_{max} and AUC were reduced when calcium carbonate and L-T4 were co-administered (133). Calcium carbonate, citrate and acetate all appear to have similar effects, with absorption studies in healthy volunteers showing a decrement in absorption of approximately 20% (134).

In a retrospective analysis, initiation of therapy with a proton pump inhibitor was associated with an increase in the serum TSH values of L-T4-treated patients, compared with a control group in whom such therapy was not initiated (135). L-T4 absorption was unaltered with use of proton pump inhibitors (146, 147) and histamine-2 blockers (147) for a one-week period in two other studies in healthy volunteers. These conflicting findings may suggest that only chronic oral therapy is associated with decreased L-T4 absorption.

Two studies have implicated bile acid sequestrants as being responsible for binding L-T4 within the intestine (136, 137). Both of these reports incorporated pharmacokinetic studies in healthy volunteers showing reduced absorption with co-administration of the agent and L-T4. The effects of the phosphate binder sevelamer has been examined in both a retrospective study (139) and a pharmacokinetic study (138). In the retrospective analysis, patients taking this agent needed higher L-T4 doses to normalize their serum TSH than patients taking calcium products as phosphate binders (139). The pharmacokinetic study showed decreased L-T4 absorption when these agents were co-administered (138).

The effect of ferrous sulfate has been examined in a trial (140) and a case report (141). During the trial, the TSH values of 14 hypothyroid patients increased from a mean of 1.6 mIU/L to a mean of 5.4 mIU/L with simultaneous ingestion of ferrous sulfate and L-T4. A need for increased L-T4 while taking ferrous sulfate was observed in the case report (141). Following documentation of increased L-T4 requirement in a patient taking an aluminum-containing

antacid (142), the same investigators showed an increase in TSH levels in five patients who were asked to take aluminum hydroxide with their L-T4 (143). Studies of sucralfate are consistent with impaired absorption (144, 145). Both a case report of elevated TSH levels, and an absorption study in healthy volunteers showing decreased and delayed L-T4 absorption, are consistent with binding of L-T4 by sucralfate (144). A blinded crossover study of 9 patients taking L-T4 failed to show a statistically significant difference in TSH while patients were taking either placebo or sucralfate in addition to their L-T4, although the study may have been underpowered and the mean serum TSH values for the placebo and sucralfate groups were 2.69 and 4.63 mIU/L respectively (145).

Although the impact of multivitamins on L-T4 absorption does not appear to have been studied, their calcium and ferrous salt content would be expected to result in impaired absorption. Based on this supposition they are included in lists of medications potentially impairing L-T4 absorption (3). Effects of several additional medications have been documented in individual cases reports (148-151). These data regarding the effect of medications on L-T4 are summarized in the table 4. Table 4a summaries pharmacokinetics studies, while table 4b shows the trials and case reports.

3c. Are there gastrointestinal conditions that should be considered when a patient's levothyroxine dose is much higher than expected?

Recommendation

In patients in whom levothyroxine dose requirements are much higher than expected, evaluation for gastrointestinal disorders such as *Helicobacter pylori*-related gastritis, atrophic gastritis, or celiac disease should be considered. Furthermore, if such disorders are detected and effectively treated, re-evaluation of thyroid function and levothyroxine dosage is recommended.

Strong recommendation. Moderate quality of evidence.

Discussion of the clinical literature

Literature review identified 18 studies addressing this topic. Several gastrointestinal disorders appear to affect either L-T4 absorption or serum TSH levels, possibly mediated through an impact on gastric acidity. These effects have been show in retrospective studies, although reduction of L-T4 dosage requirement with treatment of *Helicobacter pylori* gastritis and celiac disease has been documented prospectively.

In a prospective, non-randomized study treatment of *Helicobacter pylori* was associated with reduction of serum TSH levels from 30.5 to 4.2 mIU/L in patients who were considered non-responsive to high doses of L-T4 (152). In another study, comparison of patients with gastritis, related either to *Helicobacter pylori* or atrophic gastritis, with a reference group without gastric disorders showed that the daily L-T4 requirement was up to 34% higher in those with gastritis (2.05 versus 1.5 mcg/kg/day) (153). Furthermore, eradication of *Helicobacter pylori* infection and initiation of omeprazole were associated with decreased and increased TSH values respectively. In addition, in patients receiving L-T4 therapy, the magnitude of their L-T4 requirement was correlated with the presence or absence of serum parietal cell antibodies (154). Higher L-T4 doses were required in those with positive antibodies, and the L-T4 dose was positively associated with the antibody titer and the severity of the gastritis. Autoimmune atrophic gastritis is particularly prevalent in older patients with Hashimoto's thyroiditis and hypothyroidism. In one study, 45% of patients older than age 60 with Hashimoto's thyroiditis also had chronic atrophic gastritis (155).

Celiac disease is also more common in patients with underlying AITD. Two retrospective studies documented higher L-T4 requirements in patients with celiac disease, compared with unaffected hypothyroid patients (156, 157). Institution of a gluten-free diet reduced the requirement. There are also case reports of increased L-T4 requirements in individuals with celiac disease (158, 159), lactose intolerance (160), and intestinal giardiasis (161) with reduction in the L-T4 requirement occurring after institution of a gluten-free or lactose-restricted diet, and treatment of the infection respectively. Data comparing the magnitude of increased L-T4 requirement in these different gastrointestinal conditions appear to be lacking. However, dramatic increases in serum TSH appear to be possible in patients with more than one factor contributing to impaired L-T4 absorption, as occurred in a patient with both celiac disease and calcium carbonate use (162).

In addition to the gastrointestinal conditions discussed above, clinicians should be alert for other conditions that may affect L-T4 requirement. Examples of factors that are also associated with decreased absorption are advancing age (35), and extreme obesity (body mass index (BMI) > 40 kg/m²) (163). Although there are case reports of increased L-T4 requirements after intestinal bypass surgery (164-166), when studied directly, L-T4 absorption appears to be preserved after Roux-en-Y surgery (167) and in 32 patients undergoing various other gastric

bypass procedures (168). Such reports are consistent with the ileum being the main site of L-T4 absorption.

3d. Are different levothyroxine products associated with different absorption, such that a switch to a different brand name or generic is associated with a significantly different serum TSH?

Recommendation

Because use of different levothyroxine products may sometimes be associated with altered serum TSH values, a change in an identifiable formulation of levothyroxine (brand name or generic) should be followed by reevaluation of serum TSH at steady state.

Weak recommendation. Low quality of evidence.

Discussion of the clinical literature

Assuming that their potency is similar, and adherence is similarly maintained, if different identifiable formulations of L-T4 of the same dose result in different serum TSH values during chronic therapy, this is likely to be due to different absorption. A simulation study in which either L-T4 tablet potency or absorption were varied showed that altered absorption could result in achievement of different TSH values (102). Substitution of L-T4 preparations potentially having different absorption characteristics has, historically, lead to changes in serum TSH in some studies (101), but in other studies it has not (99, 100, 169). As these three studies antedated the current FDA guidelines for the manufacture of L-T4 products, they illustrate the concept of formulation differences, but are not directly applicable to the identifiable formulations currently available. Anecdotal reports of TSH changes associated with different L-T4 products exist (170). Similar anecdotal reports of changes in serum TSH when a patient's L-T4 is changed either from one brand name to another, or from a brand name to generic product, or from one generic to another have been gathered using an independent "Thyroid Pharmacovigilance" Web site (171). A point to be considered when evaluating these reports is that serum TSH may also fluctuate while a patient is maintained on a particular product, due to variable adherence and other factors. As mentioned in the discussion of recommendation 2a, a recent prospective, crossover trial, conducted in the pediatric population, showed that similar doses of a branded product and a generic considered by the FDA to be interchangeable resulted in significantly different TSH values in children being treated for congenital hypothyroidism (107). This study is interesting, but may not be generalizable to the adult population.

Taken together, such evidence favors consistent use of the same identifiable formulation of L-T4 in order to avoid altered absorption potentially resulting in a different serum TSH. As mentioned previously, if a patient's L-T4 product is switched, the endocrine societies recommend that the patient undergo repeat assessment of their thyroid status once steady state has been achieved (97). Altered TSH values associated with changes between L-T4 products have only been documented either with products no longer marketed in the same form, in anecdotal reports, and now, in a randomized study in children. Systematic studies of currently available L-T4 products in patients over 18 years of age could lead to a stronger conclusion regarding the differential impact of their absorption on the TSH values achieved during therapy in adults.

3e. What medications may alter a patient's levothyroxine requirement by affecting either metabolism or binding to transport proteins?

Recommendation

Initiation or discontinuation of estrogen and androgens should be followed by reassessment of serum TSH at steady state, since such medications may alter levothyroxine requirement. Serum TSH should also be reassessed in patients who are started on agents such as tyrosine kinase inhibitors that affect thyroxine metabolism and thyroxine or triiodothyronine deiodination. Serum TSH monitoring is also advisable when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are started.

Strong recommendation. Low quality of evidence.

Discussion of the clinical literature

Many medications may necessitate an adjustment in L-T4 dose by virtue of altering T4 metabolism or changing the concentration of thyroxine-binding globulin. T4 and T3 are primarily metabolized by de-iodination, but are also metabolized by conjugation with glucuronates and sulfates in the liver. All studies cited are either case reports or non-randomized prospective studies.

The major enzymes involved in conjugation are the mixed function oxidases and the uridine diphosphate-glucuronosyltransferases. Literature review revealed several relevant studies conducted in hypothyroid patients. Examples of drugs that have either been shown to increase hepatic metabolism of T4 and T3 via their induction of these enzymes, or are presumed or hypothesized to have this effect, include phenobarbital, phenytoin, carbamazepine, rifampin,

sertraline, and possibly imatinib (172). The effect of phenobarbital to increase T4 and T3 metabolism has been documented in rodents (173) and humans (174, 175), but effects on thyroid function are more notable in rats (172). Often patients or healthy volunteers taking phenytoin remain euthyroid (176, 177). A case report describes the increased TSH seen in a patient prescribed phenytoin, while she maintained her L-T4 dose (178). Other case reports also describe the development of hypothyroidism in patients treated with L-T4, who were prescribed phenytoin (179, 180). Decreased T4 and T3 concentrations without an alteration in TSH were reported in 13 patients without preexisting hypothyroidism (176) and 9 hypothyroid patients (181) after initiation of carbamazepine therapy. A similar phenomenon (normal TSH and low FT4) has been attributed to a measurement artifact in the case of free thyroid hormone concentrations (182). Longer therapy with two months of carbamazepine caused a substantial increase in TSH in 3 of 5 hypothyroid children receiving L-T4 (183). Case reports in a single athyreotic patient (184) and 3 patients with Hashimoto's hypothyroidism (185) document a substantially increased TSH and subsequent need for increased L-T4 dose with introduction of rifampin. An increase in TSH associated with sertraline therapy was reported in 11 patients (186), although another study did not report such an increase (187). All the above studies highlight the need to be alert for the possibility of increased L-T4 requirement in patients receiving drugs that can affect L-T4 metabolism by conjugation.

The need for a substantially increased dose of L-T4 has been reported in athyreotic patients prescribed tyrosine kinase inhibitors such as imatinib (188), motesanib (189), sorafenib (190), sunitinib and vandetanib (191). Accelerated conversion of T3 to rT3 because of activation of D3 has been suggested to be one of the mechanisms by which tyrosine kinase inhibitors increase the L-T4 requirement in hypothyroid patients (190, 191). The activity of other deiodinases may also be affected by these agents (191).

With respect to agents that alter D2 activity, a need for an increased dose of L-T4 has been reported with initiation of amiodarone therapy in 2 patients (192), and this drug has been shown to inhibit D2 in rodents (193). The iodine content of amiodarone could also be responsible for worsening of hypothyroidism in patients with intact thyroid glands. Although there are reports in humans that propranolol and glucocorticoids also inhibit T4 to T3 conversion (194, 195), there do not seem to be data indicating that these agents increase the requirement for L-T4 in hypothyroid patients. Growth hormone (GH) replacement therapy in GH-deficient subjects

decreases serum T4 and rT3 levels, with a concomitant rise in serum T3 levels (196, 197). This suggests a stimulatory effect of GH and/or IGF-I on the activity of D1. As a consequence, L-T4 dose may need to be adjusted when growth hormone therapy is initiated. Although consumptive hypothyroidism has most usually been reported in children with hemangiomas, it has also rarely been reported as a cause of increased L-T4 requirement in adults. Vascular tumors (198), fibroblastic tumors (199), and gastrointestinal stromal tumors (200) may each overexpress D3 and result in a need for an increased dose of L-T4.

If drugs that increase the serum thyroxine-binding globulin (TBG) concentrations, and thus increase total T4 levels, are started in hypothyroid patients receiving L-T4, their TSH levels may rise above the reference range, thus signaling the need for a higher dose of L-T4 to compensate and restore the steady state. Examples of drugs that increase serum TBG from insignificant to significant degrees, include estrogen (201), tamoxifen (202), raloxifene (203), clofibrate (204), opioids (205), mitotane (206), fluorouracil (207), and capecitabine (208). With the exception of estrogen, these drugs have either not been associated with an altered TSH (202-207), or were shown in case reports only (208). With respect to the classic case of estrogen treatment in post-menopausal women, such therapy was associated with an increase in mean TSH concentration from 0.9 mIU/L to approximately 3.2 mIU/L 12 weeks after initiation of estrogen therapy in a prospective non-randomized study (201). Rapid estrogen increase during *in vitro* fertilization is associated with increased TBG (209), and increased TSH values in treated hypothyroid women (210). Data addressing the importance of reversing such acute changes in TSH are lacking. Androgens have the opposite effect and decrease the serum TBG concentrations, thus necessitating a decrease in L-T4 dose, as seen in an observational study of 4 patients (211).

Levothyroxine dosage

4a. What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum TSH goal?

Recommendation

When deciding on a starting dose of levothyroxine, the patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of TSH elevation, age, and general clinical context, including the presence of cardiac disease, should all be considered. In

addition, the serum TSH goal appropriate for the clinical situation should also be considered.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

Many factors can affect the L-T4 dose required to normalize a particular patient's TSH. Most studies examining this issue were retrospective chart reviews (47, 212-224), but some studies were prospective (38, 225-229). Much of these data are based on retrospective or cross-sectional studies, although the conclusions of these studies are generally consistent with each other.

There is consistent evidence that actual body weight, TSH goal (normal versus sub-normal), ideal body weight, etiology of hypothyroidism, degree of serum TSH elevation, pregnancy, and age can influence dose requirement. Based on body weight, hypothyroid patients with minimal endogenous thyroid function require L-T4 doses of 1.6 -1.8 mcg per kilogram of actual body weight (38, 47, 212, 213, 215-217, 226, 227), although some studies estimate higher doses of 2.0 - 2.1 mcg/kg for some patient groups (212, 213, 226). Two studies have shown that ideal body weight is a better predictor of L-T4 dose than actual body weight (214, 225), thus suggesting that L-T4 dose requirement may depend on lean body mass. L-T4 doses in thyroid cancer patients requiring TSH suppression are generally higher and on the order of 2.1-2.7 mcg/kg (38, 212, 215).

The etiology of a patient's hypothyroidism affects their L-T4 dose (212, 226), likely reflecting the amount of residual functional thyroid tissue. Patients who are athyreotic as a consequence of thyroidectomy generally require a higher L-T4 dose than patients with Hashimoto's thyroiditis. Patients who have received radioiodine therapy for Graves' hyperthyroidism may have a variable need for L-T4, depending on whether they have remaining functional autonomous thyroid tissue. Pre-treatment serum TSH may also determine dose requirement (229). Indeed, the magnitude of the serum TSH elevation in patients newly diagnosed with hypothyroidism has been used to accurately predict a patient's L-T4 requirement at the time that their serum TSH was first rendered normal on two successive occasions (229).

Women being treated for hypothyroidism typically require an increase in their L-T4 dose early in the first trimester of pregnancy (228). The magnitude of the increase is greater in patients with little residual thyroid function (218). L-T4 replacement doses tend to decrease with age when they are titrated based on serum TSH (213, 215, 216, 219, 220). This occurs despite

the previously mentioned decrease in L-T4 absorption with advancing age (35), illustrating that the relationship between L-T4 dose requirement and age is complex.

In contrast to consistency of the findings reported in the above studies, studies examining the effect of sex (214, 215, 221), menopausal status (214, 215, 221), and the presence of the type 2 deiodinase gene (DIO2) Thr92Ala polymorphism (222, 224) have produced inconsistent findings. Differences in dose requirement based on sex and menopausal status have been reported in three studies (214, 215, 221). However, although all the studies found a lower dose requirement in post-menopausal women, different conclusions were reached about the dose requirement of men. One study suggested that sex differences were best demonstrated when dose requirement was based on ideal body weight or degree of overweight was included in the model (214). This study concluded that the effect of sex on L-T4 dose requirement was not removed by accounting for sex differences in ideal body weight or degree of overweight. Another study, in contrast, suggested that differences in lean body mass accounted for sex differences (225).

Two different studies have examined the effect of deiodinase polymorphisms on the L-T4 dose required to reach a target TSH concentration. One study showed that the DIO2-Thr92Ala polymorphism predicted the need for a higher dose of L-T4 in order to achieve near suppression of the serum TSH of thyroid cancer patients (224). Another larger study, in contrast, found no effect of this polymorphism on the L-T4 dose needed to achieve TSH suppression in thyroid cancer patients, or TSH normalization in patients with Hashimoto's hypothyroidism (222). Thus, the study by Torlontano et al. (224) suggests a blunting in the thyrotroph response associated with diminished T4 to T3 conversion, such that a higher dose of L-T4 is needed to suppress TSH. However, this theory may not be supported by the fact that the FT4 and FT3 levels did not differ between the two genotypes being studied. There are no data regarding the impact of this polymorphism in non-pituitary, brain tissues. However, the pituitary is highly enriched in D2, hence it could be more sensitive (compared to other tissues) to the effects of relative defects in the D2 enzymatic activity. Given the inconsistent results of these two studies (222, 224), further studies will be needed to determine if a patient's genetic composition truly determines their L-T4 requirement (see discussion in section 13a).

With respect to the effect of age on L-T4 requirement, analyses of age-related changes have not always incorporated adjustments for both the weight and sex of patients. In one study that adjusted for body weight only, older patients still required a lower L-T4 dose (213). In

another study that investigated females and males separately, the decreased L-T4 requirement with age was only documented in men (220). Two other studies have suggested that declining lean body mass (219) or alterations in body composition and/or changes associated with menopause (214) accounted for the reduced L-T4 requirement with age. Interestingly, sick patients older than 65 years, who are taking other medications in addition to L-T4 for a variety of co-morbidities, require lower weight-based doses of L-T4 to normalize their serum TSH than do healthy controls of a similar age who are taking only L-T4 (223).

4b. What is the best approach to initiating and adjusting levothyroxine therapy?

Recommendation

Thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal. Dose adjustments should be made when there are large changes in body weight, with aging, and with pregnancy, with TSH assessment 4-6 weeks after any dosage change.

Strong recommendation. Moderate quality of evidence.

Discussion of the clinical literature

Several approaches to initiating L-T4 therapy are acceptable. One approach is to base the starting dose on the serum TSH level, with full replacement doses (roughly 0.73 mcg/lb or 1.6 mcg/kg body weight) being required when the serum TSH is markedly elevated, and lower doses (e.g., 25-50 mcg) being required in milder degrees of hypothyroidism, e.g., where the serum TSH is ≤ 10 mIU/L or the patient has SCH (3, 229). Other factors to consider when initiating L-T4 therapy include patient age (220) and underlying comorbidities (223), both of which tend to decrease the daily hormonal requirement. The daily L-T4 dose is more dependent on lean body mass than total body weight (225), which explains why the elderly often require lower doses of L-T4 (219). Medications being taken concurrently may also affect the dose required (230).

The full calculated daily L-T4 dose (based on body weight) may be given initially to young and middle aged patients who are otherwise healthy, but many experts recommend that elderly patients and those with cardiovascular disease “start low and go slow”, for fear of precipitating cardiac events. However, one randomized trial showed that even elderly hypothyroid patients who are free of cardiovascular disease, as assessed by a dobutamine stress

echocardiogram and bicycle ergometry at 12 and 24 weeks, may be safely started on the full replacement dose (227). However, it was also observed that thyroid functional parameters improved more rapidly in those given the full dose rather than lower doses. There was no difference in the time it took for hypothyroid symptoms to resolve, although the initial assessment of symptoms did not take place until 12 weeks. This has led to the recommendation by some experts that the practice of starting L-T4 therapy slowly in the elderly not be abandoned, since it appears that there is little to be gained in elderly patients by starting with a full dose, and there are potential risks, unless it has been documented that the patient is free of cardiovascular disease (231). Patients with known coronary artery disease (CAD) should always be started on a low L-T4 dose (12.5-25 mcg/day), with gradual increases based on symptoms and serum TSH levels. Patients who have been rendered profoundly hypothyroid for radioiodine scanning and treatment for thyroid cancer, or who became hypothyroid after treatment for hyperthyroidism, would be an exception to the recommendation to “go slow”, as these patients were recently either hyperthyroid or euthyroid and have experienced hypothyroidism of limited duration.

With the exception of secondary (central) hypothyroidism, rare instances of peripheral thyroid hormone resistance, and analytic interference with its measurement, the serum TSH is the parameter that is used to adjust the L-T4 dose, with the target TSH typically being 0.5 to 3.5 or 4 mIU/L. Dose adjustments are usually made 4-6 weeks after thyroid hormone is initiated, based on the half-life of L-T4, which reaches steady state levels and serum TSH, which reaches its nadir at the same time. The target serum TSH may vary depending on patient age and underlying comorbidities. In general, L-T4 dose adjustments of 12.5 to 25 mcg/day are made, either up or down, depending on whether the serum TSH is high or low, respectively; the serum TSH is then repeated in 4-6 weeks, until the TSH target has been reached. Thereafter, serum TSH should be measured in 4-6 months and then yearly to assure stability. Changes in L-T4 requirements occur with progression of thyroid failure (higher), aging (lower), weight loss (lower), and pregnancy (higher), and many other factors, such as concomitant medications, altered intestinal absorption, and medication adherence, to name a few. Interestingly, patients being prescribed lower doses of L-T4 appear to have more stable TSH values over time than those taking higher doses (232).

4c. What are the potential deleterious effects of excessive levothyroxine?

Recommendation

The deleterious health effects of iatrogenic thyrotoxicosis include atrial fibrillation and osteoporosis. Because of these effects we recommend avoiding thyroid hormone excess and subnormal serum TSH values, particularly TSH values below 0.1 mIU/L, especially in older persons and postmenopausal women.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

Unfortunately, many patients treated with L-T4 are over-treated, based on subnormal serum TSH levels. In one study of older individuals taking L-T4, 36% of patients over age 65 years had a subnormal serum TSH (233). Excess levels of thyroid hormones, especially levels that lead to serum TSH <0.1 mIU/L, have been shown in many studies to be associated with adverse outcomes, especially related to the cardiovascular system and the skeleton in older persons or postmenopausal women. For example, in one study, patients > age 65 with serum TSH levels <0.1 mIU/L, the majority of whom were taking L-T4, had a three-fold increase in the risk of atrial fibrillation over a 10 year observation period compared to euthyroid controls (234). The risk for low bone density and fractures is also elevated in postmenopausal (but not premenopausal) women taking L-T4 (235), especially if the serum TSH levels are undetectable (236). The hazard ratios for inpatient admissions and deaths due to cardiovascular disease, dysrhythmias, and osteoporotic fractures were higher for those with suppressed TSH values in the same study of L-T4 treated patients (236). Balancing the risks and benefits of subnormal TSH values in individuals with differentiated thyroid cancer will not be addressed in this document.

4d. What are the potential deleterious effects of inadequate levothyroxine?

Recommendation

The adverse effects of thyroid hormone deficiency include detrimental effects on the serum lipid profile and progression of cardiovascular disease. We recommend that patients with overt hypothyroidism be treated with doses of levothyroxine that are adequate to normalize serum TSH levels, in order to reduce or eliminate these undesirable effects.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

Just as L-T4 therapy is frequently associated with over-treatment, under-treatment is common as well (233). Whether this is due to poor medication adherence or inadequate monitoring by the provider and failure to appropriately adjust the L-T4 dose is not known. To the extent that the goal of treating hypothyroidism is to reverse the adverse effects of thyroid hormone deficiency on all body systems, inadequate therapy would be expected to be associated with the same co-morbidities as untreated disease, especially dyslipidemia (81), atherosclerotic cardiovascular disease (237), and congestive heart failure (238), although likely to a less severe degree. Severe hypothyroidism is also a cause of reversible cardiomyopathy (239).

In mild (subclinical) hypothyroidism, however, it has been difficult to show that the mildly elevated serum TSH levels typical of this state are associated with adverse outcomes when left untreated, so that inadequate treatment would not necessarily be associated with morbidity. However, a recent report suggested that treatment of mild hypothyroidism was of benefit in reducing the risk of cardiac events in patients aged 40-70 years, providing some preliminary evidence in favor of normalizing the serum TSH in this age group (53). In this same study, however, no benefit of treatment was seen in persons over age 70 years, making it difficult to state that inadequate L-T4 therapy of SCH has deleterious effects in older persons. Indeed, the target serum TSH in the elderly may be higher than in younger persons, in light of data showing that normal older persons have a shift to the right in the serum TSH distribution, making the concept of inadequate therapy even more problematic in this age group (see recommendation 6a).

The particular importance of avoiding under-treatment of hypothyroidism during pregnancy is discussed in section 6b.

Levothyroxine and other non-hypothyroid medical conditions

5a. What is the appropriate management of perceived allergy to the constituents of levothyroxine or intolerance to levothyroxine?

Recommendation

Perceived allergy or intolerance to levothyroxine can be managed by changing the dose or product, including consideration of gel capsules, and possibly by treating concomitant iron deficiency anemia. In selected cases, a consultation with an allergist may be appropriate.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

The vast majority of patients taking L-T4 tolerate the medication without adverse effects. Since L-T4 is identical to the molecule produced by the body, it is difficult to understand how patients can be “allergic” to the medication, but occasional patients perceive adverse reactions from the medication, including headaches, palpitations, anxiety, and other nonspecific symptoms even when their thyroid hormone levels are still low and serum TSH levels are elevated. A reasonable approach in such instances would be to reduce the L-T4 dose and advance it slowly. One report of symptoms with institution of L-T4 therapy documented resolution of the symptoms when concomitant iron deficiency was corrected (240), highlighting that the correct attribution of the cause of symptoms is not always easy. Allergy to the dye in the tablet may rarely occur (241), and can be managed using 50 mcg tablets, which are colorant-free. A recent report of an allergy in the form of a rash, that developed in a patient taking a L-T4 preparation manufactured in Korea and containing tartrazine yellow No. 4 and red No. 3, was circumvented by treating the patient with a different levothyroxine product (242). Purported intolerance to other excipients in L-T4 tablets, e.g., lactose, acacia, or even gluten is anecdotal. However, some brands of L-T4 contain lactose and/or acacia, and others do not, so trying an alternate product, including gel capsules, to see if putative allergic symptoms resolve is a reasonable strategy. If problems persist, a referral to an allergist may be helpful to rule out other allergens in food or in the home, reactions to which may have been attributed to the patient’s thyroid medication.

5b. How do co-existent medical conditions (e.g. atherosclerotic coronary artery disease) affect the management of levothyroxine replacement therapy?

Recommendation

We recommend considering patients’ underlying medical conditions (such as atherosclerotic heart disease) in order to establish realistic treatment goals and avoid exacerbation of underlying comorbidities.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

Renal and liver disease: There are no adjustments in L-T4 dosing that are required in cases of cirrhosis or renal failure. Nephrotic syndrome, with its large urinary protein losses that include the thyroid hormone transport proteins TBG, transthyretine and albumin, can be a cause of increased L-T4 requirements due to excessive urinary thyroid hormone losses (243).

Cardiac disease: Thyroid hormone therapy, with its inotropic and chronotropic effects on the heart, is a potential cause of angina in patients with severe CAD (244, 245). This is the reason for starting patients with low doses of L-T4, and building the dose up slowly, while monitoring for the development of angina or other cardiac symptoms such as tachyarrhythmias. With the current use of beta adrenergic blocking drugs, most patients with CAD can be fully replaced with L-T4 without difficulty. If patients are unable to tolerate the full L-T4 dose required to normalize the serum TSH, additional measures (medical or surgical) to treat the CAD would be indicated.

Gastrointestinal disease: see recommendation 3c for discussion of gastric, celiac disease, and intestinal by-pass surgery

5c. How do co-existent psychosocial, behavioral, and mental health conditions (such as addiction, somatization disorder, and depression) affect the management of levothyroxine therapy?

Recommendation

The treatment goals of hypothyroidism are the same for patients with psychosocial, behavioral, and mental health conditions, as for the general population. However, referral to a mental health professional should be considered if the severity of the symptoms is not sufficiently explained by the severity of the biochemically-confirmed thyroid dysfunction or another medical condition, or if the mental health condition is impairing effective management of levothyroxine replacement therapy.

Strong recommendation. Low quality evidence.

Discussion of the clinical literature

Underlying mental health problems, such as depression, personality disorders (e.g. borderline personality), and addictions may complicate treatment of hypothyroidism and become frank barriers to informed consent and may impact perception of health state and adversely affect rational decision-making capacity. Patients in these categories should have a formal capacity assessment by a mental health expert (psychiatrist; clinical psychologist or social worker;

licensed addiction therapist, etc.) to rule out underlying mental health conditions.

One mental health disorder that has been hypothesized to be overlooked in the context of hypothyroidism is somatization disorder, which warrants evaluation and possible treatment by a mental health professional. Somatization disorder is a complex disorder in which a range of physiological sensations and complaints manifest in response to a complex psychological or abuse history (246-249). It is not a factitious disorder or malingering. It has been hypothesized that patients with somatization disorders, who have been treated for hypothyroidism, may persistently complain of a range of symptoms associated with hypothyroidism despite normal laboratory testing (250). Such patients are typically driven to a range of multiple practitioners, who may do multiple work-ups, and even unnecessary procedures. Such patients are frequently at risk for a range of iatrogenic harms, such as risks from unnecessary surgeries. They may also pay large sums of money for non-standard alternative therapies to deal with their physiologic complaints in an attempt to “prove” they are real (as to the patient, they are), and may become belligerent and combative when told they are euthyroid. Patients with somatization disorders are frequently misdiagnosed and mismanaged, with complicated medical histories – frequently because they seek out so many subspecialists. Somatization disorder is overwhelmingly diagnosed in females, with current hypotheses that it may be a disorder of affect regulation (251) or a complication or manifestation of a history of physical or sexual abuse (252). Recent data suggest that 1 in 3 women worldwide have been sexually or physically abused in their lifetimes [domesticviolencestatistics.org]. Somatization disorder should be managed in conjunction with a mental healthcare provider to rule out other underlying psychiatric problems, including personality disorders.

In patients with persistent complaints of hypothyroidism, and chronic pain and malaise, all organic causes should be ruled out, followed by referral to a mental health practitioner to screen for somatoform disorder. Patients suspected of somatoform disorders should be provided with sensitive discussion in which the referral is explained, in which trust is maintained. Patients should understand and appreciate that their symptoms are not factitious, and are “real” and may have causes that are rooted in psychological trauma, rather than an organic problem with physiologic causes.

Levothyroxine therapy in specific sub-populations

6a. How should levothyroxine therapy be managed in the elderly with hypothyroidism?

Recommendation

In general, levothyroxine should be initiated with low doses, and the dose titrated slowly based on serum TSH measurements. It should be recognized that normal serum TSH ranges are higher in older populations (such as those over 65 years), and that higher serum TSH targets may be appropriate.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

In elderly persons (those older than 65-70 years) who are without known heart disease or without major risk factors for heart disease, L-T4 therapy can be initiated at the full dose (227), although the method of starting with a low dose and increasing it slowly is still preferred by some experts (231). The final L-T4 dose that normalizes the serum TSH is generally lower in the elderly compared to younger persons (213, 220), related to decreases in thyroxine turnover with age, in turn caused by decreases in lean body mass (253). However, other factors in the elderly, such as decreased thyroid hormone absorption, concomitant drug use, which is more common in the elderly, and other co-morbidities may serve to negate the effects of decreased thyroxine metabolism, leading to an L-T4 dose that is closer to what would be predicted in a younger person.

The elderly are more susceptible to the adverse effects of thyroid hormone excess, especially atrial fibrillation (234), and osteoporotic fractures (235, 236, 254), so that careful titration of the L-T4 dose to avoid iatrogenic thyrotoxicosis is essential in this population. Studies specifically examining methods for dose titration in the elderly could not be identified, thus making clinical judgment of paramount importance. In addition to the lower dose requirements related to thyroxine metabolism, the target serum TSH should likely be raised in older persons, especially the oldest old (patients >80 years), given data showing that serum TSH levels rise with age in normal individuals who are free of thyroid disease (255-257). Indeed, the 97.5% confidence interval for serum TSH in healthy elderly persons is 7.5 mIU/L (255). There are observational data showing decreased mortality rates (258) and improved measures of well-being (259) in elderly persons with TSH levels that are above the traditional reference range (i.e., 0.5-4.5 mIU/L) for the general population. Furthermore, there are also observational data showing that higher FT4 concentrations are associated with mortality in the elderly (257). On the

other hand, some data suggest that that subclinical hypothyroidism may be associated with increased mortality, possibly limited to those with cardiac disease such as congestive heart failure (260).

No randomized controlled trials of L-T4 treatment in elderly patients with hypothyroidism comparing different TSH target values are available. However, based on the current evidence it is reasonable to raise the target serum TSH to 4-6 mIU/L in persons greater than age 70-80 years. Given that many individuals taking L-T4 are either undertreated or overtreated (49, 233), and that, in addition, those aged 85 years and older are more frequently started on L-T4 than younger age groups (261), the elderly, who comprise an increasing proportion of the United States population, should be targeted for particularly careful monitoring of therapy. If maintaining a regular daily schedule of L-T4 therapy is problematic in an elderly individual, consideration could be given to a guardian or visiting nurse giving all the L-T4 pills once weekly (or half the pills twice weekly), if appropriate.

L-T4 management in the case of elderly who are incapacitated and require guardianship is beyond the scope of this document. However, elderly patients who are no longer competent/capacitated may be overlooked with respect to effective treatment of hypothyroidism, and should be considered to be a vulnerable group.

6b. How should levothyroxine therapy be managed in pregnant women with hypothyroidism?

Recommendation

Women with overt hypothyroidism should receive levothyroxine replacement therapy with the dose titrated to achieve a TSH concentration within the trimester-specific reference range. Serial serum TSH levels should be assessed every four weeks during the first half of pregnancy in order to adjust levothyroxine dosing to maintain TSH within the trimester specific range. Serum TSH should also be re-assessed during the second half of pregnancy. For women already taking levothyroxine, two additional doses per week of the current levothyroxine dose, given as one extra dose twice weekly with several days separation, may be started as soon as pregnancy is confirmed.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

The treatment of hypothyroidism during pregnancy must be considered within the context of trimester-specific alterations in thyroid physiology as well as the etiology of the thyroid disease.

The TSH range for each trimester should be defined within the medical system where care is being provided, with a generalized range as follows; 0.1-2.5 mIU/L for the first trimester, 0.2 to 3.0 mIU/L for the second trimester, and 0.3 to 3.0 mIU/L for the third trimester, as outlined in the ATA guidelines for the management of thyroid disease during pregnancy (1). Several studies, including the Generation R study by Medici et al., have reported a higher TSH reference range during pregnancy, suggesting that ethnicity-based polymorphisms and dietary factors may play an important role in the thyroid axis response to pregnancy (262-266). The use of FT4 immunoassays to further define the thyroid status during pregnancy is complicated by interferences associated with physiological changes during pregnancy. These changes include increases in TBG and non-esterified fatty acids, as well as lower concentrations of albumin. Liquid chromatography, tandem mass spectrometry (LC/MS/MS) assays eliminate some of these confounding factors (267). However, these assays are time consuming and more expensive. The increasing availability of LC/MS/MS assays may increase their acceptance and decrease their cost. LC/MS/MS appears to be associated with improved accuracy and reliability of FT4 measurements (268) and is the method endorsed by the ATA guidelines for the diagnosis and management of thyroid disease during pregnancy (1).

Overt hypothyroidism (OH) is associated with an increased rate of maternal complications, including decreased fertility, increased miscarriage or stillbirth, hypertension, and post-partum hemorrhage (269, 270). In addition, OH is also associated with increased risks of fetal/infant complications, including preterm delivery, low-birth weight, and irreversible cognitive deficits (271-274). In women previously treated for hypothyroidism or found to have OH during pregnancy, L-T4 replacement therapy should be continued or initiated if not previously started (1). Ideally, the L-T4 dose should be adjusted to achieve a pre-conception TSH level below 2.5 mIU/L (1). For women taking L-T4 prior to pregnancy, the initial adjustment in L-T4 dose may be accomplished by increasing the current dose by two-tablets per week (228). Thyroid function should be monitored every 4-6 weeks, at least for the first and second trimesters (generally the time when thyroid hormone requirements are changing (228)) in order to determine if and when additional adjustments in L-T4 dose are needed. Thyroid function should also be re-assessed during the third trimester. Up to 70% of women will require adjustments of 30% or more from the pre-conception dose (228, 269, 275-277). Proper treatment of maternal hypothyroidism is associated with improvement in some maternal and

neonatal/infant outcomes (278, 279). Although not ideal, the rare circumstance of late treatment with L-T4 does not universally result in poor neurodevelopmental outcome. In a recent case report by Downing et al. (280), near normal cognitive development was achieved for 3 children born to mothers who had untreated hypothyroidism during the first trimester when compared to unaffected siblings, when maternal thyroid function was normalized prior to the 3rd trimester. Women typically return to their lower pre-pregnancy requirement for L-T4 after delivery.

6c. How should levothyroxine therapy be managed in infants and children with overt hypothyroidism?

Recommendation, infants

Levothyroxine replacement at a dose of 10-15 mcg/kg/day should be initiated once newborn screening is positive, pending the results of confirmatory testing. Higher doses may be required for infants with severe congenital hypothyroidism. The aim of therapy is to maintain the serum thyroxine in the mid- to upper half of the pediatric reference range and the serum TSH in the mid- to lower half of the pediatric reference range. The target should be to normalize serum thyroxine approximately 2-4 weeks after initiation of therapy. Once the proper dose is identified, surveillance testing with a serum TSH and thyroxine should be performed every 1 to 2 months during the first year of life with decreasing frequency as the child ages.

Strong recommendation. High quality evidence.

Recommendation, children

All children with overt hypothyroidism should receive levothyroxine replacement therapy to normalize their biochemical parameters and reverse their signs and symptoms of hypothyroidism.

Strong recommendation. High quality evidence.

6d. How should levothyroxine therapy be managed in children with subclinical hypothyroidism?

Recommendation

In children with subclinical hypothyroidism, due to the low risks of L-T4 replacement therapy, many clinicians still consider it reasonable to initiate treatment to avoid any potential risk of negative impact on growth and development. Treatment is generally not recommended when the TSH is 5-10 mIU/L. For patients with SCH and a TSH > 10 mIU/L with signs and symptoms consistent with primary thyroid disease and/or risk factors associated with progression, L-T4 replacement may be reasonable.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

The management of hypothyroidism in children is similar to adults, however, there are unique differences based on the requirement of normal thyroid function for neurocognitive development as well as growth and development. A reflection of the unique differences between child and adult physiology is the increased weight-based requirements for thyroid hormone replacement in children and adolescents compared to adults. As the child advances through the pediatric age into adulthood thyroid hormone replacement doses decrease, with newborns typically requiring 10 mcg/kg/day, one year old children 4-6 mcg/kg/day, adolescents 2-4 mcg/kg/day, with transition to the average adult dose of 1.6 mcg/kg/day once endocrine maturation is complete (215, 281).

Thyroid dysgenesis is the most common etiology of CH, affecting approximately 1:2000 to 1:4000 newborns (282). While there is no consensus on the optimal starting dose of L-T4 (283-286), standard or low dose therapy is defined by a range of 5 to 10 mcg/kg/day, while high-dose regimens is defined as a range of 10-15 mcg/kg/day (287, 288). A systematic review of the literature summarizing data from 14 cohort studies with a total of 1321 patients reported no association between the starting dose of L-T4 therapy and the standardized mean IQ or developmental quotient scores measured between 1 and 14 years of age (288). However, there are conflicting data with several reports showing higher full-scale IQ scores associated with higher starting doses (283, 286). While the controversy remains, there is reasonable agreement that the severity of the CH at the time of diagnosis (the maximum TSH level), and the length of time to achieve normal thyroid function (TSH and T4), may ultimately have a greater impact on neurocognitive outcome than the initial starting dose (283, 286, 289). In addition to the degree of TSH elevation, a distal femur plain radiograph may also help determine the severity of the hypothyroidism with a bony nucleus diameter <3mm in a term infant being associated with severe CH and decreased psychomotor development in the first year of life (290).

Optimal outcome appears to be achieved when thyroid hormone levels are normalized within 2 weeks of initiating therapy. Starting doses of 10-15 mcg/kg/day have been reported to normalize T4 levels within 2 to 3 weeks while doses less than 8 mcg/kg/day result in normalization within 6 to 8 weeks (288). Tailoring the dose based on the severity of initial TSH and T4 deficit may be the most reasonable approach. Further study of appropriate L-T4 dosing in patients with CH treated with L-T4 is certainly indicated. The addition of L-T3 to L-T4 has not been adequately studied to determine risk or benefit, but in a subgroup of patients with persistent

elevations in TSH despite T4 levels in the mid to upper part of the reference range, the addition of L-T3 may result in normalization of TSH (291). Within the United States, there are no liquid formulations and there are no compounding recipes that produce a stable concentration of L-T4 in suspension. Efforts to create suspensions should be avoided and are associated with marked extremes in dosing. To improve the likelihood of compliance, L-T4 should be administered during the same time of day, crushed and mixed with water, non-soy formula or breast milk and administered via a spoon. Older children may chew or swallow the pill. Soy, iron, calcium and infant colic drops (simethicone) can decrease the absorption of L-T4 and concurrent ingestion should be avoided (292, 293).

The aim of treatment is to keep the T4 level in the mid to upper half of the reference range and the TSH in the mid to the lower half of the reference range, optimally between 0.5 to 2.0 mIU/L (287). Once the proper dose is identified, based on normalization of TSH and T4, surveillance testing with a TSH and T4 should be performed every 1 to 2 months during the first year of life with decreasing frequency as the child ages (287). Linear growth and development should be followed closely in conjunction with regularly scheduled, well-child health visits as recommended by the American Academy of Pediatrics. For patients with severe CH, monthly surveillance during the first 6 to 12 months may be indicated (294). For patients with mild CH and no change in the L-T4 dose over the first 3 years of life, a trial off L-T4 therapy is reasonable in an effort to determine if the patient has transient or permanent CH (287). Permanent CH is established if the TSH rises and the T4 decreases on repeat testing 4 to 6 weeks after stopping L-T4 therapy. For further information on the evaluation and management of congenital hypothyroidism, please refer to the recent joint consensus statement from the European Society for Pediatric Endocrinology (295).

Autoimmune thyroiditis is the most common cause of acquired hypothyroidism, is more common in females compared to males, and the incidence increases during adolescence (296). Linear growth failure and concomitant bone age delay are the most common clinical signs of untreated acquired OH. Uncommonly, children may present with severe hypothyroidism, with TSH values > 1000 mIU/L (297). The most likely etiology is late-onset CH or delayed diagnosis of autoimmune hypothyroidism. Several approaches to care have been attempted without much impact on improving compromised adult height, a common outcome. These approaches include initiation of small doses of L-T4 with slowly advancing dose or the addition of GnRH agonist

therapy as soon as signs or puberty are witnessed or if the pace of pubertal advancement appears rapid (297, 298). Reduction in pre-treatment weight gain should not be presumed with the initiation of L-T4 replacement therapy (299). L-T4 replacement therapy is the treatment of choice for patients with OH with the dose adjusted for weight or body surface area (BSA) (281). The L-T4 dose for patients 1 to 3 years of age is 4 to 6 mcg/kg/day, for patients 3 to 10 years the L-T4 dose is 3 to 5 mcg/kg/day, and for patients 10 to 16 years the L-T4 dose is 2 to 4 mcg/kg/day (281). L-T4 may also be dosed based on BSA calculated at 100 mcg/m²/day. The method of administration and the target values for TSH and T4 are similar to that previously described for neonatal L-T4 replacement dosing.

SCH is similarly defined with a similar lack of consensus on if and/or when to initiate treatment (300-302). The majority of pediatric patients with SCH will not progress to OH and there does not appear to be a significant risk associated with not treating (303). In a large, retrospective study of 121,052 pediatric patients 6 months to 16 years of age, 73.6% of subjects with a TSH $> 5.5 - \leq 10$ mIU/L normalized their TSH over 5 years of follow-up. In subjects with a TSH > 10 mIU/L, 40% had normalization of their TSH values, 33.1% had reduction of their TSH values, and only 25% had maintenance or increase of their TSH values (304).

The presence of anti-thyroid antibodies may help identifying a subpopulation at increased risk of progression to OH. In a study following 382 patients, including 323 pediatric patients with Hashimoto's thyroiditis and 59 patients with isolated hyperthyrotropinemia (IH), the presence of TPOAb increased the risk of developing OH by 3.4 fold. However, after 3-years of follow-up, 78% of subjects with Hashimoto's thyroiditis and 86% of patients with IH did not develop OH (303).

In addition to a lack of evidence showing an increased risk of progression, there are no data showing short-term or long-term negative consequences associated with untreated SCH in the pediatric population, including no adverse effect on linear growth and no increase in cardiovascular risk, behavioral disorders, or problems with cognition (301, 305-309). Normalization of TSH values in the range often seen in SCH ($> 5.5 - \leq 10$ mIU/L) may also occur in association with weight loss in obese pediatric patients, suggesting that the alterations in the thyroid axis are a consequence rather than a cause of the obesity (310).

In several subgroups of patients, however, the potential benefit of L-T4 replacement therapy may be more significant, and measurable, so the decision about whether to initiate L-T4

replacement should be based not only on the level of TSH but also on the clinical scenario in which the test was ordered as well as the age and risk of progression. For patients with SCH and concern over linear growth, the presence of a goiter on exam, or evidence of autoimmune disease (including TPOAb positivity and/or an associated autoimmune disorder such as celiac disease or diabetes), initiation of L-T4 should be strongly considered secondary to potential benefit and an increased risk of progression (309). In addition, although there are no prospective data to show clear benefit from L-T4 replacement, patients with SCH and an increased total cholesterol with elevated LDL fraction may also benefit from initiation of therapy (310, 311). Lastly, L-T4 should also be considered in pediatric patients with a history of exposure to radiation for the treatment of a benign condition or non-thyroid malignancy due to an increased risk for progression from SCH to OH, as well as evidence suggesting a lower risk of thyroid nodule formation with L-T4 treatment (312). In a study examining 426 subjects previously treated for benign conditions with radiation, 14.2% of patients treated with L-T4 developed recurrent nodules compared to 34.2% of 198 subjects that did not receive L-T4 therapy (313).

6e. How should levothyroxine therapy be managed in individuals who have elevated serum TSH values due to non-adherence?

Recommendation

If prescription of daily levothyroxine is not successful in maintaining a normal serum TSH, weekly oral administration of the full week's dose of levothyroxine should be considered in individuals in whom adherence cannot otherwise be sustained.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

If patients maintain the same L-T4 dose, their serum TSH levels should remain within a fairly narrow range (37, 314-316). If patients experience unexpected fluctuations in their serum TSH, or persistently elevated TSH concentrations despite the prescription of large doses of L-T4, factors affecting L-T4 formulation, absorption, and metabolism can be investigated as potential culprits. Loss of potency due to use of L-T4 that is beyond its expiry date, or use of pills that have deteriorated due to environmental causes such as excessive heat or moisture are other considerations. With respect to excessive heat, tablets may be heated during transport (particularly if shipped from a remote site) or may be stored in the heat (as may occur in patients

whose jobs involve lengthy periods of travel in automobiles). If, however, such factors do not appear to be responsible, variable adherence or non-adherence to L-T4 therapy should be considered (317). There are various reports in the literature in which patients with high TSH values while being prescribed L-T4 were shown to be able to absorb L-T4 normally (317-322), and based upon this documentation were thought to have poor adherence. Absorption testing can be conducted by administering a specific oral dose of L-T4 under supervised conditions, measuring T4 concentrations at specific time points thereafter, and comparing the observed and predicted Cmax and AUC. A Cmax and AUC that is significantly less than the expected values would support impaired absorption. The principle is similar to that using for bioequivalence testing (see section 2a). Doses of L-T4 of 600 mcg to 2 mg have been employed in absorption testing (317-322).

If a combination of a high TSH and a normal or high T4 concentration is documented by laboratory testing, this pattern could be consistent with the syndrome of thyroid hormone resistance, a TSH-secreting pituitary adenoma, a macro-TSH phenomenon in which TSH complexes with an immunoglobulin and cannot be filtered by the kidney (323), or recent resumption of L-T4 therapy (324). One survey of patients prescribed L-T4 found a self-reported non-adherence rate of 22% (325).

Adherence may be made difficult for those taking multiple other medications including those that require specific administration conditions (e.g. bisphosphonates). As L-T4 is generally a life-long medication, it is important for patients to identify a medication schedule that facilitates adherence. In addition, patients can be educated about what approach to take if they forget a dose. Given, the long half-life of L-T4, patient can safely be advised to make up any omitted doses. A weekly pill box may be helpful for identifying any omitted doses. Patients may also be taking medications that impair L-T4 absorption. Variable absorption is clearly of less concern than omitted doses, so it may be necessary to compromise the goal of unimpaired absorption in order to facilitate adherence. There has been speculation that some cases of failure to adhere to a prescribed L-T4 regimen may be linked to a psychiatric disorder manifest as a desire to remain a patient (326). Other psychosocial causes for non-compliance may include barriers to accessing medication, difficulties with insurance coverage, literacy issues, and lack of understanding regarding the benefits of taking L-T4 as a medication.

Thyroid hormone concentrations in hypothyroid patients receiving large weekly doses of L-T4 have been studied in the past, prior to routine documentation of TSH values (327, 328). Normalization of serum TSH in patients suspected of being non-adherent to their therapy, with weekly or twice weekly oral therapy has been reported in case reports (319, 326, 329) and a study of a group of 23 patients (322). Literature review revealed four relevant controlled studies (330-332). Intuitively, patient education regarding the benefits of euthyroidism and the risks of iatrogenic thyroid disease would seem to a logical approach to reducing non-adherence. However, a randomized study providing education in the form of booklets mailed to patients' homes compared with usual care did not affect serum TSH, which was used as a surrogate marker of adherence (330). A randomized crossover trial of once weekly oral administration of 7 times the usual daily L-T4 dose versus daily dosage administration showed that weekly therapy was associated with supra-therapeutic concentrations of T4 for about 24 hours, although T3 levels remained within the reference range (331). Mean serum cholesterol was higher during weekly therapy, but other markers of L-T4 action such as SHBG, osteocalcin, heart rate, and left ventricular ejection time did not differ between regimens over the 6-week duration of the trial. Patient symptoms and well-being also did not differ. A second similar crossover trial of 6 week's duration showed greater increases in T4 after the weekly dose compared with the daily dose, with no associated symptoms or echocardiographic manifestations of hyperthyroidism (333). A small crossover trial of daily oral therapy versus twice-weekly oral therapy showed no significant differences in trough and peak T4, T3, and TSH concentrations and no differences in systolic time intervals over a one-month duration of therapy (332).

Parenteral L-T4 therapy does not appear to have been rigorously studied. A case report in a patient with uncharacterized malabsorption, rather than non-compliance, has been described (334). Mathematical modeling of twice weekly or weekly administration of intramuscular L-T4 showed some fluctuations of T4 levels, but with these levels remaining in the reference range (335).

In conclusion, if efforts to encourage regular daily consumption of L-T4 are unsuccessful, options include observed therapy (329), or reduction of the frequency of L-T4 ingestion to twice weekly (332), or weekly (331) with a starting dose equal to the weight-adjusted dose one would prescribe in a daily administration regimen (i.e. 7 times the daily dose). However, the three crossover trials of such oral therapy were not long-term, and none were conducted in a patient

group previously reported as manifesting non-adherence (331-333). No differences in clinical or end organ parameters of thyroid hormone action, other than higher serum cholesterol with weekly therapy, were reported in these short-term trials. Parenteral administration of L-T₄ is also possible (334, 335), although no trials of such therapy were identified.

Levothyroxine and T₃ concentrations

7a. Are variations in serum triiodothyronine concentrations within the reference range of physiologic or clinical significance? In addition, are mildly low serum triiodothyronine concentrations of clinical significance?

Summary statement:

The significance of perturbations in serum triiodothyronine concentrations within the reference range, or of mildly low serum triiodothyronine concentrations, is unknown.

Mechanistic background

Animal studies suggest that the thyroid axis has multiple homeostatic mechanisms that defend plasma T₃. Rodents subjected to iodine deficiency maintain their serum T₃ levels (336, 337). However, when severe iodine deficiency is accompanied by a fall in serum T₃, one of the tissues that is unable to sustain normal T₃ concentrations is the brain (336). Interestingly, other rodent studies do not show deficient T₃ levels in the brain with L-T₄ monotherapy, although deficiency is seen in other tissues (338). Strikingly, animals with genetic inactivation of D1, D2, or both have serum T₃ levels within the normal range, though brain T₃ levels are low (339-341). Even if the D2 inactivation is restricted to the TSH-producing cells of the pituitary gland, there is resetting of the hypothalamic thyrotropin releasing hormone (TRH) production and TSH biological activity in order to preserve serum T₃ (342). These observations, and the finding that other thyroid parameters such as T₄ and TSH are deranged in these animals, support the concept that the maintenance of circulating levels of T₃ is of primary importance in the thyroid axis homeostasis.

Plasma T₃ is the main, and perhaps the only, source of T₃ for tissues that lack D2, such as the liver (23). Even in D2 expressing tissues, approximately 50% of the intracellular T₃ is estimated to originate from the plasma based on rodent studies (23). Thus, if plasma T₃ were to fall to low levels, thyroid hormone signaling would be expected to decrease systemically. The minimum sustained decrease in plasma T₃ that results in biologically important effects remains

to be determined. A general caveat for this discussion is that variation in T3 assay performance represents one methodological limitation affecting attempts to extract data regarding T3 concentrations from the existing literature. Another caveat of applying rodent studies to human physiology is that the T4:T3 ratio in rodents is skewed towards T3, with a ratio of about 6:1 compared with 14:1 in humans, as pointed out by the authors in their study of plasma and tissue levels of T4 and T3 in thyroidectomized rats (338).

Discussion of the clinical literature

The interest in the use of combination therapies (see recommendation 13) or T3 monotherapy (see recommendation 14) implies that T3 levels are important. This concept would be a shift in traditional thinking. According to the current model, normalizing serum TSH is generally considered the target of therapy, and serum T3 is typically not measured or monitored (343). Direct evidence addressing the question of whether small decrements in plasma T3 have clinically important sequelae is lacking. A critical question, therefore, is whether changes in T3 concentrations are important, and more specifically whether decrements in T3 that remain within the reference range are actually of any clinical significance.

Some data in humans suggest that maintenance of serum T3 concentrations is of physiologic importance. It is well known that in mild primary hypothyroidism, serum T3 is kept normal in the face of a low serum T4 and mildly elevated TSH (4). In individuals living in areas of iodine deficiency, serum T3 levels are normal even when T4 and TSH are altered (344). In one study of 15 athyreotic patients taking L-T4, a progressive 30% fall in T3 induced by PTU therapy over 8 days led to a doubling of TSH, even though T4 was constant (18). Given the wide inter-individual variability of the serum T3, a 30% decrease could occur with the actual T3 value nevertheless remaining in the normal reference range.

Serum T3 (345) and FT3 (346) levels vary in a circadian fashion in healthy adult subjects, with estimates of the delta ranging from 14-35%. These changes likely follow the well-known circadian variation in TSH. Currently used therapies do not replicate the circadian rhythm of T3 or FT3. For example, patients taking L-T4 monotherapy exhibit minimal variations in serum T3 (347). It is not known whether replication of this circadian rhythm is of biologic importance, or whether mirroring this rhythm affects the ability to reverse hypothyroidism. In contrast to the steady levels of T3 achieved with L-T4 monotherapy, unless given multiple times

daily, L-T3 monotherapy is characterized by peaks and troughs in T3 concentration (348). The serum concentration of T3 following its oral administration can be predicted based on a two-compartment gut model (349). The peaks and troughs may not impact the genomic effects of T3, but may be important for non-genomic effects.

Study results are mixed as to whether T3 levels mirror other parameters that are generally thought to reflect thyroid status. Some studies show that T3 is unaltered when other thyroid-related parameters change. For example, in one study increases in L-T4 dose that were reflected by increases in resting energy expenditure were not accompanied by significant changes in serum T3 concentration (51). In other studies, at least some thyroid-related parameters change with changes in T3. With respect to the diagnosis of hypothyroidism, total cholesterol and SHBG correlated well with T3, but had no correlation with TSH levels (350). In one study in which increasing L-T4 dose also increased serum T3, there were accompanying changes in cholesterol and SHBG, but no changes in well-being (50). In another study of L-T3 monotherapy, raising T3 levels to the higher end of the reference range was accompanied by weight loss, decreased cholesterol, and increased SHBG (347). In a study of hypothyroid patients, those with low T3 levels had higher scores of hypothyroidism than those with normal T3 levels (58). However, the latter group also had lower TSH concentrations. Despite this, the hypothyroidism score did not correlate with TSH. There are some cases in which T3 seems to be necessary for normalizing TSH. For example, there are case reports of children whose TSH values could only be normalized with a combination of both L-T4 and L-T3 (291). Concomitant L-T4 and PTU therapy that resulted in normal serum T4 levels, but low serum T3 was associated with an elevated serum TSH (18).

A critical issue related to the importance of serum T3 levels is the performance of assays used to measure T3 and FT3. The disagreement between immunoassays and the more specific LC/MS/MS methodology is particularly noticeable at the lower end of the assay range, in the area where documentation of T3 concentrations would be most important if these levels were suspected to be deficient (351). LC/MS/MS assays have theoretical advantages and may be the assay method of choice in the future (352).

7b. Does levothyroxine therapy that returns the serum TSH levels of hypothyroid patients to the reference range also result in normalization of their serum triiodothyronine levels?

Summary statement

Patients with hypothyroidism treated with levothyroxine to achieve normal serum TSH values may have serum triiodothyronine concentrations that are at the lower end of the reference range, or even below the reference range. The clinical significance of this is unknown.

Discussion of the clinical literature

L-T4 is an effective, convenient, and cost-effective treatment for hypothyroidism (see recommendation 1a). One of the underlying concerns expressed about L-T4 as a treatment for hypothyroidism in general is whether physiologic concentrations of T3 are provided by such therapy in patients who only retain minimal endogenous thyroid function. The implication is that inadequate T3 levels in either the circulation or in tissues may be responsible for failure to reverse symptoms of hypothyroidism.

There are at least eight studies (38-43, 353, 354) examining the issue of serum T3 levels in humans being treated with L-T4, although only two were prospective (38, 39). Two studies used subjects as their own controls (39, 42), five used matched controls (38, 40, 41, 43), and two used comparison to the laboratory reference range only (353, 354). A small prospective study of athyreotic patients with each patient serving as their own control showed maintenance of T3 concentrations within the group as a whole, although a higher FT4/T3 ratio was necessary to achieve this (39). A minority of individuals within the group was noted to have lower serum T3 levels while taking L-T4. An additional prospective study also showed a comparable free T3 index in patients treated with L-T4 (38). Further cross-sectional studies suggested maintenance of T3 concentrations in treated patients, but the reference range was the sole comparator (353, 354). However, three cross-sectional studies comparing L-T4 treated patients with control subjects showed that despite similar TSH values the patients had significantly lower T3 concentrations (40, 41, 43). The log linear relationship between TSH and T3 was steeper (greater change in TSH for a given change in T3) in treated hypothyroid patients than in control individuals (41, 43). This has been interpreted by the authors as indicating an abnormal thyroid-pituitary feedback, with a reduced sensitivity compared to euthyroid controls. Finally, a recent retrospective study found that low TSH levels were necessary in order to achieve the same T3 levels during L-T4 therapy that were observed in patients prior to their thyroidectomy (42). However, in this study patients underwent phlebotomy 2-4 hours after taking their L-T4 tablets,

leaving open the possibility that TSH concentrations were sampled during the trough of the diurnal TSH pattern, which could have resulted in lower TSH values than were present during the remainder of the day (314, 315, 355). In addition, any comparison using the T4/TSH and T4/T3 relationship from the study data would be confounded by the fact that the investigators likely sampled the peak T4 levels. None of these studies examined patient satisfaction with therapy.

Another consideration in interpreting most of these studies is the rigor with which any population with confounding medications and coexistent illnesses were excluded, as these factors are known to affect serum T3 concentrations (356). In addition, such studies should take patient age into account, as not only does TSH increase with advancing age, but also serum T3 levels decrease within older age groups (257).

In summary, all these studies show relatively high FT4 levels and either an increased FT4/T3 or FT4/FT3 ratio in L-T4 treated patients. Whether these altered biochemical parameters have clinical consequences is unknown. For example, while excess T4 could in theory lead to increased T3 production in D2-expressing tissues, the regulation of D2 by the ubiquitination-proteasomal system would tend to minimize this effect by inhibiting D2 activity and shortening its half-life (357). In addition, these studies differ with regard to the proportion of patients that can achieve normal T3 levels without lowering the serum TSH below the reference range. In one of the prospective studies, serum T3 levels were maintained as long as the serum TSH was less than 4.5 mIU/L (39). In one retrospective study, 15% of patients has serum FT3 concentrations that were below the levels in euthyroid controls (41). In another retrospective study, serum FT3 was only maintained if the patient's serum TSH was below 0.3 mIU/L (42). However, when taken together, several non-prospective studies do indicate that L-T4 monotherapy is characterized by low T3 levels in either some or many patients (40-43). Whether these altered biochemical parameters have clinical consequences is unknown.

7c. Is there evidence of discordance between the thyroid hormone status of different tissues and the serum TSH concentration?

Summary statement

There are specific instances in which there appears to be discordance between the thyroid status of the pituitary gland, as reflected by the serum TSH, and the thyroid status of other tissues as indicated by various biomarkers. The clinical significance of this is not known.

Mechanistic background

Under normal, physiological conditions, thyroid hormone signaling in the various organs and tissues is finely modulated at the target level, with different biological consequences. This diversity results from the fact that cells and tissues vary in terms of their expression of transmembrane transporters, deiodinases, nuclear thyroid hormone receptor (TR) subtypes, and coregulators (9, 358, 359). For example, the transporter MCT8 seems to be mostly important in the brain; D2 is expressed in the brain but not the liver; and the heart and skeleton are TR-alpha (TR- α) predominant tissues whereas the liver is TR-beta (TR β) predominant. The consequences of differential deiodinase expression are striking: rodent studies indicate that the thyroid hormone receptors in brain cells are almost fully occupied under normal conditions, whereas in the liver cells the receptors are only about half occupied (360). Furthermore, while nuclear T3 content ultimately determines the intensity of the TR mediated signaling, the set of genes affected by the TRs is cell type-specific. Thus, systemic thyroid status is the integration of all of the individual thyroid statuses of the different cell-types of the body at a given level of circulating T3 and T4.

Animal data strongly indicate that different tissues can have different concentrations of T3, and thus different levels of thyroid hormone signaling at a given time, i.e. tissues can have variable “tissue-specific thyroid status”. Furthermore normalization of the TSH does not ensure uniform T3 levels in various tissues, though no data are available regarding the adequacy of thyroid signaling per se. This has been demonstrated in vitro utilizing L-T4 infusion in animals, during which some tissues were demonstrated to be relatively T3-deficient even though all were exposed to the same plasma T3 and T4 concentrations and in some cases had normal serum TSH levels (338, 361). The best understood mechanism underlying tissue-specific thyroid status derives from the differential sub-cellular localizations of the deiodinases. While D2 and D3 are intracellular enzymes, D1 functions at the plasma membrane. Thus, D2 can directly alter the intracellular T3 content without immediately altering plasma T3 concentration. Thus, the differences in tissue distribution of the various forms of deiodinases result in tissue-specific supplies of T3. In vitro data and rodent studies have established that primary changes in D2 or D3 in a given tissue can lead to tissue-specific changes in thyroid status without affecting circulating T3, T4, or TSH (362, 363); human studies have not been reported.

Discussion of the clinical literature

In a 1971 study of myxedematous patients in whom therapy with L-T₄ was initiated, lowering of their elevated serum TSH values was shown to correlate with the dose of L-T₄ given (46). The serum TSH correlated well with both the administered dose ($r = -0.99$) and the serum FT₄ concentration achieved ($r = -1.0$). In the years following, data have accumulated about the predictable (364), albeit complex (365-367), relationship between FT₄ and TSH. Part of the complexity of this relationship is due to higher TSH values in older individuals, but at the same time a less robust response to hypothyroxinemia in older individuals, resulting in two overlapping sigmoidal curves (367). Serum TSH has been accepted as a robust, sensitive, and reproducible indicator of thyroid status (368). Serum TSH is thought to integrate signals from both T₃ and T₄ and its dynamic relationship with these parameters has led to its establishment as the best single test for determining systemic thyroid status. The logarithmic relationship between TSH and thyroid hormone bestows sensitivity: even if circulating T₃ and T₄ are in the normal range, it cannot be assumed that the subject is euthyroid. The inter-individual ranges for T₃ and T₄ are much broader than the individual variance (369), such that measuring T₃ and T₄ is a suboptimal way to assess thyroid status.

Despite the time-honored concept that a normal serum TSH indicates that there is euthyroidism in all tissues, there are some data that do not support this concept. A caveat to using serum TSH as the sole indicator of systemic thyroid status can be proposed based on the observation that the TSH remains normal in some L-T₄ treated hypothyroid subjects with a high T₄:T₃ ratio, even when T₃ levels are lower than the normal range (39-43) (see section 7b). In these subjects, it is possible that in the pituitary, the low T₃ is counterbalanced by the higher T₄ (370). However, it is unknown whether all of the other tissues of the body, with their differing expression of deiodinases, transporters, and TRs, can maintain normal thyroid signaling in the face of this altered T₄:T₃ ratio, especially when T₃ is low. Other examples of situations in which T₃ may be low in the face of normal serum TSH include starvation (371) and the polar T₃ syndrome (372).

Other examples of discordant tissue response to therapy exist. In a study of daily monotherapy, a dose of L-T₃ that normalized cardiac parameters, serum cholesterol, serum creatine phosphokinase, and basal metabolic rate did not normalize TSH, which in fact remained elevated (370). A recent crossover study of L-T₃ monotherapy and L-T₄ monotherapy that

resulted in normal serum TSH concentrations during both arms of therapy was accompanied by weight loss, decreased cholesterol, and increased SHBG during the L-T3 treatment phase (347). In another study in which resting energy expenditure was correlated with TSH levels, there were no concurrent TSH-associated changes in ACE concentration, SHBG levels, and the lipid profile (51). It has previously been suggested that L-T4 therapy provides a signal of greater magnitude to the thyrotrophs than L-T3 because T3 is provided not only by the circulating levels but also from intrapituitary conversion of T4 to T3 (370). Other investigators, after performing TRH stimulation testing in patients receiving either L-T4 or L-T3 treatment reached a different conclusion, namely that differential responses to therapy were mediated peripherally and not at the pituitary gland level (373). Such studies indicate discordance between the signal emanating from the pituitary and other tissues.

A recent study examined the relationships between TSH, FT4, and FT3 in approximately 2,000 patients who were either untreated or L-T4-treated (374). Mathematical modeling showed different correlations between TSH *versus* FT4 and TSH *versus* FT3 in the treated and untreated groups. The authors noted that in subjects treated with L-T4 monotherapy, the gradient between TSH and FT3 increased with L-T4 dosage. They observed that increments of L-T4 monotherapy were progressively more effective in suppressing TSH production, but simultaneously less effective in restoring FT3. They suggested that D2 levels within the pituitary are uniquely increased in order to maintain T3 production in the setting of high T4 levels (358), thus lowering TSH levels. The lowered TSH levels could subsequently result in failure to maintain FT3 levels. The authors suggested that their data and analyses (374, 375) provide evidence that TSH may not be the only standard for assessing euthyroidism and that T3 levels might need to be considered as well (374).

The clinical syndromes of resistance to thyroid hormone (RTH), caused by inactivating mutations in TR α (RTH α) or TR β (RTH β) could perhaps also be considered as a very particular example of how TSH may not necessarily reflect thyroid hormone signaling in other tissues than the pituitary and the hypothalamus. Patients with RTH α have normal levels of TSH in combination with a low FT4 and high T3, and suffer from local hypothyroidism in tissues that predominantly express TR α (376, 377). Patients with RTH β have normal or elevated levels of TSH despite elevated levels of FT4 and FT3, and suffer from thyroid hormone overexposure in TR α -expressing tissues (378, 379). Thus the molecular pathology of RTH β is an unbalanced

hormonal signaling due to the combination of defective TR β and otherwise normal TR α receptors exposed to supra-physiologic levels of thyroid hormone. The result is a mix of hypothyroid symptoms and signs related to tissues such as the liver where the β -isoform is present in higher concentrations, and hyperthyroid symptoms and signs in tissues enriched with TR α such as the myocardium (380).

7d. Should levothyroxine therapy for hypothyroidism, particularly in specific sub-groups such as those with obesity, depression, dyslipidemia, or who are athyreotic, be targeted to achieve high-normal T3 levels or low-normal TSH levels?

Recommendation

There is insufficient evidence of benefit to recommend that treatment with levothyroxine be targeted to achieve low-normal TSH values or high-normal T3 values in those patients with hypothyroidism who are overweight, or those who have depression, dyslipidemia, or who are athyreotic.

Strong recommendation. Moderate quality of evidence.

Discussion of the clinical literature

Theoretically, it is possible that raising T3 levels to the upper part of the normal range or achieving TSH values in the lower part of the normal range during replacement for hypothyroidism may be beneficial for those with residual signs or symptoms that overlap with those of hypothyroidism, such as dyslipidemia, obesity, depression, or dissatisfaction with their therapy. Serum T3 would potentially be raised either by increasing a patient's L-T4 dose to both lower the TSH and raise the T3 concentration (39, 41-43), although feedback mechanisms would presumably limit the degree to which T3 could be raised. Alternatively T3 levels could be raised by use of combination therapy with L-T3 (see discussion in section 13b).

There are a handful of studies that potentially address the issue of raising T3 levels or lowering TSH levels by L-T4 dosage adjustment in treated hypothyroid patients who have lipid disorders, depression, are dissatisfied with their therapy, or are overweight. In a recent study, hypothyroid patients were maintained at low-normal or high-normal TSH values for a year and had resultant T3 levels of 123 and 113 ng/dL. This study showed no decrement in cholesterol, body mass index, or percentage body fat associated with the higher L-T4, despite an increase in resting energy expenditure (381). In a crossover trial, 56 patients with primary hypothyroidism

were treated for 8-week periods with 3 doses of L-T4 in a random order, with achievement of TSH values of 2.8, 1, and 0.3 mIU/L and free T3 values of 2.5, 2.7, and 3.1 pg/mL respectively. There was progressive lowering of total cholesterol with the higher free T3 values (50). However, the significance of this reduction seemed to be due to lowering of cholesterol in the group that included many patients with subclinical hyperthyroidism. Psychologic well-being, treatment satisfaction, and body weight did not change across the three different groups.

Two retrospective studies have examined weight changes in hypothyroid patients. One of these examined weight changes in individuals after either replacement or suppressive doses of L-T4 for post-surgical hypothyroidism and found no significant weight changes (382). A second study compared weight changes during a one-year period in patients who had just undergone thyroidectomy without ever becoming hypothyroid with patients already taking L-T4 for primary hypothyroidism or thyroid cancer, and also patients without a diagnosis of hypothyroidism (383). This study, in contrast, found those with hypothyroidism gained more weight than those without. The magnitude of the weight gain from greatest to least was 1) recently thyroidectomized, 2) pre-existing hypothyroidism, and 3) pre-existing thyroid cancer diagnosis. Although this latter study could be interpreted as showing that L-T4 treatment to achieve a normal TSH fails to normalize some aspect of weight regulation, the cautions about drawing conclusions from retrospective studies applies.

A 2006 cross-sectional analysis examined correlations between psychological well-being, as assessed by General Health Questionnaire (GHQ) scores, and thyroid analytes in hypothyroid patients being treated with L-T4. There was a relationship between both the log-transformed TSH and psychological well-being, and also between FT4 concentrations and well-being, but no relationship existed between free T3 and well-being (67). In summary, these three studies, in which patients with AITD comprised 75-80% of the population, suggest that dosage adjustments resulting in higher T3 concentrations do not decrease weight or BMI, improve patient well-being or satisfaction, but may possibly decrease serum cholesterol.

Use of combination synthetic L-T4 and L-T3 therapy has not proven beneficial with respect to reducing body weight or improving lipid profile (see recommendation 13b), although analysis of sub-groups with unfavorable lipid profiles or obesity have not been conducted. Symptoms such as anxiety and depression have not been shown to be less common in patients treated with combination therapy. Neither have patients with fatigue (384), dissatisfaction with

their therapy (385), self-reported multidimensional psychopathology symptoms (386), or depression (387, 388) been shown to respond better to combination therapy. However, small numbers of patients were available for some of these comparisons, for example 4 depressed patients versus 29 non-depressed patients in the study by Bunevicius et al. (387), and 14 patients with low fatigue levels and 14 with high fatigue levels in the study by Rodriguez et al. (384).

If there is a possibility of low T3 concentrations during L-T4 therapy in the general population, and if the levels achieved are of concern, there may be another sub-population for whom this theoretically is of even greater concern. This population would be patients with athyreosis. Those who are athyreotic as a result of thyroidectomy do not retain the ability to generate T3 from intrathyroidal sources, an ability that may be retained in patients with AITD who still have some endogenous function. The ability to assess whether athyreotic patients, in particular, benefit from combination therapy that includes T3 is precluded by the small number of such patients who have been studied. Although the presence of athyreotic patients has been suggested to account for the positive outcome from one study of combination therapy (387), a meta-analysis performed in 2006 (389) did not find an association between positive outcomes from combination therapy and the athyreotic state. Another population who might potentially benefit from combination therapy is those patients who have the specific DIO2 polymorphism DIO2-Thr92Ala (390), although low serum T3 levels have not been documented in this sub-population, and abnormal D2 activity has not been confirmed in this population either. This topic is fully addressed in recommendation 13b.

Levothyroxine therapy in secondary hypothyroidism

8a. What biochemical goals should be employed for levothyroxine replacement in patients with secondary hypothyroidism?

Recommendation

In patients with secondary hypothyroidism, the primary biochemical treatment goal should be to maintain the serum free thyroxine values in the upper half of the reference range. However, the serum free thyroxine target level may be reduced in older patients or patients with comorbidities, who may be at higher risk of complications of thyroid hormone excess.

Strong recommendation. Moderate quality evidence

Discussion of the clinical literature

Secondary (central) hypothyroidism is characterized by insufficient pituitary production of TSH. This disorder affects 1:100,000 individuals and accounts for a small percentage of all cases of hypothyroidism (391). The treatment of secondary hypothyroidism, and the more common primary hypothyroidism, require different approaches based on the ability of the serum TSH concentration to serve as a reliable signaling mechanism (391, 392). Thus, in patients with primary hypothyroidism the serum TSH concentration is considered to be the best marker of thyroid status, and is used as the basis for adjusting thyroid hormone dose. When the etiology of hypothyroidism is a pituitary deficit of TSH, this extremely sensitive and convenient indicator of thyroid status can, unfortunately, no longer be employed. Not only is serum TSH an unreliable indicator, but it may also become undetectable with small increments in L-T4 that still leave the serum FT4 in the hypothyroid range (393).

The dilemma with respect to treating secondary hypothyroidism is that it cannot be determined what is the “normal” FT4 for the individual patient. Patients with an intact pituitary and subclinical thyroid dysfunction have, by definition, abnormal TSH values but FT4 values within the reference range. Subclinical thyroid dysfunction is well known to have adverse effects on lipid metabolism, the cardiovascular system, and the skeleton (4). Patients treated for secondary hypothyroidism could thus potentially be exposed to adverse effects of inadequate or excessive thyroid hormone without the usual signal from an abnormal TSH. Thus, an alternative measure of thyroid status may be required for treating secondary hypothyroidism.

Literature review revealed 8 potentially relevant studies. Only one of these was a randomized controlled trial and this was of short duration (85). Six studies were retrospective examinations of groups of patients with hypothyroidism (394-399), and another was a prospective study of patients with secondary hypothyroidism alone, with no comparison group (393). These studies show that there are changes in physiologic parameters with dosage changes, but they were not specifically designed to address when a change in L-T4 dose should be made. In addition, there are no long-term studies comparing different dosing of L-T4, the resultant FT4 concentrations, and the subsequent outcomes in patients with central hypothyroidism.

The randomized controlled trial crossed patients over from the “empiric” L-T4 dose that had been selected by their treating physician (mean 1 mcg/kg/day) to a body weight-adjusted dose of 1.6 mcg/kg/day (85). The dose of 1.6 mcg/kg/day produced higher FT4 levels that

reached the upper part of the reference range and was associated with lower body weight, lower BMI, lower cholesterol (total, LDL, and HDL), less clinical signs of hypothyroidism based on the Zulewski score, and a lower creatine kinase value. However, no differences in well-being and cognitive function were observed. The prospective study examined biochemical parameters in patients at three time points: when they were considered euthyroid on L-T4, after discontinuing L-T4, and then after resumption of L-T4 (393). The L-T4 dose used was the long-term treatment dose that had been selected by their prescribing physician. The mean dose was 1.5 mcg/kg, and this produced normal FT4 and FT3 values in most, but not all patients. Two out of 37 patients had low FT4 and FT3 levels, while 3 out of 37 patients had high FT3 concentrations while taking this dose. L-T4 therapy was associated with significantly increased SHBG levels, ACE concentrations, and markers of bone turnover. No assessments of quality of life were made.

Some cross-sectional studies show that patients being treated for secondary hypothyroidism have lower FT4 values than patients being treated for primary hypothyroidism. One study compared FT4 values in patients being treated with L-T4 for secondary hypothyroidism with values in patients being treated for primary hypothyroidism who had TSH values within the laboratory reference range (395). Approximately 20% of those with secondary hypothyroidism had a FT4 values below the 10th percentile, compared with less than 3% of patients with primary hypothyroidism (395). A study from 1999 found lower FT4 levels in treated patients with secondary hypothyroidism, compared with a group with primary hypothyroidism (398). Another study found that 1.6 mcg/kg L-T4 produced normal FT4 values in 94% of patients, but normal FT3 values in only 49% (394). The other retrospective studies show varying findings (396, 397).

The randomized controlled trial described demonstrated that FT4 levels in the upper half of the reference range best reversed the clinical signs of hypothyroidism (85). A retrospective study also suggested that higher FT4 values within the normal range had most benefit on lipid parameters and body composition (399). Other recommendations in the literature include keeping FT4 concentrations within the reference range (391), keeping L-T4 in the middle of the laboratory reference range (392, 393), and keeping the FT4 levels in the same range as the FT4 levels seen in patients being treated for primary hypothyroidism (395).

Only one study of combination therapy has been conducted in a population of patients with hypopituitarism (85). This was the randomized controlled crossover study already

discussed. Lower creatine kinase and faster ankle reflex time were seen with the combination therapy, compared with patients receiving L-T4 at a dose of 1.6 mcg/kg, but the free T3 levels were supra-physiologic during combination therapy. The Zulewski score and working memory test were improved during combination therapy, but only compared with the 1.0 mcg/kg/day, not the higher 1.6 mcg/kg dose. As there is insufficient evidence to recommend for combination therapy in patients with secondary hypothyroidism, no recommendation can be made regarding appropriate treatment goals.

As a separate observation, growth hormone replacement may necessitate either initiation of L-T4 or an increase in the L-T4 dose in patients with hypopituitarism (400). It has been suggested that growth hormone may inhibit peripheral conversion of T4 to T3 and also have a central inhibitory effect on TSH release.

8b. Are clinical parameters useful for assessing adequacy of levothyroxine replacement in patients with secondary hypothyroidism?

Recommendation

Although it may be helpful to follow changes in clinical parameters in patients treated for secondary hypothyroidism, such parameters alone lack sensitivity and specificity. There is a limited amount of evidence suggesting that clinical parameters are helpful as secondary means of judging adequacy of replacement with levothyroxine in patients with secondary hypothyroidism in whom biochemical assessment is limited to serum free thyroxine levels.

Weak recommendation. Moderate quality evidence

Discussion of the clinical literature

Literature review revealed 1 potentially relevant study (85). This previously described randomized controlled trial utilized a crossover design with 29 patients either taking an “empiric” dose that had been selected by their treating physician (mean 1 mcg/kg/day), a body weight-adjusted dose of 1.6 mcg/kg/day (85), or body weight adjusted combination therapy. This study examined body weight, BMI, ankle reflex time, Zulewski score, and neurocognitive testing to assess well-being and cognitive function on the three regimens. Both body weight adjusted regimens were associated with higher FT4 levels, lower body weight, lower BMI, lower cholesterol (total, LDL, and HDL), and less clinical signs of hypothyroidism based on the Zulewski score. The only component of the neurocognitive test that differed between regimens

was improved working memory in patients taking combination therapy. Ankle reflex time was only normalized by the combination therapy. In summary, clinical parameters such as body weight, BMI, and clinical score of hypothyroidism appear to mirror an increased dose of L-T4 in a single small study.

8c. Are tissue markers of thyroid hormone action helpful for management of levothyroxine replacement in patients with secondary hypothyroidism?

Recommendation

In patients with secondary hypothyroidism in whom the only available biochemical thyroid parameters are thyroid hormone levels, tissue markers of thyroid hormone action may be used, in addition to thyroid hormone parameters, as an adjunctive means of judging the adequacy of levothyroxine replacement.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

Literature review revealed 2 potentially relevant studies. One of these was the previously identified randomized controlled trial (85). The other was a prospective study of 37 patients with secondary hypothyroidism undergoing reinstatement of their L-T4 therapy (393). In the latter study L-T4 therapy was associated with significantly increased concentrations of FT4, FT3, SHBG, ACE, soluble interleukin-2 receptors, carboxyl-terminal telopeptides of type I collagen, and bone GLA protein. There was a significant positive correlation with FT3 concentration and the serum concentrations of soluble interleukin-2 receptors, carboxyl-terminal telopeptides of type I collagen, and bone GLA protein. The authors suggested that soluble interleukin-2 receptor concentration would be a useful parameter to monitor therapy as it was unaffected by concomitant therapy with growth hormone, sex steroids, and glucocorticoids. During the former randomized trial creatine kinase decreased in response to the higher TH levels seen with the body weight-adjusted therapy. In summary, although raising TH levels in patients with secondary hypothyroidism correlated with biochemical parameters, no long-term studies of the use of these parameters to adjust therapy are available.

9a. What tools may be useful in the clinical or research setting, to measure the impact of levothyroxine replacement for primary hypothyroidism on patients' physical or psychological well-being, treatment satisfaction, or treatment preferences?

Recommendation

Of the established instruments used to measure hypothyroid symptoms, data are lacking regarding their sensitivity and specificity in the “everyday” clinical setting to recommend their routine clinical use. Further studies are needed to determine if and how to combine general psychological screening instruments, hypothyroidism-specific tools, and laboratory assessment of thyroid function to measure the impact of levothyroxine replacement therapy on psychological well-being, treatment satisfaction, and preference in clinical practice. A combination of general instruments, combined with hypothyroidism-specific tools, may be the most effective way to examine psychological well-being in the levothyroxine-treated population in the research setting.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

Numerous organ systems are impacted by thyroid hormone deficiency. Assessment of discrete end-organ responses to L-T4 replacement in patients with primary hypothyroidism has focused on cardiovascular, neuromuscular, and cognitive measures. Assays of lipid parameters are commonly employed in both clinical and research settings, whereas echocardiography, cardiopulmonary exercise testing, and pulse wave velocity measures are used primarily in research studies. Likewise, neuromuscular and cognitive testing is usually restricted to the research setting. Numerous instruments have been applied to assess perceived health status, well-being, quality of life, and symptoms in research studies of L-T4 replacement, though not all have been validated and some are not well suited for studying the impact of L-T4 replacement (as reviewed in (401)). The Short-Form-36 (SF-36) (402) and the Nottingham Health Profile (403) have each been used to examine perceived health status and may be compared to normative data in other clinical populations. The SF-36 may be more sensitive to differences in the hypothyroid population (401). The GHQ (404) and Hospital Anxiety and Depression Scale (405) are general tools that measure psychological well-being.

Hypothyroidism-specific instruments have also been developed to measure health status (Chronic Thyroid Questionnaire (406)), quality of life (Underactive-Thyroid-Dependent Quality of Life Questionnaire (407, 408) and ThyPro (409)), and symptoms (Billewicz index (66), Zulewski score (58), Thyroid Symptom Questionnaire (68), Colorado Health Fair Thyroid Disease Symptom Survey (49), and Underactive Thyroid Treatment Satisfaction Questionnaire

(407, 410)). These instruments have not been directly compared, so that the superiority of a specific instrument has not been determined. However, of those listed, only the Thyroid Symptom Questionnaire has not been validated. A combination of general instruments that can be compared to reference populations without thyroid disease and hypothyroidism-specific tools that are more sensitive to change may be the most effective way to examine psychological well-being in the L-T4-treated population in the research setting.

9b. What approach should be taken in patients treated for hypothyroidism who have normal serum TSH values but still have unresolved symptoms?

Recommendation

A minority of patients with hypothyroidism, but normal serum TSH values, may perceive a suboptimal health status of unclear etiology. Acknowledgement of the patients' symptoms and evaluation for alternative causes is recommended in such cases. Future research into whether there are specific sub-groups of the population being treated for hypothyroidism who might benefit from combination therapy should be encouraged.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

Two case-control studies have examined the question of residual hypothyroid symptoms in patients taking L-T4. Saravanan et al. conducted a case-control study in which 397 euthyroid L-T4 users showed impaired psychological well-being and more thyroid symptoms compared to 551 age- and sex-matched controls (68). In this study, a survey was sent to both control patients not taking L-T4 and patients taking L-T4 who were matched for age and sex. More euthyroid patients being treated for hypothyroidism (34 %) had impairment in their sense of psychological well-being (GHQ score ≥ 3) compared to controls (25 %). Approximately 10% more hypothyroid patients were dissatisfied based on a thyroid symptom questionnaire. The differences remained significant even after adjustment for other medical conditions, which were generally more prevalent in the group receiving treatment for hypothyroidism. This was not confirmed in a smaller, similarly designed case-control study from Eskelinen et al. (411). However, a third study also showed more fatigue in euthyroid patients than in euthyroid controls (412). A fourth study, in which subjects were recruited by letter and then subsequently took part in cognitive testing and completed questionnaires assessing well-being, also showed lower scores in both these areas in the euthyroid patients taking L-T4, but the comparison was with standard

reference values, rather than a formal control group (413). The difficulty in interpreting these types of studies is that their findings are highly dependent on the health of the control group, the fact that recruitment methods may elicit a higher response rate from individuals who are dissatisfied, and the likelihood that patients with hypothyroidism are highly attuned to potential symptoms of hypothyroidism.

Three studies have addressed the relationship between symptoms of hypothyroidism and serum TSH levels in L-T4 users. A cross-sectional analysis of 697 patients taking L-T4 showed a correlation between higher TSH levels and more hypothyroid symptoms, even within the subset of 470 patients who were euthyroid (67). On the other hand, another cross-sectional study did not find a relationship between well-being and two categories of TSH values of less than and greater than 2 mIU/L (413). Moreover, in a randomized, controlled crossover trial by Walsh et al. of three different L-T4 doses that achieved TSH levels below the lower limit of the reference range, in the lower half of the reference range, and in the upper half of the reference range, there were no differences in symptoms or significant treatment preferences (50). This study suggests that L-T4 users do not experience symptomatic benefit from lower serum TSH levels.

It has been argued that the serum TSH level should not be the sole way to determine euthyroidism, and that clinical symptoms should be incorporated into the determination of the optimal L-T4 dose (414). In a study by Carr et al., patients were symptomatically improved on a L-T4 dose that was 50 mcg/day higher than their optimal dose and resulted in low serum TSH levels (415). However, it should be noted that this was a non-randomized, open label study of short duration, and therefore subject to participant bias. In summary, patients treated with L-T4 to euthyroid serum TSH goals may experience more symptoms of hypothyroidism than people who do not have treated hypothyroidism. However, data from one randomized clinical trial show that increasing the L-T4 dose does not affect these symptoms.

The question that these studies do not answer is why some patients with hypothyroidism have residual symptoms despite serum TSH levels that fall within the reference range. Inadequacy of L-T4 to resolve hypothyroid symptoms has been invoked to explain residual symptoms. However, other explanations should be considered. For example, there are studies suggesting that the presence of thyroid peroxidase antibodies *per se*, even in patients who have maintained endogenous euthyroidism, may be associated with more symptoms than are reported by euthyroid patients without thyroid autoimmunity. One study found more symptoms and lower

quality of life in those with elevated titers of thyroid peroxidase antibodies (416), whereas another study reported more depression (417). Simply being labeled as a patient with hypothyroidism could be associated with feeling unwell. In addition, it has been shown that, individuals referred for thyroid testing by their primary care physicians had rates of psychological distress that were approximately twice as high as the general population under the care of a physician, with 54% versus 19% having GHQ scores >3 (418). This was despite the fact that the rate of hypothyroidism in the referred patients was not higher than that in the general population. Thus, it is more likely that those with psychological distress will have SCH not only detected, but also treated, even if the psychological distress is not causally related to SCH. Moreover, symptoms thought to indicate the presence of hypothyroidism, but not actually related to the hypothyroid state, will presumably not resolve with the application of L-T4.

Even though serum T3 concentrations are typically not measured during an evaluation of hypothyroidism, if they are in fact measured, it is theoretically appealing from a physiological standpoint to attempt to normalize them, along with other biochemical parameters. A recent survey of practice patterns found that 22% of clinicians would measure serum T3 levels when confronted by a biochemically euthyroid patient with persistent symptoms (419). No published studies have demonstrated that relatively low T3 levels have negative consequences for patients with normal serum TSH values, so this is an, as yet, untested hypothesis. If symptomatic patients, who are euthyroid based on their serum TSH values, also have relatively low serum T3 levels during L-T4 therapy in the absence of non-thyroidal illness (39-43), they could be considered for referral for future clinical trials of L-T3-containing combination therapy (see discussion in *recommendation 13 and Future Directions*). As practicing clinicians, we are aware that T3 therapy is being administered to selected patients under these circumstances. The previously mentioned survey of practice patterns found that 3.6% of physicians would prescribe L-T3 under such circumstances (419). A recent review discussed the addition of L-T3 to L-T4 therapy in persistently symptomatic patients with biochemical euthyroidism under carefully monitored conditions (420). An individual trial of T3 therapy to normalize the serum T3 levels without driving serum TSH below the normal range is unsupported by data and therefore is an unproven approach, but, following extensive discussion, some task force members thought it could be considered on an individual basis. This would be considered innovative therapy, which occurs when a practitioner uses a treatment in a way that deviates from commonly accepted

practice. When such new treatments are used repeatedly, they should be made the object of formal research at an early stage, in order to determine whether the innovation is both safe and effective. When T3 therapy is used outside of a trial it is difficult to determine whether the therapy had the desired response in the individual patient and the patient's uncontrolled experience does not contribute to determining the effectiveness of the therapy.

Use of levothyroxine in euthyroid individuals

10a. Is there a role for the use of levothyroxine to treat biochemically euthyroid patients with symptoms that overlap with those of hypothyroidism?

Recommendation

We strongly recommend against the use of levothyroxine treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use of levothyroxine in this situation.

Strong recommendation. High quality evidence.

Discussion of the clinical literature

In a randomized placebo controlled crossover trial in patients with symptoms suggestive of hypothyroidism but biochemical euthyroidism, L-T4 was no more effective than placebo in improving cognitive and psychological well-being scores despite increases in serum FT4 and decreases in serum TSH when study subjects were receiving L-T4 (421). A study employing 12 months of TSH suppression therapy in euthyroid patients with thyroid nodules did not detect any changes in parameters such as weight, fat mass, waist circumference, and exercise performance compared with patients untreated with L-T4, suggesting that L-T4 also does not alter body composition or muscle function in euthyroid individuals (422). In part, the negative outcomes of these studies may be explained by the finding that symptoms do not always accurately predict hypothyroidism. In one case-control study of patients identified through laboratory records, when patients with biochemical hypothyroidism were compared with euthyroid individuals, there did not seem to be specific symptoms that separated one group from another (57). The number of symptoms experienced by patients may be helpful in detecting hypothyroidism: hypothyroid patients had seven symptoms or more, and were also more likely to have experienced a change in their symptoms (57). In another study, a symptom score correlated well with Achilles reflex time

and cholesterol, but not TSH (58). Based on these data, there does not appear to be a substantiated role for the use of L-T4 therapy to treat symptoms in biochemically euthyroid patients with symptoms that overlap with those of hypothyroidism. Furthermore, there may be harm in treating euthyroid patients with L-T4 due to potential iatrogenic hyperthyroidism and potential deflection of attention away from any underlying non-thyroidal disorders, including somatization disorders.

10b. Is there a role for the use of levothyroxine to treat euthyroid patients with depression?

Recommendation

We recommend against the routine use of levothyroxine for the treatment of euthyroid individuals with depression, due to a paucity of controlled data examining treatment efficacy in this setting.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

Depression. Individuals referred for thyroid testing are frequently found to have symptoms of psychologic distress (418). However, there is no simple association between a diagnosis of hypothyroidism and depression. Most individuals with depression do not exhibit signs or symptoms of hypothyroidism (423); similarly most individuals with hypothyroidism do not exhibit symptoms of depression (424). Although overall the incidence of hypothyroidism does not appear to be greater in those with depression, depression may be found more often in those previously diagnosed with hypothyroidism than in those newly diagnosed with hypothyroidism (424). When the thyroid function of depressed patients was compared with controls, those with depression had a slightly higher TSH (1.9 *versus* 1.5 mIU/L) (425). Overall, the association between depression and thyroid dysfunction is relatively weak (424) and could potentially be due to the thyroid disease itself, unmasking of depression following treatment of thyroid dysfunction, or coping with a chronic medical illness.

Depression is seen in some overtly hypothyroid patients (426), and usually resolves with treatment (427). On the other hand, depression is not more common in patients with SCH (428, 429), and when it does coexist with mild hypothyroidism, L-T4 therapy does not improve it (430).

To our knowledge, there are no controlled studies of L-T4 therapy in depression. Data from open label studies using supra-physiologic doses of L-T4 (250-500 mcg/day) in bipolar disorders (431, 432) and refractory depression (433) have yielded positive results. However, there are no randomized placebo controlled trials of L-T4 therapy for bipolar disorder or depression, with or without concomitant antidepressant therapy. One randomized trial of thyroid hormone potentiation of tricyclic antidepressant non-responders compared 37.5 mcg daily of L-T3 to 150 mcg daily of L-T4, and found greater responses to L-T3 compared to L-T4, but the study had no placebo arm (434). See section 15a for a more detailed discussion on the use of L-T3 in euthyroid patients with depression.

10c. Is there a role for the use of levothyroxine to treat euthyroid patients with obesity?

Recommendation

We recommend against the treatment of obesity with levothyroxine in euthyroid individuals, due to a lack of treatment efficacy for this condition

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

Obesity rates are increasing in the United States (435, 436), possibly contributed to by an abundant food supply and sedentary lifestyles. Cross sectional studies have demonstrated increasing BMI or body weight associated with increasing TSH values (437-439), but autoimmunity itself may be linked with obesity (440), or obesity may be the trigger for changes in thyroid parameters (441, 442), rendering difficulty in assigning cause and effect. Moreover, increased TSH values seen in obese patients may revert to normal after weight loss (442). Although hypothyroidism is often perceived to be a cause of obesity by the public, most of the weight gain (and weight loss with therapy) in thyroid hormone deficiency states is due to fluid retention. There is no significant loss of fat mass, even after therapy of severe hypothyroidism, despite increases in resting energy expenditure (443). Similarly, there are no significant changes in body weight after L-T4 treatment of SCH (84, 444). Although thyroid hormones have been used as a means to attempt to induce weight loss in the past (e.g., (445)), negative nitrogen balance (446) and other deleterious effects on the heart and bone (234-236) dictate against the

use of thyroid hormone to treat obesity. Furthermore, a recent meta-analysis has shown that L-T4 is an ineffective treatment for obesity (447).

10d. Is there a role for the use of levothyroxine to treat euthyroid patients with urticaria?

Recommendation

We recommend against the treatment of urticaria with levothyroxine in euthyroid individuals, due to a lack of treatment efficacy for this condition

Strong recommendation. Moderate quality evidence.

Chronic urticaria is often seen in patients with underlying AITD, especially Hashimoto's thyroiditis. Approximately 25% of patients with chronic idiopathic urticaria seem to have evidence of thyroid autoimmunity (448). Anecdotal reports have suggested that L-T4 therapy may be of use in the treatment of urticaria in euthyroid individuals with positive thyroid autoantibodies (e.g., (449)). However, a retrospective study did not show any benefit of L-T4 treatment that restored euthyroidism in hypothyroid patients with AITD, compared to patients with urticaria without AITD, when the activity of the urticaria in both groups was monitored for 6 months (450). A small, randomized trial showed no improvement with L-T4 when taken with an antihistamine in euthyroid patients with AITD compared to an antihistamine alone (451). Other studies in the literature are generally underpowered and uncontrolled (448).

10e. What is the recommended approach to treating factitious thyrotoxicosis?

Recommendation

Factitious thyrotoxicosis should be treated with discontinuation of the exogenous thyroid hormone with education and/or psychiatric consultation as appropriate.

Strong recommendation. Low quality evidence.

Discussion of the clinical literature

Factitious thyrotoxicosis (thyrotoxicosis factitia) has traditionally been defined as a syndrome wherein patients surreptitiously ingest thyroid hormone (452). It can be associated with Münchausen's syndrome (where physical symptoms and signs of illness are intentionally produced), and is also associated with neuroses related to poor body image and concerns about

increased body weight. More recently, the term factitious thyrotoxicosis has been expanded (453), to include instances of accidental L-T4 ingestion, such as in pediatric poisoning or pharmacy error, or through intentional or unintentional ingestion of supplements that contain thyroid gland extract (454). The treatment is the discontinuation of thyroid hormone. In individuals with psychiatric disorders who are secretly taking thyroid hormone, psychiatric consultation is warranted. Such a consult may not only provide relief for the underlying disorder, but also serves to protect the patient from thyrotoxic-related events. Factitious thyrotoxicosis has not been studied in a systematic manner. A strong recommendation is made despite low quality evidence because there are benefits, but few risks.

Clinical ethics considerations in levothyroxine treatment

11. What are the ethical obligations of clinicians in treating hypothyroidism?

Recommendation

Clinical ethical principles in levothyroxine treatment for hypothyroidism revolve around two core ethical principles in medicine: the Principles of Beneficence and Non-Maleficence, which guide the risk/benefit analysis in clinical practice, and protect clinicians from deviating from practice to satisfy inappropriate patient demands. Additional ethical obligations revolve around the professional virtues of competence and intellectual honesty.

Ungraded

Discussion of the clinical ethics literature

Clinical ethics is a field of practice that refers to the “bedside” ethical issues and dilemmas that arise in the everyday delivery of patient care. Among the four core medical ethical principles introduced and codified in the 1970s in most developed countries, the relevant ethical principle in the treatment of hypothyroidism is the Principle of Beneficence, which guides healthcare providers to maximize clinical benefits and minimize clinical harms; and the Principle of Non-Maleficence, the obligation not to intentionally introduce harms to patients, or intentionally initiate a therapy that is known to have no therapeutic benefit. The Principle of Non-Maleficence also directs practitioners to warn third parties of imminent harms, if the patient appears to be a threat to an identifiable third party or the public (455); this is also a legal standard, codified in health law doctrine.

Offering patients formulations of thyroid hormones or other preparations that are known

to be inferior to the standard of care, potentially futile, or even harmful, contravenes the Principles of Beneficence and Non-Maleficence. Failing to fulfill the Duty to Warn, by notifying third parties or authorities when severely hypothyroid patients are driving, for example, and are known threats to public safety or even child safety (if driving children), is a violation of Non-Maleficence (455).

Most practitioners are taught that patient autonomy means that they should cater to patient preferences. However, if patients are requesting inappropriate therapies this is a misinterpretation. The Principle of Respect for Persons is a principle that dually guides practitioners to respect patient autonomy, but to also *protect* patients who do not have full decision-making capacity from pointless harm. Autonomy can only be enabled with valid informed consent, which comprises full disclosure and explanations of all procedures and treatments; decision-making capacity, which means that patients must demonstrate understanding, appreciation, rationality and expression of a choice; and voluntariness, in which there is no coercion.

Goals of care should be guided by autonomous patients' preferences, but there are limits to what practitioners may offer if patients are demanding therapies that are outside the standard of care, or potentially harmful. In the context of hypothyroidism, patients may express a preference to feel well and be restored to euthyroid levels, yet refuse synthetic L-T4 therapy because it is not "natural". This stated preference could indicate the patient does not understand and appreciate the pharmacologic properties of L-T4, which can be explained as restoring "natural" physiologic function. In this common example, the patient's preference can be understood as a preference not to have drug side effects or be harmed. Respecting the patient's preference, in this context, would be to ensure the patient has a truer understanding of hypothyroidism and L-T4 action; only when the patient understands and appreciates that choosing thyroid extract therapy rather than L-T4 could expose them to certain risks such as elevated serum T3 levels, would this constitute informed refusal of standard therapy. If there is inability of autonomous patients to demonstrate understanding, appreciation, rationality, and expression of a choice, this indicates there is a barrier to decision-making capacity, and thus, valid informed consent cannot be claimed. Several articles provide more information about informed consent, decision-making capacity, and surrogacy in the thyroidology context (456, 457).

Beneficent care thus recognizes there are limits to patient autonomy when patients or their surrogates request substandard, unsound or untested medical procedures or therapies that could be either futile or harmful. It should be recognized that while autonomous patients may accept or refuse therapies, they should not be abandoned to “autonomy” when they seek therapies that violate beneficent care (458-460) by being provided with inappropriate care because they request it. When Beneficence and Non-Maleficence are violated, there may be legal consequences and licensure revocation, as these ethical violations constitute medical negligence. Two recent judgments in high profile medical negligence cases (461, 462) involved practitioners acceding to patients’ demands for unsound medical therapies. In these cases, the physicians abandoned primary obligations to beneficence and non-maleficence, and treated the patients as their customers. In one judgment, the practitioner was stripped of his medical license (461, 463); in the other, he was convicted of involuntary manslaughter for iatrogenic harms caused by a therapy the patient demanded (462).

All medical practitioners have professional ethical duties to be competent in their fields of practice, which includes intellectual honesty (464, 465), and referring patients to other colleagues in areas where knowledge is insufficient. Practitioners who state they are experts in treating hypothyroidism when they have no demonstrable accredited training or board certification (e.g. “integrated medicine”) violate professional ethical standards of practice, as it overtly deceives patients. Additionally, competently trained medical experts who misuse their medical knowledge to personally profit, deceive patients, or purvey non-standard, risky innovative therapies in hypothyroidism are violating basic standards of care.

Finally, there are special ethical considerations for prenatal and pediatric contexts. For more information about these special populations, as well as the full range of clinical and professional ethical considerations relevant in thyroidology, we refer clinicians to the Clinical and Professional Ethics Guidelines published by the ATA Ethics Advisory Committee (456) and a recent review article (457).

SECTION II. THERAPIES OTHER THAN LEVOTHYROXINE ALONE

Thyroid extracts

12. In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is treatment with thyroid extracts superior to treatment with levothyroxine alone?

Recommendation

We recommend that levothyroxine be considered as routine care for patients with primary hypothyroidism, in preference to use of thyroid extracts. Although there is preliminary evidence from a short-duration study that some patients may prefer treatment using thyroid extracts, high quality controlled long-term outcome data are lacking to document superiority of this treatment compared to levothyroxine therapy. Furthermore, there are potential safety concerns related to the use of thyroid extracts, such as the presence of supraphysiologic serum triiodothyronine levels and a paucity of long-term safety outcome data.

Strong recommendation. Moderate quality evidence.

Mechanistic background

The thyroid gland secretes a variety of iodinated and non-iodinated molecules that collectively play important roles during prenatal and adult lives. Understanding what these molecules are and what they do informs our understanding of the therapy for hypothyroidism. The main non-iodinated molecule secreted by the thyroid is calcitonin, an endogenous hormone with probable effects on calcium and bone metabolism. The other iodine-containing molecules include T4, T3, reverse T3, 3,3'-diiodothyronine (3,3'-T2), 3,5-diiodothyronine (3,5-T2), monoiodothyronine (T1), and their decarboxylated forms known as thyronamines.

While the traditional view has been that T3 is important as the main iodothyronine with significant binding to nuclear TRs at physiological concentrations, and T4 is important as a precursor of T3 (466), the use of desiccated thyroid extracts for therapy of hypothyroidism is based on the hypothesis that other molecules present in the thyroid gland may have important effects. A growing number of in vitro studies have indicated that administration of pharmacologic doses of 3,5-T2 has metabolic effects, possibly mediated via non-genomic mechanisms (467-469). Note that the mechanism by which 3,5-T2 is generated in humans is unclear; furthermore the circulating levels of 3,5-T2 is two orders of magnitude lower than T3 (470, 471). Finally, thyronamines have been shown to interact with the G-protein coupled receptor Transcript Antisense to Ribosomal RNA (TAR1), with 3-iodothyronamine being the most potent agonist. In pharmacologic doses, 3-iodothyronamine triggers diverse effects such as hypothermia, behavioral inactivity, bradycardia, and decreased cardiac output. Metabolic

effects such as a shift from carbohydrate to fat metabolism and stimulation of food intake have also been described (472).

In summary, current evidence supports the classical view that T3 and T4 are the only biologically important secreted products of the thyroid; none of the alternate signaling molecules have been definitely shown to have physiologic relevance in humans at endogenous concentrations. It is not known whether oral use of thyroid extracts would provide any of these “alternate” components to patients, since studies of their retention during product preparation, their absorption into the blood from the gastrointestinal tract, and subsequent concentrations achieved have not been published. The available literature does suggest that pharmacologic administration of 3,5-T2 and iodothyronamines could have metabolic effects.

Discussion of the clinical literature

Desiccated thyroid or thyroid extract refers to preparations that are derived from the thyroid gland of animals. These preparations were the primary therapy for hypothyroidism until the advent of synthetic thyroxine preparations in the 1960's. All commercially available prescription desiccated preparations are derived from pigs. As per the United States Pharmacopeia (USP), desiccated thyroid is “the cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by humans.” Tablets are measured for T4 and T3 content and are formulated into doses expressed as “grains” with one grain (65 mg) tablets containing 38 mcg of T4; 9 mcg of T3; protein-bound iodine; and unmeasured quantities of diiodothyronine, monoiodothyronine, and calcitonin, to which inactive ingredients are added for tablet stability. Varying strengths from fractions to multiples of a grain are commercially available. One process used to achieve specific dosage strengths is to mix different batches of the product during manufacture. The bioavailability of the T4 and T3 components has been shown to be the same between desiccated thyroid and synthetic preparations (473).

There are two main clinical concerns with the use of desiccated thyroid preparations, both of which center on their T3 component. The ratio of T4:T3 in desiccated thyroid preparations is 4.2:1, which is significantly lower than the 14:1 ratio of secretion by the human thyroid gland. This relative excess of T3 leads to supraphysiologic levels of T3 (474-477). In addition, due to the shorter half-life of T3, fluctuations of T3 occur over the course of the day, with peak levels

shortly after dosing (475, 477). Thus, there is concern for thyrotoxicosis if thyroid extract therapy is not adjusted according to the serum TSH. One nonrandomized crossover study documented a larger number of hyperthyroid symptoms when individuals were taking desiccated thyroid preparations compared with levothyroxine preparations, which was attributed to T3 effects (474). There are claims from proponents of each type of therapy regarding the superiority of their preparation (478, 479). However, there is only one randomized clinical trial comparing desiccated thyroid to L-T4 in the therapy of hypothyroidism (480) (see table 5a). Although this crossover study did suggest that in selected individuals there was patient preference for the extract and minimal weight loss associated with its use, the study, which was designed as a superiority trial, and powered for quality of life endpoints, not safety endpoints, was essentially a negative study in that improved quality of life was not also seen over the 16 weeks of treatment.

It is worth noting that when evaluating health outcomes, measures such as quality of life and mortality are clearly health outcomes (481, 482). However, demonstration of patient preference without use of a validated questionnaire may not truly be a health outcome, and traditionally has not been considered to be a health outcome (482). In addition, the preference outcome may need to be interpreted in the context of another validated health outcome, such as quality of life. There was also no routine documentation of the daily excursion in T3 concentration that was associated with thyroid extract use (only two patients had serum T3 levels measured on one occasion 3 hours after taking the thyroid extract) (480), thus not providing data to counter the older studies (474-477) showing hypertriiodothyroninemia 2-5 hours after thyroid extract use. The clinical consequences of such serum T3 excursions are unknown. These high T3 levels may be of particular concern in patients receiving suppressive therapy for thyroid cancer using a thyroid extract.

There are no published controlled long-term outcome trials of the use of desiccated thyroid extract. Furthermore, data from studies of combinations of L-T4 and L-T3 therapy (as reviewed in recommendation 13b) do not suggest additional benefit from the addition of L-T3 to L-T4 replacement therapy. However, the long term therapeutic efficacy of the T4:T3 ratio found in porcine desiccated thyroid and of the remaining components of porcine thyroids found in these tablets has not been assessed, leaving the direct benefits and risks of desiccated thyroid therapy untested. Moreover, use of thyroid extract should not be contemplated during pregnancy. Delivery of T4 is thought to be crucial for the developing fetal brain (483) and using a thyroid

hormone preparation where the T4 concentration may be lower than that in L-T4 could be deleterious.

Synthetic combination therapy and the rationale for its use

13a. Do genetic variants in thyroid hormone pathway genes (deiodinases or thyroid hormone transporters) affect the serum or tissue levels of thyroid hormones in healthy euthyroid individuals or hypothyroid patients taking replacement therapy?

Summary Statement

Specific polymorphisms in the deiodinases are consistently associated with very small changes in serum thyroid hormone levels. Insufficient data exist to draw any conclusion about the clinically relevant effects of deiodinase or transporter polymorphisms on tissue thyroid hormone levels.

Mechanistic background

*Twin and family studies have shown that between 26 and 65% of the variation in serum thyroid function tests is due to genetic factors (484, 485). Genetic variants can be divided into two broad classes, based on their frequency and their functional effects on the target gene. Polymorphisms are common genetic variants that occur frequently in the population, and generally have only very modest effects on gene function. In contrast, mutations are rare genetic variants with major effects on gene function leading to monogenic disorders such as *RTHα*, *RTHβ* (see section 7c and section 24), or the Allan-Herndon-Dudley syndrome due to mutations in the thyroid hormone transporter *MCT8* (486). While no patients have been identified with functionally important deiodinase mutations, 7 patients with mutations in *SECISBP2*, a gene critical for the synthesis of selenocysteine containing proteins including the deiodinases, have been identified. Affected individuals have a mild phenotype but do exhibit decreased serum T3 levels (487).*

Candidate gene studies have been widely used to study associations of polymorphisms in thyroid hormone pathway genes with thyroid function tests. Such studies are straightforward to perform, and can be powered to detect small effects of specific alleles. Care must be taken to avoid false positive results arising from small sample size, lack of replication in an independent cohort, lack of standardized phenotyping and genotyping, and population stratification when insufficient care has been paid to matching cases and controls (488). Alternatively, genome-wide association studies (GWAS) can be performed with genotyping of large numbers of polymorphisms across the genome rather than focusing on a single candidate gene. GWAS

studies require much larger sample sizes than candidate gene studies in order to have adequate statistical power.

In recent years, it has been demonstrated that certain polymorphisms are consistently associated with serum TSH and iodothyronine levels. A recent large meta-analysis of GWAS for serum levels of TSH and FT4 in up to 26,420 and 17,520 euthyroid subjects, respectively, identified 26 independent associations. Some were in loci that had previously been identified in candidate gene analyses, but many novel loci that were significantly associated with TSH and FT4 were identified as well (489). Together, these genetic markers explain 5.64% of the trait variation in TSH, and 2.30 % of the variation in FT4, suggesting that many other genetic markers remain to be identified.

Evaluating whether mutations or polymorphisms are important for a protein's function can be done in cells or with mouse studies in which the altered gene is knocked into the germline of the animal. Such studies may be limited because of the possibility of cell-specific or species-specific effects, and also because proteins may have functions unknown to the investigators that are therefore overlooked. The effects on protein function have not been established for most of the polymorphisms associated with TSH and FT4, not even for the most consistent single nucleotide polymorphisms (SNPs) in the type D1 gene (DIO1) (489, 490).

Similarly, in vitro studies have as yet failed to reveal any consistent functional effect of the widely-studied D2 gene (DIO2) polymorphism (rs225014) that results in a Thr92Ala substitution in the enzyme (491). The polymorphism is located in an instability loop of the protein and about 9-16% of the population is homozygous for the substitution (492). The D2 Thr92Ala variant is associated with decreased D2 enzyme velocity in skeletal muscle and thyroid tissue samples of patients with type 2 diabetes mellitus who were homozygous for the variant (493). In contrast, cells transiently expressing the Thr92Ala form of D2 display similar kinetic properties with either T4 or rT3 as substrate as compared to controls (493, 494). This being the case, the clinical associations with this polymorphism may result from an unstudied function of the polymorphism, or from linkage disequilibrium with another unidentified locus in the genome.

On the other hand, another D2 polymorphism with reported clinical associations, the DIO2-258A/G (rs12885300) was associated with an increased ratio of T3/T4, consistent with an increase in deiodinase activity (495). In vitro studies suggest that this polymorphism may cause an increase in D2 expression (496). Pharmacogenomic studies designed to interrogate the role

of the DIO2-Thr92Ala (497) and the DIO2-258A/G (498) polymorphisms on the hypothalamic-pituitary thyroid axis indicate that these polymorphisms have distinct, small, but significant modulatory effects on the TSH secretion and on the pattern of thyroid hormone secretion. Homozygous subjects showed a delayed rise in serum T3 (497) and a blunted rise in FT4 and normal T3 release (498) respectively, indicating subtle alterations in intrathyroidal conversion of T4 into T3, with opposite effects on the T3 product, associated with these two polymorphisms.

The D1 polymorphisms DIO1-C785T (rs11206244) and DIO1-A1814G (rs12095080) appear to be associated with decreased and increased activity of D1 respectively, possibly by altering mRNA stability or folding (499). It should be noted that data are lacking as to whether polymorphisms in thyroid hormone pathway genes, including the deiodinases and transmembrane transporters, are associated also with differences in tissue T3 levels. In the case of D2, which is critical for local T3 generation, studies in rodents with inactivating D2 mutations have shown T3 deficiency in D2-dependent tissues such as the brain (339-341). Thus, the possible effects of genetic variants in D2 on tissue T3 levels in human subjects should be a subject of future research.

Similarly, effects of polymorphisms in thyroid hormone transporters on transport function and thus tissue T3 levels have not been reported. The possibility that a genetic transport abnormality caused by a polymorphism could be physiologically relevant seems possible based on the observation that inactivating mutations of MCT8 in hemizygous males have been found to cause severe psychomotor retardation, known as the Allan-Herndon-Dudley syndrome (AHDS). These individuals have peripheral hypermetabolism and abnormal serum thyroid levels with elevated serum T3, low serum T4, and slightly high TSH (486, 500, 501).

Discussion of the clinical literature

A number of studies have looked for associations between deiodinase polymorphisms and differences in circulating thyroid hormone levels. While some polymorphisms are associated with statistically significant differences across genotypes, these differences are very small, such that T3, T4, and reverse T3 remain in their respective normal ranges (489, 495, 502, 503). For example, the DIO1-C785T polymorphism has been associated with a small decrease in serum T3, trending from 131.8 ng/dL (CC) to 127.7 ng/dL (TT) (502). The C allele of the DIO1 polymorphism rs2235544 has, on the other hand, been associated with an increase in the FT3

concentration in both L-T4 treated and non-treated individuals in a meta-analysis (504) and the D1-A1814G allele is associated with a higher T3/rT3 ratio (494). The best-studied polymorphism in DIO2 (DIO2- Thr92Ala) is, in fact, not associated with any change in circulating thyroid hormone levels (502), while another DIO2 polymorphism DIO2-258A/G (D2-ORFa-Gly3Asp) was associated with lower serum T4 and FT4 levels and an increased T3/T4 ratio, but was not associated with serum T3 levels (495).

A few studies have investigated whether genetic variants thyroid hormone pathway genes (i.e. the deiodinases) are associated with altered function of the thyroid axis in human patients taking L-T4 monotherapy. For example, when present as the homozygous Ala/Ala form, the Thr92Ala polymorphism has been associated with a higher requirement for L-T4 in order to achieve near-suppression of serum TSH in patients who have undergone total thyroidectomy (224). However, a subsequent study found no effect of the Thr92Ala D2 polymorphism on the L-T4 dose needed to achieve TSH suppression in thyroid cancer patients or TSH normalization in patients with Hashimoto's hypothyroidism (222). The relationship between FT4 and TSH in patients appears to be affected by their DIO2-258A/G (DIO2-ORFa-Gly3Asp) polymorphism status. The negative feedback of FT4 on TSH is weaker in homozygous patients being treated with L-T4 (505). Given this limited amount of data, it remains to be proven that these D2 polymorphisms have a clinically important effect on thyroid hormone economy.

A large number of studies have looked for associations between genetic variants in the thyroid hormone pathway genes and other clinical syndromes. For example, a recent GWAS identified 22 polymorphisms that were associated with serum TSH, 4 of which were also significantly associated with the risk of thyroid cancer (506). Most studies however, have focused on the role of the DIO2-Thr92Ala D2 polymorphism, which was initially identified as being clinically relevant in a study associating it with insulin resistance and increased BMI (491). Subsequently, this polymorphism has been associated with various phenotypes including mental retardation (507), hypertension (508), osteoarthritis (509), accelerated bone turnover (510), and response to lung injury (511), although subsequent studies could not confirm the associations with hypertension (512). Ultimately, understanding the connections between the deiodinase polymorphisms and these other entities will depend upon the discovery of an enzyme property affected by the polymorphism, or an effect on tissue levels of T3 conveyed by these polymorphisms, or linkage to another critical genetic locus or loci.

MCT8 has also been studied to determine whether there is any impact of polymorphisms on serum thyroid hormone parameters. Results from these studies are mixed with associations between SNPs and FT4 and FT3 shown in one study (513), but not in others (30).

13b. In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?

Recommendation:

There is no consistently strong evidence of superiority of combination therapy over monotherapy with levothyroxine. Therefore, we recommend against the routine use of combination treatment with levothyroxine and liothyronine as a form of thyroid replacement therapy in patients with primary hypothyroidism, based on conflicting results of benefits from randomized controlled trials comparing this therapy to levothyroxine therapy alone and a paucity of long-term outcome data.

Weak recommendation. Moderate quality evidence.

13c. In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?

Recommendation

For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone (in the absence of an allergy to levothyroxine constituents or an abnormal serum TSH), there is currently insufficient evidence to support the *routine* use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or N of 1 trial, due to uncertainty in long-term risk benefit ratio of the treatment and uncertainty as to the optimal definition of a successful trial to guide clinical decision-making. Additional research targeting those with relatively low serum T3 concentrations, but normal TSH levels during monotherapy is needed to address whether there is a subgroup of patients who might benefit from combination therapy.

Insufficient evidence

Mechanistic background

A fundamental characteristic of D2 is that its enzymatic activity is tightly coupled to plasma T4 levels by the ubiquitin-proteasomal system (358). As circulating T4 falls in hypothyroid subjects, the fractional conversion rate of T4-to-T3 increases (514). In hypothyroid rodents, this increase occurs via a PTU-insensitive pathway (515), i.e. D2. The flux of T4 through the D2 activation pathway increases due to increased enzyme activity, such that serum T3 levels remain normal, at

least until the fall in serum T4 is substantial. In D2 expressing tissues such as the brain, much of the intracellular T3 is generated from circulating T4 (340, 516); thus, these tissues are particularly protected from mild T4 deficiency. The existence of the D2 pathway for conversion of T4 to T3, and the homeostatic function of D2 for maintenance of intracellular T3 in the face of mild T4 deficiency, explain why L-T4 monotherapy can be so effective in the treatment of hypothyroidism. Treatment with PTU in patients reliant on L-T4 therapy reduces their serum T3 levels significantly by about 20 ng/dL. Presumably this reduction is due to inhibition of the PTU-susceptible D1, illustrating both that D1 contributes in part to maintenance of serum T3 and that D2 contributes importantly to maintenance of serum T3 levels (19).

At the same time, data indicate that a small but significant proportion of thyroidectomized patients on L-T4 monotherapy have low circulating T3 in spite of normal range TSH and high-normal serum T4 (39-43). It is possible that in these subjects, the D2 pathway does not fully compensate for the absence of the thyroidal T3 production; the significance of the low serum T3 levels in these patients is discussed in section 7a and 7b. Note that even D2-expressing tissues would be expected to be relatively T3 deficient since D2 is not upregulated significantly by decreases in serum T3. The serum TSH remains in the normal range likely because the decreased serum T3 is counterbalanced by the increased serum T4. If this concept is correct, the question then becomes how to simultaneously normalize the concentration of T3 in all tissues? Increasing L-T4 dose would raise serum T3, thus raising tissue T3 content in all tissues, but at the cost of lowering serum TSH, and at the theoretical risk of inducing mild hyperthyroidism in D2-expressing tissues. Hypothetically, replacing some of the administered L-T4 dose with L-T3 could help normalize tissue T3 without necessarily lowering serum TSH. Data supporting the concept that combination therapy can be effective in normalizing tissue T3 across all tissues are available from rodent studies (361), but corresponding data in humans are not available. Animal studies have shown that some tissues are relatively T3-deficient during L-T4 infusions (338, 361). However the cerebral cortex was an exception, as in this tissue T3 homeostasis was maintained over a wide range of T4 and T3 infusions (338). An infusion of a combination of L-T4 and L-T3 allowed for normalization of serum TSH and levels of T4 and T3 in all tissues tested (361).

Discussion of the clinical literature

In order to evaluate whether the combination of L-T4 with L-T3, also referred to as combination therapy, was clinically superior to L-T4 alone, in thyroid hormone replacement of adults with primary hypothyroidism, we reviewed the results of 13 original randomized controlled trials (384-388, 517-524), as well as 4 systematic reviews or meta-analyses of selected randomized controlled trials (389, 525-527). The reason for reviewing all original studies, rather than only the published reviews or meta-analyses, was that some trials were published after these reviews or meta-analyses were conducted. We did not include a randomized trial published by Smith et al. in 1970, since the dosages of L-T4 that were used were higher than those typically used in current clinical practice, and the study pre-dated utilization of TSH measurements, both of which may have contributed to thyroid hormone over-replacement in the study (528). We did not include a controlled crossover design trial from Regalbuto et al. (529), given that there was no evidence of randomization of patients reported in the methods section of the paper.

The characteristics of the included original trials are described in Table 5b. The studies included a variety of L-T4/L-T3 dose combinations, administered either once or twice a day, and the duration of treatments ranged from 5 weeks to 1 year, with the majority of studies being 6 months or shorter in treatment duration (Table 5b). The majority of patients in most studies had primary autoimmune hypothyroidism, but some studies included patients who had thyroid surgery or radioactive iodine treatment (Table 5b). Females accounted for the vast majority of participants studied in all of the studies (80% or more of the study population in respective trials) (384-388, 517-524). Some trials provided information regarding pre-trial screening for relevant symptoms such as depression and fatigue using validated questionnaires (404, 530-533) and described inclusion/exclusion criteria based on these symptoms (Table 5c). All included trials had some level of blinding, except for one study focusing on laboratory parameter outcomes by Fadayeve et al. (520). Of the 12 included trials comparing the effect of combination L-T4/L-T3 treatment to L-T4 alone, seven had a crossover design, (384, 385, 387, 517, 519, 521, 523), and the rest had a parallel design (386, 388, 518, 520, 522, 524). The impact of combination L-T4/L-T3 treatment on serum TSH levels measured at study completion was as follows: a) no significant difference compared to L-T4 therapy alone – 8 studies (384, 387, 388, 517, 518, 520, 521, 524), b) significantly higher TSH measurement in the combination therapy group compared to the L-T4 group – 3 studies (385, 519, 522), or c) significantly lower TSH measurement in the combination therapy group compared to L-T4 alone – 2 studies (386, 523), including one study

where the serum TSH in the highest dose combination group (5:1 ratio of L-T4 to L-T3), was suppressed to 0.07 mIU/L (386).

Among the 12 trials examining health-related quality of life, or mood (384-388, 517-519, 521-524), there was marked unexplained clinical heterogeneity of L-T4/L-T3 treatment effects, categorized as follows: a) marked superiority of combination treatment on multiple measures – 2 trials (Bunevicius et al. from 1999 (387) and Nygaard et al. from 2009 (521)), b) superiority of combination treatment on a minority of measurements – 2 trials, with 1 trial from Saravanan et al. reporting some improvements in mood at 3 months but not 12 months (522), and another trial from Valizadeh et al. reporting improvement of an insomnia/anxiety subscale with other measures not significantly different (524), or c) no statistically significant superiority of combination treatment over L-T4 treatment – 8 trials (384-386, 388, 517-519, 523). It is important to note that it was not uncommon for psychological or quality of life measurements to improve in both treatment groups, suggesting an important placebo effect. Among the 10 trials reporting measures of neurocognitive functioning or behavior, there was marked unexplained clinical heterogeneity of L-T4/L-T3 treatment effect, with the results summarized as follows: a) marked superiority of combination treatment on multiple measures – 1 trial by Bunevicius et al. from 1999 (387), b) superiority of combination treatment on a minority of measurements – 1 trial by Escobar-Morreale et al. (519), c) no statistically significant superiority of combination treatment over L-T4 treatment – 8 trials (384-386, 388, 517, 518, 522, 523), including a study by Clyde et al., where cognitive performance on a Grooved Peg Board test was better in the L-T4 group, compared to the combination therapy.

Thyroid-related symptoms and thyroid-related health outcomes are clinically relevant outcomes examined in many of the included trials. There was no significant difference in thyroid-specific symptom questionnaires between treatment groups in the 7 trials measuring these outcomes (384, 385, 517-520, 522). Of the 9 trials examining the outcome of body weight (384-386, 517-519, 521, 522, 524), the end of trial weight was significantly reduced in the combination therapy group compared to the L-T4 group in only one trial at a TSH suppressive dose of combination therapy (L-T4:L-T3 5:1 ratio) (386), with no significant differences observed in the other studies (384, 385, 517-519, 521, 522, 524). Bone mineral densitometry, measured after 6 months of treatment, was not significantly different with combination treatment compared to L-T4 alone, in one study of pre-menopausal women, examining this outcome (520).

Skeletal fracture outcomes were not reported in any studies. The effect of combination L-T4/L-T3 treatment compared to L-T4 alone on resting heart rate was evaluated in 11 trials (384-387, 517-520, 522-524), and the effects were characterized as follows: a) significantly increased heart rate in the combination therapy group compared to the L-T4 group – 1 trial by Appelhof et al. (386), at the 5:1 L-T4 to L-T3 ratio dose of combination therapy, b) significantly reduced heart rate in the combination therapy group compared to the L-T4 group – 3 trials, including those from Bunevicius et al. from 1999 (387), Escobar-Morreale et al. (519), and Walsh et al. (385), respectively, or c) no significant difference between treatment groups in 7 trials (384, 517, 518, 520, 522-524). Too few of the combination therapy trials have assessed lipid and cardiovascular parameters to allow comments about benefits related to these outcomes.

Another relevant consideration is treatment preference of patients (see comment in recommendation 12 about use of preference measures as health outcomes). An important limitation in interpreting data on patient preference from randomized trials of combination therapy is a lack of validation and standardization of measurement of this construct, among trials. Among the 5 blinded, crossover design trials comparing treatment preference (385, 387, 517, 519, 521), combination L-T4/L-T3 treatment was preferred to L-T4 in 4 trials (387, 517, 519, 521), whereas there was no significant difference in treatment preference in only one trial (385). It is important to note that the total number of patients who completed the studies in these 4 positive crossover design preference trials was only 128 (387, 517, 519, 521), which is comparable to the 101 patients who completed follow-up in the trial where combination treatment was not preferred (385). The mean serum TSH was significantly higher in the combination therapy group (3.1 mIU/L) compared to the L-T4 group (mean 1.5 mIU/L) in the negative crossover design preference trial (385); in the crossover trials where combination treatment was preferred, the mean serum TSH was not significantly different between groups in 3 studies (387, 517, 521), but significantly higher in the combination L-T4/L-T3 group compared to the L-T4 group in one study from Escobar-Morreale et al. (mean TSH 2.5 mIU/L in the combination therapy group and 1.95 mIU/L in L-T4 group) (519). In blinded parallel design randomized trials evaluating patient preference or subjective patient evaluation of improved well-being on experimental treatment, combination treatment was preferred over L-T4 alone in a study examining data from 130 individuals from Appelhof et al. (386), but not in a study examining data from 573 individuals from Saravanan et al. (522). The observed treatment

preferences of L-T4/L-T3 combination therapy over L-T4 treatment alone in the described studies cannot be reliably explained by any significant consistent benefit of combination treatment on measures of mood, quality of life, neurocognitive functioning, classic hypothyroid symptoms, weight, or TSH. Thus, the reason why L-T4/L-T3 combination therapy was preferred over L-T4 alone by some patients is not well understood and there is some question about validity of this measurement, given the lack of standardized evaluation methods for this construct among studies.

We also reviewed the results of recent systematic reviews or meta-analyses, comparing the effect of combination L-T4/L-T3 treatment compared to L-T4 treatment alone (389, 525-527). For respective meta-analyses, the timing of review and number of trials included was as follows: a) review by Grozinsky-Glasberg et al. conducted in September 2005 in which data were pooled from 11 trials (including one unpublished study) (389), b) a review by Joffe et al. (2007) in which data were pooled from 9 trials (including one unpublished trial) (526), c) a review by Ma et al. conducted in 2008 (527) in which data were pooled from 10 trials (including potentially partially duplicated results of one trial (387)). The authors of these meta-analyses reported that based on their pooled analyses, there was no significant benefit of combination L-T4/L-T3 treatment compared to L-T4 treatment alone, on mood/health-related quality of life (389, 526, 527), nor cognitive functioning (389, 527). Of note, statistical heterogeneity of some of these pooled analyses was noted (389, 527), and for some measures reported by Ma et al., L-T4 alone appeared to be superior to combination treatment (527). Pooled adverse event rates were not significantly different between treatment arms (389). In a meta-regression analysis, Grozinsky-Glasberg et al. reported no significant association among length of follow-up, percentage of athyreotic patients, nor dose of L-T3 and psychologic outcomes (389). In pooling data from 4 trials examining treatment preference, Joffe et al. reported that combination treatment was significantly preferred over L-T4 treatment alone (526). A systematic review, without meta-analysis, was also published by Escobar-Morreale et al. in 2005 (525), in which data from 9 trials (including the 1970 trial from Smith et al. (528)), were reviewed. Escobar-Morreale et al. also concluded that data on benefits of combination treatment on psychological outcomes were heterogeneous and not reproducible, and that the treatment preference for combination treatment was not explained based on results of psychologic or psychometric tests (525).

In conclusion, in reviewing data from 13 published randomized controlled trials (384-388, 517-524), and 4 systematic reviews or meta-analyses of trials (389, 525-527), we found important unexplained clinical heterogeneity of studies, in terms of therapeutic dose combinations utilized, and important study results, such as the following: end of trial TSH, psychological status or health-related quality of life, neurocognitive functioning or behavior, and treatment preference. Measurements on thyroid-related symptom questionnaires generally did not appear to be significantly superior with L-T4/L-T3 combination therapy compared to L-T4 alone. Serious adverse events did not appear to be reported at higher rates in combination treatment compared to L-T4 alone, however the majority of trials are limited by relatively short follow-up periods. The potential for adverse effects of long-term use of combination therapy, such as fractures, or cardiovascular events, are not known. There is also a paucity of data collected on the use of combination therapy in men with primary hypothyroidism. Longer-term outcome research is generally needed in this field, given that thyroid hormone replacement therapy is generally life-long. Furthermore, randomized controlled trials incorporating the use of sustained release T3 preparations would be of interest. However at the current time, based on a lack of clear consistent evidence of benefit of combination therapy using L-T4/L-T3 over established L-T4 therapy and the lack of a proven reproducibly efficacious dose combination using currently available preparations, as well as the lack of long-term outcome data (on safety and efficacy) on the use of L-T4/L-T3 combination therapy, we believe that the *routine* use of L-T4/T3 in treatment of primary hypothyroidism is not justified.

Published trials of combination therapy have not targeted patients who have relatively low serum T3 values during monotherapy. In addition, the serum T3 values achieved during combination therapy have not been a specific endpoint of these trials. It is possible that future trials that included as an entry criterion having both a relatively low serum T3 and a normal serum TSH concentration during monotherapy, in the absence of non-thyroidal illness, might have different outcomes from the trials conducted thus far. Future research addressing this subgroup of patients should be encouraged, as currently this is an unproven approach. As outlined in the discussion of recommendation 9b, some of our task force members felt that, at the discretion of the practitioner, innovative therapy with T3 could be attempted. Such treatment would be solely used to attempt to enhance the well-being of an individual patient, but would not formally test a hypothesis, permit conclusions to be drawn, or contribute to knowledge that would

generalizable for future patients.

Our view is generally in keeping with a recent joint statement from the AACE and the ATA, indicating that “the evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism” (3). However, the joint AACE/ATA hypothyroidism treatment guideline acknowledged that there are “still-unresolved issues raised by studies that reported some patients prefer and some patient subgroups may benefit from a combination of L-thyroxine and L-triiodothyronine” (3). In a recent clinical practice guideline, the ETA has also stated that “there is insufficient evidence that L-T4 and L-T3 combination therapy serves the hypothyroid patient better than T4 monotherapy” and that “L-T4 remains the standard treatment for hypothyroidism” (5). However, the ETA has suggested that “L-T4 and L-T3 combination therapy might be considered as an experimental approach in compliant L-T4–treated hypothyroid patients who have persistent complaints despite serum TSH values in the reference range, provided they have previously been given support to deal with the chronic nature of their disease and associated auto-immune diseases have been ruled out.” This document outlines methods for calculating L-T4 and L-T3 doses for physicians who are considering using a trial of combination therapy in their patients. A range of widely differing opinions about combination therapy has been offered since the publications of the AACE/ATA and ETA guidelines (534-539). However, both the AACE/ATA hypothyroidism guideline (3) and the ETA guideline (5) have strongly discouraged the use of L-T4/L-T3 combination therapy in pregnant women. We also agree that in pregnancy, where delivery of T4 is thought to be crucial for fetal brain development (483), use of a treatment regimen containing T3, in which the T4 concentration may be relatively reduced, could be deleterious and should be avoided.

We would like to stress that if any experimental therapy (such as combination T4/T3 therapy) is considered in humans, it must meet professional and institutional ethical standards, as outlined in section 18 (ethical considerations in hypothyroidism research). We believe that high quality randomized controlled clinical trials are needed to prove if any specific subgroup of patients with primary hypothyroidism may specifically benefit from the use of T4/T3 combination therapy over the use of T4 alone. Such trials need to track relevant adverse effects, and ideally, examine long-term outcomes.

13d. Should genetic characterization according to type 2 deiodinase gene polymorphism status be used to guide the use of combination synthetic T3 and T4 therapy in hypothyroidism, in order to optimize biochemical and clinical outcomes?

Recommendation:

Currently, genetic testing is not recommended as a guide to selecting therapy for 3 reasons.

i) Although there are data suggesting that specific polymorphisms of the type 2 deiodinase gene might be associated with therapeutic response to combination synthetic triiodothyronine and levothyroxine therapy, controlled confirmatory studies are needed. ii) Currently genetic testing for these specific deiodinase polymorphisms is only available in the research setting. iii) The small effect of the type 2 deiodinase gene variants identified so far that do affect thyroid hormone concentrations (see section 13a), suggests that other factors (e.g. yet unidentified genetic variants) may play a far greater role in determining an individual patient's thyroid hormone concentrations.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

We examined the medical literature to determine whether a therapeutic strategy of tailoring the use of combination L-T4/L-T3 treatment, according to genetic characterization of the primary hypothyroid adult patient, improves health outcomes, as opposed to a strategy of routine L-T4 treatment for all patients. We included 3 studies on secondary analyses (390, 540, 541), stemming from two prospective trials comparing L-T4/L-T3 combination therapy to L-T4 alone in primary hypothyroidism (386, 522), in our review. Such secondary analyses of trials, in which treatment allocation was not stratified a priori according to genetic characterization, should be considered hypothesis-generating. In addition, given the modest effects that we now know these polymorphisms exert, this may limit their clinical relevance for the individual patient.

Using data from a randomized controlled trial by Saravanan et al. (522), Panicker et al. (390) explored in a secondary analysis whether common genetic variants (polymorphisms) of three deiodinase genes (DIO1, DIO2, and DIO3), predicted baseline psychological morbidity, and response to combination L-T4/L-T3 treatment in 552 patients. Panicker et al. reported that the presence of two SNPs in the DIO2 gene, DIO2-Thr92Ala (also known as rs225014) and rs225015, which are in strong linkage disequilibrium ($R^2 = 0.88$), were respectively significantly associated with baseline measures of psychological well-being (390). Although 16 polymorphisms were tested, no multiple testing correction was applied because this study, despite being the largest study to date, was underpowered to detect all but very large differential

gene-treatment effects. For this reason, the authors choose to report the P values and associations, which should be considered suggestive, and qualified their findings by stating clearly that the results need replicating as a risk of type I statistical error exists (390). Moreover, Panicker et al. reported a significant interaction between the less common variant of DIO2-Thr92Ala, and combination L-T4/L-T3 treatment compared to L-T4 treatment, on the outcomes of psychological well-being, thyroid symptoms, and satisfaction, in absence of any significant effect on circulating thyroid hormone levels (390). In addition, there was no association between being homozygous for the DIO2 polymorphism and having a lower pre-intervention serum free T3 concentration than the remainder of the study population. 16% of the population in this study was homozygous for the polymorphism (390). In contrast, analyzing data from a randomized controlled trial by Appelhof et al. comparing L-T4 monotherapy with L-T4 and L-T3 combination therapy in two ratios (386), the same group (Appelhof et al.) found no significant association of DIO2-Thr92Ala and another DIO2 polymorphism DIO2-258A/G (rs12885300, DIO2-ORFa-Gly3Asp) with measures of well-being, neurocognitive functioning or treatment preference (data from 92 patients) (540). Polymorphisms in DIO1, although associated with altered serum T3 levels (495, 502), have not been associated with altered response to combination therapy (390).

In another secondary analysis of 92 patients from the same study by Appelhof et al. (386), van der Deure et al. reported that the presence of two polymorphisms of OATP1C1, a T4 transporter expressed in brain tissue, were significantly associated with measures of fatigue and depression, but did not explain differences in neurocognitive functioning nor preference for L-T4/ L-T3 combination therapy in patients with primary hypothyroidism (541). An important limitation of these studies examining associations with SNPs was that respective treatment allocation to the combination L-T4/L-T3 treatment or L-T4 alone, was not randomized with attention to polymorphism status, and thus the results should be considered hypothesis-generating. In addition, the differences between the treatment groups were significant, but small, with considerable overlap between the groups. As a consequence, it is unlikely that genetic characterization of only these polymorphisms will result in superior health outcomes.

With whole exome and whole genome sequencing becoming ever more easily available, less common variants that may, in part, have larger effects are likely to be detected. Large randomized controlled trials are needed to know whether a strategy of tailoring type of thyroid

hormone replacement therapy (i.e. L-T4/L-T3 or L-T4 alone), according to genetic characterization, may result in superior health outcomes, compared to the currently recommended strategy of routine L-T4 treatment for adults with primary hypothyroidism.

T3 monotherapy for hypothyroidism

14. Are there data regarding therapy with triiodothyronine alone, either as standard liothyronine or as sustained release triiodothyronine, that support the use of triiodothyronine therapy alone for the treatment of hypothyroidism?

Recommendation

Although short-term outcome data in hypothyroid patients suggest that thrice-daily synthetic liothyronine may be associated with beneficial effects on parameters such as weight and lipids, longer-term controlled clinical trials using a longer acting form of triiodothyronine are needed, before considering the endorsement of synthetic liothyronine therapy for routine clinical use.

Strong recommendation. Moderate quality evidence.

Mechanistic background

T4, the main product of the thyroid gland, is a pro-hormone devoid of intrinsic activity and the biological effects of thyroid hormone are the result of the interaction between T3 with its receptors (9). From this perspective T4, and by extension its reservoir of hormone bound to serum carrier proteins, assures a reserve of substrate for the deiodination to T3 and offers a buffering against fluctuations in the circulating and tissue levels of T3. On the other hand, since replacement therapy with L-T4 relies entirely on the deiodination step to provide adequate levels of serum and tissue T3, a defect in this metabolic step would result in inadequate delivery of the active hormonal form. Direct therapy with L-T3, while having the advantage of avoiding the requirement for a deiodination step, could also have the theoretical disadvantage of not permitting regulated time-specific and tissue-specific production of T3. With L-T4 therapy, D2-expressing tissues should maintain the required substrate for normal intracellular generation of T3; in addition, the D2 pathway contributes to providing normal amounts of T3 for most patients. With T3 monotherapy, multiple daily dosing is required to sustain serum T3 levels due to the shorter half-life of L-T3, compared with L-T4 (348). If normalization of serum TSH is the goal of L-T3 monotherapy, serum T3 levels must be significantly higher, approximately double, than those seen during L-T4 monotherapy; whether this leads to relative hyperthyroidism in

some tissues requires further study. The impact of L-T3 monotherapy on D2-expressing tissues other than the pituitary gland is also unknown. In rodents, normalization of serum TSH and hypothalamic TRH expression with T3 monotherapy requires serum T3 levels in the supranormal range (542).

Discussion of the clinical literature

Therapy with synthetic preparation L-T3 has the theoretical advantage of bypassing the T4 to T3 conversion step, which is obligatory in case of L-T4 treatment, hence directly delivering the bioactive drug to the various organ/tissues target of the hormonal action. Conversely, a theoretical disadvantage of the therapy with L-T3 alone is represented by the lack of a T4 as a reservoir of substrate; hence the circulating and tissue levels of T3 are entirely dependent on the pharmacokinetic characteristics of the exogenously administered hormone replacement. The available data relative to the pharmacokinetics of L-T3 are contradictory, indicating half-life values ranging from 6 to 22 hours (36, 543). The primary data were obtained from single-dose studies, and either these studies were performed by means of measurement of radioactive decay of radio-labeled L-T3 in euthyroid volunteers (543) or by measurement of serum T3 in hypothyroid patients (36, 543). Since some studies have been performed in subjects with endogenous production of thyroid hormone from the thyroid gland, it is possible that the reuptake and metabolism of iodine in the thyroid caused a spurious increase in the half-life of the drug. Calculation of L-T3 half-life in the blood may also be complicated by distribution from the blood into other compartments and re-distribution back into the blood. However, an average half-life of one day has been quoted (543).

L-T3 therapy started after L-T4 discontinuation, usually administered at a dose of 25 mcg twice-daily, has traditionally been used with the intent of ameliorating hypothyroid symptoms in situations in which induction of hypothyroidism was used as a means delivering therapy for thyroid cancer (544). However, with respect to the hypothyroidism induced in this situation, once-daily administration of 50 mcg L-T3 versus placebo did not result in a significantly different Billewicz score when documented 2 weeks after L-T4 discontinuation, perhaps because FT4 levels were still sufficient at this time point. Use of L-T3 delayed the attainment of a serum TSH greater than 30 mIU/L, but did not alter the hypothyroid symptoms at the time of scanning (44). Thus T3 does not appear to have an advantage in this setting.

Although an extended-release formulation of L-T3 has been shown in a single short-term study to reduce the peaks and troughs of L-T3 administration that were seen over a 9 hour period after T3 administration (545), currently no formal pharmacokinetic study has been published. Presumably, once in the circulation as T3, the persistence of T3 is limited by its short half-life. Thus, even though a sustained release preparation may have reduced peaks and troughs, it may still need to be administered several times day. However, interestingly, a report of a sustained release profile for serum T3 levels after administration of a single dose of T3 sulfate to hypothyroid patients was recently published (546).

A recent double blind randomized crossover study demonstrated that L-T3 can achieve an equivalent degree of serum TSH suppression as compared to L-T4 at a ratio (mcg/mcg) 1:3 when administered as a thrice-daily regimen (348). With this regimen the serum levels of T3 were significantly higher, albeit within the reference range, than the ones achieved with L-T4 therapy both in the morning and throughout the day (347), while serum TSH remained stable throughout the 24-hours. In this study, no adverse events were recorded with the exception of an episode of generalized anxiety during the treatment with L-T4; the two treatments were also equivalent with respect to cardiovascular function and glucose homeostasis. No differences were observed in quality of life endpoints, and patients were not able to distinguish which treatment arm they were assigned to (347). When treated with L-T3, patients experienced an average weight loss of 2.1 kg, a 13.3% decrease in LDL-cholesterol, and a 22.3% increase in SHBG, compared with L-T4 therapy. These investigators subsequently reported performing TRH stimulation in these patients and noted that serum TSH responses were similar in the L-T3 and L-T4 groups, suggesting that possible metabolic differences were mediated peripherally and not at the pituitary gland level (373). Taken together, the data indicate that the substitution of L-T3 for L-T4 at equivalent doses (relative to the thyrotroph) provide an increased hormonal signal to the liver in the absence of obvious toxicity.

Although the results of the double blind randomized crossover treat-to-target L-T3 vs. L-T4 study (347) seem to indicate some superiority at least relative to weight and lipid profile, it is important to note that the experimental treatment was cumbersome and required multiple adjustments; indeed volunteers required an average of 180 days to achieve a target serum TSH on a stable dose of replacement therapy. Therefore, L-T3 alone should not be advocated as a

replacement therapy modality in the absence of an extended-release formulation able to provide stable serum levels of T3.

The L-T3-only therapy appears more favorable for patients affected by dyslipidemia and obesity, but at the present time there is not sufficient evidence that this modality is superior to the standard L-T4 therapy, particularly because of the risk of over- or under-dosing, with the attendant risk of cardiac and skeletal toxicity, and because of the necessity of strict compliance to the regimen and the timing of the drug administration.

Presently no data are available on the long-term effects of L-T3-only therapy, particularly with respect to bone and mineral metabolism and overall safety profile. Long-term administration studies on large populations are required to evaluate the safety of this treatment modality, and the sustainability of the weight and lipid profile changes. Currently there is no evidence that L-T3-only therapy is cost-effective relative to the standard of care represented by L-T4. Furthermore, one can predict that this therapeutic modality will require more monitoring and presumably will be associated with longer periods of under-treatment or over-treatment as compared to L-T4 therapy.

Although not recommended, if used, the following common sense recommendations to monitoring might apply. L-T3 only therapy should be monitored with measurements of fasting serum TSH levels before the administration of the dose, aiming to target serum TSH within the lower tertile of the reference range, if aiming for TSH values seen in a normal population (54). Although data to support this approach are not available, it would seem reasonable to measure serum T3 levels in the morning (trough), and two-hours after the administration of the dose (peak), aiming to maintain the values within the reference range; serum FT4 assessment is of no value in this scenario.

At the present time there is insufficient evidence to suggest that the L-T3-only therapy is a safe and efficacious treatment of hypothyroidism in the general population, including in hypothyroid patients with obesity and dyslipidemia. This recommendation may change in the future should long-term, randomized, controlled trials of a sustained release formulation of T3 become available.

L-T3 monotherapy in euthyroid patients

15a. Is there a role for the use of liothyronine to treat biochemically euthyroid patients with depression?

Recommendation

Although some uncontrolled and non-randomized data exist concerning successful use of liothyronine in euthyroid patients with depression, larger, prospective randomized placebo controlled studies are needed to more completely define the potential role of liothyronine in this condition, balancing the risks and benefits of therapy to measurable clinical outcomes.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

Despite advances in our understanding of T3-mediated genomic as well as nongenomic actions at the cellular level (547), the role for L-T3 in optimizing thyroid hormone replacement therapy has not been clearly elucidated (534, 548-550). With increased recognition of the biologic importance of T3 at the cellular level, and the concerns that biochemical euthyroidism may not equate to tissue euthyroidism, there has been an increasing dialogue regarding whether L-T3 therapy may be effective in reducing symptoms seen in euthyroid patients as well as in patients with depression, obesity, and cardiovascular disease.

The potential use of L-T3 in the treatment of mood disorders has most commonly focused on one of two clinical strategies, either as an adjunct to help accelerate the onset of action of anti-depressant therapy or as an augmentation to therapy in an effort to enhance the effect of treatment that has not achieved the intended clinical effect (551). Hypothalamic-pituitary-thyroid axis abnormalities have been documented in depression, along with reduction in serotonin levels (552). The physiologic basis for the potential role of L-T3 is based on observations of T3-induced increased concentrations of serotonin in the cerebral cortex of mice with increased serotonin-mediated responses (553). In a meta-analysis by Aronson et al. of patients with major depressive disorder, L-T3 augmentation was associated with a 2-fold likelihood of response to tricyclic anti-depressant (TCA) therapy in 292 patients with a previous history of treatment-resistant depression (554). Altshuler et al. reported results of a meta-analysis of six studies examining the use of L-T3 to accelerate the effect of TCA with 5 of 6 studies showing greater effect of combined therapy with L-T3 over placebo, with the most pronounced impact found in studies that had larger cohorts of women (555). More recently, Cooper-Kazaz and Lerer reviewed the literature on combined L-T3 and serotonin reuptake inhibitors (SSRI)

(551). A total of eight studies were compared; five randomized controlled trials (RCTs) of which three were enhancement studies and two were augmentation studies, and three additional open augmentation studies where L-T3 was added after failure of SSRI only therapy. Of the three enhancement studies, one showed weak support for acceleration of L-T3 to therapeutic efficacy of SSRI, and in two no acceleration was found. In the five augmentation studies, including the STAR*D study comparing L-T3 augmentation to lithium augmentation (556), the use of L-T3 augmentation was associated with an overall remission rate between 25% to 36%. For all studies combined there were very few side-effects associated with the addition of L-T3 up to 50 mcg/day (551). The authors conclude that while there is evidence to support the clinical efficacy of L-T3 for the enhancement or augmentation of SSRI therapy, the data are not conclusive and further controlled studies employing uniform study design are needed to determine the appropriate dose, the timing of L-T3 initiation, and length of treatment (551). The practice guideline of the American Psychiatric Association describes the use of L-T3 in its document about treatment of major depression, but does not have a specific recommendation addressing its use (557).

If T3 therapy is in fact beneficial, it is possible that this may be due to pharmacological rather than physiological effects of T3. Nevertheless, it may occur that a psychiatrist is using adjunctive oral T3 therapy to treat a psychiatric disorder and requests an endocrinologist's opinion how to manage the patient. It would seem appropriate to monitor the patient clinically with a history and physical examination. Serum FT4, T3 and TSH levels should also be monitored recognizing that the T3 levels, and perhaps the TSH concentrations, might vary throughout the day. A clinical recommendation then can be given based on these parameters.

15b. Is there a role for the use of liothyronine to treat biochemically euthyroid patients with obesity?

Recommendation

We recommend against the use of synthetic liothyronine therapy in treating euthyroid patients with obesity, due to a lack of controlled data proving treatment efficacy for this indication.

Strong recommendation. Low quality evidence.

Discussion of the clinical literature

L-T3 has also been considered as a potential therapy to prevent the cardiovascular morbidity and mortality associated with obesity. Efforts to use L-T3 are based on studies showing decreased serum T3 with subsequent decreased basal metabolic rate in obese subjects placed on calorie-restricted diets (447, 558). In hypothyroid patients, when L-T3 is administered thrice daily, dosed to achieve a target TSH of 0.5 to 1.5 mIU/L, LT3 treatment is associated with decreased body weight, with an average weight loss of -1.8 ± 1.9 kg, as well as reduced total cholesterol, low-density lipoprotein, non-high-density lipoprotein and apolipo-protein B when compared to L-T4 therapy in the same individual (347). There have been multiple studies on the potential efficacy of L-T3 in euthyroid obese subjects, summarized in a systematic review by Kaptein et al. (447). In 13 of 14 studies, L-T3 was the exclusive therapy, with L-T4/L-T3 used in the additional study. Unfortunately, there was wide variation in study design with no clear association between L-T3 therapy and weight loss, protein breakdown, or metabolic rate. In addition, none of the studies were designed to determine one of the most important questions, i.e. whether L-T3 therapy during caloric deprivation enhances fat loss without loss of muscle mass or strength. In addition, there was evidence showing L-T3 therapy induced subclinical hyperthyroidism based on lower FT4 and TSH levels. No study performed TRH stimulation to more fully evaluate the impact of the L-T3 dose regimen on hypothalamic-pituitary function (447).

Compounded thyroid hormones

16. What is the recommendation regarding therapy with compounded thyroid hormones (either levothyroxine or liothyronine) for treatment of hypothyroidism based on current evidence?

Recommendation

We recommend against the routine use of compounded thyroid hormones due to concerns about safety and potency and due to the lack of data proving superiority to standard thyroid hormone preparations. However, in the case of suspected allergy to an excipient of standard thyroid hormone preparations that cannot be avoided with a change in brand or dose formulation, including a trial of levothyroxine gel capsules, it may be reasonable to consider use of compounded products, although a controlled study of this approach has not been published.

Strong recommendation. Low quality evidence

Discussion of the clinical literature

Compounded medications are those prepared by a specialized pharmacy that produces the drug with specific individual patient needs in mind (in response to a licensed physicians' prescription). The process usually involves modifying or altering the components of the medication or its excipients in a specific manner. There are specialized pharmacies and pharmacists that are capable of preparing compounded medications. Theoretical advantages of compounded medications include the ability to change the form of the medication (e.g., from tablet to liquid or transdermal preparation), specific excipients or dyes can be included or excluded (e.g., lactose can be excluded if a patient is lactose intolerant, erythrosine (red dye) can be excluded if the patient is allergic), and various flavors can be added to make the medication more palatable. Specific doses of medication that may not be commercially available may also be prepared. On the other hand, there are potential concerns regarding compounded medications. There are no specific guidelines or regulations governing the compounding of every medication, and the experience and consistency regarding the active ingredient(s) may vary over time and between different pharmacies and different preparations. Furthermore, compounded medications may be more expensive than commercially prepared formulations.

The Pharmacy Compounding Accreditation Board has been developed to set national standards for compounding pharmacies. The FDA does not specifically regulate every medication that is prepared individually by compounding, nor does it regulate the specific pharmacy or pharmacists. The FDA does, however, oversee the ingredients used and the facilities in which they are prepared. It was noted in 2007 (559) that the FDA considers compounded medications as "new drugs" and, as such, they do not regulate their safety or efficacy and also do not allow interstate transportation of these compounded medications unless approval is given in a specific instance. The FDA does recognize the critical role of individual states in supervising and regulating pharmacists and pharmacies that perform compounded medications. FDA-cited concerns regarding compounded medications include the consistency of the skill of compounding pharmacists and the reliability of their products. The general conceptual importance of compounded medications for individual, specific patient usage, however, was noted. Thus, it is possible that these pharmacies could serve a role if bioequivalence and stability of hormonal content could be assured. It should also be noted that a

recent fungal meningitis outbreak in Massachusetts was apparently linked to an intravenous compounded medication. This tragedy has led to comments and criticism of the present regulations governing compounding pharmacies. The FDA has suggested there be updated regulations governing compounding pharmacies with governmental oversight of the preparation, labeling and administration of compounded medications but still within a framework of maintaining the potential advantages of compounding pharmacies (560).

T4, T3, thyroid extract and combinations of these preparations have each been compounded. However, there are very few published studies regarding use of compounded thyroid hormones for treatment of hypothyroidism that meet scientific criteria for rigorous peer review. One paper published by a specific pharmacy owner lists suggested formulae for achieving a 11:1 ratio of T4:T3 in the circulation and describes preparation, but does not provide any details about outcomes of therapy with the compounded product (561). There are also no published studies that compare compounded preparations with FDA-approved preparations. Boulton et al. (562) assessed the stability of L-T4 in compounded oral liquid doses prepared from commercially available tablets. They examined stability over time (up to 90 days) and under various temperature conditions. The compounded preparations had significant degradation in each of the circumstances noted, but the compounded tablet preparations without added preservative retained more than 90% of its original concentration for 8 days, although at day 14 none of the formulations retained more than 90% potency. Thus, in order to ensure maintenance of potency, fresh supplies may need to be obtained from the compounding pharmacy at frequent intervals, with associated inconvenience to the patient. A separate issue is related to the standardization and bioequivalence of compounded T4 and T3 obtained from a given pharmacy over time, or between pharmacies. There are no peer-reviewed studies assessing these issues, thus quality control at the multiple pharmacies in existence is a concern. Errors in thyroid hormone compounding have occurred and have resulted in severe thyrotoxicosis (563).

Unfortunately placebo-controlled comparative studies of compounded thyroid hormones with their FDA-approved counterparts may not be helpful for guiding their use because the compounding arm of such a trial would be specific only to the particular pharmacist and compounding pharmacy. In other words, in light of the heterogeneity introduced by compounding pharmacists, if equivalence is demonstrated this would not be generalizable to other pharmacies. Therefore, randomized controlled clinical trials will be useful only when a

uniform standard of regulation is instituted. When such trials are performed *in vitro* studies should also determine the amount of thyroid hormone in each preparation.

A general statement regarding the comparison of costs to the patient for a compounded thyroid hormone and a commercially available product cannot be made. Patient costs for an individual compounded agent depends on multiple factors, to include the individual compounding pharmacy, the specific medication, the constituents of the compounding formulation, and insurance issues.

Until all the concerns above are addressed, potential use of compounding pharmacies should only be considered if there is no alternative, such as allergy to an excipient. However, it is theoretically possible that this indication may be obviated by the availability of L-T4 soft gel capsules. The use of a non-excipient gel capsule would be preferable to the use of compounded L-T4.

Nutraceuticals

17. Is there a role for the use of dietary supplementation, nutraceuticals, and over-the-counter products in either hypothyroid or euthyroid individuals?

Recommendation

We recommend against the use of dietary supplements, nutraceuticals, or other over the counter products either in euthyroid individuals or as a means of treating hypothyroidism. We particularly caution against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism in those with intact thyroid glands susceptible to becoming further dysregulated because of underlying thyroid pathology.

Strong recommendation. Low quality evidence.

Discussion of the clinical literature

The FDA 1994 Dietary Supplement Health and Education Act expanded the definition of dietary supplements to include any non tobacco product that is intended to supplement the diet and contains at least one of the following ingredients: a mineral, vitamin, herb or other botanical, an amino acid, or any dietary substance in humans utilized to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.

Nutraceuticals is a term formulated to reflect its “nutrition” origin and “pharmaceutical” action, but it does not have a “regulatory definition”. Nutraceuticals 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” (564). Use of such products, including vitamin preparations and herbal supplements, is common (565). Approximately 20% of the subset of the hypothyroid population who are being treated for thyroid cancer use such supplements (566).

The AACE has published an excellent summary with guideline recommendations for dietary supplements and nutraceuticals (567), with some updated information provided in the recent Guidelines for Hypothyroidism in Adults (3). In general, the government mandates three possible types of claims of dietary supplement labels: (1) nutrient content (such as “high in calcium”); (2) “structure-function” or nutrition support (for example, “vitamin C prevents scurvy” or “calcium builds strong bones”), and (3) disease claims. The “disease claims” alone requires FDA authorization after a thorough scientific evaluation of relevant studies. All other products must include the following statement: “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, mitigate, or prevent any disease.” Interested individuals should refer to the original comprehensive AACE document (567). Certain dietary supplements or nutraceuticals are purported to have the capacity to enhance thyroid function. These agents or compounds can be allocated to one of several categories; iodine-containing substances, tyrosine-containing substances, and thyroid hormone extracts or analogs.

Iodine containing substances (e.g., kelp) can, indeed, have multiple actions on the thyroid gland, as illustrated in a recent series of case reports (568). These effects on the thyroid gland can have significant clinical consequences. Excess iodine may precipitate thyroid dysfunction, particularly in patients with underlying thyroid autonomy, Hashimoto’s thyroiditis, or multinodular thyroid glands. Large amounts of iodine (e.g., SSKI or Lugol’s solution) can be used to decrease thyroid gland T4 and T3 secretion and is used in the treatment of hyperthyroid patients (569). However, there can be escape from thyroidal inhibition of organification (i.e., escape from the Wolff-Chaikoff effect) (570), and exacerbation of hyperthyroidism can occur, especially in hyperthyroid patients treated with iodine solutions for at least several weeks or who are not receiving antithyroid agents concurrently. These studies demonstrate various and multiple effects of iodine supplementation on thyroid function including the inducement of

hyperthyroidism, hypothyroidism and thyroiditis. There is no doubt, of course, that a minimal amount of iodine (about 150 mcg daily) is required for normal thyroid function in euthyroid non pregnant individuals, but when iodine supplementation is used by otherwise normal individuals to enhance thyroid function it is generally used in much larger doses, with the possibility of causing adverse effects. However, there is little evidence that iodine supplementation in pharmacologic amounts can beneficially improve thyroid function in euthyroid individuals. As a result, the AACE guidelines note that “No data support the role of iodine in enhancing thyroid function (patient advised to discontinue use).”

Tyrosine is an amino acid that that forms the basis for synthesis of T4 and T3, and it has been speculated that giving tyrosine supplementation to euthyroid individuals would improve thyroid gland function. Nonetheless, as noted in the AACE guidelines “No published data, however, support the claim that ingestion of tyrosine increases the production of thyroid hormone (patient advised to discontinue use).” Commercially available supplements sold for “thyroid health” or “thyroid support” may also contain measurable amounts of T4 and T3, potentially exposing the public to iatrogenic thyrotoxicosis (571).

The AACE guidelines note that multiple substances have been utilized as dietary supplements for thyroid conditions. They list the following substances as being utilized for “functional hypothyroidism” in biochemically normal individuals: carnosic acid, *Commiphora molmol* (myrrh), desiccated animal thyroid extract, linoleic acid, omega-3 fatty acids, organic iodide, selenium, methionine, 3,5,3'-triiodothyroacetic acid or tiratricol (TRIAC), tyrosine, vitamin A, vitamin D, vitamin E, *Withania somnifera*, and zinc glycinate. They also note possible interactions between thyroid hormone absorption or action with several compounds to include bugleweed, red yeast, kelp, calcium, iron, and bone meal. Soy protein has been studied and may interfere with levothyroxine absorption. Sathyapalan et al. (572) performed a double-blind crossover study and demonstrated that there was an increased risk of developing OH in patients who originally had SCH, when they received a vegetarian diet (containing 30 g soy protein and 16 mg phytoestrogen) as compared to a Western diet (containing 30 g soy protein and 2 mg phytoestrogens).

The use of various thyroid hormone analogs that can be purchased over the internet to enhance thyroid function is a very controversial area. TRIAC is a naturally occurring metabolite of L-T4 that has significant metabolic action. It can bind to the T3 receptor and it can decrease

TSH secretion. It may have a role in managing cases of resistance to thyroid hormone (573). However, TRIAC administration in pharmacologic doses can cause toxicity like that caused by thyroid hormone (574-578). Although TRIAC has effects similar to thyroid hormone (in selected circumstances), there is a lack of evidence it is beneficial when administered to euthyroid individuals and there is also a lack of evidence that it more beneficial than L-T4 when administered to hypothyroid subjects (579). 3,5-diiodothyronine is advertised on the internet as an agent for weight-loss and enhancement of cardiovascular training. However, reports of its safety and efficacy for these purposes could not be identified, other than in a single short term study in 2 patients (580). Given the lack of substantive available evidence, the use of a thyroid analog to enhance thyroid activity is not recommended.

Strong recommendation against nutraceuticals is provided despite low quality evidence, because there are potential risks but few proven benefits.

Ethical considerations in hypothyroidism research

18. What are the research ethics issues involved in evaluating or designing clinical trials for the treatment of hypothyroidism?

Recommendation

There should be recognition that there is not enough data to resolve clinical disagreement amongst thyroid experts (called “clinical equipoise”) regarding treatment for hypothyroidism. Clinical equipoise is disturbed only by the results of well-designed randomized controlled trials that have the statistical power to settle the question of efficacy between monotherapy and combination therapy, or other forms of therapy.

Ungraded

Discussion of the clinical research literature

In evaluating published research and original studies of thyroid hormone replacement, only those studies demonstrating ethically sound design and responsible conduct of research (RCR), in which there was study oversight and Institutional Review Board approval, should be considered. Well-designed small studies without the statistical power to resolve clinical disagreement, or disturb “clinical equipoise” (see further), cannot be considered to be a high level of evidence of a null effect, superior or inferior efficacy.

The fact that a study is published does not mean that it meets criteria for RCR. A well-

executed meta-analysis of high quality RCTs, with no clinically or statistically significant heterogeneity of pooled results, could be used to influence clinical practice. However, narrative review articles, editorials, and opinion letters are insufficient to disturb clinical equipoise. There are fundamental challenges with editorship and reviewership, which can influence what types of studies are published (581). Although most industry-funded studies incorporate appropriate design and clear declaration of conflict, such studies can also be problematic. Studies funded by a drug manufacturer showing that the drug is effective or superior, need to be very carefully evaluated, as the opportunity for biased results is clear. In this respect, perceived conflicts of interest are treated the same as overt conflicts of interest.

Clinical Equipoise in Thyroid Hormone Therapy. The concept of “clinical equipoise” was introduced in 1987 by research ethicist Benjamin Freedman (582). A state of clinical equipoise exists when a “community of experts” responsible for setting the standards of care are uncertain as to whether Therapy A is better than Therapy B. Thus, clinical equipoise provides the ethical basis for conducting a randomized controlled trial of the two therapies in order to resolve the question about which therapy is superior. In current thyroidology, clinical equipoise exists about the issue of L-T4/L-T3 combination therapy for hypothyroidism as described in the literature review for recommendations 13b and 13c and table 5b. In this case, clinical equipoise may be considered to exist due to conflicting findings of trials in the literature and heterogeneity in the dose and frequency of the treatment utilized in the existing studies. There is also some uncertainty about which, if any, patients may benefit from combination therapy.

A critical question that must be addressed is: *Who comprises the community of experts?* There are some practitioners who feel that their own clinical observations in practice “count” as evidence, and form the basis for “innovative therapies”. Such practitioners may widely disseminate their therapeutic opinions to patients directly through published trade books or through the Internet. What separates a valid community expert from an invalid community expert is scientific integrity, in which there is honest clinical disagreement. However, practitioners who intentionally misuse their professional training to profiteer or deceive patients, or misrepresent themselves as “thyroid experts” or thyroidologists when they can demonstrate no objective training in endocrinology, are not considered ethical actors who are part of a serious clinical community with beneficent intentions. Clinical investigators who fail to meet basic standards in ethical conduct or scientific integrity must also be excluded from the community of experts. An

example would be publishing results of new therapies without evidence of RCR. As for critics of TSH testing and proponents of antiquated diagnostic tools such as basal body temperature readings, or other therapies, some (583), must be viewed as ethical actors within a history of medicine context if they were practicing in an era prior to the development of TSH testing as a standard of care. In this context, practitioners who questioned what would have been a “new” laboratory test in the 1960s and 1970s were actually practicing evidence-based medicine, and were cautious about adopting a new standard of care until it proved to be a superior diagnostic tool. However, any practitioner who currently promotes antiquated ideas, and judges them as “current” or still relevant, misrepresents medical history. This would be similar to a diabetologist promoting the use of antiquated therapies for diabetes and recommending a patient with type 1 diabetes go on the special diets promoted in the early 20th century instead of taking insulin.

Resolving Clinical Equipoise: RCT Design. The need to resolve collective professional uncertainty, or “community of experts” uncertainty, over efficacy and safety of Therapy A (combination therapy) versus Therapy B (standard of care/monotherapy) is critically needed for patient care. **However, we could not find sufficient consistent data from studies of long-term therapy to resolve these issues.**

The community of experts in thyroid hormone therapy remain divided over T4 monotherapy and L-T4/L-T3 combination therapy, and even formulations of T4. This is creating problems in patient care, patient trust and informed consent. The thyroid clinical community has an ethical obligation to disturb clinical equipoise regarding thyroid hormone therapy in order to set a consistent standard of care that does not lead patients to question beneficent care. A robust RCT (power =80%) has yet to be conducted that recruits from a representative population of hypothyroid patients worldwide; tests therapies at dosages that cannot be disputed; accounts for regional disparities; discloses no potential conflicts of interest; and continues long enough for results to be replicated and to “resolve the dispute among clinicians.” (582).

Design Criteria, in addition to incorporating clinically meaningful endpoints, ought to include the following (582):

- Who is enrolled? Clinical equipoise requires a representative sample of the target clinical population. One must be able to generalize the results to the conditions of clinical practice across healthcare systems and countries; narrow trials designed to resolve some theoretical question may render it useless for influencing clinical decisions, even if

successfully completed. For example, studies performed in white males may not be applicable to women or minorities. There may be dosing discrepancies based on the pharmacogenetics of groups typically excluded from clinical trials.

- **Sample Size:** If the sample is too small, it's unlikely to answer the question. A robust RCT (power = 80%) would be likely to disturb equipoise even if the RCT result was "negative"
- **What gets tested?** Clinical equipoise requires honest, professional disagreement as to the preferred treatment: standard of care (monotherapy) vs. new treatment (combination therapy) at dosages that are chosen based upon strong preliminary "proof-of-concept" data, and using doses and formulations that would not to be contested by its proponents (584).
- **When will the study be complete?** The RCT ought to continue until sufficient evidence has been gathered to "resolve the dispute among clinicians." (582). This includes replication of results.
- **Conflicts of Interest: Real or Perceived.** Studies receiving funding from a company with a financial interest in the study outcome may not disturb clinical equipoise due to perceived bias. Clinicians may also wish to be aware of the funding received from pharmaceutical companies by journals in which studies are published.

N of 1 Trials. N of 1 trials have been referenced in other reviews on this topic (5). In the few meta-analyses that have reviewed N of 1 trials (585), few even meet the criteria for an IRB-approved study; most fall into the category of innovative therapy, which, in the thyroid hormone context, is sometimes called "individualized" combination therapy. Innovative therapy refers to a non-standard or even experimental therapy designed to optimize beneficent care for one, individual patient, which is not intended for generalizable knowledge. Such studies may also report "measurable effects" in individual patients that have no clinical significance. N of 1 trials may be useful for "enhancing therapeutic precision" or evaluating individual treatment effects for a patient (585). In order to be generalizable, a valid N of 1 trial is a well-designed, IRB-approved multiple crossover study conducted with informed consent in a single individual as a tool to estimate the heterogeneity of treatment effects in a population. To date, no N of 1 studies in thyroidology meet this criteria; all of the N of 1 trials evaluated in the thyroid literature meet

the standard of innovative therapy. Innovative therapies do not require IRB approval if data are not being collected for the purpose of generalizable knowledge and publication, and they are ethically permissible. Investigators who are using innovative therapies, in contrast to a situation where an “N of 1” trial is being conducted, are not truly engaged in research. Thus, any reports of innovative therapies cannot be used to validate or refute evidence; nor does innovative therapy resolve clinical equipoise.

Wilson’s Syndrome

19. Is there evidence for the existence of “Wilson’s temperature syndrome” and a rationale for use of escalating doses of triiodothyronine?

Recommendation:

There are no credible scientific data to support the existence of “Wilson’s Syndrome” and we recommend against the use of triiodothyronine escalation therapy for this indication, due to a lack of proven treatment benefit and safety concerns relating to the risk of thyrotoxicosis.

Strong recommendation. Low quality evidence.

Discussion of the clinical literature

Wilson’s Syndrome or Wilson’s Temperature Syndrome is described as having the hallmarks of fatigue, anxiety, depression, headaches, insomnia, and muscle aches, with a low body temperature being the feature that distinguishes it from Chronic Fatigue Syndrome (586-588). The ATA statement on “Wilson’s Syndrome” was updated on May 24, 2005 (589). The summary statement is as follows:

The American Thyroid Association has found no scientific evidence supporting the existence of “Wilson’s syndrome.” The theory proposed to explain this condition is at odds with established facts about thyroid hormone. Diagnostic criteria for “Wilson’s syndrome” are imprecise and could lead to misdiagnosis of many other conditions. The T3 therapy advocated for “Wilson’s syndrome” has never been evaluated objectively in a properly designed scientific study. Furthermore, administration of T3 can produce abnormally high concentrations of T3 in the blood, subjecting patients to new symptoms and potentially harmful effects on the heart and bones.

The ATA supports efforts to learn more about the causes of somatic symptoms that affect many individuals, to test rigorously the idea that some as yet unidentified abnormality in thyroid hormone action might account for even a small subset of these symptoms, and to pursue properly designed clinical trials to assess the effectiveness of lifestyle, dietary, and pharmacological treatments for these

common ailments. However, unsupported claims, such as those made for “Wilson’s syndrome,” do nothing to further these aims.

The task force reviewed this statement and performed a current literature review. As part of this review, the task force reviewed the Wilson’s syndrome doctors handbook (587). In addition, the posting from Wikipedia, the free encyclopedia, (590) was also reviewed to determine what information the public has access to. The task force believes that the prior ATA statement accurately reflects our current state of knowledge. The protocol recommended by Dr. Wilson on his website remains of great concern, given that protocol describes escalating a dose of compounded T3 from 7.5 mcg twice daily by 15 mcg increments. A patient taking 7.5 mcg T3 twice a day and increasing the dose by 15 mcg every day could potentially suffer serious iatrogenic T3 thyrotoxicosis. For example, see the section “patient death and medical license suspension” from the Wikipedia article on Wilson’s syndrome.

A review article published since the 2005 ATA statement was identified (586). However, this article provided only the results of uncontrolled trials in support of T3 therapy, including an in-house trial of T3 therapy for chronic fatigue syndrome. It also quoted an uncontrolled trial of T3 therapy in individuals with persistent symptoms while taking L-T4 performed prior to the availability of TSH monitoring (591). See also recommendation 16 for a discussion of compounded thyroid hormones and recommendation 18 regarding the ethics of trials for the therapy of hypothyroidism. An ongoing dialogue with patients affected by the symptoms outlined on the Wilson’s temperature website is essential. To quote from an article by Dr. Weetman (250), “communication lies at the heart of managing patients whose health problems cannot be explained and the focus should be on the patient’s concerns, the relief of symptoms and the avoidance of alienation.”

SECTION III. HOSPITALIZED PATIENTS

Levothyroxine in hospitalized patients

20a. In hospitalized but not critically ill patients with known pre-existing hypothyroidism, should levothyroxine therapy be re-evaluated based on an elevated serum TSH measurement?

Recommendation

In hospitalized patients with a pre-established diagnosis of hypothyroidism who are found to have an elevated TSH measurement, consideration should be given to institution or

adjustment of levothyroxine replacement. Factors such as the degree of clinical and biochemical hypothyroidism, active co-morbidities, and details of administration of levothyroxine (e.g. dosage, timing, and other factors impacting absorption), are relevant considerations in this situation.

Strong recommendation. Low quality evidence.

20b. In hospitalized but not critically ill patients in whom levothyroxine replacement is instituted or increased, should the therapeutic goal be normalization of serum TSH?

Recommendation

The therapeutic goal of levothyroxine replacement in non-critically ill patients is long-term normalization of serum TSH when steady state thyroid hormone levels are achieved. We do not recommend titrating the levothyroxine dose to serum free thyroxine levels unless serum TSH cannot be relied upon, e.g. following pituitary surgery.

Strong recommendation. Low quality evidence.

20c. In hospitalized but not critically ill patients treated with levothyroxine replacement what formulation and route of administration are recommended?

Recommendation:

For hospitalized but not critically ill patients, oral levothyroxine treatment is recommended. If this is not feasible, other enteral routes can be used. However, if there are concerns about significant malabsorption or there are other clinical reasons why a patient cannot be given enteral levothyroxine, intravenous levothyroxine may be administered, until enteral absorption improves. If using intravenous levothyroxine, the equivalent intravenous dose is approximately 75%, assuming the enteral levothyroxine dose had achieved euthyroidism.

Weak recommendation. Low quality evidence.

20d. In hospitalized but not critically ill patients about to be treated with levothyroxine should the possibility of adrenal insufficiency be excluded?

Recommendation:

For hospitalized but not critically ill patients who are about to be treated with levothyroxine, the possibility of adrenal insufficiency should be considered. If there is sufficient clinical or biochemical evidence to consider this diagnosis, adrenal insufficiency should be ruled out or empiric treatment should be provided.

Strong recommendation. Low quality evidence.

Discussion of the clinical literature

When a patient with pre-existing hypothyroidism is admitted to the hospital, it is not unusual to find that TSH levels are abnormal. The clinician must carefully investigate whether factors prior to the admission and/or factors relating to the admission itself are complicating the treatment of hypothyroidism, e.g. omission of doses of L-T4, or administration of medications that interfere with its absorption. When the patient is not critically ill, this process is usually straightforward. Best practice in this case is based on logic and observational studies or cases series, rather than clinical trials.

The situation is considerably more complicated if a patient with preexisting hypothyroidism develops a separate critical illness. The non-thyroidal illness syndrome (NTIS) (also known as the sick euthyroid syndrome or the low T3 syndrome) occurs when patients with normal thyroid function become critically ill; in this setting, a progressive depression of the thyroid axis occurs such that circulating T3 decreases, followed by declines in serum TSH and/or T4, and then declines in FT4 in some sicker patients (592, 593). In current practice, these patients are not treated with thyroid hormone replacement (see recommendation 22 regarding the NTIS).

In contrast, patients with established hypothyroidism are maintained on thyroid hormone when they become critically ill, even though they too may exhibit the physiologic changes of the NTIS. This is logical, since untreated hypothyroidism itself can lead to critical illness in the form of myxedema coma. A rise in TSH during the worsening stages of critical illness is typically indicative of thyroid hormone deficiency, and thyroid hormone replacement is thus instituted or increased until TSH normalizes. Interpretation of thyroid function tests is more complicated in the intensive care unit (ICU) setting because of medication effects on the hypothalamic-pituitary axis. For example, dopamine and dobutamine may lower serum TSH, such that some patients with primary hypothyroidism could be under-replaced if following a TSH-dependent dosing scheme. L-T4 may need to be given intravenously in the ICU setting since malabsorption can occur not only as a result of gastrointestinal disease, but also because of iatrogenic factors such as the use of proton pump inhibitors and specialized tube feedings. If using intravenous L-T4, the equivalent intravenous dose is approximately 75%, assuming the enteral L-T4 dose had achieved euthyroidism.

It should be noted that increased L-T4 replacement therapy may lead to TSH normalization without normalization of T3 (594), presumably due to accelerated metabolism of T3. However, as the NTIS is considered adaptive, logic dictates that “correction” of the low T3 may not be an appropriate goal of replacement, even for patients with a known history of hypothyroidism being maintained on L-T4. Indeed, using L-T3 for replacement is problematic, as the appropriate target range for serum T3 is not defined in this setting; furthermore, high doses of T3 have been linked to adverse outcomes (595). High quality randomized placebo controlled trials of various thyroid hormone regimens in NTIS addressing whether thyroid axis derangements are adaptive or pathophysiologic are needed, but would be challenging to design. As patients recover from their critical non-thyroidal illness, a rebound in TSH can occur. Thus, proper dose adjustment requires serial TSH measurements and correlation with overall clinical status.

The possibility of adrenal insufficiency must also be considered in this setting, since treatment of hypothyroidism might accelerate cortisol metabolism (596). There are case reports of adrenal insufficiency unmasked by thyroid hormone (597, 598).

Myxedema coma

21a. In patients with myxedema coma being treated with levothyroxine, what route of administration should be used?

Recommendation

Initial thyroid hormone replacement for myxedema coma should be levothyroxine given intravenously. A loading dose of 200 to 400 mcg of levothyroxine may be given, with lower doses given for smaller, older patients and those with a history of coronary disease or arrhythmia. A daily replacement dose of 1.6 mcg/kg body weight, reduced to 75% as long as being intravenously administered, can be given thereafter. Oral therapy, or other enteral therapy if the oral route cannot be employed, may be instituted after the patient improves clinically.

Strong recommendation. Low quality evidence.

21b. In patients with myxedema coma being treated with levothyroxine, should empiric glucocorticoid coverage be provided?

Recommendation

Empiric glucocorticoid coverage should be employed as part of the initial therapy for myxedema coma, with intravenous glucocorticoid administration, at doses appropriate for the stressed state, preceding levothyroxine administration.

Strong recommendation. Low quality evidence.

21c. In patients with myxedema coma being treated with levothyroxine, should liothyronine therapy also be initiated?

Recommendation

Given the possibility that thyroxine conversion to triiodothyronine may be decreased in patients with myxedema coma, intravenous liothyronine may be given in addition to levothyroxine. High doses should be avoided given the association of high serum triiodothyronine during treatment with mortality. A loading dose of 5 to 20 mcg can be given, followed by a maintenance dose of 2.5 to 10 mcg every 8 hours, with lower doses chosen for smaller, older patients and those with a history of coronary artery disease or arrhythmia. Therapy can continue until the patient is clearly recovering (e.g. until the patient regains consciousness and clinical parameters have improved).

Weak recommendation. Low quality evidence.

21d. In patients with myxedema coma being treated with levothyroxine, what therapeutic endpoints should be targeted?

Recommendation

Intravenous levothyroxine treatment in severely hypothyroid patients may lead to improvement in cardiovascular, renal, pulmonary, and metabolic parameters within a week. Serum thyroxine and triiodothyronine concentrations may improve or normalize with a similar time frame, with more gradual improvement in serum TSH. Thus, the therapeutic endpoints in myxedema coma should be improved mental status, improved cardiac function, and improved pulmonary function. Measurement of thyroid hormones every 1-2 days is reasonable to ensure a favorable trajectory in the biochemical parameters. While optimal levels for serum TSH and thyroid hormones are not well defined in this circumstance, failure of TSH to trend down or for thyroid hormone levels to improve could be considered indications to increase levothyroxine therapy and/or add liothyronine therapy, whereas high serum triiodothyronine could be considered an indication to decrease therapy given safety concerns.

Weak recommendation. Low quality evidence.

Discussion of the clinical literature

In the extreme case of myxedema coma, the literature clearly supports the use of thyroid hormone replacement as the disease has a high mortality rate (595, 599). There are case reports demonstrating death without treatment (600-602). In the setting of myxedema coma thyroid hormone therapy should be instituted, or increased if a patient is already receiving treatment. L-T4 should be given initially. L-T3 can be given as well, though case series suggest that higher doses of L-T3 may be associated with adverse outcomes (595).

Therapy can, and should be, instituted based on clinical suspicion alone, and should not be delayed while waiting for blood test results. If the patient has been taking thyroid hormone, it must be assumed that the dose or route is inappropriate, and more aggressive replacement instituted immediately. In this setting, primary hypothyroidism may itself be the inciting cause of critical illness, or might complicate a non-thyroidal critical illness if unrecognized and untreated (603). Thyroid hormone replacement is vital for the survival of these patients, even though the NTIS physiology still applies; because hypothyroidism is considered a primary motivator of illness in this setting, concerns about abnormal T4 to T3 conversion become relevant, and replacement with L-T3 may be more reasonable.

It must be remembered that the degree of TSH elevation may not be an accurate indicator of the severity of the hypothyroidism based on the wide range of serum TSH values seen in myxedema coma (595), possibly due to variable suppression of the hypothalamic-pituitary axis by the illness. Also, a lesser magnitude of TSH elevation may be seen in older patients (366), at least in the outpatient setting. An inappropriate TSH may also be seen if hypothyroidism is caused by TSH deficiency, e.g. secondary hypothyroidism in patients with panhypopituitarism.

Initial thyroid hormone replacement for myxedema coma should be L-T4 given intravenously. A loading dose of 200 to 400 mcg of L-T4 may be given, with lower doses given for smaller, older patients and those with a history of coronary disease or arrhythmia. A daily replacement dose of 1.6 mcg/kg body weight, reduced to 75% as long as being intravenously administered, can be given thereafter.

A study of a group of hypothyroid patients with mean serum TSH values of approximately 80 mIU/L treated with 100 mcg intravenous L-T4 daily showed normalization of thyroid hormone levels in 4 days, with significant improvement in serum TSH and other clinical parameters within a week (604). These dramatic improvements occurred without a loading dose of LT-4. With administration of a loading dose in patients with myxedema coma, there may be a

greater increase in T4 and T3 based on the dose administered, the volume of distribution, and the occupancy of binding proteins. Therapeutic endpoints to target would mainly be those clinical parameters related to the various organ systems affected, e.g. mental status, temperature, respiratory function, cardiovascular status, electrolytes, and biochemical measures of thyroid status. While equilibrium levels of TSH would not be anticipated until well after clinical improvement should be seen, serially measuring the serum TSH, FT4 or T4, and T3 in patients being treated for myxedema coma could provide supportive evidence that the therapy is working, and could insure that very high levels of T3 are avoided. In addition, checking the serum T4 and T3 concentrations 1-2 days after initiation of therapy will allow assessment of the response to the loading dose. Therapy should be aggressive: if the clinical picture is not improving, L-T4 could be increased and/or L-T3 could be increased or added. Safety concerns include tachycardia, arrhythmia, and myocardial infarction. Oral therapy, or other enteral therapy if the oral route cannot be employed, may be instituted after the patient improves clinically.

Given the possibility that T4 conversion to T3 may be decreased in patients with myxedema coma, intravenous L-T3 may be given in addition to L-T4. High doses should be avoided given their association with mortality (595). A loading dose of 5 to 20 mcg can be given, followed by a maintenance dose of 2.5 to 10 mcg every 8 hours, with lower doses chosen for smaller, older patients and those with a history of coronary artery disease or arrhythmia. If intravenous therapy with L-T3 is initiated, there are no data addressing optimum duration of such therapy. However, it would seem reasonable to continue intravenous therapy with L-T3 until there is a clinical response that indicates that the patient is clearly recovering such as regained consciousness, improved mental status, improved pulmonary function, improved cardiac function, and improvement of clinical parameters. Use of intravenous L-T3 monotherapy administered at doses of either 25 or 50 mcg daily in hypothyroid patients with serum TSH values in the range of 68-81 mIU/L lead to normalization of various cardiovascular, pulmonary, metabolic parameters within a week (605). TSH values decreased significantly within the same time period, although less so than the TSH response to intravenous L-T4 observed by the same authors in a similar cohort of patients (604).

Given the rarity of myxedema coma, randomized clinical trials are not feasible, and so recommendations regarding the type, route, and outcomes measures for replacement are based solely on expert opinion and case reports (595, 599, 606-619). In addition to aggressive thyroid

hormone replacement, it is widely accepted that supportive measures directed at treating hypothermia, hypoventilation, and hyponatremia are important. In addition to supportive measures for hypothermia, hypoventilation, volume depletion, hypoglycemia, and hyponatremia, most clinicians favor empiric treatment of concomitant conditions. Empiric glucocorticoid therapy at stress doses should be initiated at the start of therapy for myxedema coma. Serum cortisol should ideally be measured prior to initiation of therapy. Empiric broad-spectrum antibiotic coverage should be administered if sepsis is in the differential diagnosis.

Low T3 concentrations in hospitalized patients

22a. In hospitalized adult patients exhibiting the “non-thyroidal illness syndrome,” should thyroid hormone replacement be instituted with levothyroxine?

Recommendation

We recommend against the use of levothyroxine as a form of therapy for hospitalized patients experiencing critical illness exhibiting the “non-thyroidal illness syndrome”. The few randomized controlled trials comparing levothyroxine therapy to no treatment have not shown significant clinical benefit, and have raised safety concerns that limit support for this approach.

Strong recommendation. Moderate quality evidence.

22b. In hospitalized adult patients exhibiting the “non-thyroidal illness syndrome,” should thyroid hormone replacement be instituted with liothyronine?

Recommendation

We recommend against the use of liothyronine as a form of therapy for hospitalized patients experiencing critical illness exhibiting the “non-thyroidal illness syndrome”. Although low doses of liothyronine have not been linked to harm in clinical trials, data showing any significant clinical benefit are also lacking.

Weak recommendation. Moderate quality evidence.

Mechanistic background

There seem to be differences between the acute and chronic phases of critical illness (28). During acute illness there are changes in thyroid hormone binding, alteration in thyroid hormone uptake by cells, decreased T4 to T3 conversion due to the effects of endogenous circulating cortisol, cytokines, free fatty acids, and various drugs on D1. There may also be

increased T3 catabolism due to changes in the deiodinases, namely D3, in peripheral tissues. All these effects lead to low circulating T3 levels. As illness becomes more prolonged, superimposed upon these changes is central suppression of the hypothalamic pituitary axis, with decreases in circulating TSH and T4.

While decreased T4 to T3 conversion has been posited as an etiologic cause of the NTIS, more recent data suggest that increased T3 catabolism because of ectopically upregulated D3 in tissues such as liver, skeletal muscle, and heart has a greater impact in lowering T3 (26). Studies in animal models have linked D3 induction to hypoxia, with direct upregulation of the D3 gene by Hypoxia-inducible Factor 1 (HIF-1), the major regulator of the hypoxic response (363, 620, 621).

The underlying physiology of chronic NTIS involves a down-regulation of the hypothalamic-pituitary-thyroid axis such that production and release of thyroid hormones decrease as the degree of illness worsens. (622). Similar changes in circulating iodothyronines are seen regardless of the etiology of the underlying illness; most authorities have interpreted this, teleologically, to indicate that the depression of the axis represents a physiologic response, though dissenting voices exist. A minority view holds that the changes seen, while perhaps a common pathway, are nonetheless pathologic (623, 624). The literature regarding mechanisms of the NTIS is based largely on rodent studies. Several important steps may ultimately lead to the NTIS. For example, caloric restriction leads to decreased leptin signaling, which in turn reduces TRH and TSH production (625, 626). Animal models of NTIS featuring either caloric restriction or endotoxin administration have been associated with increased D2 expression and activity in the mediobasal hypothalamus. An increase in D2-mediated T4 to T3 conversion would be expected to increase the local supply of T3, thus decreasing TRH and TSH production rates (627). An increase in D2 mediated T4 to T3 conversion would be expected to increase the supply of T3 to important regulatory centers in the brain controlling the thyroid axis.

The extent to which central hypothyroidism, versus reduced D2 activity, and increased D3-mediated clearance in peripheral tissues cause the NTIS remains to be determined, but one study of critically ill patients in which central hypothyroidism was corrected via TRH infusion suggests that the central effect predominates (622). Furthermore, a complete understanding of the NTIS will not be possible without further studies of the effects of illness-related cytokine

fluxes on thyroid hormone binding, transport and tissue activation, particularly in the settings of both acute inflammation and chronic severe illness (28, 628).

Discussion of the clinical literature

As patients with normal thyroid function become critically ill, a progressive decline in circulating T3 is observed, followed by decreases in serum T4 and TSH if the clinical course does not improve. This stereotypic pattern, known as the NTIS or alternatively the “Non-thyroidal Illness Syndrome” or “Euthyroid-Sick Syndrome”, occurs without regard to the etiology of the primary illness, suggesting a physiologic, adaptive role. At the same time, since untreated hypothyroidism can itself lead to critical illness in the form of myxedema coma, debate continues as to whether NTIS patients might benefit from thyroid hormone replacement.

Data from randomized controlled trials are limited, with studies involving relatively small numbers of patients suffering from heterogeneous life-threatening illnesses. These trials have failed to show benefits as far as major clinical endpoints such as survival are concerned, though it must be noted that their statistical power has typically been low. In some cases, replacement has been linked to harm, in particular with higher doses of L-T3, and one study showed increased mortality with L-T4 therapy in patients with acute renal failure (629). On the other hand, lower doses of L-T3 have been suggested to alter certain clinical parameters in ways that could potentially be beneficial. In current practice, most clinicians interpret the data as not favoring thyroid hormone replacement, and accept as dogma that the NTIS is an adaptive process.

In order to evaluate whether hospitalized patients in the intensive care unit with NTIS should be treated with L-T4 or L-T3, we first had to define which group of patients should be included. Given that our focus is adult patients in the intensive care unit, we excluded studies of pediatric patients (less than 17 years old), brain dead potential organ donor patients (as this is a very specific clinical situation), and fasting patients. We excluded studies of peri-operative (cardiac surgery) L-T3 therapy from this section, since most of these studies included patients being given dopamine, which is known to suppress TSH and can cause iatrogenic hypothyroidism (630).

Randomized controlled data are limited with regards to this clinical question. Review of 10 recent review articles indicates that a large majority of experts do not advocate the initiation of L-T3 therapy in this clinical setting (28, 356, 447, 624, 631-636).

Kaptein et al. have performed comprehensive reviews of this subject, published in 2009 (447). They also performed a review of the post-operative literature in 2010 (632). They excluded studies that examined patients less than 18 years of age (except for Brent and Hershman 1986 (637)), studies of peri-operative patients, studies with before and during study design, and studies of thyroid hormone use for less than 24 hours. They also excluded studies for “data not extractable or end-points not included” as well (discussed below). Thus the results of 7 randomized controlled trials (629, 637-642), the most recent of which was published in 2004 were included. Five of the studies utilized L-T4 (629, 637, 639-641), and two utilized L-T3 (638, 642) (see table 6). PubMed search of the literature revealed no relevant studies published since the Kaptein review.

Therefore, recommendation 22b regarding the use of L-T3 in critically ill subjects is based on only two published studies identified by Kaptein and colleagues. Becker et al. (638) studied burn patients (14 controls, 14 treated) in 1982, with the finding that 200 mcg oral L-T3 did not alter mortality (4 patients died in each group), or the high metabolic rate typically observed in burn patients. In 2004 Sirlak et al. (642) treated patients (40 controls, 40 treated) with 125 mcg L-T3 or placebo daily orally for 7 days prior to coronary artery bypass surgery and continued therapy until discharge. T3 levels were higher in the treated group before surgery and after (but were similar during cardiopulmonary bypass). Inotropic requirements were decreased in the T3 group. Length of ICU stay was decreased in the T3 group. Three patients died in each group. Atrial fibrillation was not increased in the T3 group. Morbidity and mortality were otherwise unaffected.

One notable study by Pingitore and colleagues published in 2008 (643) was excluded by the Kaptein et al. analysis for “data not extractable”. The endpoints were hemodynamic and neurohormonal testing. This trial (10 control, 10 T3 treated) employed intravenous infusion of L-T3 for 3 days such that levels were higher than normal on day 1, then normal. No adverse outcomes were reported with T3. It should be noted that studies with L-T3 administration <24 hours were omitted from the analysis by Kaptein et al., as were patients treated with L-T3 in the peri-operative period (in subjects who may or may not have had the NTIS). However, these studies are, nevertheless, cited by other authors to support the potential safety of short-term L-T3 replacement. For example, Acker et al. 2002 (644) studied patients with delayed graft function in cadaveric renal transplantation, finding the intravenous infusion of L-T3 (to levels still within

the reference range) for 24 hours had no effect on the course, either beneficial or with regards to morbidity and mortality. This was excluded from the review by Kaptein et al. given the short duration of therapy.

DeGroot's review in 2006 (624) suggests that if L-T3 therapy is to be initiated, it should be at a "replacement dose" of approximately 50 mcg/day in divided doses. This is much lower than used in the two trials above (Becker et al. 1982 (638) and Sirlak et al. 1984 (642)). The review also suggests that T3 be followed and adjusted such that it is "at least low normal" before the next scheduled dose. DeGroot also advocates starting L-T4 (624), though no data for use of combination therapy in this situation could be identified. Interestingly, one *post mortem* study analyzing 31 patients that had died in the ICU and had been treated with 150 mcg T4 and 0.6 mcg T3/kg daily compared to 48 patients that had not been treated with thyroid hormones, provided clear evidence for tissue specific regulation of tissue T4 and T3 concentrations in critical illness (645). Patients treated with T4 and T3 had approximately 1.5 times higher levels of serum and muscle T3, whereas liver T3 concentrations were more than 4 times higher in patients receiving T4 and T3 therapy. However, this study did not address any potential benefits of thyroid hormone use, as all subjects died in the ICU and there was no appropriate control group directed to answering this question.

22c. In hospitalized adult patients with cardiac dysfunction, such as advanced heart failure, and low serum triiodothyronine concentrations, should thyroid hormone replacement be instituted with liothyronine?

Recommendation

We recommend against the routine use of liothyronine as a form of therapy for hospitalized patients with heart failure and low serum triiodothyronine concentrations given the mixed data from short-term trials, the hypothetical risks, and pending further randomized trials confirming benefit and safety.

Weak recommendation. Moderate quality evidence.

Discussion of the clinical literature

The clinical findings of both hypothyroidism and hyperthyroidism illustrate the dramatic effect of T3 alterations on cardiac output, contractility, vascular resistance, and blood pressure, as well as cholesterol metabolism (646). On a cellular level, similar to other tissues, T3 has both genomic and non-genomic effects on the cardiac myocyte. However, cardiac cells may be more

reliant on adequate serum T3 levels for normal function based on data suggesting decreased transport of T4 into the cardiac myocyte (647). The role of T3 in cardiovascular disease is highlighted by the NTIS in which the physiologic response to illnesses such as heart failure are characterized by a decrease in total and free T3 with normal T4 and TSH levels. NTIS is typically considered an adaptive response, however, there is continued discussion over whether L-T3 replacement therapy may be worthwhile in an effort to reduce the negative consequences associated with NTIS including alterations in cardiac tissue remodeling (646). Hamilton et al. reported on the safety of short term L-T3 infusion in 23 patients with advanced heart failure showing that administration of L-T3 (cumulative dose 0.15 to 2.7 mcg/kg) was well tolerated with no significant change in heart rate, metabolic rate or core temperature (648). In addition, the L-T3 infusion was associated with increased cardiac output and reduced systemic vascular resistance in patients who received the largest dose (648). Subsequently, in the only randomized, placebo controlled study to date, Pingitore et al. reported a similar positive effect of L-T3 on cardiac function in 20 patients with dilated cardiomyopathy (643). At a starting dose of 20 mcg/m², adjusted to obtain a normal serum T3 level, L-T3 infusion for a three-day period was associated with an increase in left-ventricular end-diastolic volume and stroke volume as well as reduced plasma noradrenaline, n-terminal pro-B-Type natriuretic peptide, and aldosterone when compared to placebo controls. Again, there was no increase in heart rate or other side effects associated with L-T3 therapy (643), but cardiovascular outcomes with longer term therapy are needed. While these studies are encouraging (649), the question remains whether serum T3 may be better considered as a marker of disease status rather than a focus of therapy. The recent study by D'Aloia et al. highlights this consideration where short-term dobutamine therapy resulted in statistically improved cardiac status associated with reduced brain natriuretic peptide reduction and increased FT3 levels (650).

SECTION IV. USE OF THYROID HORMONE ANALOGS

Thyroid hormone analogs and euthyroid patients

23. Should thyroid hormone analog therapy be used in euthyroid individuals with non-hypothyroid-related medical conditions (such as dyslipidemia) based on current evidence?

Recommendation

Although pre-clinical data suggest that the concept of thyromimetic use for treatment of non-hypothyroid-related medical conditions may be promising, we recommend against the use of such drugs outside of the research setting, due to concerns about the lack of clear benefit or excessive side effects, of currently available preparations.

Strong recommendation. Low quality evidence.

Mechanistic background

T3 exerts its genomic effects via binding to its nuclear thyroid hormone receptors (TRs) (9). TRs function as hormone modulated transcription factors and their binding interactions with target genes either activate or repress transcription. There are two TR isoforms, TR α and TR β , encoded by separate genes. TR mRNAs can be alternatively spliced; in humans, three main splice variants are found, namely TR α 1, TR α 2, and TR β 2. Of note, these TR isoforms are differentially expressed throughout the body such that some tissues can be said to be dominant with respect to a given TR isoform (8, 9). For example, TR β is the prevalent isoform in the liver and pituitary, whereas TR α is predominant in the heart, brain, and the skeleton. Thyroid hormone analogs may have significantly greater affinity for TR β than TR α , in the order of 22-fold greater for Eprotirome (651), 10-fold greater for Sobetirome (652), 14-15 fold greater for KB141 (653) and MB07344 (654), and 40-fold greater for GC-24 (655). The various thyroid hormone analogs, their relative selectivity for the TR β , and potential uses based on this selectivity are shown in table 7.

Thyroid hormone analogs thus have potential clinical utility because they may promote tissue specific effects (656). A tantalizing goal of research in this area has been to determine whether some of the beneficial effects of T3 excess can be isolated pharmacologically while avoiding unwanted effects. For example, given the predominance of TR β in the liver, it has been postulated that selective TR β agonist drugs could be used to lower cholesterol without the adverse TR α -driven cardiac and skeletal effects that would be seen with pharmacologic T3 administration. Animal studies using TR β agonists have verified that this strategy is indeed possible (657-659). Furthermore, pre-clinical studies show that highly TR β -selective agonists may have other metabolic benefits, such as accelerating energy expenditure in rodents by increasing metabolic rate (660, 661), reducing body weight (662), and conferring protection against diet-induced obesity (660).

Thyroid hormone analogs have also been studied because they may have higher binding

affinities for the TRs than does T3. For example, bindings studies suggest that TRIAC exhibits ~3.5-fold greater affinity for TR β and ~1.5-fold greater affinity for TR α when compared to T3 (579), spurring interest in this compound in the treatment of RTH (663). On the other hand, 3,5-diiodothyropropionic Acid (DITPA) is an analog with much lower binding affinity for TRs than T3 (664). A number of animal studies have suggested that DITPA may have some degree of cardioselectivity, though the mechanism is unclear given that this drug binds TR α and TR β with similar affinity (664). Studies of DITPA in animals have provided some promising effects such as improved left ventricular performance, reduced end-diastolic pressure, and cardiac remodeling after myocardial infarction (665, 666). However, one study of post-ischemic cardiac function showed an increased incidence of arrhythmias during ischemia and reperfusion with the use of DITPA (667).

Discussion of the clinical literature

A number of thyroid hormone analogs have been evaluated in clinical trials. While several have shown potentially beneficial effects, significant side effects have also been seen that have limited enthusiasm with regards to their further development for clinical use. Clinical studies of Eprotirome and other TR β -selective agonists or liver-specific TR ligands show consistently that there is a therapeutic window through which these drugs lower serum cholesterol without significantly affecting cardiovascular parameters or bone metabolism, and only minimally affecting thyroid hormone economy (668, 669). Eprotirome therapy was associated with decreases in serum LDL, apolipoprotein B, triglycerides, and Lp(a) lipoprotein when added to statin therapy (668), and given as single therapy in primary hypercholesterolemia (670). However, a recent phase III trial of Eprotirome for patients with heterozygous familial hypercholesterolemia (NCT01410383) was terminated in February 2012 after some liver injury was seen in participants and after dog toxicology studies revealed that 12 months of exposure to the drug led to cartilage damage (671). Although cartilage damage was not seen in study participants, these two findings lead the company to terminate all clinical trials with this drug (672).

Sobetirome (GC-1) is a highly selective TR β agonist that currently has an active investigational new drug (IND) status. A clinical trial started at Oregon Health Sciences University in the Fall of 2012 (NCT01787578) in patients with X-linked adrenoleukodystrophy

based on pre-clinical data indicating that T3 or TR β agonists upregulate the gene ABCD2; upregulation of ABCD2 can compensate for the mutation in ABCD1 (adrenoleukodystrophy gene) carried by these patients.

DITPA has been tested in two clinical trials focused on its potential cardiovascular benefits in heart failure patients. Despite the promising effects in animal studies, although DITPA improved some hemodynamic parameters, there was no overall benefit in patients with congestive heart failure (673). In fact, two clinical trials (Titan Pharmaceuticals-NCT00103519; VA- NCT00032643) were terminated in 2006 and 2009, respectively. Another clinical trial of DITPA in a heart failure population reported improved body weight and low-density lipoprotein levels, but also a high dropout rate and negative effects on the skeleton (674). Of interest, DITPA has been effective in reversing some of the abnormalities seen in four children with MCT8 deficiency treated with this agent on compassionate grounds (501). The success of this therapy is presumably due to the fact that DITPA can enter brain tissues without the need for the MCT8 transporter.

Two studies of TRIAC have been reported, showing that this analog can lower serum FT4 without a compensatory increase in serum TSH, suggesting a suppressive effect on TSH secretion. At the same time, plasma LDL and total cholesterol levels decreased while serum osteocalcin and urinary excretion of calcium and pyridinium cross-links increased (675, 676). Should future analogs have specific TSH suppressive potential, they might be useful agents for the management of thyroid cancer.

It should be noted that none of the analogs have been tested in large randomized clinical trials in euthyroid individuals, and none are FDA-approved. Thus, more research is needed with new analogs to see if the potential for tissue-specific pharmacologic control of thyroid hormone action can be achieved.

Thyroid hormone analogs and resistance to thyroid hormone

24a. What are the clinical and biochemical goals for treatment of patients who have genetic syndromes of resistance to thyroid hormone?

Recommendation

The therapeutic goals of the treatment of patients with genetic syndromes of resistance to thyroid hormone are to improve the symptoms caused by excessive TR-alpha signaling, while minimizing the symptoms caused by deficient TR-beta signaling.

Weak recommendation. Low quality evidence.

24b. What is the role of thyroid hormone analogs in treating patients who have genetic syndromes of resistance to thyroid hormone?

Recommendation

Although preliminary data from small case series suggest that the use of TRIAC in patients with genetic syndromes of resistance to thyroid hormone may be promising, more clinical research is needed before the use of thyroid hormone analogs can be recommended for this indication.

Weak recommendation; low quality evidence

Mechanistic Background

Resistance to Thyroid Hormone (RTH), (OMIM identifier # 188570) (677) is a rare genetic disease characterized by increased serum levels of thyroid hormones and inappropriately normal or increased TSH (678). RTH is caused by inactivating mutations in TR α (RTH α) or TR β (RTH β). Patients with RTH α have normal levels of TSH in combination with a low FT4 and high T3, and suffer from local hypothyroidism in tissues that predominantly express TR α (376, 377). Patients with RTH β have normal or elevated levels of TSH despite elevated levels of FT4 and FT3. Symptoms in these latter patients are due to a combination of low thyroid hormone action in predominantly TR β -expressing tissues, and thyroid hormone overexposure in TR α -expressing tissues (378, 379).

The majority of RTH forms are caused by autosomal dominant mutations in the TR β gene (679), but in a significant percentage no mutation was identified (380), suggesting that mutations in other loci may cause RTH (680-683). Approximately 1000 patients in 350 families with mutations in TR β have been described to date. These mutations may be associated with impaired ability to bind T3, and/or may prevent the normal TR-mediated gene transactivation. The mutant TR β /corepressor complexes remain bound to the T3-responsive genes and transcriptional repression cannot be lifted by the presence of T3. Thus, mutant TR β molecules exhibit a “dominant negative” effect.

TR β mediates the negative TSH feedback mechanism in the pituitary gland. The lack of adequate negative feedback results in an inappropriately normal or elevated TSH and a hyperactive goiter with variable degrees of increased serum levels of T4 and T3. In effect, RTH

patients exhibit unbalanced hormonal signaling due to the combination of defective $TR\beta$ and otherwise normal $TR\alpha$ receptors exposed to supra-physiologic levels of thyroid hormone. The result is a mix of hyperthyroid symptoms and signs arising from organs enriched with the $TR\alpha$ such as the heart, skeletal muscle, and brain, and hypothyroid signs related to tissues such as the liver where the β -isoform is predominant (380).

Hypothetically, a thyroid hormone analog with a preference for $TR\beta$ might be useful in treatment of RTH patients, since it would normalize TSH and lower thyroid hormone production, while normalizing thyroid hormone signaling directly in $TR\beta$ dominant tissues. Treatment with TRIAC, which has a higher affinity for $TR\beta$ than for $TR\alpha$ has been used in a number of patients based on this rationale.

Discussion of the clinical literature

Literature on the treatment of RTH is limited to case reports given the rarity of the syndrome. Most patients with RTH can be managed symptomatically with selective beta-blockers to minimize symptoms of hyperthyroidism arising from $TR\alpha$ dominant tissues such as tachycardia and tremor; in $TR\beta$ dominant tissues, the excess thyroid hormone is balanced for the most part by the relative insensitivity of the mutant $TR\beta$. Quite often, RTH patients are erroneously diagnosed as thyrotoxic and treated with radioablation or thyroid surgery (684). In such cases, use of L-T4 therapy requires supraphysiological dosing if $TR\beta$ -dominant tissues are to be made “euthyroid”. However, this will potentially lead to hyperthyroidism in the $TR\alpha$ dominant tissues (685). Thus, L-T4 can be combined with beta-blockers to prevent $TR\alpha$ related cardiac symptoms (380). Treatment must be individualized, and no target thyroid hormone or TSH value can be defined *a priori* as adequate replacement. Indeed, the replacement therapy should be adjusted to the patient’s symptoms and signs. Aside from the use of the L-T3 suppression test (Werner’s test) as a diagnostic dynamic test between RTH and TSH producing adenomas, L-T3 is generally not considered part of therapy, although it has been employed as a treatment modality for RTH children also affected by Attention Deficient Hyperactivity Disorder (686).

Small case series indicate that the use of TRIAC in RTH is effective in suppressing the TSH with no evidence of cardiac toxicity (573, 687). One case involved a treatment duration of 3 years (663). Unfortunately, this drug is not currently available in the United States. Hence the treatment options are limited to L-T4 coupled with cardiac-selective beta-blockers. Although not

currently tested in humans, TR β -mutant-selective analogs may represent a more targeted therapeutic option for the treatment of RTH (688).

FUTURE DIRECTIONS

Despite the advances that have occurred in the field of therapy for hypothyroidism, there are still many unanswered questions. For example, with respect to targeting biochemical parameters and achieving amelioration of symptoms and patient satisfaction, it is not known whether replicating an individual's set point, as opposed to targeting a particular part of the laboratory reference would be beneficial. Even if this approach did optimize therapy, there is no current routine means of determining an individual's set point in advance of them developing thyroid dysfunction, precluding replication of these parameters during subsequent therapy. Similarly, it is possible that replication of the endogenous circadian rhythm in T3 may also optimize therapy. However, current exogenous therapies do not reproduce endogenous serum T4 excursions or serum T3 rhythms.

It has been clearly established that L-T4 therapy results in a higher serum T4/T3 ratio than is observed in the non-athyreotic state. It is not known whether there is a detrimental effect of this abnormal serum T4/T3 ratio. For example, as T4 is a primary inhibitor of D2 activity, does excessive circulating T4 ultimately lower the activity of D2, and result in any adverse consequences?

Another question relates to the best marker of thyroid status. Serum TSH is considered to be the best marker currently available. However, there are specific instances in which a normal serum TSH may be documented despite biochemical parameters indicating that specific tissues are in a hypothyroid or hyperthyroid state. In addition, there is some evidence that serum T3 values in the lower part of the normal range may not always be reflected by elevated serum TSH values, or even serum TSH values in the upper part of the normal range (39-43). A related issue, particularly in specific sub-populations, is that the biologic activity of serum TSH is not always concordant with its measured concentrations. Of particular note, the questions 7a-7d raised by task force members, which relate to the significance of serum T3 concentrations and the thyroid status of different tissues, could only be addressed with summary statements, not formal recommendations, illustrating the need for additional studies in these areas. Another

consideration is that serum T3 levels are known to be affected by age and disease state, adding further difficulty to their interpretation.

Yet another aspect of treatment of hypothyroidism is how to assess tissue euthyroidism. Animal studies show that a normal serum T3 is not necessarily accompanied by a normal T3 concentration in all tissues. The ability of tissue T3 to mirror serum T3 is dependent on the particular tissue's complement of deiodinases. Gene profiling can demonstrate the genomic actions of thyroid hormone within particular tissues. However, commercially available tests to indicate tissue status in humans are not available.

If the premise that L-T4 does not provide optimum therapy for hypothyroidism were true, it would be anticipated that some of the many trials of combination therapy would have yielded positive results. However, other than an individual patient preference for combination therapy seen in some trials, there have generally been few benefits documented. Moreover, even a study that appeared to show a benefit at 6 months no longer showed maintenance of this benefit at 12 months. This is an important consideration given that thyroid hormone therapy is generally lifelong. It is interesting that, assuming trials of combination therapy have been driven by a concern about low serum T3 levels, the serum T3 response has not been rigorously assessed in many trials, and restoration of serum T3 levels to "normal" has generally not been an endpoint.

It is possible that trials have not been more successful because the correct population has not yet been targeted. This target might include those with genetic variants of the deiodinases or other thyroid hormone signaling elements, or those with disproportionately lower serum T3 levels while taking L-T4 monotherapy. If N of 1 trials were being considered these might also logically be conducted in those with low or low-normal serum T3 concentrations. It is also possible that trials of once or twice daily L-T3 therapy added to L-T4 monotherapy have not had more positive outcomes because of the non-physiologic nature of the L-T3 dosing. A sustained release preparation, or even a preparation with a new delivery system that mimics the normal diurnal rhythm of serum T4 and T3, may be necessary in order to reveal a benefit. Large, prospective, long-term outcome studies examining clinically significant outcomes are needed to clarify the optimal formulation or combination of formulations of thyroid hormone replacement therapies, and which patients may benefit from any specific therapies. More research is also needed to identify biomarkers that are most strongly associated with clinically relevant endpoints, long-term outcomes and benefits of therapies. In addition to studying clinically relevant

endpoints in future studies, long-term parallel studies rather than shorter term cross over studies may be most helpful.

Finally, qualitative research may be informative in exploring the nature of patient preferences for particular thyroid hormone preparations. There is an absence of qualitative research in the area of evaluating therapies for hypothyroidism, which raises questions about the validity of many of the quantitative instruments used in assessing patient well-being on various formulations and dosages. Qualitative data are traditionally used to form the basis of more precise quantitative instruments; it also helps to inform about covert socio-ethical barriers to well-being, which may affect how data are collected and/or analyzed.

Clearly, there have been great advances in the understanding and management of thyroid hormone replacement, but nevertheless more research is needed. Areas in which future research should be encouraged include, but are not limited to:

- 1) strategies to avoid iatrogenic thyroid disease in individuals treated for hypothyroidism
- 2) research into strategies to aid compliance with L-T4 therapy
- 3) better understanding of maternal-fetal physiology during pregnancy with development of improved titration of L-T4 therapy in hypothyroid pregnant patients
- 4) further studies of soft gel L-T4 capsules to determine their proper place in the therapeutic armamentarium
- 5) further study, and improved standardization, of compounded formulations of L-T4 and/or L-T3
- 6) development of additional biomarkers of euthyroidism, which may supplement the use of serum TSH as a biomarker
- 7) development of a better understanding of how T3 levels are affected by age and disease status, with consideration of reference ranges indexed to age and health status
- 8) clarification of the relative importance of maintaining specific serum T3 concentrations
- 9) research into the relationship between serum T3 and T3 concentrations in specific tissues
- 10) development of more accurate assays to measure serum concentrations of free T3, total T3, and free T4
- 11) development of a sustained release T3 preparation that can then be prospectively tested in clinical trials (e.g. in combination with L-T4 in a physiologic ratio of about 14:1)
- 12) in the absence of the availability of a sustained release T3 preparation, study of when, if

ever, the use of L-T3 would be beneficial in selected patients with apparent decreased T4 to T3 conversion and disproportionately low serum T3 levels

- 13) longterm outcome research using thyroid extracts that includes documentation of the consequences of excursions in serum T3 concentrations
- 14) development of thyroid hormone analogs with a favorable benefit to risk profile
- 15) pursuit of research into developing thyroid stem cells as a potential avenue for understanding thyrocyte physiology and as a possible future treatment for hypothyroidism.

Answers to questions such as these will advance our understanding of how to effectively and completely reverse the derangements that are a hallmark of untreated hypothyroidism, and will contribute to our ability to improve the lives of our patients with hypothyroidism.

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Table 1. The American College of Physicians' Guideline Grading System

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden OR Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

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Table 2. Interpretation of the American College of Physicians' Guideline Grading System

Grade of Recommendation	Benefit Versus Risks and Burdens	Methodological Quality of Supporting Evidence	Interpretation	Implications
Strong recommendation; high-quality evidence	Benefits clearly outweigh risks and burden or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances without reservation	For patients, most would want the recommended course of action and only a small proportion would not; a person should request discussion if the intervention was not offered.
Strong recommendation; moderate-quality evidence	Benefits clearly outweigh risks and burden or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies		For clinicians, most patients should receive the recommended course of action.
Strong recommendation; low-quality evidence	Benefits clearly outweigh risks and burden or vice versa	Observational studies or case series		For policymakers, the recommendation can be adopted as a policy in most situations.
Weak recommendation; high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values	For patients, most would want the recommended course of action but some would not—a decision may depend on an individual's circumstances.
Weak recommendation; moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies		For clinicians, different choices will be appropriate for different patients, and a management decision consistent with a patient's values, preferences, and circumstances should be reached.
Weak recommendation; low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risks, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable	For policymakers, policymaking will require substantial debate and involvement of many stakeholders.
Insufficient	Balance of benefits and risks cannot be determined	Evidence is conflicting, poor quality, or lacking	Insufficient evidence to recommend for or against routinely providing the service	For patients, decisions based on evidence from scientific studies cannot be made; for clinicians, decisions based on evidence from scientific studies cannot be made; for policymakers, decisions based on evidence from scientific studies cannot be made.

RCT = randomized, controlled trial.

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Table 3. Main properties and roles of iodothyronine deiodinases found in human tissues

	D1	D2	D3
Position of iodine in substrate molecule	5' or 5	5'	5
Preferred substrate	rT3>T4	T4>rT3	T3>T4
Predominant tissue localization	Liver, kidney, thyroid	Pituitary gland, CNS, BAT, skin, heart	CNS, skin, placenta, tumors
Subcellular localization	Plasma membrane	Endoplasmic reticulum	Plasma membrane, nuclear membrane
Hypothyroidism	↓	↑	↓
Hyperthyroidism	↑	↓	↑
K _m (T4)	2 μM	2 nM	37 nM
Selective activator	none	cAMP	Hypoxia/HIF-1
Selective inhibitor	PTU	none	none
Main role in thyroid hormone economy and signaling	Contributes to approximately 20% of extrathyroidal T3 production; neutral for intracellular T3 levels	Contributes to approximately 80% of extrathyroidal T3 production; increases intracellular T3 levels	Main contributor to the clearance of T3; decreases intracellular T3 levels

Brown adipose tissue: BAT, central nervous system: CNS, substrate concentration at which the reaction rate is half maximum velocity: K_m, Hypoxia-inducible Factor 1: HIF-1

Table 4a. Medications affecting levothyroxine absorption, as shown in pharmacokinetic studies

Medications	Type of study	Hypothyroid versus Healthy Subjects	Number of subjects	Pharmacokinetic study showing reduced absorption?	Reference
Calcium carbonate	Randomized, crossover absorption study	Healthy	7	Yes, maximum absorption 84% vs 58 %	Singh, 2001 (133)
Calcium carbonate, citrate, acetate	4 period absorption study with random crossover to calcium preparations	Healthy	8	Yes, T4 response area with calcium 75-81% (100% without)	Zamfirescu, 2011 (134)
Proton pump inhibitor (pantoprazole)	Crossover absorption study after one week of PPI vs no PPI	Healthy	20 (10 no PPI first; 10 PPI first)	No, T4 AUC unaffected by PPI	Dietrich, 2006 (146)
PPI (pantoprazole) and H2 – blocker (famotidine)	Randomized to absorption study with drug after absorption study without	Healthy	20	No, T4 peak and T4 AUC unaffected by PPI and H2-blocker	Ananthakrishnan, 2008 (147)
Cholestyramine	6 absorption studies each in 5 healthy	Healthy	5	Yes, best absorption with 5 hr separation of drug and LT4	Northcutt, 1969 (136)
Colesevelam	Non-randomized, crossover study with and without drug	Healthy	6	Yes, response area 3.8% with (100% without)	Weitzman, 2009 (137)
Selevamer	Randomized to absorption study with drug after absorption study without	Healthy	7	Yes, T4 response area 50% with selevamer (100% without)	John-Kalarickal, 2007 (138)
Sucralfate	Absorption study with and without drug	Healthy	5	Yes, reduced and delayed peak absorption	Sherman, 1994 (144)
Raloxifene	Absorption study with and without drug	Hypothyroid	1	Yes, lower peak T4 levels with raloxifene	Siraj, 2003 (148)

Table 4b. Medications reducing levothyroxine absorption, as shown in trials and case studies in hypothyroid patients (n/a = not applicable)

Medications	Type of study	Number of subjects	TSH values mIU/L (w/o medication, c/w with medication)	Binding study?	Reference
Calcium carbonate	Prospective, crossover trial	20	1.6 vs 2.7	Yes, LT4 adsorbs to calcium	Singh, 2000 (132)
Proton pump inhibitor (lansoprazole)	Retrospective chart review of PPI initiation	55 controls, 37 taking PPI	Increased by 0.11 vs 0.69	n/a	Sachmechi, 2007 (135)
Cholestyramine	Case reports	2	Increased while taking cholestyramine	Yes, cholestyramine bound to LT4	Northcutt, 1969 (136)
Selevamer	Retrospective chart review	67	Mean TSH 20 with selevamer	n/a	Diskin, 2007 (139)
Ferrous sulfate	Non-randomized, prospective trial	14	TSH 1.6 vs 5.4	Yes, T4 formed a complex with iron	Campbell, 1992 (140)
Ferrous sulfate	Case report (patient also pregnant and post-partum)	1	TSH 1.3 c/w 29		Shakir, 1997 (141)
Aluminum-containing antacid	Case report	1	TSH 1.1 vs 36	n/a	Sperber, 1992 (142)
Aluminum-containing antacid	Non-randomized, prospective study	5	TSH increased from 2.6 to 7.2	Yes, T4 adsorbed to antacid	Liel, 1994 (143)
Sucralfate	Case report	1	TSH increased from normal to 30	n/a	Sherman, 1994 (144)
Sucralfate	Placebo-controlled, randomized	9	TSH 2.7 vs 4.6	n/a	Campbell, 1994 (145)
Raloxifene	Case report	1	TSH normal vs 9.4	n/a	Siraj, 2003 (148)
Orlistat	Case report	1	TSH 0.03 vs 73	n/a	Madhava, 2005 (150)
Cation exchange resin	Case report	1	TSH 0.67 vs 139	Yes, T4 adsorbed to sodium polystyrene sulphonate	McLean, 1993 (151)

Table 5a. Characteristics of the randomized controlled trial comparing health and psychological effects in hypothyroid patients treated with thyroid extract (containing T4 and T3) compared to L-T4 alone

Author, year (reference)	Treatment dosing*	Etiology primary hypothyroidism	Design	Number of patients randomized (completed follow-up)	Treatment duration	End of study TSH differences between groups
Hoang, 2013 (480)	T4: usual Thyroid extract: 1 mg extract for each 1.667 mcg usual T4 Dosing: Once daily	Mixed: Autoimmune, post-RAI, thyroid surgery, post-EBRT, no thyroid cancer	Randomized, double blind cross-over study	78 (70)	16 weeks	Thyroid extract > LT4

Table 5b. Characteristics of randomized controlled trials comparing health and psychological effects in hypothyroid patients treated with synthetic combination L-T4/L-T3 therapy compared to L-T4 alone

Author, year (reference)	Treatment dosing*	Etiology primary hypothyroidism	Design	Number of patients randomized (completed follow-up)	Treatment duration	End of study TSH differences between groups
Appelhof, 2005 (386)	T4: usual dose LT4/LT3: 10:1 or 5:1 ratio of T4 to T3 ratio, respectively Dosing: Twice daily	Autoimmune	Parallel, blinded	141 (130)	15 weeks	LT4/LT3 < LT4 (TSH significantly lower only in the 5:1 T3:LT4 dose group)
Bunevicius, 1999 (387)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 12.5 µg/day Dosing: Once daily	Mixed – Autoimmune, thyroid cancer	Cross-over, blinded	35 (33)	5 weeks	NS‡ difference
Bunevicius, 2002 (517)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 10 µg/day Dosing: Once daily	All Graves disease, history of subtotal thyroidectomy	Cross-over, blinded	13 (10)	5 weeks	NS‡ difference
Clyde, 2003 (518)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 15 µg/d Dosing: Twice daily	Mixed – Autoimmune, post-RAI, thyroid surgery, post-EBRT, 1 patient thyroid cancer	Parallel, blinded	46 (44)	4 months	NS‡ difference
Escobar-Morreale, 2005 (519)	T4: 100 µg/day LT4/LT3: LT4 75 µg/day and T3 5 µg/d Dosing: Once daily	Mixed - Autoimmune, post-RAI	Cross-over, blinded	28 (26)	8 weeks	LT4/LT3 > LT4
Fadeyev, 2010 (520)	T4: 1.6 µg/kg/day LT4/LT3: estimated T4 dose minus 25 µg/day with T3 12.5 µg/day Dosing: Once daily†	Untreated overt hypothyroidism, etiology not reported	Parallel, unblinded	36 (36)	6 months	NS‡ difference
Nygaard, 2009 (521)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 20 or 50 µg/day, respectively Dosing: Once daily	Autoimmune	Cross-over, blinded	68 (59)	12 weeks	NS‡ difference
Rodriguez, 2005 (384)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 10 µg/day Dosing: Once daily†	Mixed – Autoimmune, post-RAI, thyroid surgery	Cross-over, blinded	30 (27)	6 weeks	NS‡ difference
Saravanan, 2005 (522)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 10 µg/day	Primary hypothyroidism, no thyroid cancer	Parallel, blinded	697 (573)	12 Months (outcomes assessed 3 and 12 months)	LT4/LT3 > LT4

	Dosing: Once daily					
Sawka, 2003 (388)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 total 25 µg/day Dosing: Twice daily T3, once daily T4	Primary hypothyroidism, no thyroid cancer, no thyroidectomy, no history of hyperthyroidism	Parallel, blinded	40 (33)	15 weeks	NS‡ difference
Siegmund, 2004 (523)	T4: usual LT4/LT3: usual T4 dose minus 5% with T3 5% (aim 14:1 ratio LT4 to T3) Dosing: Once daily†	Mixed – Autoimmune, post-RAI£, thyroid surgery, no thyroid cancer	Cross-over, blinded	26 (23)	12 weeks	LT4/LT3< LT4
Valizadeh, 2009 (524)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 total 12.5 µg/day Dosing: Twice daily T3, T4 once daily	Mixed – Autoimmune, post-RAI£, thyroid surgery, but no one on TSH suppressive therapy	Parallel, blinded	71 (60)	4 months	NS‡ difference
Walsh, 2003 (385)	T4: usual LT4/LT3: usual T4 dose minus 50 µg/day with T3 10 µg/day Dosing: Once daily†	Mixed – Autoimmune, post-RAI£, thyroid surgery, but no thyroid cancer on TSH suppressive therapy	Cross-over, blinded	110 (101)	10 weeks	LT4/LT3> LT4

*Starting treatment doses are shown (prior to adjustments within trials according to thyroid function tests)

†Dosing not reported, assume once daily

£Post-RAI, history of radioactive iodine treatment

µPost-EBRT, history of external beam radiation treatment

Table 5c. Trials from those listed in table 5b that provide information regarding mood and fatigue symptoms in the trial participants

Author, Year (reference)	Information about Mood and Fatigue
Escobar-Morreale, 2005 (519)	Individuals with mental illness or affective disorders were not allowed to participate in this trial
Rodriguez, 2005 (384)	The participants in this trial were pre-screened for fatigue and mood using validated questionnaires (Piper Fatigue Scale and General Health Questionnaire-30 [GHQ-30]), respectively. The sampling of participants was stratified according to severity of fatigue level, however individuals with scores >45 on the GHQ-30 were excluded, due to an increased probability of depression). (530, 532, 533)
Sawka, 2003 (388)	This trial was conducted in individuals with primary hypothyroidism who were had evidence of depressive symptoms at baseline (General Health Questionnaire administered on 2 occasions prior to randomization). (404, 531)
Valizadeh, 2009 (524)	Individuals with psychiatric disorders were not allowed to participate in this trial

Walsh, 2003 (385)	Individuals with untreated major depression were not allowed in this trial, but patients on stable doses of antidepressants were allowed if the depression treatment was unlikely to change
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Table 6. Characteristics of randomized controlled trials comparing “clinical endpoints” in hospitalized patients treated with either L-T3 or L-T4

Author, year, reference	Treatment dosing	Patient population	Design	Number of patients randomized
Becker, 1982 (638)	T3: 200 µg/day Dosing: Once daily	Burn Patients	Parallel, blinded	28
Brent, 1986 (637)	T4: 1.5 µg/kg Dosing: Once daily	Mixed ICU Patients	Parallel, unblinded	23
Moruzzi, 1994 (640)	T4: 100 µg/day Dosing: Once daily	Cardiomyopathy	Parallel, blinded	20
Moruzzi, 1996 (639)	T4: 100 µg/day Dosing: Once daily	Cardiomyopathy	Parallel, blinded	20
Acker, 2002 (644)	T4: 150 µg/day Dosing: Twice daily	Acute Renal Failure	Parallel, blinded	59
Lu, 2003 (641)	T4: 50 µg/day Dosing: Once daily	CHF III/IV	Parallel, unblinded	28
Sirlak, 2004 (642)	T3: 125 µg/day versus placebo	Cardiac surgery patients	Parallel, blinded	80

Table 7. The Selectivity and Potential Uses of Thyroid Hormone Analogues

Analogue	Selectivity for TR β (compared with TR α)	Potential Use
Eprotirome (KB2115)	22-fold greater	Cholesterol lowering
DIPTA	Equal affinity	Cholesterol lowering Cardiac inotropic
GC-1 (Sobetirome)	10-fold greater	Cholesterol lowering Obesity treatment
KB141	14-fold greater	Cholesterol lowering
MB07344	15-fold greater	Cholesterol lowering
GC-24	40-fold greater	Obesity treatment
TRIAC	2-3 fold greater	RTH
Tetrac	Metabolized to TRIAC	RTH
CO23	TR β vs TR α selectivity not seen in rodents	Effects on behavior (if TR α -selective)

Abbreviations	
American Association of Clinical Endocrinologists	AACE
American College of Physicians	ACP
American Thyroid Association	ATA
Angiotensin-converting enzyme	ACE
Autoimmune thyroid disease	AITD
Area under the curve	AUC
Body mass index	BMI
Body surface area	BSA
Coronary artery disease	CAD
3,5-Diiodothyropropionic Acid	DITPA
Deiodinase type 1	D1
Deiodinase type 2	D2
Deiodinase type 3	D3
Deiodinase type 1 gene	DIO1
Deiodinase type 2 gene	DIO2
Deiodinase type 3 gene	DIO3
General Health Questionnaire	GHQ
Genome wide association studies	GWAS
High density lipoprotein	HDL
Hypoxia-inducible factor 1	HIF-1
Intensive care unit	ICU
Institutional Review Board	IRB
Investigational new drug	IND
Isolated hyperthyrotropinemia	IH
Levothyroxine	L-T4
Liothyronine	L-T3
Liquid chromatography, tandem mass spectrometry	LC/MS/MS
Low density lipoprotein	LDL
Maximum concentration	Cmax
Micrograms	mcg
Monocarboxylate transporter	MCT
Non-thyroidal illness syndrome	NTIS
Organic anion transporting polypeptide	OATP
Overt hypothyroidism	OH
Proton pump inhibitor	PPI
Randomized, controlled trial	RCT
Responsible conduct of research	RCR
Serotonin reuptake inhibitors	SSRI
Sex hormone binding globulin	SHBG
Single nucleotide polymorphisms	SNPs
Subclinical hypothyroidism	SCH
Syndrome of resistance to thyroid hormone	RTH
Syndrome of resistance to thyroid hormone with mutation in TR α	RTH α
Syndrome of resistance to thyroid hormone with mutation in TR β	RTH β

Thyroid hormone	TH
Thyroid peroxidase antibodies	TPOAb
Thyroid binding globulin	TBG
Thyrotropin releasing hormone	TRH
Thyroxine	T4
Thyroid hormone receptor	TR
Thyroid hormone receptor-alpha	TR α
Thyroid hormone receptor-beta	TR β
Thyroid stimulating hormone or thyrotropin	TSH
3,5,3'-triiodothyroacetic acid	TRIAC
Tri-cyclic anti-depressant	TCA
Triiodothyronine	T3
Urinary n-telopeptides	NTX
United States Pharmacopeia	USP

SECTION I. LEVOTHYROXINE THERAPY		
Number	Question	Page
	<i>Levothyroxine therapy and endpoints during therapy</i>	
1a	Why is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?	13
Strong Rec, Mod Q	Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost.	
1b	What are the clinical and biochemical goals for levothyroxine replacement in primary hypothyroidism?	16
Strong Rec, Mod Q	Levothyroxine replacement therapy has three main goals. These are (i) to provide resolution of patients' symptoms and hypothyroid signs, including biological and physiologic markers of hypothyroidism, (ii) to achieve normalization of serum TSH with improvement in thyroid hormone concentrations, and (iii) to avoid overtreatment (iatrogenic thyrotoxicosis) especially in the elderly.	
1c	Are clinical parameters such as cold sensitivity and dry skin useful by themselves for assessing adequacy of levothyroxine replacement in primary hypothyroidism?	17
Strong Rec, Low Q	Although it may be helpful to follow changes in clinical symptoms longitudinally in patients treated for hypothyroidism, symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment. Therefore, symptoms should be followed, but considered in the context of serum TSH values, relevant co-morbidities, and other potential causes	
1d	Are tissue markers of thyroid hormone action helpful in determining the adequacy of levothyroxine replacement in primary hypothyroidism?	19
Weak Rec, Low Q	Tissue biomarkers of thyroid hormone action are not recommended for routine clinical use, outside of the research setting, since these parameters are not sensitive, specific, readily available, or standardized.	
	<i>Choice of levothyroxine product</i>	
2a	Is there a clinical rationale for prescribing brand name levothyroxine preparations in preference to generic levothyroxine?	20
Weak Rec, Low Q	Prescription of brand name levothyroxine, or alternatively maintenance of the same generic preparation (i.e. maintenance of an identifiable formulation of levothyroxine), is advised. Switches between levothyroxine products could potentially result in variations in the administered dose and should generally be avoided for that reason.	
2b	Are there situations in which therapy with levothyroxine dissolved in glycerin and supplied in gelatin capsules may have advantages over standard levothyroxine?	24
Weak Rec, Low Q	Although there are preliminary small studies suggesting that levothyroxine dissolved in glycerin and supplied in gelatin capsules may be better absorbed than standard levothyroxine in selected circumstances such as concomitant use	

	of proton pump inhibitors or concomitant coffee consumption, the present lack of controlled long term outcome studies does not support a recommendation for the use of such preparations in these circumstances. Switch to a gel capsule might be considered in the rare case of putative allergies to excipients.	
	<i>Levothyroxine absorption and metabolism</i>	Page
3a	How should levothyroxine administration be timed with respect to meals and beverages in order to maintain maximum, consistent absorption?	25
Weak Rec, Mod Q	Because co-administration of food and levothyroxine is likely to impair levothyroxine absorption, we recommend that, if possible, levothyroxine be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal), for optimal, consistent absorption.	
3b	Are there medications and supplements that should not be co-administered with levothyroxine in order to avoid impaired absorption?	28
Weak Rec, Low Q	We recommend that where feasible, levothyroxine should be separated from other potentially interfering medications and supplements (e.g. calcium carbonate and ferrous sulfate). A 4-hour separation is traditional, but untested. Other medications (e.g. aluminum hydroxide and sucralfate) may have similar effects, but have been insufficiently studied.	
3c	Are there gastrointestinal conditions that should be considered when a patient's levothyroxine dose is much higher than expected?	30
Strong Rec, Mod Q	In patients in whom levothyroxine dose requirements are much higher than expected, evaluation for gastrointestinal disorders such as <i>Helicobacter pylori</i> -related gastritis, atrophic gastritis or celiac disease should be considered. Furthermore, if such disorders are detected and effectively treated, re-evaluation of thyroid function and levothyroxine dosage is recommended	
3d	Are different levothyroxine products associated with different absorption, such that a switch to a different brand name or generic is associated with a significantly different serum TSH?	32
Weak Rec, Low Q	Because use of different levothyroxine products may sometimes be associated with altered serum TSH values, a change in an identifiable formulation of levothyroxine formulation (brand name or generic) should be followed by reevaluation of serum TSH at steady state.	
3e	What medications may alter a patient's levothyroxine requirement by affecting either metabolism or binding to transport proteins?	33
Strong Rec, Low Q	Initiation or discontinuation of estrogen and androgens should be followed by reassessment of serum TSH at steady state, since such medications may alter levothyroxine requirement. Serum TSH should also be reassessed in patients who are started on agents such as tyrosine kinase inhibitors that affect thyroxine metabolism and thyroxine or triiodothyronine deiodination. Serum TSH monitoring is also advisable when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are started.	
	<i>Levothyroxine dosage</i>	Page
4a	What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum TSH goal?	35
Strong	When deciding on a starting dose of levothyroxine, the patient's weight, lean	

Rec, Mod Q	body mass, pregnancy status, etiology of hypothyroidism, degree of TSH elevation, age, and general clinical context, including the presence of cardiac disease, should all be considered. In addition, the serum TSH goal appropriate for the clinical situation should also be considered.	
4b	What is the best approach to initiating and adjusting levothyroxine therapy?	
Strong Rec, Mod Q	Thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal. Dose adjustments should be made when there are large changes in body weight, with aging, and with pregnancy, with TSH assessment 4-6 weeks after any dosage change.	38
4c	What are the potential deleterious effects of excessive levothyroxine?	
Strong Rec, Mod Q	The deleterious health effects of iatrogenic thyrotoxicosis include atrial fibrillation and osteoporosis. Because of these effects we recommend avoiding thyroid hormone excess and subnormal serum TSH values, particularly TSH values below 0.1 mIU/L, especially in older persons and postmenopausal women.	40
4d	What are the potential deleterious effects of inadequate levothyroxine?	
Strong Rec, Mod Q	The adverse effects of thyroid hormone deficiency include detrimental effects on the serum lipid profile and progression of cardiovascular disease. We recommend that patients with overt hypothyroidism be treated with doses of levothyroxine that are adequate to normalize serum TSH, in order to reduce or eliminate these undesirable effects.	40
	<i>Levothyroxine and other non-hypothyroid medical conditions</i>	Page
5a	What is the appropriate management of perceived allergy to the constituents of levothyroxine or intolerance to levothyroxine?	
Weak Rec, Low Q	Perceived allergy or intolerance to levothyroxine can be managed by changing the dose or product, including consideration of gel capsules, and possibly by treating concomitant iron deficiency anemia. In selected cases, a consultation with an allergist may be appropriate.	41
5b	How do co-existent medical conditions (e.g. atherosclerotic coronary artery disease) affect the management of levothyroxine replacement therapy?	
Weak Rec, Low Q	We recommend considering patients' underlying medical conditions (such as atherosclerotic heart disease) in order to establish realistic treatment goals and avoid exacerbation of underlying comorbidities.	42
5c	How do co-existent psychosocial, behavioral, and mental health conditions (such as addiction, somatization disorder, and depression) affect the management of levothyroxine therapy?	
Strong Rec, Low Q	The treatment goals of hypothyroidism are the same for patients with psychosocial, behavioral, and mental health conditions, as for the general population. However, referral to a mental health professional should be considered if the severity of the symptoms is not sufficiently explained by the severity of the biochemically-confirmed thyroid dysfunction or another medical condition, or if the mental health condition is impairing effective management of levothyroxine replacement therapy.	43
	<i>Levothyroxine therapy in specific sub-populations</i>	Page
6a	How should levothyroxine therapy be managed in the elderly with	45

	hypothyroidism?	
Strong Rec, Low Q	In general, levothyroxine should be initiated with low doses, and the dose titrated slowly based on serum TSH measurements. It should be recognized that normal serum TSH ranges are higher in older populations (such as those over 65 years), and that higher serum TSH targets may be appropriate.	
6b	How should levothyroxine therapy be managed in pregnant women with hypothyroidism?	
Strong Rec, Mod Q	Women with overt hypothyroidism should receive levothyroxine replacement therapy with the dose titrated to achieve a TSH concentration within the trimester-specific reference range. Serial serum TSH levels should be assessed every four weeks during the first half of pregnancy in order to adjust levothyroxine dosing to maintain TSH within the trimester specific range. Serum TSH should also be re-assessed during the second half of pregnancy. For women already taking levothyroxine, two additional doses per week of the current levothyroxine dose, given as one extra dose twice weekly with several days separation, may be started as soon as pregnancy is confirmed.	46
6c	How should levothyroxine therapy be managed in infants and children with overt hypothyroidism?	
Strong Rec, High Q	<p>Recommendation, infants Levothyroxine replacement at a dose of 10-15 mcg/kg/day should be initiated once newborn screening is positive, pending the results of confirmatory testing. Higher doses may be required for infants with severe congenital hypothyroidism. The aim of therapy is to maintain the serum thyroxine in the mid- to upper half of the pediatric reference range and the serum TSH in the mid- to lower half of the pediatric reference range. The target should be to normalize serum thyroxine approximately 2-4 weeks after initiation of therapy. Once the proper dose is identified, surveillance testing with a serum TSH and thyroxine should be performed every 1 to 2 months during the first year of life with decreasing frequency as the child ages.</p> <p>Recommendation, children All children with overt hypothyroidism should receive levothyroxine replacement therapy to normalize their biochemical parameters and reverse their signs and symptoms of hypothyroidism.</p>	48
6d	How should levothyroxine therapy be managed in children with subclinical hypothyroidism?	
Weak rec, Low Q	In children with subclinical hypothyroidism, due to the low risks of L-T4 replacement therapy, many clinicians still consider it reasonable to initiate treatment to avoid any potential risk of negative impact on growth and development. Treatment is generally not recommended when the TSH is 5-10 mIU/L. For patients with SCH and a TSH > 10 mIU/L with signs and symptoms consistent with primary thyroid disease and/or risk factors associated with progression, L-T4 replacement may be reasonable.	48
6e	How should levothyroxine therapy be managed in individuals who have elevated serum TSH values due to non-adherence?	52
Weak	If prescription of daily levothyroxine is not successful in maintaining a normal	

Rec, Low Q	serum TSH, weekly oral administration of the full week's dose of levothyroxine should be considered in individuals in whom adherence cannot otherwise be sustained.	
	<i>Levothyroxine and serum triiodothyronine concentrations</i>	Page
7a	Are variations in serum triiodothyronine concentrations within the reference range of physiologic or clinical significance? In addition, are mildly low serum triiodothyronine concentrations of clinical significance?	55
SS	The significance of perturbations in serum triiodothyronine concentrations within the reference range, or of mildly low serum triiodothyronine concentrations, is unknown.	
7b	Does levothyroxine therapy that returns the serum TSH levels of hypothyroid patients to the reference range also result in normalization of their serum triiodothyronine levels?	57
SS	Patients with hypothyroidism treated with levothyroxine to achieve normal serum TSH values may have serum triiodothyronine concentrations that are at the lower end of the reference range, or even below the reference range. The clinical significance of this is unknown.	
7c	Is there evidence of discordance between the thyroid hormone status of different tissues and the serum TSH concentration?	59
SS	There are specific instances in which there appears to be discordance between the thyroid status of the pituitary gland, as reflected by the serum TSH, and the thyroid status of other tissues as indicated by various biomarkers. The clinical significance of this is not known.	
7d	Should levothyroxine therapy for hypothyroidism, particularly in specific subgroups such as those with obesity, depression, dyslipidemia, or who are athyreotic, be targeted to achieve high-normal serum triiodothyronine levels or low-normal serum TSH levels?	63
Strong Rec, Mod Q	There is insufficient evidence of benefit to recommend that treatment with levothyroxine be targeted to achieve low-normal serum TSH values or high-normal serum triiodothyronine values in patients with hypothyroidism, including those who are overweight, or those who have depression, dyslipidemia, or who are athyreotic.	
	<i>Levothyroxine therapy in secondary hypothyroidism</i>	Page
8a	What biochemical goals should be employed for levothyroxine replacement in patients with secondary hypothyroidism?	65
Strong Rec, Mod Q	In patients with secondary hypothyroidism, the primary biochemical treatment goal should be to maintain the serum free thyroxine values in the upper half of the reference range. However, the serum free thyroxine target level may be reduced in older patients or patients with comorbidities, who may be at higher risk of complications of thyroid hormone excess.	
8b	Are clinical parameters useful for assessing adequacy of levothyroxine replacement in patients with secondary hypothyroidism?	68
Weak Rec, Mod Q	Although it may be helpful to follow changes in clinical parameters in patients treated for secondary hypothyroidism, such parameters alone lack sensitivity and specificity. There is a limited amount of evidence suggesting that clinical parameters are helpful as secondary means of judging adequacy of	

	replacement with levothyroxine in patients with secondary hypothyroidism in whom biochemical assessment is limited to serum free thyroxine levels.	
8c	Are tissue markers of thyroid hormone action helpful for management of levothyroxine replacement in patients with secondary hypothyroidism?	69
Weak Rec, Low Q	In patients with secondary hypothyroidism in whom the only available biochemical thyroid parameters are thyroid hormone levels, tissue markers of thyroid hormone action may be used, in addition to thyroid hormone parameters, as an adjunctive means of judging the adequacy of levothyroxine replacement.	
	<i>Patient satisfaction with levothyroxine therapy</i>	Page
9a	What tools may be useful in the clinical or research setting, to measure the impact of levothyroxine replacement for primary hypothyroidism on patients' physical or psychological well-being, treatment satisfaction, or treatment preferences?	69
Strong Rec, Mod Q	Of the established instruments used to measure hypothyroid symptoms, data are lacking regarding their sensitivity and specificity in the "everyday" clinical setting to recommend their routine clinical use. Further studies are needed to determine if and how to combine general psychological screening instruments, hypothyroidism-specific tools, and laboratory assessment of thyroid function to measure the impact of levothyroxine replacement therapy on psychological well-being, treatment satisfaction, and preference in clinical practice. A combination of general instruments, combined with hypothyroidism-specific tools, may be the most effective way to examine psychological well-being in the levothyroxine-treated population in the research setting.	
9b	What approach should be taken in patients treated for hypothyroidism who have normal serum TSH values but still have unresolved symptoms?	71
Weak Rec, Low Q	A minority of patients with hypothyroidism, but normal serum TSH values, may perceive a suboptimal health status of unclear etiology. Acknowledgement of the patients' symptoms and evaluation for alternative causes is recommended in such cases. Future research into whether there are sub-groups of the population being treated for hypothyroidism who might benefit from combination therapy should be encouraged.	
	<i>Use of levothyroxine in euthyroid individuals</i>	Page
10a	Is there a role for the use of levothyroxine to treat biochemically euthyroid patients with symptoms that overlap with those of hypothyroidism?	74
Strong Rec, High Q	We strongly recommend against the use of levothyroxine treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use of levothyroxine in this situation.	
10b	Is there a role for the use of levothyroxine to treat euthyroid patients with depression?	75
Weak Rec, Low Q	We recommend against the routine use of levothyroxine for the treatment of euthyroid individuals with depression, due to a paucity of controlled data examining treatment efficacy in this setting.	
10c	Is there a role for the use of levothyroxine to treat euthyroid patients with obesity?	76
Strong	We recommend against the treatment of obesity with levothyroxine in	

Rec, Mod Q	euthyroid individuals, due to a lack of treatment efficacy for this condition	
10d	Is there a role for the use of levothyroxine to treat euthyroid patients with urticaria?	77
Strong Rec, Mod Q	We recommend against the treatment of urticaria with levothyroxine in euthyroid individuals, due to a lack of treatment efficacy for this condition	
10e	What is the recommended approach to treating factitious thyrotoxicosis?	77
Strong Rec, Mod Q	Factitious thyrotoxicosis should be treated with discontinuation of the exogenous thyroid hormone with education and/or psychiatric consultation as appropriate.	
	<i>Clinical ethics considerations in levothyroxine treatment</i>	Page
11	What are the ethical obligations of clinicians in treating hypothyroidism?	78
Not graded	Clinical ethical principles in levothyroxine treatment for hypothyroidism revolve around two core ethical principles in medicine: the Principles of Beneficence and Non-Maleficence, which guide the risk/benefit analysis in clinical practice, and protect clinicians from deviating from practice to satisfy inappropriate patient demands. Additional ethical obligations revolve around the professional virtues of competence and intellectual honesty.	
SECTION II. THERAPIES OTHER THAN LEVOTHYROXINE ALONE		
Number	Question	
	<i>Thyroid extracts</i>	Page
12	In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is treatment with thyroid extracts superior to treatment with levothyroxine alone?	81
Strong Rec, Mod Q	We recommend that levothyroxine be considered as routine care for patients with primary hypothyroidism, in preference to use of thyroid extracts. Although there is preliminary evidence from a short-duration study that some patients may prefer treatment with extracts, high quality controlled long-term outcome data are lacking to document superiority of this treatment compared to levothyroxine therapy. Furthermore, there are potential safety concerns related to the use of thyroid extracts, such as the presence of supraphysiologic serum triiodothyronine levels and a paucity of long-term safety outcome data.	
	<i>Synthetic combination therapy and the rationale for its use</i>	Page
13a	Do genetic variants in thyroid hormone pathway genes (deiodinases or thyroid hormone transporters) affect the serum or tissue levels of thyroid hormones in healthy euthyroid individuals or hypothyroid patients taking replacement therapy?	84
SS	Specific polymorphisms in the deiodinases are consistently associated with very small changes in serum thyroid hormone levels. Insufficient data exist to draw any conclusion about the clinically relevant effects of deiodinase or transporter polymorphisms on tissue thyroid hormone levels.	
13b	In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is combination treatment including liothyronine and levothyroxine superior to the use of levothyroxine alone?	88
Weak	There is no consistently strong evidence of superiority of combination therapy	

Rec, Mod Q	over monotherapy with levothyroxine. Therefore, we recommend against the routine use of combination treatment with liothyronine and levothyroxine as a form of thyroid replacement therapy in patients with primary hypothyroidism, based on conflicting results of benefits from randomized controlled trials comparing this therapy to levothyroxine therapy alone and paucity of long-term outcome data.	
13c	In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	
Insufficient	For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone (in the absence of an allergy to levothyroxine constituents or an abnormal serum TSH), there is currently insufficient evidence to support the routine use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or N of 1 trial, due to uncertainty in long-term risk benefit ratio of the treatment and uncertainty as to the optimal definition of a successful trial to guide clinical decision-making. Additional research targeting those with low serum T3 concentrations, but normal TSH levels during monotherapy is needed to address whether there is a subgroup of patients who might benefit from combination therapy.	88
13d	Should genetic characterization according to type 2 deiodinase gene polymorphism status be used to guide the use of combination synthetic T3 and T4 therapy in hypothyroidism, in order to optimize biochemical and clinical outcomes?	
Strong Rec, Mod Q	Currently, genetic testing is not recommended as a guide to selecting therapy for 3 reasons. i) Although there are data suggesting that specific polymorphisms of the type 2 deiodinase gene might be associated with therapeutic response to combination synthetic triiodothyronine and levothyroxine therapy, controlled confirmatory studies are needed. ii) Currently genetic testing for these specific deiodinase polymorphisms is only available in the research setting. iii) The small effect of the type 2 deiodinase gene variants identified so far that do affect thyroid hormone concentrations (see section 13a), suggests that other factors (e.g. yet unidentified genetic variants) may play a far greater role in determining an individual patient's thyroid hormone concentrations.	96
	<i>Liothyronine monotherapy for hypothyroidism</i>	Page
14	Are there data regarding therapy with triiodothyronine alone, either as standard liothyronine or as sustained release triiodothyronine, that support the use of triiodothyronine therapy alone for the treatment of hypothyroidism?	
Strong Rec, Mod Q	Although short-term outcome data in hypothyroid patients suggest that thrice-daily synthetic liothyronine may be associated with beneficial effects on parameters such as weight and lipids, longer-term controlled clinical trials using a longer acting form of triiodothyronine are needed, before considering the endorsement of synthetic liothyronine therapy for routine clinical use.	98
	<i>Liothyronine monotherapy in euthyroid patients</i>	Page

15a	Is there a role for the use of liothyronine to treat biochemically euthyroid patients with depression?	102
Weak Rec, Low Q	Although some uncontrolled and non-randomized data exist concerning successful use of liothyronine in euthyroid patients with depression, larger, prospective randomized placebo controlled studies are needed to more completely define the potential role of liothyronine in this condition, balancing the risks and benefits of therapy to measurable clinical outcomes.	
15b	Is there a role for the use of liothyronine to treat biochemically euthyroid patients with obesity?	103
Strong Rec, Low Q	We recommend against the use of synthetic liothyronine therapy in treating euthyroid patients with obesity, due to a lack of controlled data proving treatment efficacy for this indication.	
	<i>Compounded thyroid hormones</i>	Page
16	What is the recommendation regarding therapy with compounded thyroid hormones (either levothyroxine or liothyronine) for treatment of hypothyroidism based on current evidence?	104
Strong Rec, Low Q	We recommend against the routine use of compounded thyroid hormones due to concerns about safety and potency and due to the lack of data proving superiority to standard thyroid hormone preparations. However, in the case of suspected allergy to an excipient of standard thyroid hormone preparations that cannot be avoided with a change in brand or dose formulation, including a trial of levothyroxine gel capsules, it may be reasonable to consider use of compounded products, although a controlled study of this approach has not been published.	
	<i>Nutraceuticals</i>	Page
17	Is there a role for the use of dietary supplementation, nutraceuticals, and over-the-counter products in either hypothyroid or euthyroid individuals?	107
Strong Rec, Low Q	We recommend against the use of dietary supplements, nutraceuticals, or other over the counter products either in euthyroid individuals or as a means of treating hypothyroidism. We particularly caution against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism in those with intact thyroid glands susceptible to becoming further dysregulated because of underlying thyroid pathology.	
	<i>Ethical considerations in hypothyroidism research</i>	Page
18	What are the research ethics issues involved in evaluating or designing clinical trials for the treatment of hypothyroidism?	110
Not graded	There should be recognition that there is not enough data to resolve clinical disagreement amongst thyroid experts (called “clinical equipoise”) regarding treatment for hypothyroidism.. Clinical equipoise is disturbed only by the results of well-designed randomized controlled trials that have the statistical power to settle the question of efficacy between monotherapy and combination therapy, or other forms of therapy.	
	<i>Wilson’s Syndrome</i>	Page
19	Is there evidence for the existence of “Wilson’s temperature syndrome” and a rationale for use of escalating doses of triiodothyronine?	114
Strong	There are no credible scientific data to support the existence of “Wilson’s	

Rec, Low Q	Syndrome” and we recommend against the use of triiodothyronine escalation therapy for this indication, due to a lack of proven treatment benefit and safety concerns relating to the risk of thyrotoxicosis.	
SECTION III. HOSPITALIZED PATIENTS		
Number	Question	
	<i>Levothyroxine in hospitalized patients with hypothyroidism</i>	Page
20a	In hospitalized but not critically ill patients with known pre-existing hypothyroidism, should levothyroxine therapy be re-evaluated based on an elevated serum TSH measurement?	115
Strong Rec, Low Q	In hospitalized patients with a pre-established diagnosis of hypothyroidism who are found to have an elevated TSH measurement, consideration should be given to institution or adjustment of levothyroxine replacement. Factors such as the degree of clinical and biochemical hypothyroidism, active co-morbidities, and details of administration of levothyroxine (e.g. dosage, timing, and other factors impacting absorption), are relevant considerations in this situation.	
20b	In hospitalized but not critically ill patients in whom levothyroxine replacement is instituted or increased, should the therapeutic goal be normalization of serum TSH?	116
Strong Rec, Low Q	The therapeutic goal of levothyroxine replacement in non-critically ill patients is long-term normalization of serum TSH when steady state thyroid hormone levels are achieved. We do not recommend titrating the levothyroxine dose to serum free thyroxine levels unless serum TSH cannot be relied upon, e.g. following pituitary surgery.	
20c	In hospitalized but not critically ill patients treated with levothyroxine replacement what formulation and route of administration are recommended?	116
Weak Rec, Low Q	For hospitalized but not critically ill patients, oral levothyroxine treatment is recommended. If this is not feasible, other enteral routes can be used. However, if there are concerns about significant malabsorption or there are other clinical reasons why a patient cannot be given enteral levothyroxine, intravenous levothyroxine may be administered, until enteral absorption improves. If using intravenous levothyroxine, the equivalent intravenous dose is approximately 75%, assuming the enteral levothyroxine dose had achieved euthyroidism.	
20d	In hospitalized but not critically ill patients about to be treated with levothyroxine should the possibility of adrenal insufficiency be excluded?	116
Strong Rec, Low Q	For hospitalized but not critically ill patients who are about to be treated with levothyroxine, the possibility of adrenal insufficiency should be considered. If there is sufficient clinical or biochemical evidence to consider this diagnosis, adrenal insufficiency should be ruled out or empiric treatment should be provided.	
	<i>Myxedema coma</i>	Page
21a	In patients with myxedema coma being treated with levothyroxine, what route of administration should be used?	118
Strong Rec,	Initial thyroid hormone replacement for myxedema coma should be levothyroxine given intravenously. A loading dose of 200 to 400 mcg of	

Low Q	levothyroxine may be given, with lower doses given for smaller, older patients and those with a history of coronary disease or arrhythmia. A daily replacement dose of 1.6 mcg/kg body weight, reduced to 75% as long as being intravenously administered, can be given thereafter. Oral therapy, or other enteral therapy if the oral route cannot be employed, may be instituted after the patient improves clinically.	
21b	In patients with myxedema coma being treated with levothyroxine, should empiric glucocorticoid coverage be provided?	118
Strong Rec, Low Q	Empiric glucocorticoid coverage should be employed as part of the initial therapy for myxedema coma, with intravenous glucocorticoid administration, at doses appropriate for the stressed state, preceding levothyroxine administration.	
21c	In patients with myxedema coma being treated with levothyroxine, should liothyronine therapy also be initiated?	119
Weak Rec, Low Q	Given the possibility that thyroxine conversion to triiodothyronine may be decreased in patients with myxedema coma, intravenous liothyronine may be given in addition to levothyroxine. High doses should be avoided given the association of high serum triiodothyronine during treatment with mortality. A loading dose of 5 to 20 mcg can be given, followed by a maintenance dose of 2.5 to 10 mcg every 8 hours, with lower doses chosen for smaller, older patients and those with a history of coronary artery disease or arrhythmia. Therapy can continue until the patient is clearly recovering (e.g. until the patient regains consciousness and clinical parameters have improved).	
21d	In patients with myxedema coma being treated with levothyroxine, what therapeutic endpoints should be targeted?	119
Weak Rec, Low Q	Intravenous levothyroxine treatment in severely hypothyroid patients may lead to improvement in cardiovascular, renal, pulmonary, and metabolic parameters within a week. Serum thyroxine and triiodothyronine concentrations may improve or normalize with a similar time frame, with more gradual improvement in serum TSH. Thus, the therapeutic endpoints in myxedema coma should be improved mental status, improved cardiac function, and improved pulmonary function. Measurement of thyroid hormones every 1-2 days is reasonable to ensure a favorable trajectory in the biochemical parameters. While optimal levels for serum TSH and thyroid hormones are not well defined in this circumstance, failure of TSH to trend down or for thyroid hormone levels to improve could be considered indications to increase levothyroxine therapy and/or add liothyronine therapy, whereas high serum triiodothyronine could be considered an indication to decrease therapy given safety concerns.	
	<i>Low triiodothyronine concentrations in hospitalized patients</i>	Page
22a	In hospitalized adult patients exhibiting the “non-thyroidal illness syndrome,” should thyroid hormone replacement be instituted with levothyroxine?	122
Strong Rec, Mod Q	We recommend against the use of levothyroxine as a form of therapy for hospitalized patients experiencing critical illness exhibiting the “non-thyroidal illness syndrome”. The few randomized controlled trials comparing levothyroxine therapy to no treatment have not shown significant clinical	

	benefit, and have raised safety concerns that limit support for this approach.	
22b	In hospitalized adult patients exhibiting the “non-thyroidal illness syndrome,” should thyroid hormone replacement be instituted with liothyronine?	122
Weak Rec, Mod Q	We recommend against the use of liothyronine as a form of therapy for hospitalized patients experiencing critical illness exhibiting the “non-thyroidal illness syndrome”. Although low doses of liothyronine have not been linked to harm in clinical trials, data showing any significant clinical benefit are also lacking.	
22c	In hospitalized adult patients with cardiac dysfunction, such as advanced heart failure, and low serum triiodothyronine concentrations, should thyroid hormone replacement be instituted with liothyronine?	126
Weak Rec, Mod Q	We recommend against the routine use of liothyronine as a form of therapy for hospitalized patients with heart failure and low serum triiodothyronine concentrations given the mixed data from short-term trials, the hypothetical risks, and pending further randomized trials confirming benefit and safety.	
	SECTION IV. USE OF THYROID HORMONE ANALOGS	
	<i>Thyroid hormone analogs and euthyroid patients</i>	Page
23	Should thyroid hormone analog therapy be used in euthyroid individuals with non-hypothyroid-related medical conditions (such as dyslipidemia) based on current evidence?	127
Strong Rec, Low Q	Although pre-clinical data suggest that the concept of thyromimetic use for treatment of non-hypothyroid-related medical conditions may be promising, we recommend against the use of such drugs outside of the research setting, due to concerns about the lack of clear benefit or excessive side effects, of currently available preparations.	
	<i>Thyroid hormone analogs and resistance to thyroid hormone</i>	Page
24a	What are the clinical and biochemical goals for treatment of patients who have genetic syndromes of resistance to thyroid hormone?	130
Weak Rec, Low Q	The therapeutic goals of the treatment of patients with genetic syndromes of resistance to thyroid hormone are to improve the symptoms caused by excessive TR-alpha signaling, while minimizing the symptoms caused by deficient TR-beta signaling.	
24b	What is the role of thyroid hormone analogs in treating patients who have genetic syndromes of resistance to thyroid hormone?	131
Weak Rec, Low Q	Although preliminary data from small case series suggest that the use of TRIAC in patients with genetic syndromes of resistance to thyroid hormone may be promising, more clinical research is needed before the use of thyroid hormone analogs can be recommended for this indication.	