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SPECIAL ARTICLE

Guidelines for the Treatment of Hypothyroidism

Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement

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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; it 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 each clinical recommendation was assessed, using the American College of Physicians 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 the development of superior biomarkers of euthyroidism to supplement thyrotropin measurements, mechanistic research on serum triiodothyronine

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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 subgroup effects). Additional research is also needed to develop thyroid hormone analogs with a favorable benefit to risk profile.

INTRODUCTION

Background, Objectives, and Rationale

Levothyroxine (LT_4) 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 feel that LT_4 therapy is not efficacious in restoring optimum health.

Several recent advances in our understanding of thyroid physiology may shed light on why some patients feel unwell while taking LT_4 monotherapy. For example, much has been learned about the sources and regulation of triiodothyronine (T_3) in the plasma and within specific tissues, as well as about the regulation of thyrotropin (TSH). In addition, new data have emerged on dissatisfaction with LT_4 therapy being associated with genetic variation in deiodinases, and fatigue and depression in treated hypothyroid patients being linked with genetic variations in thyroid hormone transporters. The mandate of this task force was to review the goals of LT_4 therapy, examine sources of dissatisfaction with LT_4 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, liothyronine (LT_3) 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 are 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 if it is 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 LT_4 and LT_3 were published (5). We acknowledge these guidelines, and our document was prepared with a goal of minimizing redundancy. We intended that the features that would distinguish this document from these guidelines would be (i) attention to the basic science and translational underpinning for the various thyroid hormone therapies, (ii) extensive consideration of ethical issues, (iii) focus on treatment itself, as opposed to other aspects of diagnosis and management, and most importantly (iv) focus on evaluation of treatment alternatives. We also wished to explore promising preclinical 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 ATA. We formed in the summer of 2011 and our composition included members with particular expertise in mechanistic and translational science (four members), members with particular expertise in clinical thyroidology (six 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 redirected 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 seven interim discussions using conference calls. A spring meeting of the ATA that was open to all potential stakeholders (e.g., health care providers, patients, public) was held on April 25 and 26, 2013, 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 treatment 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. 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. Opportunity for revision existed 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 in which 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 articles 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, or because the question did not lend itself to a recommendation, 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 at least once. 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 articles and reviews, as well as articles suggested by other task force members. For the clinical topic reviews, the authors preferentially selected articles 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.

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

	Strength of recommendation	
Quality of evidence	*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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Our final guidelines document was approved by the board of directors of the ATA, underwent a 1-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.

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. For clinicians, most patients should receive the recommended course of action. For policymakers, the recommendation can be adopted as a policy in most situations.
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		
Strong recommendation; low-quality evidence	Benefits clearly outweigh risks and burden or vice versa	Observational studies or case series	Strong recommendation, but may change when higher-quality evidence becomes available	
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. 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. For policymakers, policymaking will require substantial debate and involvement of many stakeholders.
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		
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	
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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ORGANIZATION OF GUIDELINES:
SECTION I. LEVOTHYROXINE THERAPY

Number	*Question*	*Page*
	Levothyroxine Therapy and Endpoints During Therapy	
1a	Is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?	1676
1b	What are the clinical and biochemical goals for levothyroxine replacement in primary hypothyroidism?	1677
1c	Are clinical parameters such as cold sensitivity and dry skin useful by themselves for assessing adequacy of levothyroxine replacement in primary hypothyroidism?	1678
1d	Are tissue markers of thyroid hormone action helpful in determining the adequacy of levothyroxine replacement in primary hypothyroidism?	1679
	Choice of Levothyroxine Product	
2a	Is there a clinical rationale for prescribing brand-name levothyroxine preparations in preference to generic levothyroxine?	1679
2b	Are there situations in which therapy with levothyroxine dissolved in glycerin and supplied in gelatin capsules may have advantages over standard levothyroxine?	1681
	Levothyroxine Absorption and Metabolism	
3a	How should levothyroxine administration be timed with respect to meals and beverages in order to maintain maximum, consistent absorption?	1681
3b	Are there medications and supplements that should not be co-administered with levothyroxine in order to avoid impaired absorption?	1682
3c	Are there gastrointestinal conditions that should be considered when a patient's levothyroxine dose is much higher than expected?	1683
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 thyrotropin?	1684
3e	What medications may alter a patient's levothyroxine requirement by affecting either metabolism or binding to transport proteins?	1685
	Levothyroxine Dosage	
4a	What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum thyrotropin goal?	1686
4b	What is the best approach to initiating and adjusting levothyroxine therapy?	1687
4c	What are the potential deleterious effects of excessive levothyroxine?	1688
4d	What are the potential deleterious effects of inadequate levothyroxine?	1688
	Levothyroxine and Other Nonhypothyroid Medical Conditions	
5a	What is the appropriate management of perceived allergy to the constituents of levothyroxine or intolerance to levothyroxine?	1689
5b	How do co-existent medical conditions (e.g., atherosclerotic coronary artery disease) affect the management of levothyroxine replacement therapy?	1689
5c	How do coexistent psychosocial, behavioral, and mental health conditions (such as addiction, somatization disorder, and depression) affect the management of levothyroxine therapy?	1689
	Levothyroxine Therapy in Specific Subpopulations	
6a	How should levothyroxine therapy be managed in the elderly with hypothyroidism?	1690
6b	How should levothyroxine therapy be managed in pregnant women with hypothyroidism?	1691
6c	How should levothyroxine therapy be managed in infants and children with overt hypothyroidism?	1691
6d	How should levothyroxine therapy be managed in children with subclinical hypothyroidism?	1691
6e	How should levothyroxine therapy be managed in individuals who have elevated thyrotropin values due to nonadherence?	1693
	Levothyroxine and Serum Triiodothyronine 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?	1694
7b	Does levothyroxine therapy that returns the serum thyrotropin levels of hypothyroid patients to the reference range also result in normalization of their serum triiodothyronine levels?	1695
7c	Is there evidence of discordance between the thyroid hormone status of different tissues and the serum thyrotropin concentration?	1696
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 thyrotropin levels?	1697

(*continued*)

SECTION I. LEVOTHYROXINE THERAPY (CONTINUED)

Number	Question	Page
	Levothyroxine Therapy in Secondary Hypothyroidism	
8a	What biochemical goals should be employed for levothyroxine replacement in patients with secondary hypothyroidism?	1698
8b	Are clinical parameters useful for assessing adequacy of levothyroxine replacement in patients with secondary hypothyroidism?	1699
8c	Are tissue markers of thyroid hormone action helpful for management of levothyroxine replacement in patients with secondary hypothyroidism?	1699
	Patient Satisfaction with Levothyroxine Therapy	
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?	1700
9b	What approach should be taken in patients treated for hypothyroidism who have normal serum thyrotropin values but still have unresolved symptoms?	1700
	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?	1701
10b	Is there a role for the use of levothyroxine to treat euthyroid patients with depression?	1702
10c	Is there a role for the use of levothyroxine to treat euthyroid patients with obesity?	1702
10d	Is there a role for the use of levothyroxine to treat euthyroid patients with urticaria?	1703
10e	What is the recommended approach to treating factitious thyrotoxicosis?	1703
	Clinical Ethics Considerations in Levothyroxine Treatment	
11	What are the ethical obligations of clinicians in treating hypothyroidism?	1703

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?	1704
	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?	1706
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?	1707
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?	1707
13d	Should genetic characterization according to type 2 deiodinase gene polymorphism status be used to guide the use of combination synthetic levothyroxine and liothyronine therapy in hypothyroidism, in order to optimize biochemical and clinical outcomes?	1712
	Liothyronine 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?	1713
	Liothyronine Monotherapy in Euthyroid Patients	
15a	Is there a role for the use of liothyronine to treat biochemically euthyroid patients with depression?	1714
15b	Is there a role for the use of liothyronine to treat biochemically euthyroid patients with obesity?	1715
	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?	1715
	Nutraceuticals	
17	Is there a role for the use of dietary supplementation, nutraceuticals, and over-the-counter products in either hypothyroid or euthyroid individuals?	1716
	Ethical Considerations in Hypothyroidism Research	
18	What are the research ethics issues involved in evaluating or designing clinical trials for the treatment of hypothyroidism?	1718
	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?	1719

(*continued*)

Number	Question	Page
	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 thyrotropin measurement?	1720
20b	In hospitalized but not critically ill patients in whom levothyroxine replacement is instituted or increased, should the therapeutic goal be normalization of serum thyrotropin?	1720
20c	In hospitalized but not critically ill patients treated with levothyroxine replacement what formulation and route of administration are recommended?	1720
20d	In hospitalized but not critically ill patients about to be treated with levothyroxine should the possibility of adrenal insufficiency be excluded?	1720
	Myxedema Coma	
21a	In patients with myxedema coma being treated with levothyroxine, what route of administration should be used?	1721
21b	In patients with myxedema coma being treated with levothyroxine, should empiric glucocorticoid coverage be provided?	1721
21c	In patients with myxedema coma being treated with levothyroxine, should liothyronine therapy also be initiated?	1721
21d	In patients with myxedema coma being treated with levothyroxine, what therapeutic endpoints should be targeted?	1721
	Low Triiodothyronine Concentrations in Hospitalized Patients	
22a	In hospitalized adult patients exhibiting the ''nonthyroidal illness syndrome,'' should thyroid hormone replacement be instituted with levothyroxine?	1722
22b	In hospitalized adult patients exhibiting the ''nonthyroidal illness syndrome,'' should thyroid hormone replacement be instituted with liothyronine?	1722
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?	1724
	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?	1725
	Thyroid Hormone Analogs and Thyroid Hormone Resistance	
24a	What are the clinical and biochemical goals for treatment of patients who have genetic syndromes of resistance to thyroid hormone?	1726
24b	What is the role of thyroid hormone analogs in treating patients who have genetic syndromes of resistance to thyroid hormone?	1726

SECTION I. LEVOTHYROXINE THERAPY

Levothyroxine Therapy and Endpoints During Therapy

1a. 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 LT_4 in the treatment of hypothyroidism lies in the peripheral conversion of the exogenously administered pro-hormone thyroxine (T_4) into its active metabolite T_3 (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 T_4 and T_3 (11). Understanding the impact of the deiodinases on thyroid hormone action requires knowledge of their kinetics, tissue distribution, subcellular 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 T_3 (D1 is estimated to

contribute approximately 24% of circulating T_3 in healthy individuals) and also preserving iodide by removing iodine from inactive metabolites of T_3 and T_4 in the liver and kidney (conjugated iodothyronines) (13). Of note, the D1 gene is up-regulated by T_3, and thus in hyperthyroidism the proportion of circulating T_3 arising from the D1 pathway is significantly increased (11). Propylthiouracil (PTU) 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 T_4 to T_3; approximately 60% of circulating T_3 is estimated to originate from the D2 pathway in healthy individuals (18–20). Expressed in the endoplasmic reticulum (21,22), D2 generated T_3 first accumulates in the cell long enough to contribute to the nuclear T_3 pool (23); thus, changes in D2 activity can cause intracrine tissue-specific changes in thyroid signaling. Intracrine refers to the conversion of T_4 into T_3 within the cell resulting in a cell-specific modulation of the hormonal signaling. Subsequently, D2-generated T_3 exits the cells, thus contributing to thyroid signaling in surrounding tissues (paracrine effects) and to the plasma pool of T_3 affecting thyroid signaling in other tissues. D1 on the other hand resides in the plasma membrane and does not seem to alter the intracellular T_3 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 T_3 to T_2 (3′,5′-T_2), and T_4 to reverse T_3 (rT_3: 3,3′,5′-T_3). Thus, the role of D3 is to clear T_3. Like D2, D3 is thought to have tissue-specific effects, preventing circulating T_3 from entering the nucleus. In disease states, and particularly in hypoxic states, D3 expression can be found ectopically in a wide range of tissues (26); the resultant increase in T_3 clearance promotes both tissue-specific and systemic lowering of T_3 and has been implicated in the pathogenesis of the ''nonthyroidal 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 T_4 and lower serum T_3 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 T_3. 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 1970s, the mainstay of thyroid hormone replacement therapy was desiccated thyroid extracts. Three factors were likely responsible for LT_4 becoming the predominant therapy in the latter half of the 20th century: first, the isolation of T_4 in 1927 by Kendall (31); second, the synthesis of T_4 (32) and its better-absorbed sodium salt by Chalmers *et al.* (33); and third, the demonstration that the biologically active T_3 was generated from T_4 in humans (10).

Approximately 85 μg of T_4 is secreted by the thyroid gland daily. Of the total daily T_3 production of about 33 μg in normal man, approximately 80% (about 26 μg) arises from peripheral conversion from T_4, and only about 20% (approximately 6.5 μg) derives from direct thyroidal secretion (34). It is now well established that while T_4 is the major secretory product of the thyroid gland, thyroid hormone action in peripheral tissues is due to the effects of T_3 binding to its nuclear receptor, defining T_4 as a pro-hormone for T_3.

Gastrointestinal absorption of the tablet formulation of LT_4 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 T_4 and T_3 (36). With such therapy, there will be a transient peak in serum T_4 and free (F)T_4 levels of about 15% magnitude about 4 hours after LT_4 administration (37). Moreover, in athyreotic individuals treated with LT_4 to achieve a normal serum TSH, the serum FT_4 is usually higher and the serum T_3 is either normal (38,39) or lower than the values seen in normal individuals (39–43). Steady-state levels of T_4 and TSH are generally achieved in 6 weeks (approximately five to six half-lives) after initiation of therapy (38). Although there are no randomized clinical trials comparing LT_4 to placebo to treat hypothyroidism, it has clearly been demonstrated that LT_4 or LT_3 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 thyrotropin 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 LT_4 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 (RCT) demonstrated that patients are unable to detect differences in the symptoms associated with hypothyroidism when the LT_4 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

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	$rT_3 > T_4$	$T_4 > rT_3$	$T_3 > T_4$
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	↑	↓	↑
Km (T_4)	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 T_3 production in athyreotic individuals; neutral for intracellular T_3 levels	Contributes to approximately 80% of extrathyroidal T_3 production in athyreotic individuals; increases intracellular T_3 levels	Main contributor to the clearance of T_3; decreases intracellular T_3 levels

BAT, brown adipose tissue; CNS, central nervous system; Km, substrate concentration at which the reaction rate is half maximum velocity; HIF-1, hypoxia-inducible factor 1; rT_3, reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine.

changes in the LT_4 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 RCTs 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 cross-over 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).

In some cases, LT_4 alone may fail to restore the T_3 levels to a value 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 T_3 levels are chosen as one of the therapeutic targets, it is reasonable to titrate the therapy to achieve circulating levels of T_3 similar to the presurgery values while maintaining the TSH value within the range of normality. Levels of FT_4 above the reference range are often observed during replacement therapy with LT_4 (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 thyrotropin values, relevant comorbidities, 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 often have an insidious onset and overlap significantly between patients with thyroid disease and those without. 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 the 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 it 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 LT_4 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 LT_4 (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 T_3 bound to the thyroid hormone receptor (TR) over time, with increasing amounts of T_3 establishing a greater thyroid hormone transcriptional "footprint" in any given tissue. This is because T_3 binding to TR modulates the expression of specific sets of T_3-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 because 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 sex hormone binding globulin (SHBG), osteocalcin, urinary n-telopeptides, total cholesterol, low-density lipoprotein (LDL) cholesterol, lipoprotein(a), creatine kinase, ferritin, myoglobin, and enzymes such as tissue plasminogen activator, angiotensin converting enzyme (ACE), and glucose 6-phosphate dehydrogenase (61,75–81). The results of RCTs have indicated that cholesterol (50,82–86), and SHBG levels (50) are particularly affected by the administration of LT_4. Similarly, RCTs have demonstrated that LT_4 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 LT_4 dose, correlated well with TSH, and was more sensitive to dose alterations than either lipid profile, SHBG concentrations, or 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 LT_4 products available only outside of the United States. There is a long history of regulatory and clinical discussion regarding LT_4 products (94,95). The Food and Drug Administration (FDA) defines an LT_4 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 (Cmax) of serum T_4 fall within 80%–125% of a reference product when a comparable dose is administered to healthy volunteers. In this analysis, the LT_4 dose is only tested at a single oral dose of 600 μg, 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 LT_4 administered (i.e., 600 μg) 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 LT_4 preparations (97).

Blakesley *et al.* (98), in a study funded by Abbott Laboratories, studied the FDA-recommended pharmacokinetic process of comparing LT_4 products. Even when correction was made for endogenous serum T_4 levels in healthy individuals, enabling the detection of differences in the administered dose of 25% and 33%, they could not distinguish acute LT_4 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 LT_4 preparations by assessing for comparable serum T_4, T_3, 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 LT_4 (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 two proprietary LT_4 products (one of which has been reformulated since this evaluation) and two generic LT_4 products (neither of which is currently available) and also concluded that they were bioequivalent and therapeutically equivalent. In contrast, Mayor *et al.* (101) of Knoll pharmaceuticals reanalyzed the data by Dong *et al.* (100) using correction for baseline T_4 levels and the TSH data obtained during the trial, and found that the LT_4 products that seemed to be pharmacokinetically bioequivalent were, in fact, not equivalent therapeutically. No prospective studies assessing this question 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 FT_4, T_3, 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 LT_4 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 LT_4 products be reassessed as though they were new drugs (105). When a generic or branded LT_4 preparation meets the criteria noted above for bioequivalence and potency, the FDA has determined that LT_4 preparations can be substituted for one another by the pharmacy, unless specifically designated to be dispensed 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 LT_4 preparation to another to ensure the goal TSH (and FT_4 and T_3) 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, 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 LT_4 preparations in preference to generic LT_4?'' This issue would not arise if a patient could be maintained on an identifiable formulation of LT_4 (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 LT_4 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 LT_4 product stability. A recent retrospective study of children treated for congenital hypothyroidism (CH) exclusively with either brand-name or generic LT_4 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 comparable TSH values (107). In this study, 30 children with primary hypothyroidism (20 with CH; 11 with autoimmune thyroiditis) and an initial TSH greater than 100 mIU/L were studied. Following 8 weeks of brand name LT_4, the serum TSH was statistically significantly lower ($p = 0.002$) as compared to 8 weeks of generic LT_4. 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 CH. The authors concluded that branded LT_4 was not bioequivalent to an AB-rated generic LT_4 preparation. The authors stated ''It would therefore seem prudent not to substitute LT_4 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 LT_4 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 LT_4 is not based on an anticipated inherent superiority of one particular LT_4 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 LT_4 products not only to various generic formulations, but should also compare brand LT_4 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 evidence.

Discussion of the clinical literature

An oral gel preparation that contains only LT_4, glycerin, gelatin, and water has been developed. The gelatin capsule contains LT_4 as a liquid (109). This formulation is in contrast to standard solid LT_4 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 LT_4 preparations in terms of the serum FT_4, T_3, 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 LT_4, allowed suppression of serum TSH during chronic therapy in patients with thyroid disease that could not be achieved by ingestion of standard LT_4 with Italian style coffee (112). An uncontrolled retrospective study noted lower serum TSH concentrations in patients who were switched from LT_4 tablets to the same dose of LT_4 as a soft gel capsule (113). A case report describes a patient taking a PPI whose serum TSH was higher during treatment with LT_4 tablets than with the same dose given as a gel capsule. An absorption study showed better absorption of the LT_4 from 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 LT_4 tablets. An alternative approach to switching to a soft gel capsule, in situations of suspected poor absorption, is to increase the dose of the LT_4 tablet with periodic monitoring of thyroid function tests.

A liquid formulation of LT_4 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 LT_4 is consumed with breakfast (115,116). When the liquid LT_4 preparation contained in these ampoules is added to breakfast beverages the T_4 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 LT_4 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 LT_4 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 LT_4 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 LT_4 is co-administered with food, absorption is reduced 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 LT_4 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 LT_4 ingestion underwent absorption testing (121). The ingestion of food and LT_4 in close proximity to each other was associated with an LT_4 absorption curve that was characterized by delayed absorption. After a 1-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 LT_4 absorption. However, fiber did not appear to affect absorption in a study of LT_4 in healthy volunteers (127). A summary of several case studies of increased TSH values in hypothyroid patients ingesting their LT_4 with espresso coffee has been reported (122). Absorption studies performed in these patients and in volunteers support the role of coffee in reducing LT_4 absorption. Compared with water, coffee reduced both the maximum concentration (Cmax) 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 LT_4, 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 LT_4 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 LT_4 administration influences the serum TSH values of hypothyroid patients receiving treatment. Three of these had a cross-over design and thus are the most rigorous studies. The previously mentioned case study from 1995 examined four patients in whom TSH suppression therapy was difficult to achieve while they were eating breakfast 15–20 minutes after LT_4 ingestion (121). Consuming breakfast within 20 minutes after taking LT_4 resulted in a higher TSH, compared with when these same patients had breakfast 60 minutes after taking their LT_4, suggesting impaired absorption with a separation of less than 60 minutes. In contrast, a retrospective study of elderly nursing home residents showed that serum TSH values were unaffected when the timing of LT_4 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 postprandial. Another parallel design study, in which patients newly diagnosed with hypothyroidism were prescribed LT_4 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 cross-over studies had different findings with the lowest serum TSH values being seen either 1 hour before breakfast or at bedtime (128,129). In one of these studies, patients took their LT_4 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 LT_4 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 LT_4 ingestion (129). A third cross-over study found higher, more variable TSH values when LT_4 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 nonfasting 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.

To put the summarized data in context, it is important to consider not only when LT_4 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 LT_4 1 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 LT_4 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 LT_4 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

The literature review revealed 20 relevant articles. Studies documenting altered LT_4 absorption in animals were not included. The list of medications that can alter the absorption of LT_4 is extensive and includes calcium carbonate (132–134), PPIs (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 cross-over 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 nonrandomized, noncontrolled trials. The prospective study of aluminum hydroxide was performed in only five 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 LT_4 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 LT_4 to calcium at acidic pH levels. A subsequent absorption study showed that both the Cmax and AUC were reduced when calcium carbonate and LT_4 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 PPI was associated with an increase in the serum TSH values of LT_4-treated patients, compared with a control group in whom such therapy was not initiated (135). LT_4 absorption was unaltered with use of PPIs (146,147) and histamine-2 blockers (147) for a 1-week period in two other studies in healthy volunteers. These conflicting findings may suggest that only chronic oral therapy is associated with decreased LT_4 absorption.

Two studies have implicated bile acid sequestrants as being responsible for binding LT_4 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 LT_4. 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 LT_4 doses to normalize their serum TSH than patients taking calcium products as phosphate binders (139). The pharmacokinetic study showed decreased LT_4 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 LT_4. A need for increased LT_4 while taking ferrous sulfate was observed in the case report (141). Following documentation of increased LT_4 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 LT_4 (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 LT_4 absorption are consistent with binding of LT_4 by sucralfate (144). A blinded cross-over study of nine patients taking LT_4 failed to show a statistically significant difference in TSH while patients were taking either placebo or sucralfate in addition to their LT_4, 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 LT_4 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 LT_4 absorption (3). Effects of several additional medications have been documented in individual cases reports (148–151). These data regarding the effect of medications on LT_4 absorption are summarized in Tables 4 and 5. Table 4 summaries pharmacokinetics studies, while Table 5 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 LT_4 absorption or serum TSH levels, possibly mediated through an impact on gastric acidity. These effects have been shown in retrospective studies, although reduction of LT_4 dosage requirement with treatment of *Helicobacter pylori* gastritis and celiac disease has been documented prospectively.

In a prospective, nonrandomized study treatment of *H. pylori* was associated with reduction of serum TSH levels from 30.5 to 4.2 mIU/L in patients who were considered nonresponsive to high doses of LT_4 (152). In another study, comparison of patients with gastritis, related either to *H. pylori* or atrophic gastritis, with a reference group without gastric disorders showed that the daily LT_4 requirement was up to 34% higher in those with gastritis (2.05 vs. 1.5 μg/kg/d) (153). Furthermore, eradication of *H. pylori* infection and initiation of omeprazole were associated with decreased and increased TSH values, respectively. In addition, in patients receiving LT_4 therapy, the magnitude of their LT_4 requirement was correlated with the presence or absence of serum parietal cell antibodies (154). Higher LT_4 doses were required in those with positive antibodies, and the LT_4 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 LT_4 requirements in patients with celiac disease,

Table 4. Medications Affecting Levothyroxine Absorption, as Shown in Pharmacokinetic Studies

Medications	*Type of study*	*Hypothyroid versus healthy subjects*	*No. of subjects*	*Pharmacokinetic study showing reduced absorption?*	*Reference*
Calcium carbonate	Randomized, cross-over absorption study	Healthy	7	Yes, maximum absorption 84% vs. 58 %	133
Calcium carbonate, citrate, acetate	Four-period absorption study with random cross-over to calcium preparations	Healthy	8	Yes, T_4 response area with calcium 75%–81% (100% without)	134
PPI (pantoprazole)	Crossover absorption study after 1 week of PPI versus no PPI	Healthy	20 (10 no PPI first; 10 PPI first)	No, T_4 AUC unaffected by PPI	146
PPI (pantoprazole) and H2-blocker (famotidine)	Randomized to absorption study with drug after absorption study without	Healthy	20	No, T_4 peak and T_4 AUC unaffected by PPI and H2-blocker	147
Cholestyramine	Six absorption studies each in five healthy participants	Healthy	5	Yes, best absorption with 5 h separation of drug and LT_4	136
Colesevelam	Nonrandomized, cross-over study with and without drug	Healthy	6	Yes, response area 3.8% with (100% without)	137
Selevamer	Randomized to absorption study with drug after absorption study without	Healthy	7	Yes, T_4 response area 50% with selevamer (100% without)	138
Sucralfate	Absorption study with and without drug	Healthy	5	Yes, reduced and delayed peak absorption	144
Raloxifene	Absorption study with and without drug	Hypothyroid	1	Yes, lower peak T_4 levels with raloxifene	148

AUC, area under the curve; H2-blocker, acid blocker; LT_4, levothyroxine; PPI, proton pump inhibitor.

compared with unaffected hypothyroid patients (156,157). Institution of a gluten-free diet reduced the requirement. There are also case reports of increased LT_4 requirements in individuals with celiac disease (158,159), lactose intolerance (160), and intestinal giardiasis (161) with reduction in the LT_4 requirement occurring after institution of a gluten-free or lactose-restricted diet and treatment of the infection, respectively. Data comparing the magnitude of increased LT_4 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 LT_4 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 LT_4 requirement. Examples of factors that are also associated with decreased absorption are advancing age (35) and extreme obesity (body mass index [BMI] > 40 kg/m^2) (163). Although there are case reports of increased LT_4 requirements after intestinal bypass surgery (164–166), when studied directly LT_4 absorption appeared 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 LT_4 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 re-evaluation of serum TSH at steady state.

Weak recommendation. Low-quality evidence.

Discussion of the clinical literature

Assuming that their potency is similar and adherence is similarly maintained, if different identifiable formulations of LT_4 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 LT_4 tablet potency or absorption were varied showed that altered absorption could result in achievement of different TSH values (102). Substitution of LT_4 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

TABLE 5. MEDICATIONS REDUCING LEVOTHYROXINE ABSORPTION, AS SHOWN IN TRIALS AND CASE STUDIES IN HYPOTHYROID PATIENTS

Medications	*Type of study*	*No. of subjects*	*TSH values mIU/L (w/o medication, c/w with medication)*	*Binding study?*	*Reference*
Calcium carbonate	Prospective, cross-over trial	20	1.6 vs. 2.7	Yes, LT_4 adsorbs to calcium	132
PPI (lansoprazole)	Retrospective chart review of PPI initiation	55 controls, 37 taking PPI	Increased by 0.11 vs. 0.69	n/a	135
Cholestyramine	Case reports	2	Increased while taking cholestyramine	Yes, cholestyramine bound to LT_4	136
Selevamer	Retrospective chart review	67	Mean TSH 20 with selevamer	n/a	139
Ferrous sulfate	Nonrandomized, prospective trial	14	TSH 1.6 vs 5.4	Yes, T_4 formed a complex with iron	140
Ferrous sulfate	Case report (patient also pregnant and post partum)	1	TSH 1.3 c/w 29		141
Aluminum-containing antacid	Case report	1	TSH 1.1 vs. 36	n/a	142
Aluminum-containing antacid	Nonrandomized, prospective study	5	TSH increased from 2.6 to 7.2	Yes, T_4 adsorbed to antacid	143
Sucralfate	Case report	1	TSH increased from normal to 30	n/a	144
Sucralfate	Placebo-controlled, randomized	9	TSH 2.7 vs. 4.6	n/a	145
Raloxifene	Case report	1	TSH normal vs. 9.4	n/a	148
Orlistat	Case report	1	TSH 0.03 vs. 73	n/a	150
Cation exchange resin	Case report	1	TSH 0.67 vs. 139	Yes, T_4 adsorbed to sodium polystyrene sulfonate	151

n/a, not applicable; TSH, thyrotropin.

(99,100,169). As these three studies antedated the current FDA guidelines for the manufacture of LT_4 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 LT_4 products exist (170). Similar anecdotal reports of changes in serum TSH when a patient's LT_4 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'' website (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, cross-over 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 CH (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 LT_4 to avoid altered absorption potentially resulting in a different serum TSH. As mentioned previously, if a patient's LT_4 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 LT_4 products have only been documented 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 LT_4 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 thyrotropin at steady state, since such medications may alter the levothyroxine requirement. Serum thyrotropin 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 thyrotropin monitoring is also advisable when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are started.

Strong recommendation. Low-quality evidence.

Discussion of the clinical literature

Many medications may necessitate an adjustment in LT_4 dose by virtue of altering T_4 metabolism or changing the concentration of thyroxine-binding globulin (TBG). T_4 and T_3 are primarily metabolized by deiodination, but are also metabolized by conjugation with glucuronates and sulfates in the liver. All studies cited are either case reports or nonrandomized 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 T_4 and T_3 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 T_4 and T_3 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 LT_4 dose (178). Other case reports also describe the development of hypothyroidism in patients treated with LT_4, who were prescribed phenytoin (179,180). Decreased T_4 and T_3 concentrations without an alteration in TSH were reported in 13 patients without pre-existing hypothyroidism (176) and nine hypothyroid patients (181) after initiation of carbamazepine therapy. A similar phenomenon (normal TSH and low FT_4) 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 three of five hypothyroid children receiving LT_4 (183). Case reports in a single athyreotic patient (184) and three patients with Hashimoto's hypothyroidism (185) document a substantially increased TSH and subsequent need for increased LT_4 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 of these studies highlight the need to be alert for the possibility of increased LT_4 requirement in patients receiving drugs that can affect LT_4 metabolism by conjugation.

The need for a substantially increased dose of LT_4 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 T_3 to rT_3 because of activation of D3 has been suggested to be one of the mechanisms by which tyrosine kinase inhibitors increase the LT_4 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 LT_4 was reported with initiation of amiodarone therapy in two 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 T_4 to T_3 conversion (194,195), there do not seem to be data indicating that these agents increase the requirement for LT_4 in hypothyroid patients. Growth hormone (GH) replacement therapy in GH-deficient subjects decreases serum T_4 and rT_3 levels, with a concomitant rise in serum T_3 levels (196, 197). This suggests a stimulatory effect of GH and/or insulin-like growth factor 1 on the peripheral deiodination of T_4. As a consequence, LT_4 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 LT_4 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 LT_4.

If drugs that increase the serum TBG concentrations, and thus increase total T_4 levels, are started in hypothyroid patients receiving LT_4, their TSH levels may rise above the reference range, thus signaling the need for a higher dose of LT_4 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 postmenopausal 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 nonrandomized 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 LT_4 dose, as seen in an observational study of four 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 thyrotropin elevation, age, and general clinical context, including the presence of cardiac disease, should all be considered. In addition, the serum thyrotropin 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 LT_4 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 subnormal), 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 LT_4 doses of 1.6–1.8 μg/kg of actual body weight (38,47,212,213,215–217,226,227), although some studies estimate higher doses of 2.0–2.1 μg/kg for some patient groups (212,213,226). Two studies have shown that ideal body weight is a better predictor of LT_4 dose than actual body weight (214,225), thus suggesting that LT_4 dose requirement may depend on lean body mass. LT_4 doses in thyroid cancer patients requiring TSH suppression are generally higher and on the order of 2.1–2.7 μg/kg (38,212,215).

The etiology of a patient's hypothyroidism affects their LT_4 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 LT_4 dose than patients with Hashimoto's thyroiditis. Patients who have received radioiodine therapy for Graves' hyperthyroidism may have a variable need for LT_4, depending on whether they have remaining functional autonomous thyroid tissue. Pretreatment 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 LT_4 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 LT_4 dose early in the first trimester of pregnancy (228). The magnitude of the increase is greater in patients with little residual thyroid function (218). LT_4 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 LT_4 absorption with advancing age (35), illustrating that the relationship between LT_4 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 postmenopausal 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 LT_4 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 LT_4 dose required to reach a target TSH concentration. One study showed that the DIO2-Thr92Ala polymorphism predicted the need for a higher dose of LT_4 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 LT_4 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 T_4 to T_3 conversion, such that a higher dose of LT_4 is needed to suppress TSH. However, this theory may not be supported by the fact that the FT_4 and FT_3 levels did not differ between the two genotypes being studied. There are no data regarding the impact of this polymorphism in nonpituitary 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 LT_4 requirement (see discussion in section 13a).

With respect to the effect of age on LT_4 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 LT_4 dose (213). In another study that investigated females and males separately, the decreased LT_4 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 LT_4 requirement with age. Interestingly, sick patients older than 65 years, who are taking other medications in addition to LT_4 for a variety of comorbidities, require lower weight-based doses of LT_4 to normalize their serum TSH than do healthy controls of a similar age who are taking only LT_4 (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 thyrotropin as the goal. Dose adjustments should be made when there are large changes in body weight, with aging, and with pregnancy, with thyrotropin assessment 4–6 weeks after any dosage change.

Strong recommendation. Moderate quality of evidence.

Discussion of the clinical literature

Several approaches to initiating LT_4 therapy are acceptable. One approach is to base the starting dose on the serum TSH level, with full replacement doses (roughly 0.73 μg/lb or 1.6 μg/kg body weight) being required when the serum TSH is markedly elevated, and lower doses (e.g., 25–50 μg) being required in milder degrees of hypothyroidism; for example, if the serum TSH is $\leq$ 10 mIU/L or the patient has SCH (3,229). Other factors to consider when initiating LT_4 therapy include patient age (220) and underlying comorbidities (223), both of which tend to decrease the daily hormonal requirement. The

daily LT_4 dose is more dependent on lean body mass than total body weight (225), which explains why the elderly often require lower doses of LT_4 (219). Medications being taken concurrently may also affect the dose required (230).

The full calculated daily LT_4 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). It was also observed that thyroid functional parameters improved more rapidly in patients 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 LT_4 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 LT_4 dose (12.5–25 μg/d), 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'' because they 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 LT_4 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 LT_4, which reaches steady-state levels by then, 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, LT_4 dose adjustments of 12.5–25 μg/d 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 LT_4 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 LT_4 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 thyrotropin values, particularly thyrotropin 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 LT_4 are overtreated, based on subnormal serum TSH levels. In one study of older individuals taking LT_4, 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 older than age 65 with serum TSH levels <0.1 mIU/L, the majority of whom were taking LT_4, had a threefold 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 LT_4 (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 LT_4-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 thyrotropin levels, in order to reduce or eliminate these undesirable effects.

Strong recommendation. Moderate quality evidence.

Discussion of the clinical literature

Just as LT_4 therapy is frequently associated with overtreatment, undertreatment 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 LT_4 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 comorbidities 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 LT_4 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 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 undertreatment of hypothyroidism during pregnancy is discussed in section 6b.

Levothyroxine and Other Nonhypothyroid 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 LT_4 tolerate the medication without adverse effects. Since LT_4 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 LT_4 dose and advance it slowly. One report of symptoms with institution of LT_4 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 μg tablets, which are colorant-free. A recent report of an allergy in the form of a rash that developed in a patient taking an LT_4 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 LT_4 tablets (e.g., lactose, acacia, or even gluten) is anecdotal. However, some brands of LT_4 contain lactose and/or acacia, and others do not, so trying an alternate product, including gel capsules, to see if 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 LT_4 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 LT_4 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 LT_4, and increasing the dose slowly, while monitoring for the development of angina or other cardiac symptoms such as tachyarrhythmias. With the current use of β-adrenergic blocking drugs, most patients with CAD can be fully treated with LT_4 without difficulty. If patients are unable to tolerate the full LT_4 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 gastritis, 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 (e.g., psychiatrist, clinical psychologist or social worker, licensed addiction therapist) 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 involves 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 nonstandard alternative therapies to deal with their physiologic complaints in an attempt to ''prove'' they are real (as to the patient, they are), and they may become belligerent and combative when told they are euthyroid. Patients with somatization disorders are frequently misdiagnosed and mismanaged and have complicated medical histories. Frequent misdiagnosis may occur 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 one in three women worldwide have been sexually or physically abused in their lifetimes (domesticviolencestatistics.org). Somatization disorder should be managed in conjunction with a mental health care provider to rule out other underlying psychiatric problems, including personality disorders.

In patients with persistent complaints of hypothyroidism as well as 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 they may have causes that are rooted in psychological trauma, rather than an organic problem with physiologic causes.

Levothyroxine Therapy in Specific Subpopulations

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 thyrotropin measurements. It should be recognized that normal serum thyrotropin ranges are higher in older populations (such as those over 65 years), and that higher serum thyrotropin 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, LT_4 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 LT_4 dose that normalizes the serum TSH is generally lower in the elderly compared to younger persons (213,220), related to decreases in T_4 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 comorbidities may serve to negate the effects of decreased T_4 metabolism, leading to an LT_4 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 LT_4 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 T_4 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 FT_4 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 RCTs of LT_4 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 LT_4 are either undertreated or overtreated (49,233), and that, in addition, those aged 85 years and older are more frequently started on LT_4 than younger age groups (261), the elderly, who comprise an increasing proportion of the U.S. population, should be targeted for particularly careful monitoring of therapy. If maintaining a regular daily schedule of LT_4 therapy is problematic in an elderly individual, consideration could be given to a guardian or visiting nurse giving all the LT_4 pills once weekly (or half the pills twice weekly), if appropriate.

LT_4 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 thyrotropin concentration within the trimester-specific reference range. Serial serum thyrotropin levels should be assessed every 4 weeks during the first half of pregnancy in order to adjust levothyroxine dosing to maintain thyrotropin within the trimester specific range. Serum thyrotropin should also be reassessed 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 in which care is being provided, with a generalized range as follows: 0.1–2.5 mIU/L for the first trimester, 0.2–3.0 mIU/L for the second trimester, and 0.3–3.0 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.* (262), 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 FT_4 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 nonesterified 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 FT_4 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 postpartum 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, LT_4 replacement therapy should be continued or initiated if not previously started (1). Ideally, the LT_4 dose should be adjusted to achieve a preconception TSH level below 2.5 mIU/L (1). For women taking LT_4 prior to pregnancy, the initial adjustment in LT_4 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 LT_4 dose are needed. Thyroid function should also be reassessed during the third trimester. Up to 70% of women will require adjustments of 30% or more from the preconception 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 LT_4 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 three 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 third trimester. Women typically return to their lower prepregnancy requirement for LT_4 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 μg/kg/d 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 thyrotropin 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 thyrotropin 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 levothyroxine 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 thyrotropin is 5–10 mIU/L. For patients with subclinical hypothyroidism and thyrotropin >10 mIU/L with signs and symptoms consistent with primary thyroid disease and/or risk factors associated with progression, levothyroxine 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 μg/kg/d, 1-year-old children 4–6 μg/kg/d, adolescents 2–4 μg/kg/d, with transition to the average adult dose of 1.6 μg/kg/d 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 LT_4 (283–286), standard or low-dose therapy is defined by a range of 5–10 μg/kg/d, while high-dose regimens are defined as a range of 10–15 μg/kg/d (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 LT_4 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 T_4) 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 <3 mm 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 μg/kg/d have been reported to normalize T_4 levels within 2–3 weeks, while doses <8 μg/kg/d result in normalization within 6–8 weeks (288). Tailoring the dose based on the severity of initial TSH and T_4 deficit may be the most reasonable approach. Further study of appropriate LT_4 dosing in patients with CH treated with LT_4 is certainly indicated. The addition of LT_3 to LT_4 has not been adequately studied to determine risk or benefit, but in a subgroup of patients with persistent elevations in TSH despite T_4 levels in the mid to upper part of the reference range, the addition of LT_3 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 LT_4 in suspension. Efforts to create suspensions should be avoided and are associated with marked extremes in dosing. To improve the likelihood of compliance, LT_4 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 LT_4 and concurrent ingestion should be avoided (292,293).

The aim of treatment is to keep the T_4 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 and 2.0 mIU/L (287). Once the proper dose is identified, based on normalization of TSH and T_4, surveillance testing with a TSH and T_4 should be performed every 1–2 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 6–12 months may be indicated (294). For patients with mild CH and no change in the LT_4 dose over the first 3 years of life, a trial off LT_4 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 T_4 decreases on repeat testing 4–6 weeks after stopping LT_4 therapy. For further information on the evaluation and management of CH, 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 LT_4 with slowly advancing dose or the addition of gonadotropin-releasing hormone agonist therapy as soon as signs or puberty are witnessed or if the pace of pubertal advancement appears rapid (297,298). Reduction in pretreatment weight gain should not be presumed with the initiation of LT_4 replacement therapy (299). LT_4 replacement therapy is the treatment of choice for patients with OH with the dose adjusted for weight or body surface area (281). The LT_4 dose for patients 1–3 years of age is 4–6 μg/kg/d, for patients 3–10 years the LT_4 dose is 3–5 μg/kg/d, and for patients 10–16 years the LT_4 dose is 2–4 μg/kg/d (281). LT_4 may also be dosed based on body surface area calculated at 100 $\mu g/m^2/d$. The method of administration and the target values for TSH and T_4 are similar to that previously described for neonatal LT_4 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 to ≤ 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, the presence of thyroid peroxidase antibodies (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 isolated hyperthyrotropinemia 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 to ≤ 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 LT_4 replacement therapy may be more significant and measurable, so the decision about whether to initiate LT_4 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 LT_4 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 LT_4 replacement, patients with SCH and an increased total cholesterol with elevated LDL fraction may also benefit from initiation of therapy (310,311). Lastly, LT_4 should also be considered in pediatric patients with a history of exposure to radiation for the treatment of a benign condition or nonthyroid 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 LT_4 treatment (312). In a study examining 426 subjects previously treated for benign conditions with radiation, 14.2% of patients treated with LT_4 developed recurrent nodules compared to 34.2% of 198 subjects that did not receive LT_4 therapy (313).

6e. How should levothyroxine therapy be managed in individuals who have elevated serum thyrotropin values due to nonadherence?

■ **RECOMMENDATION**

If prescription of daily levothyroxine is not successful in maintaining a normal serum thyrotropin, 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 LT_4 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 LT_4, factors affecting LT_4 formulation, absorption, and metabolism can be investigated as potential culprits. Loss of potency due to use of LT_4 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 nonadherence to LT_4 therapy should be considered (317). There are various reports in the literature in which patients with high TSH values while being prescribed LT_4 were shown to be able to absorb LT_4 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 LT_4 under supervised conditions, measuring T_4 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 LT_4 of 600 μg to 2 mg have been employed in absorption testing (317–322).

If a combination of a high TSH and a normal or high T_4 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 LT_4 therapy (324). One survey of patients prescribed LT_4 found a self-reported nonadherence 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). Since LT_4 is generally a lifelong 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 LT_4, patients 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 LT_4 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 LT_4 regimen may be linked to a psychiatric disorder manifest as a desire to remain a patient (326). Other psychosocial causes for noncompliance may include barriers to accessing medication, difficulties with insurance coverage, literacy issues, and lack of understanding regarding the benefits of taking LT_4 as a medication.

Thyroid hormone concentrations in hypothyroid patients receiving large weekly doses of LT_4 have been studied in the past, prior to routine documentation of TSH values (327,328). Normalization of serum TSH in patients suspected of being nonadherent 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 nonadherence. 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 cross-over trial of once weekly oral administration of 7 times the usual daily LT_4 dose versus daily dosage administration showed that weekly therapy was associated with supratherapeutic concentrations of T_4 for about 24 hours, although T_3 levels remained within the reference range (331). Mean serum cholesterol was higher during weekly therapy, but other markers of LT_4 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 cross-over trial of 6 weeks' duration showed greater increases in T_4 after the weekly dose compared with the daily dose, with no associated symptoms or echocardiographic manifestations of hyperthyroidism (333). A small cross-over trial of daily oral therapy versus twice weekly oral therapy showed no significant differences in trough and peak T_4, T_3, and TSH concentrations and no differences in systolic time intervals over a 1-month duration of therapy (332).

Parenteral LT_4 therapy does not appear to have been rigorously studied. A case report in a patient with uncharacterized malabsorption, rather than noncompliance, has been described (334). Mathematical modeling of twice weekly or weekly administration of intramuscular LT_4 showed some fluctuations of T_4 levels, but with these levels remaining in the reference range (335).

In conclusion, if efforts to encourage regular daily consumption of LT_4 are unsuccessful, options include observed therapy (329) or reduction of the frequency of LT_4 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 cross-over trials of such oral therapy were not long term, and none were conducted in a patient group previously reported as manifesting nonadherence (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 LT_4 is also possible (334,335), although no trials of such therapy were identified.

Levothyroxine and Triiodothyronine 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 T_3. Rodents subjected to iodine deficiency maintain their serum T_3 levels (336,337). However, when severe iodine deficiency is accompanied by a fall in serum T_3, one of the tissues that is unable to sustain normal T_3 concentrations is the brain (336). Interestingly, other rodent studies do not show deficient T_3 levels in the brain with LT_4 monotherapy, although deficiency is seen in other tissues (338). Strikingly, animals with genetic inactivation of D1, D2, or both have serum T_3 levels within the normal range, though brain T_3 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 T_3 (342). These observations and the finding that other thyroid parameters such as T_4 and TSH are deranged in these animals support the concept that the maintenance of circulating levels of T_3 is of primary importance in the thyroid axis homeostasis.

Plasma T_3 is the main, and perhaps the only, source of T_3 for tissues that lack D2, such as the liver (23). Even in D2-expressing tissues, approximately 50% of the intracellular T_3 is estimated to originate from the plasma based on rodent studies (23). Thus, if plasma T_3 was to fall to low levels, thyroid hormone signaling would be expected to decrease systemically. The minimum sustained decrease in plasma T_3 that results in biologically important effects remains to be determined. A general caveat for this discussion is that variation in T_3 assay performance represents one methodological limitation affecting attempts to extract data regarding T_3 concentrations from the existing literature. Another caveat of applying rodent studies to human physiology is that the T_4:T_3 ratio in rodents is skewed towards T_3, 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 T_4 and T_3 in thyroidectomized rats (338).

Discussion of the clinical literature

The interest in the use of combination therapies (see recommendation 13) or T_3 monotherapy (see recommendation 14) implies that T_3 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 T_3 is typically not measured or monitored (343). Direct evidence addressing the question of whether small decrements in plasma T_3 have clinically important sequelae is lacking. A critical question, therefore, is whether changes in T_3 concentrations are important and more specifically whether decrements in T_3 that remain within the reference range are actually of any clinical significance.

Some data in humans suggest that maintenance of serum T_3 concentrations is of physiologic importance. It is well known that in mild primary hypothyroidism, serum T_3 is kept normal in the face of a low serum T_4 and mildly elevated TSH (4). In individuals living in areas of iodine deficiency, serum T_3 levels are normal even when T_4 and TSH are altered (344). In one study of 15 athyreotic patients taking LT_4, a progressive 30% fall in T_3 induced by PTU therapy over 8 days led to a doubling of TSH, even though T_4 was constant (18). Given the wide interindividual variability of the serum T_3, a

30% decrease could occur with the actual T_3 value nevertheless remaining in the normal reference range.

Serum T_3 (345) and FT_3 (346) levels vary in a circadian fashion in healthy adult subjects, with estimates of the delta ranging from 14% to 35%. These changes likely follow the well-known circadian variation in TSH. Currently used therapies do not replicate the circadian rhythm of T_3 or FT_3. For example, patients taking LT_4 monotherapy exhibit minimal variations in serum T_3 (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 T_3 achieved with LT_4 monotherapy, unless given multiple times daily, LT_3 monotherapy is characterized by peaks and troughs in T_3 concentration (348). The serum concentration of T_3 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 T_3, but may be important for nongenomic effects.

Study results are mixed as to whether T_3 levels mirror other parameters that are generally thought to reflect thyroid status. Some studies show that T_3 is unaltered when other thyroid-related parameters change. For example, in one study increases in LT_4 dose that were reflected by increases in resting energy expenditure were not accompanied by significant changes in serum T_3 concentration (51). In other studies, at least some thyroid-related parameters change with changes in T_3. With respect to the diagnosis of hypothyroidism, total cholesterol and SHBG correlated well with T_3, but had no correlation with TSH levels (350). In one study in which increasing LT_4 dose also increased serum T_3, there were accompanying changes in cholesterol and SHBG, but no changes in well-being (50). In another study of LT_3 monotherapy, raising T_3 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 T_3 levels had higher scores of hypothyroidism than those with normal T_3 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 T_3 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 LT_4 and LT_3 (291). Concomitant LT_4 and PTU therapy that resulted in normal serum T_4 levels, but low serum T_3 was associated with an elevated serum TSH (18).

A critical issue related to the importance of serum T_3 levels is the performance of assays used to measure T_3 and FT_3. 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 T_3 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 thyrotropin 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

LT_4 is an effective, convenient, and cost-effective treatment for hypothyroidism (see recommendation 1a). One of the underlying concerns expressed about LT_4 as a treatment for hypothyroidism in general is whether physiologic concentrations of T_3 are provided by such therapy in patients who only retain minimal endogenous thyroid function. The implication is that inadequate T_3 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 T_3 levels in humans being treated with LT_4, 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 T_3 concentrations within the group as a whole, although a higher FT_4/T_3 ratio was necessary to achieve this (39). A minority of individuals within the group was noted to have lower serum T_3 levels while talking LT_4. An additional prospective study also showed a comparable free T_3 index in patients treated with LT_4 (38). Further cross-sectional studies suggested maintenance of T_3 concentrations in treated patients, but the reference range was the sole comparator (353,354). However, three cross-sectional studies comparing LT_4-treated patients with control subjects showed that despite similar TSH values the patients had significantly lower T_3 concentrations (40,41,43). The log linear relationship between TSH and T_3 was steeper (greater change in TSH for a given change in T_3) 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 T_3 levels during LT_4 therapy that were observed in patients prior to their thyroidectomy (42). However, in this study patients underwent phlebotomy 2–4 hours after taking their LT_4 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 T_4/TSH and T_4/T_3 relationship from the study data would be confounded by the fact that the investigators likely sampled the peak T_4 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 co-existent illnesses were excluded because these factors are known to affect serum T_3 concentrations (356). In addition, such studies should take patient age into

account because not only does TSH increase with advancing age, but serum T_3 levels decrease within older age groups as well (257).

In summary, all these studies show relatively high FT_4 levels and either an increased FT_4/T_3 or FT_4/FT_3 ratio in LT_4-treated patients. Whether these altered biochemical parameters have clinical consequences is unknown. For example, while excess T_4 could in theory lead to increased T_3 production in D2-expressing tissues, the regulation of D2 by the ubiquination-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 T_3 levels without lowering the serum TSH below the reference range. In one of the prospective studies, serum T_3 levels were maintained as long as the serum TSH was less than 4.5 mIU/L (39). In one retrospective study, 15% of patients had serum FT_3 concentrations that were below the levels in euthyroid controls (41). In another retrospective study, serum FT_3 was only maintained if the patient's serum TSH was below 0.3 mIU/L (42). However, when taken together, several nonprospective studies do indicate that LT_4 monotherapy is characterized by low T_3 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 thyrotropin 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 cells and tissues varying in terms of their expression of transmembrane transporters, deiodinases, nuclear 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 TRα predominant tissues whereas the liver is TRβ predominant. The consequences of differential deiodinase expression are striking: rodent studies indicate that the TRs 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 T_3 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 T_3 and T_4.

Animal data strongly indicate that different tissues can have different concentrations of T_3, and thus different levels of thyroid hormone signaling at a given time; that is, tissues can have variable "tissue-specific thyroid status." Furthermore, normalization of the TSH does not ensure uniform T_3 levels in various tissues, though no data are available regarding the adequacy of thyroid signaling per se. This has been demonstrated in vitro *by utilizing LT_4 infusion in animals, during which some tissues were demonstrated to be relatively T_3-deficient even though all were exposed to the same plasma T_3 and T_4 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 subcellular localizations of the deiodinases. While D2 and D3 are intracellular enzymes, D1 functions at the plasma membrane. Thus, D2 can directly alter the intracellular T_3 content without immediately altering plasma T_3 concentration. Thus, the differences in tissue distribution of the various forms of deiodinases result in tissue-specific supplies of T_3.* 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 T_3, T_4, 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 LT_4 was initiated, lowering of their elevated serum TSH values was shown to correlate with the dose of LT_4 given (46). The serum TSH correlated well with both the administered dose ($r = -0.99$) and the serum FT_4 concentration achieved ($r = -1.0$). In the years following, data have accumulated about the predictable (364), albeit complex (365–367), relationship between FT_4 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 T_3 and T_4 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 T_3 and T_4 are in the normal range, it cannot be assumed that the subject is euthyroid. The interindividual ranges for T_3 and T_4 are much broader than the individual variance (369), such that measuring T_3 and T_4 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 LT_4-treated hypothyroid subjects with a high T_4:T_3 ratio, even when T_3 levels are lower than the normal range (39–43) (see section 7b). In these subjects, it is possible that in the pituitary, the low T_3 is counterbalanced by the higher T_4 (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 T_4:T_3 ratio, especially when T_3 is low. Other examples of situations in

which T_3 may be low in the face of normal serum TSH include starvation (371) and the polar T_3 syndrome (372).

Other examples of discordant tissue response to therapy exist. In a study of daily monotherapy, a dose of LT_3 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 cross-over study of LT_3 monotherapy and LT_4 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 LT_3 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 LT_4 therapy provides a signal of greater magnitude to the thyrotrophs than LT_3 because T_3 is provided not only by the circulating levels but also from intrapituitary conversion of T_4 to T_3 (370). Other investigators, after performing TRH stimulation testing in patients receiving either LT_4 or LT_3 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, FT_4, and FT_3 in approximately 2000 patients who were either untreated or LT_4 treated (374). Mathematical modeling showed different correlations between TSH versus FT_4 and TSH versus FT_3 in the treated and untreated groups. The authors noted that in subjects treated with LT_4 monotherapy, the gradient between TSH and FT_3 increased with LT_4 dosage. They observed that increments of LT_4 monotherapy were progressively more effective in suppressing TSH production, but simultaneously less effective in restoring FT_3. They suggested that D2 levels within the pituitary are uniquely increased in order to maintain T_3 production in the setting of high T_4 levels (358), thus lowering TSH levels. The lowered TSH levels could subsequently result in failure to maintain FT_3 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 T_3 levels might need to be considered as well (374).

The clinical syndromes of resistance to thyroid hormone (RTH), caused by inactivating mutations in TRα (RTHα) or TRβ (RTHβ) 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 RTHα have normal levels of TSH in combination with a low FT_4 and high T_3, and suffer from local hypothyroidism in tissues that predominantly express TRα (376,377). Patients with RTHβ have normal or elevated levels of TSH despite elevated levels of FT_4 and FT_3 and suffer from thyroid hormone overexposure in TRα-expressing tissues (378,379). Thus the molecular pathology of RTHβ is an unbalanced hormonal signaling due to the combination of defective TRβ and otherwise normal TRα receptors exposed to supraphysiologic 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 TRα such as the myocardium (380).

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 triiodothyronine levels or low-normal thyrotropin levels?

■ **RECOMMENDATION**

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

Strong recommendation. Moderate quality of evidence.

Discussion of the clinical literature

Theoretically, it is possible that raising T_3 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 T_3 would potentially be raised either by increasing a patient's LT_4 dose to both lower the TSH and raise the T_3 concentration (39,41–43), although feedback mechanisms would presumably limit the degree to which T_3 could be raised. Alternatively T_3 levels could be raised by use of combination therapy with LT_3 (see discussion in section 13b).

There are a handful of studies that potentially address the issue of raising T_3 levels or lowering TSH levels by LT_4 dosage adjustment in treated hypothyroid patients who have lipid disorders or 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 T_3 levels of 123 and 113 ng/dL. This study showed no decrement in cholesterol, BMI, or percentage body fat associated with the higher LT_4, despite an increase in resting energy expenditure (381). In a cross-over trial, 56 patients with primary hypothyroidism were treated for 8-week periods with three doses of LT_4 in a random order, with achievement of TSH values of 2.8, 1, and 0.3 mIU/L and free T_3 values of 2.5, 2.7, and 3.1 pg/mL respectively. There was progressive lowering of total cholesterol with the higher free T_3 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 LT_4 for postsurgical hypothyroidism and found no significant weight changes (382). A second study compared weight changes during a 1-year period in patients who had

just undergone thyroidectomy without ever becoming hypothyroid with patients already taking LT_4 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 (i) recently thyroidectomized, (ii) pre-existing hypothyroidism, and (iii) pre-existing thyroid cancer diagnosis. Although this latter study could be interpreted as showing that LT_4 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 LT_4. There was a relationship between both the log-transformed TSH and psychological well-being and also between FT_4 concentrations and well-being, but no relationship existed between FT_3 and well-being (67). In summary, these various studies, in which patients with AITD comprised 75%–80% of the population, suggest that dosage adjustments resulting in higher T_3 concentrations do not decrease weight or BMI or improve patient well-being or satisfaction, but they may possibly decrease serum cholesterol.

Use of combination synthetic LT_4 and LT_3 therapy has not proven beneficial with respect to reducing body weight or improving lipid profile (see recommendation 13b), although analysis of subgroups 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 four depressed patients versus 29 nondepressed 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 T_3 concentrations during LT_4 therapy in the general population, and if the levels achieved are of concern, there may be another subpopulation 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 T_3 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 T_3 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 T_3 levels have not been documented in this subpopulation, 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 that of 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 LT_4 that still leave the serum FT_4 in the hypothyroid range (393).

The dilemma with respect to treating secondary hypothyroidism is that it cannot be determined what is the ''normal'' FT_4 for the individual patient. Patients with an intact pituitary and subclinical thyroid dysfunction have, by definition, abnormal TSH values but FT_4 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 eight potentially relevant studies. Only one of these was a RCT, 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 LT_4 dose should be made. In addition, there are no long-term studies comparing

different dosing of LT_4, the resultant FT_4 concentrations, and the subsequent outcomes in patients with central hypothyroidism.

The RCT crossed patients over from the ''empiric'' LT_4 dose that had been selected by their treating physician (mean 1 μg/kg/d) to a body weight–adjusted dose of 1.6 μg/kg/d (85). The dose of 1.6 μg/kg/d produced higher FT_4 levels that reached the upper part of the reference range, and it was associated with lower body weight, lower BMI, lower cholesterol (total, LDL, and high-density lipoprotein [HDL]), fewer 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 LT_4, after discontinuing LT_4, and then after resumption of LT_4 (393). The LT_4 dose used was the long-term treatment dose that had been selected by their prescribing physician. The mean dose was 1.5 μg/kg, and this produced normal FT_4 and FT_3 values in most, but not all patients. Two out of 37 patients had low FT_4 and FT_3 levels, while 3 out of 37 patients had high FT_3 concentrations while taking this dose. LT_4 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 FT_4 values than patients being treated for primary hypothyroidism. One study compared FT_4 values in patients being treated with LT_4 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 FT_4 values below the 10th percentile, compared with less than 3% of patients with primary hypothyroidism (395). A study from 1999 found lower FT_4 levels in treated patients with secondary hypothyroidism, compared with a group with primary hypothyroidism (398). Another study found that 1.6 μg/kg LT_4 produced normal FT_4 values in 94% of patients, but normal FT_3 values in only 49% (394). The other retrospective studies show varying findings (396, 397).

The RCT described demonstrated that FT_4 levels in the upper half of the reference range best reversed the clinical signs of hypothyroidism (85). A retrospective study also suggested that higher FT_4 values within the normal range had most benefit on lipid parameters and body composition (399). Other recommendations in the literature include keeping FT_4 concentrations within the reference range (391), keeping FT_4 levels in the middle of the laboratory reference range (392, 393), and keeping the FT_4 levels in the same range as the FT_4 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 cross-over study already discussed. Lower creatine kinase and faster ankle reflex time were seen with the combination therapy, compared with patients receiving LT_4 at a dose of 1.6 μg/kg, but the free T_3 levels were supraphysiologic during combination therapy. The Zulewski score and working memory test were improved during combination therapy, but only compared with the 1.0 μg/kg/d, not the higher 1.6 μg/kg dose. Since 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 LT_4 or an increase in the LT_4 dose in patients with hypopituitarism (400). It has been suggested that growth hormone may enhance peripheral conversion of T_4 to T_3 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 a 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 one potentially relevant study (85). This previously described RCT utilized a cross-over design with 29 patients either taking an ''empiric'' dose that had been selected by their treating physician (mean 1 μg/kg/d), a body weight–adjusted dose of 1.6 μg/kg/d (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 FT_4 levels, lower body weight, lower BMI, lower cholesterol (total, LDL, and HDL), and fewer 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 LT_4 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 two potentially relevant studies. One of these was the previously identified RCT (85). The other was a prospective study of 37 patients with secondary hypothyroidism undergoing reinstatement of their LT_4 therapy (393). In the latter study LT_4 therapy was associated with significantly increased concentrations of FT_4, FT_3, SHBG, ACE, soluble interleukin-2 receptors, carboxyl-terminal telopeptides of type I collagen, and bone GLA protein. There was a significant positive correlation with FT_3 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 because 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 thyroid hormone (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.

Patient Satisfaction with Levothyroxine Therapy

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 TH deficiency. Assessment of discrete end-organ responses to LT_4 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 LT_4 replacement, though not all have been validated and some are not well suited for studying the impact of LT_4 replacement, as reviewed by Razvi *et al.* (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 LT_4-treated population in the research setting.

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

■ **RECOMMENDATION**

A minority of patients with hypothyroidism, but normal serum thyrotropin values, may perceive a suboptimal health status of unclear etiology. Acknowledgment of the patients' symptoms and evaluation for alternative causes is recommended in such cases. Future research into whether there are specific subgroups 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 LT_4. Saravanan *et al.* (68) conducted a case–control study in which 397 euthyroid LT_4 users showed impaired psychological well-being and more thyroid symptoms compared to 551 age- and sex-matched controls. In this study, a survey was sent to both control patients not taking LT_4 and patients taking LT_4 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 LT_4, 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 LT_4 users. A cross-sectional analysis of 697 patients taking LT_4 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 cross-over trial by Walsh *et al.* (50) of three different LT_4 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. This study suggests that LT_4 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 LT_4 dose (414). In a study by Carr *et al.* (415), patients had symptomatic improvement on an LT_4 dose that was 50 μg/d higher than their optimal dose and resulted in low serum TSH levels. However, it should be noted that this was a nonrandomized, open-label study of short duration and therefore subject to participant bias. In summary, patients treated with LT_4 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 LT_4 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 LT_4 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 patients with elevated titers of TPOAb (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 LT_4.

Even though serum T_3 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 T_3 levels when confronted by a biochemically euthyroid patient with persistent symptoms (419). No published studies have demonstrated that relatively low T_3 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 T_3 levels during LT_4 therapy (39–43) in the absence of nonthyroidal illness, they could be considered for referral for future clinical trials of LT_3-containing combination therapy (see discussion in recommendation 13 and Future Directions). As practicing clinicians, we are aware that T_3 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 LT_3 under such circumstances (419). A recent review discussed the addition of LT_3 to LT_4 therapy in persistently symptomatic patients with biochemical euthyroidism under carefully monitored conditions (420). A trial of LT_4/LT_3 therapy is mentioned in the 2012 ATA thyroid hormone treatment patient brochure. An individual trial of T_3 therapy to normalize the serum T_3 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 T_3 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 because 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 cross-over trial in patients with symptoms suggestive of hypothyroidism but biochemical euthyroidism, LT_4 was no more effective than placebo in improving cognitive and psychological well-being scores despite increases in serum FT_4 and decreases in serum TSH when study subjects were receiving LT_4 (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 LT_4, suggesting that LT_4 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 LT_4 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 LT_4 due to potential iatrogenic hyperthyroidism and potential deflection of attention away from any underlying nonthyroidal 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

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 co-exist with mild hypothyroidism, LT_4 therapy does not improve it (430).

To our knowledge, there are no controlled studies of LT_4 therapy in depression. Data from open-label studies using supraphysiologic doses of LT_4 (250–500 μg/d) in bipolar disorders (431,432) and refractory depression (433) have yielded positive results. However, there are no randomized placebo controlled trials of LT_4 therapy for bipolar disorder or depression, with or without concomitant antidepressant therapy. One randomized trial of TH potentiation of tricyclic antidepressant nonresponders compared 37.5 μg daily of LT_3 to 150 μg daily of LT_4, and found greater responses to LT_3 compared to LT_4, but the study had no placebo arm (434). See section 15a for a more detailed discussion on the use of LT_3 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 TH 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 LT_4 treatment of SCH (84,444). Although THs have been used as a means to attempt to induce weight loss in the past [e.g., Rivlin (445)], negative nitrogen balance (446) and other deleterious effects on the heart and bone (234–236) dictate against the use of TH to treat obesity. Furthermore, a

recent meta-analysis has shown that LT_4 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 LT_4 therapy may be useful in the treatment of urticaria in euthyroid individuals with positive thyroid autoantibodies [e.g., Monge *et al.* (449)]. However, a retrospective study did not show any benefit of LT_4 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 LT_4 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 TH (452). It can be associated with Münchausen's syndrome (in which 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 LT_4 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 TH. In individuals with psychiatric disorders who are secretly taking TH, 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 health care providers to maximize clinical benefits and minimize clinical harms; and the Principle of Non-Maleficence, the obligation to not intentionally introduce harms to patients or to not 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 THs 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, for example, by notifying third parties or authorities when severely hypothyroid patients are driving 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 LT_4 therapy because it is not ''natural.'' This stated preference could indicate the patient does not understand and appreciate the pharmacologic properties of LT_4, 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 LT_4 action; only when the patient understands and appreciates that choosing thyroid extract therapy rather than LT_4 could expose them to certain risks such as elevated serum T_3 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 because 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 in which 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 because it overtly deceives patients. Additionally, competently trained medical experts who misuse their medical knowledge to personally profit, deceive patients, or purvey nonstandard, 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 noniodinated 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 noniodinated molecule secreted by the thyroid is calcitonin, an endogenous hormone with probable effects on calcium and bone metabolism. The other iodine-containing molecules include T_4, T_3, rT_3, 3,3′-diiodothyronine, 3,5-diiodothyronine (3,5-T_2), monoiodothyronine, and their decarboxylated forms known as thyronamines.

While the traditional view has been that T_3 is important as the main iodothyronine with significant binding to nuclear TRs at physiological concentrations, and T_4 is important as a precursor of T_3 (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-T_2 has metabolic effects, possibly mediated via nongenomic mechanisms (467–469). Note that the mechanism by which 3,5-T_2 is generated in humans is unclear; furthermore, the circulating levels of 3,5-T_2 is two orders of magnitude lower than T_3 (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 T_3 and T_4 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-T_2 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 T_4 preparations in the 1960s. 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 T_4 and T_3 content and are formulated into doses expressed as ''grains'' with 1 grain (65 mg) tablets containing 38 μg of T_4; 9 μg of T_3; 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 T_4 and T_3 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 T_3 component. The ratio of T_4 to T_3 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 T_3 leads to supraphysiologic levels of T_3 (474–477). In addition, due to the shorter half-life of T_3, fluctuations of T_3 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 cross-over study documented a larger number of hyperthyroid symptoms when individuals were taking desiccated thyroid preparations compared with levothyroxine preparations, which was attributed to T_3 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 LT_4 in the therapy of hypothyroidism (480) (see Table 6). Although this cross-over 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 T_3 concentration that was associated with thyroid extract use (only two patients had serum T_3 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 T_3 excursions are unknown. These high T_3 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 LT_4 and LT_3 therapy (as reviewed in recommendation 13b) do not suggest additional benefit from the addition of LT_3 to LT_4 replacement therapy. However, the long-term therapeutic efficacy of the T_4:T_3 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 T_4 is thought to be crucial for the developing fetal brain (483) and using a TH preparation in which the T_4 concentration may be lower than that in LT_4 could be deleterious.

TABLE 6. CHARACTERISTICS OF THE RANDOMIZED CONTROLLED TRIAL COMPARING HEALTH AND PSYCHOLOGICAL EFFECTS IN HYPOTHYROID PATIENTS TREATED WITH THYROID EXTRACT (CONTAINING T_4 AND T_3) COMPARED TO LT_4 ALONE

Reference	*Treatment dosing*[a]	*Etiology primary hypothyroidism*	*Design*	*No. of patients randomized (completed follow-up)*	*Treatment duration*	*End of study TSH differences between groups*
480	T_4: usual Thyroid extract: 1 mg extract for each 1.667 μg usual T_4 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 > LT_4

[a]Starting treatment doses are shown (prior to adjustments within trials according to thyroid function tests).
EBRT, external beam radiation therapy; RAI, radioactive iodine.

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 TH transporter MCT8 (486). While no patients have been identified with functionally important deiodinase mutations, seven 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 T_3 levels (487).*

Candidate gene studies have been widely used to study associations of polymorphisms in TH 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 FT_4 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 FT_4 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 FT_4, 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 FT_4, 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 T_4 or rT_3 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 T_3/T_4, 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 TH secretion. Homozygous subjects showed a delayed rise in serum T_3 (497) and a blunted rise in FT_4 and normal T_3 release (498), respectively, indicating subtle alterations in intrathyroidal conversion of T_4 into T_3, with opposite effects on the T_3 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 TH pathway genes, including the deiodinases and transmembrane transporters, are also associated with differences in tissue T_3 levels. In the case of D2, which is critical for local T_3 generation, studies in rodents with inactivating D2 mutations have shown T_3 deficiency in D2-dependent tissues such as the brain (339–341). Thus, the possible effects of genetic variants in D2 on tissue T_3 levels in human subjects should be a subject of future research.

Similarly, effects of polymorphisms in TH transporters on transport function and thus tissue T_3 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. These individuals have peripheral hypermetabolism and abnormal serum thyroid levels with elevated serum T_3, low serum T_4, 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 TH levels. While some polymorphisms are associated with statistically significant differences across genotypes, these differences are very small, such that T_3, T_4, and rT_3 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 T_3, 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 FT_3 concentration in both LT_4 treated and nontreated individuals in a meta-analysis (504) and the D1-A1814G allele is associated with a higher T_3/rT_3 ratio (494). The best-studied polymorphism in *DIO2* (DIO2- Thr92Ala) is, in fact, not associated with any change in circulating TH levels (502), while another *DIO2* polymorphism DIO2-258A/G (D2-ORFa-Gly3Asp) was associated with lower serum T_4 and FT_4 levels and an increased T_3/T_4 ratio, but was not associated with serum T_3 levels (495).

A few studies have investigated whether genetic variants in the TH pathway genes (i.e., the deiodinases) are associated with altered function of the thyroid axis in human patients taking LT_4 monotherapy. For example, when present as the homozygous Ala/Ala form, the Thr92Ala polymorphism has been associated with a higher requirement for LT_4 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 LT_4 dose needed to achieve TSH suppression in thyroid cancer patients or TSH normalization in patients with Hashimoto's hypothyroidism (222). The relationship between FT_4 and TSH in patients appears to be affected by their DIO2-258A/G (DIO2-ORFa-Gly3Asp) polymorphism status. The negative feedback of FT_4 on TSH is weaker in homozygous patients being treated with LT_4 (505). Given this limited amount of data, it remains to be proven that these D2 polymorphisms have a clinically important effect on TH economy.

A large number of studies have looked for associations between genetic variants in the TH pathway genes and other clinical syndromes. For example, a recent GWAS identified 22 polymorphisms that were associated with serum TSH, four 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 T_3 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 TH parameters. Results from these studies are mixed with associations between SNPs and FT_4 and FT_3 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 thyrotopin), 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 triiodothyronine concentrations, but normal thyrotropin 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 T_4 levels by the ubiquitin-proteasomal system (358). As circulating T_4 falls in hypothyroid subjects, the fractional conversion rate of T_4-to-T_3 increases (514). In hypothyroid rodents, this increase occurs

via a PTU-insensitive pathway (515) (i.e., D2). The flux of T_4 through the D2 activation pathway increases due to increased enzyme activity, such that serum T_3 levels remain normal, at least until the fall in serum T_4 is substantial. In D2-expressing tissues such as the brain, much of the intracellular T_3 is generated from circulating T_4 (340,516); thus, these tissues are particularly protected from mild T_4 deficiency. The existence of the D2 pathway for conversion of T_4 to T_3, and the homeostatic function of D2 for maintenance of intracellular T_3 in the face of mild T_4 deficiency, explain why LT_4 monotherapy can be so effective in the treatment of hypothyroidism. Treatment with PTU in patients reliant on LT_4 therapy reduces their serum T_3 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 T_3 and that D2 contributes importantly to maintenance of serum T_3 levels (19).

At the same time, data indicate that a small but significant proportion of thyroidectomized patients on LT_4 monotherapy have low circulating T_3 in spite of normal range TSH and high-normal serum T_4 (39–43). It is possible that in these subjects, the D2 pathway does not fully compensate for the absence of the thyroidal T_3 production; the significance of the low serum T_3 levels in these patients is discussed in section 7a and 7b. Note that even D2-expressing tissues would be expected to be relatively T_3 deficient since D2 is not upregulated significantly by decreases in serum T_3. The serum TSH remains in the normal range likely because the decreased serum T_3 is counterbalanced by the increased serum T_4. If this concept is correct, the question then becomes how to simultaneously normalize the concentration of T_3 in all tissues? Increasing LT_4 dose would raise serum T_3, thus raising tissue T_3 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 LT_4 dose with LT_3 could help normalize tissue T_3 without necessarily lowering serum TSH. Data supporting the concept that combination therapy can be effective in normalizing tissue T_3 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 T_3-deficient during LT_4 infusions (338,361). However the cerebral cortex was an exception, as in this tissue T_3 homeostasis was maintained over a wide range of T_4 infusions (338). An infusion of a combination of LT_4 and LT_3 allowed for normalization of serum TSH and levels of T_4 and T_3 in all tissues tested (361).

Discussion of the clinical literature

In order to evaluate whether the combination of LT_4 with LT_3, also referred to as combination therapy, was clinically superior to LT_4 alone, in TH replacement of adults with primary hypothyroidism, we reviewed the results of 13 original RCTs (384–388,517–524), as well as four systematic reviews or meta-analyses of selected RCTs (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.* (528) in 1970, since the dosages of LT_4 that were used were higher than those typically used in current clinical practice and the study predated utilization of TSH measurements, both of which may have contributed to TH overreplacement in the study. We did not include a controlled cross-over design trial from Regalbuto *et al.* (529), given that there was no evidence of randomization of patients reported in the methods section of the article.

The characteristics of the included original trials are described in Table 7. The studies included a variety of LT_4/LT_3 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 7). 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 7). 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 pretrial 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 8). All included trials had some level of blinding, except for one study focusing on laboratory parameter outcomes by Fadayev *et al.* (520). Of the 13 included trials comparing the effect of combination LT_4/LT_3 treatment to LT_4 alone, seven had a cross-over 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 LT_4/LT_3 treatment on serum TSH levels measured at study completion was as follows: (i) no significant difference compared to LT_4 therapy alone—eight studies (384,387,388,517,518, 520,521,524); (ii) significantly higher TSH measurement in the combination therapy group compared to the LT_4 group—three studies (385,519,522); or (iii) significantly lower TSH measurement in the combination therapy group compared to LT_4 alone—two studies (386,523), including one study in which the serum TSH in the highest dose combination group (5:1 ratio of LT_4 to LT_3), 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 LT_4/LT_3 treatment effects, categorized as follows: (i) marked superiority of combination treatment on multiple measures—two trials (387,521), (ii) superiority of combination treatment on a minority of measurements—two trials, with one trial from Saravanan *et al.* (522) reporting some improvements in mood at 3 months but not 12 months, and another trial from Valizadeh *et al.* (524) reporting improvement of an insomnia/anxiety subscale with other measures not significantly different; or (iii) no statistically significant superiority of combination treatment over LT_4 treatment—eight 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 LT_4/LT_3 treatment effect, with the results summarized as follows: (i) marked superiority of combination treatment on multiple measures—one trial by Bunevicius *et al.* (387), (ii) superiority of combination treatment on a minority of measurements—one trial by

TABLE 7. CHARACTERISTICS OF RANDOMIZED CONTROLLED TRIALS COMPARING HEALTH AND PSYCHOLOGICAL EFFECTS IN HYPOTHYROID PATIENTS TREATED WITH SYNTHETIC COMBINATION LT_4/LT_3 THERAPY COMPARED TO LT_4 ALONE

Reference	*Treatment dosing*[a]	*Etiology primary hypothyroidism*	*Design*	*No. of patients randomized (completed follow-up)*	*Treatment duration*	*End of study TSH differences between groups*
386	T_4: usual dose LT_4/LT_3: 10:1 or 5:1 ratio of T_4 to T_3 ratio, respectively Dosing: twice daily	Autoimmune	Parallel, blinded	141 (130)	15 weeks	$LT_4/LT_3 < LT_4$ (TSH significantly lower only in the 5:1 LT_4/LT_3 dose group)
387	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 12.5 μg/d Dosing: once daily	Mixed: autoimmune, thyroid cancer	Cross-over, blinded	35 (33)	5 weeks	NS
517	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 10 μg/d Dosing: once daily	All Graves' disease, history of subtotal thyroidectomy	Cross-over, blinded	13 (10)	5 weeks	NS
518	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 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
519	T_4: 100 μg/d LT_4/LT_3: LT_4 75 μg/d and T_3 5 μg/d Dosing: once daily	Mixed: autoimmune, post-RAI	Cross-over, blinded	28 (26)	8 weeks	$LT_4/LT_3 > LT_4$
520	T_4: 1.6 μg/kg/d LT_4/LT_3: estimated T_4 dose minus 25 μg/d with T_3 12.5 μg/d Dosing: once daily[b]	Untreated overt hypothyroidism, etiology not reported	Parallel, unblinded	36 (36)	6 months	NS
521	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 20 or 50 μg/d, respectively Dosing: once daily	Autoimmune	Cross-over, blinded	68 (59)	12 weeks	NS
384	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 10 μg/d Dosing: once daily[b]	Mixed: autoimmune, post-RAI, thyroid surgery	Cross-over, blinded	30 (27)	6 weeks	NS
522	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 10 μg/d Dosing: once daily	Primary hypothyroidism, no thyroid cancer	Parallel, blinded	697 (573)	12 Months (outcomes assessed 3 and 12 months)	$LT_4/LT_3 > LT_4$

(*continued*)

Table 7. (Continued)

Reference	*Treatment dosing*[a]	*Etiology primary hypothyroidism*	*Design*	*No. of patients randomized (completed follow-up)*	*Treatment duration*	*End of study TSH differences between groups*
388	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 total 25 μg/d Dosing: Twice daily T_3, once daily T_4	Primary hypothyroidism, no thyroid cancer, no thyroidectomy, no history of hyperthyroidism	Parallel, blinded	40 (33)	15 weeks	NS
523	T_4: usual LT_4/LT_3: usual T_4 dose minus 5% with T_3 5% (aim 14:1 ratio LT_4 to T_3) Dosing: once daily[b]	Mixed: autoimmune, post-RAI, thyroid surgery, no thyroid cancer	Cross-over, blinded	26 (23)	12 weeks	$LT_4/LT_3 < LT_4$
524	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 total 12.5 μg/d Dosing: twice daily T_3, T_4 once daily	Mixed: autoimmune, post-RAI, thyroid surgery, but no one on TSH-suppressive therapy	Parallel, blinded	71 (60)	4 months	NS
385	T_4: usual LT_4/LT_3: usual T_4 dose minus 50 μg/d with T_3 10 μg/d Dosing: once daily[b]	Mixed: autoimmune, post-RAI, thyroid surgery, but no thyroid cancer on TSH-suppressive therapy	Cross-over, blinded	110 (101)	10 weeks	$LT_4/LT_3 > LT_4$

[a]Starting treatment doses are shown (prior to adjustments within trials according to thyroid function tests).
[b]Dosing not reported, assume once daily.
NS, not significantly different; RAI, radioactive iodine treatment; EBRT, external beam radiation treatment.

Escobar-Morreale *et al.* (519), and (iii) no statistically significant superiority of combination treatment over LT_4 treatment—eight trials (384–386,388,517,518,522,523), including a study by Clyde *et al.* (518), in which cognitive performance on a Grooved Peg Board test was better in the LT_4 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 seven trials measuring these outcomes (384,385,517–520,522). Of the nine 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 LT_4 group in only one trial at a TSH-suppressive dose of combination therapy (LT_4:LT_3 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 LT_4 alone in one study of premenopausal women examining this outcome (520). Skeletal fracture outcomes were not reported in any studies. The effect of combination LT_4/LT_3 treatment compared to LT_4 alone on resting heart rate was evaluated in 11 trials (384–387,517–520,522–524), and the effects were characterized as follows: (i) significantly increased heart rate in the combination therapy group compared to the LT_4 group—one trial by Appelhof *et al.* (386), at the 5:1 LT_4 to LT_3 ratio dose of combination therapy; (ii) significantly reduced heart rate in the combination therapy group compared to the LT_4 group—three trials, including those from Bunevicius *et al.* (387), Escobar-Morreale *et al.* (519), and Walsh *et al.* (385), respectively, or (iii) no significant difference between treatment groups in seven 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 five blinded, cross-over design trials comparing treatment preference (385,387,517,519,521), combination LT_4/LT_3 treatment was preferred to LT_4 in four 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 four positive cross-over design preference trials was only 128 (387,517,519,521), which is

Table 8. Trials from Those Listed in Table 7 That Provide Information Regarding Mood and Fatigue Symptoms in the Trial Participants

Reference	*Information about mood and fatigue*
519	Individuals with mental illness or affective disorders were not allowed to participate in this trial.
384	The participants in this trial were prescreened 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).
388	This trial was conducted in individuals with primary hypothyroidism who were had evidence of depressive symptoms at baseline (GHQ administered on two occasions prior to randomization) (404,531).
524	Individuals with psychiatric disorders were not allowed to participate in this trial.
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.

comparable to the 101 patients who completed follow-up in the trial in which 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 LT_4 group (mean 1.5 mIU/L) in the negative cross-over design preference trial (385); in the cross-over trials where combination treatment was preferred, the mean serum TSH was not significantly different between groups in three studies (387,517,521), but significantly higher in the combination LT_4/LT_3 group compared to the LT_4 group in one study from Escobar-Morreale *et al.* (519) (mean TSH 2.5 mIU/L in the combination therapy group and 1.95 mIU/L in LT_4 group). 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 LT_4 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 LT_4/LT_3 combination therapy over LT_4 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 LT_4/LT_3 combination therapy was preferred over LT_4 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 LT_4/LT_3 treatment compared to LT_4 treatment alone (389,525–527). For respective meta-analyses, the timing of review and number of trials included was as follows: (i) review by Grozinsky-Glasberg *et al.* (389) conducted in September 2005 in which data were pooled from 11 trials (including one unpublished study), (ii) a review by Joffe *et al.* (526) from 2007 in which data were pooled from nine trials (including one unpublished trial), and (iii) a review by Ma *et al.* (527) conducted in 2008 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 LT_4/LT_3 treatment compared to LT_4 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.* (527), LT_4 alone appeared to be superior to combination treatment. Pooled adverse event rates were not significantly different between treatment arms (389). In a meta-regression analysis, Grozinsky-Glasberg *et al.* (389) reported no significant association among length of follow-up, percentage of athyreotic patients, or dose of LT_3 and psychologic outcomes. In pooling data from four trials examining treatment preference, Joffe *et al.* (526) reported that combination treatment was significantly preferred over LT_4 treatment alone. A systematic review, without meta-analysis, was also published by Escobar-Morreale *et al.* (525) in 2005, in which data from nine trials [including the 1970 trial from Smith *et al.* (528)], were reviewed. Escobar-Morreale *et al.* (525) 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.

In conclusion, in reviewing data from 13 published RCTs (384–388,517–524) and four 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 LT_4/LT_3 combination therapy compared to LT_4 alone. Serious adverse events did not appear to be reported at higher rates in combination treatment compared to LT_4 alone; however, the majority of trials were 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 TH replacement therapy is generally lifelong. Furthermore, RCTs incorporating the use of sustained release T_3 preparations would be of interest. However, at the current time, based on a lack of clear consistent evidence of benefit of combination therapy using LT_4/LT_3 over established LT_4 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 LT_4/LT_3 combination therapy, we

believe that the *routine* use of LT_4/T_3 in treatment of primary hypothyroidism is not justified.

Published trials of combination therapy have not targeted patients who have relatively low serum T_3 values during monotherapy. In addition, the serum T_3 values achieved during combination therapy have not been a specific endpoint of these trials. It is possible that future trials that include having both a relatively low serum T_3 and a normal serum TSH concentration during monotherapy as entry criteria, in the absence of nonthyroidal illness, might have different outcomes from the trials conducted thus far. Future research addressing this subgroup of patients should be encouraged because this is currently 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 T_3 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 LT_4 and LT_3 combination therapy serves the hypothyroid patient better than T_4 monotherapy'' and that ''LT_4 remains the standard treatment for hypothyroidism'' (5). However, the ETA has suggested that ''LT_4 and LT_3 combination therapy might be considered as an experimental approach in compliant LT_4–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 LT_4 and LT_3 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 LT_4/LT_3 combination therapy in pregnant women. We also agree that in pregnancy, where delivery of T_4 is thought to be crucial for fetal brain development (483), use of a treatment regimen containing T_3, in which the T_4 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 T_4/T_3 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 T_4/T_3 combination therapy over the use of T_4 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 levothyroxine and liothyronine 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 three 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 levothyroxine and liothyronine 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 LT_4/LT_3 treatment, according to genetic characterization of the primary hypothyroid adult patient, improves health outcomes, as opposed to a strategy of routine LT_4 treatment for all patients. We included three studies on secondary analyses (390,540,541) stemming from two prospective trials comparing LT_4/LT_3 combination therapy to LT_4 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 RCT 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 LT_4/LT_3 treatment in 552 patients. Panicker *et al.* (390) 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. 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.* (390) reported a significant interaction between the less common variant of DIO2-Thr92Ala and combination LT_4/LT_3 treatment compared to LT_4 treatment on the outcomes of psychological well-being, thyroid symptoms, and satisfaction, in the absence of any significant effect on circulating TH levels. In addition, there was no association between being homozygous for the *DIO2* polymorphism and having a lower pre-intervention serum free T_3 concentration than the remainder of the study population. Sixteen percent of the population in this study was homozygous for the polymorphism (390). In contrast, analyzing data from a RCT by Appelhof *et al.* (386) comparing LT_4 monotherapy with LT_4 and LT_3 combination therapy in two ratios, the same group (540) 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). Polymorphisms in *DIO1*, although associated with altered serum T_3 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.* (541) reported that the presence of two polymorphisms of *OATP1C1*, a T_4 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 LT_4/ LT_3 combination therapy in patients with primary hypothyroidism. An important limitation of these studies examining associations with SNPs was that respective treatment allocation to the combination LT_4/LT_3 treatment or LT_4 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 RCTs are needed to know whether a strategy of tailoring the type of TH replacement therapy (i.e., LT_4/LT_3 or LT_4 alone), according to genetic characterization, may result in superior health outcomes, compared to the currently recommended strategy of routine LT_4 treatment for adults with primary hypothyroidism.

Triiodothyronine 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

T_4, the main product of the thyroid gland, is a prohormone devoid of intrinsic activity, and the biological effects of TH are the result of the interaction between T_3 with its receptors (9). From this perspective T_4, and by extension its reservoir of hormone bound to serum carrier proteins, ensures a reserve of substrate for the deiodination to T_3 and offers a buffering against fluctuations in the circulating and tissue levels of T_3. On the other hand, since replacement therapy with LT_4 relies entirely on the deiodination step to provide adequate levels of serum and tissue T_3, a defect in this metabolic step would result in inadequate delivery of the active hormonal form. Direct therapy with LT_3, 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 T_3. With LT_4 therapy, D2-expressing tissues should maintain the required substrate for normal intracellular generation of T_3; in addition, the D2 pathway contributes to providing normal amounts of T_3 for most patients. With T_3 monotherapy, multiple daily dosing is required to sustain serum T_3 levels due to the shorter half-life of LT_3, compared with LT_4 (348). If normalization of serum TSH is the goal of LT_3 monotherapy, serum T_3 levels must be significantly higher, approximately double, than those seen during LT_4 monotherapy; whether this leads to relative hyperthyroidism in some tissues requires further study. The impact of LT_3 monotherapy on D2-expressing tissues other than the pituitary gland is also unknown. In rodents, normalization of serum TSH and hypothalamic TRH expression with T_3 monotherapy requires serum T_3 levels in the supranormal range (542).

Discussion of the clinical literature

Therapy with synthetic LT_3 has the theoretical advantage of bypassing the T_4 to T_3 conversion step, which is obligatory in case of LT_4 treatment, hence directly delivering the bioactive drug to the various organs/tissues that are the target of hormonal action. Conversely, a theoretical disadvantage of therapy with LT_3 alone is represented by the lack of T_4 as a reservoir of substrate; hence the circulating and tissue levels of T_3 are entirely dependent on the pharmacokinetic characteristics of the exogenously administered hormone replacement. The available data relative to the pharmacokinetics of LT_3 are contradictory, indicating half-life values ranging from 6 to 22 hours (36,543). The primary data were obtained from single-dose studies, and these studies were either performed by means of measurement of radioactive decay of radio-labeled LT_3 in euthyroid volunteers (543) or by measurement of serum T_3 in hypothyroid patients (36,543). Since some studies have been performed in subjects with endogenous production of TH from the thyroid gland, it is possible that the re-uptake and metabolism of iodine in the thyroid caused a spurious increase in the half-life of the drug. Calculation of LT_3 half-life in the blood may also be complicated by distribution from the blood into other

compartments and redistribution back into the blood. However, an average half-life of 1 day has been quoted (543).

LT_3 therapy started after LT_4 discontinuation, usually administered at a dose of 25 μg 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 μg LT_3 versus placebo did not result in a significantly different Billewicz score when documented 2 weeks after LT_4 discontinuation, perhaps because FT_4 levels were still sufficient at this time point. Use of LT_3 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 T_3 does not appear to have an advantage in this setting.

Although an extended-release formulation of LT_3 has been shown in a single short-term study to reduce the peaks and troughs of LT_3 administration that were seen over a 9-hour period after T_3 administration (545), currently no formal pharmacokinetic study has been published. Presumably, once in the circulation as T_3, the persistence of T_3 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 T_3 levels after administration of a single dose of T_3 sulfate to hypothyroid patients was recently published (546).

A recent double-blind randomized cross-over study demonstrated that LT_3 can achieve an equivalent degree of serum TSH suppression as compared to LT_4 at a ratio (μg/μg) of 1:3 when administered as a thrice-daily regimen (348). With this regimen the serum levels of T_3 were significantly higher, albeit within the reference range, than the ones achieved with LT_4 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 LT_4; 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 LT_3, 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 LT_4 therapy. These investigators subsequently reported performing TRH stimulation in these patients and noted that serum TSH responses were similar in the LT_3 and LT_4 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 LT_3 for LT_4 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 cross-over treat-to-target LT_3 versus LT_4 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, LT_3 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 T_3.

The LT_3-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 LT_4 therapy, particularly because of the risk of over- or underdosing, 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 LT_3-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 LT_3-only therapy is cost-effective relative to the standard of care represented by LT_4. Furthermore, one can predict that this therapeutic modality will require more monitoring and presumably will be associated with longer periods of undertreatment or overtreatment as compared to LT_4 therapy.

Although not recommended, if used, the following common sense recommendations to monitoring might apply. LT_3-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 T_3 levels in the morning (trough) and 2 hours after the administration of the dose (peak), aiming to maintain the values within the reference range; serum FT_4 assessment is of no value in this scenario.

At the present time there is insufficient evidence to suggest that LT_3-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 T_3 become available.

Liothyronine 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 nonrandomized 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 T_3-mediated genomic as well as nongenomic actions at the cellular level

(547), the role for LT_3 in optimizing TH replacement therapy has not been clearly elucidated (534,548–550). With increased recognition of the biologic importance of T_3 at the cellular level, and the concerns that biochemical euthyroidism may not equate to tissue euthyroidism, there has been an increasing dialogue regarding whether LT_3 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 LT_3 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 antidepressant 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 LT_3 is based on observations of T_3-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.* (554) of patients with major depressive disorder, LT_3 augmentation was associated with a twofold greater likelihood of response to tricyclic antidepressant (TCA) therapy in 292 patients with a previous history of treatment-resistant depression. Altshuler *et al.* (555) reported results of a meta-analysis of six studies examining the use of LT_3 to accelerate the effect of TCA with five of six studies showing greater effect of combined therapy with LT_3 over placebo, with the most pronounced impact found in studies that had larger cohorts of women. More recently, Cooper-Kazaz and Lerer (551) reviewed the literature on combined LT_3 and serotonin re-uptake inhibitors (SSRIs). A total of eight studies were compared; five RCTs, of which three were enhancement studies and two were augmentation studies, and three additional open augmentation studies in which LT_3 was added after failure of SSRI-only therapy. Of the three enhancement studies, one showed weak support for acceleration by LT_3 of the therapeutic efficacy of SSRIs, and in two, no acceleration was found. In the five augmentation studies, including the STAR*D study comparing LT_3 augmentation to lithium augmentation (556), the use of LT_3 augmentation was associated with an overall remission rate between 25% and 36%. For all studies combined there were very few side effects associated with the addition of LT_3 up to 50 μg/d (551). The authors conclude that while there is evidence to support the clinical efficacy of LT_3 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 LT_3 initiation, and length of treatment (551). The practice guideline of the American Psychiatric Association describes the use of LT_3 in its document about treatment of major depression, but does not have a specific recommendation addressing its use (557).

If LT_3 therapy is in fact beneficial, it is possible that this may be due to pharmacological rather than physiological effects of T_3. Nevertheless, it may occur that a psychiatrist is using adjunctive oral LT_3 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 FT_4, T_3, and TSH levels should also be monitored, recognizing that the T_3 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

LT_3 has also been considered as a potential therapy to prevent the cardiovascular morbidity and mortality associated with obesity. Efforts to use LT_3 are based on studies showing decreased serum T_3 with subsequent decreased basal metabolic rate in obese subjects placed on calorie-restricted diets (447,558). In hypothyroid patients, when LT_3 is administered thrice daily, dosed to achieve a target TSH of 0.5–1.5 mIU/L, LT_3 treatment is associated with decreased body weight, with an average weight loss of -1.8 ± 1.9 kg, as well as reduced total cholesterol, LDL, non-HDL, and apolipoprotein B when compared to LT_4 therapy in the same individual (347). There have been multiple studies on the potential efficacy of LT_3 in euthyroid obese subjects, summarized in a systematic review by Kaptein *et al.* (447). In 13 of 14 studies, LT_3 was the exclusive therapy, with LT_4/LT_3 used in the additional study. Unfortunately, there was wide variation in study design with no clear association between LT_3 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; that is, whether LT_3 therapy during caloric deprivation enhances fat loss without loss of muscle mass or strength. In addition, there was evidence showing LT_3 therapy induced subclinical hyperthyroidism based on lower FT_4 and TSH levels. No study performed TRH stimulation to more fully evaluate the impact of the LT_3 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 concerning issues 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 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 (559). The FDA does recognize the critical role of individual states in supervising and regulating pharmacists and pharmacies that perform compounding of 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).

T_4, T_3, thyroid extract, and combinations of these preparations have each been compounded. However, there are very few published studies regarding use of compounded THs for treatment of hypothyroidism that meet scientific criteria for rigorous peer review. One article published by a specific pharmacy owner lists suggested formulae for achieving a 11:1 ratio of T_4:T_3 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 LT_4 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 their 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 T_4 and T_3 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 TH compounding have occurred and have resulted in severe thyrotoxicosis (563).

Unfortunately placebo-controlled comparative studies of compounded THs 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 TH in each preparation.

A general statement regarding the comparison of costs to the patient for a compounded TH 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 LT_4 soft gel capsules. The use of a nonexcipient gel capsule would be preferable to the use of compounded LT_4.

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 nontobacco 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: (i) nutrient content (such as ''high in calcium''); (ii) structure-function or nutrition support (for example, ''vitamin C prevents scurvy'' or ''calcium builds strong bones''), and (iii) 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 TH 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 T_4 and T_3 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 anti-thyroid 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 μg daily) is required for normal thyroid function in euthyroid nonpregnant 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 T_4 and T_3, 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 TH (patient advised to discontinue use).'' Commercially available supplements sold for ''thyroid health'' or ''thyroid support'' may also contain measurable amounts of T_4 and T_3, 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 TH 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 LT_4 absorption. Sathyapalan *et al.* (572) performed a double-blind cross-over 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 TH analogs that can be purchased over the internet to enhance thyroid function is a very controversial area. TRIAC is a naturally occurring metabolite of LT_4 that has significant metabolic action. It can bind to the T_3 receptor and it can decrease TSH secretion. It may have a role in managing cases of resistance to TH (573). However, TRIAC administration in pharmacologic doses can cause toxicity like that caused by TH (574–578). Although TRIAC has effects similar to TH (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 LT_4 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 two 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 are not enough data to resolve clinical disagreement among 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 TH 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 or 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 TH 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 RCT 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 LT_4/LT_3 combination therapy for hypothyroidism as described in the literature review for recommendations 13b and 13c and Table 7. 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 TH therapy remain divided over T_4 monotherapy and LT_4/LT_3 combination therapy and even formulations of T_4. 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 TH 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 health care 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) versus 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 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 institutional review board (IRB)-approved study; most fall into the category of innovative therapy, which in the TH context is sometimes called ''individualized'' combination therapy. Innovative therapy refers to a nonstandard or even experimental therapy designed to optimize beneficent care for one individual patient and 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 cross-over 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 in which 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 T_3 therapy advocated for ''Wilson's syndrome'' has never been evaluated objectively in a properly designed scientific study. Furthermore, administration of T_3 can produce abnormally high concentrations of T_3 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 Doctor's Manual (587). In addition, the posting from Wikipedia, the free encyclopedia,

was also reviewed to determine what information the public has access to (590). 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 T_3 from 7.5 μg twice daily by 15 μg increments. A patient taking 7.5 μg T_3 twice a day and increasing the dose by 15 μg every day could potentially suffer serious iatrogenic T_3 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 T_3 therapy, including an in-house trial of T_3 therapy for chronic fatigue syndrome. It also quoted an uncontrolled trial of T_3 therapy in individuals with persistent symptoms while taking LT_4 performed prior to the availability of TSH monitoring (591). See also recommendation 16 for a discussion of compounded THs 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 thyrotropin measurement?

■ **RECOMMENDATION**

In hospitalized patients with a pre-established diagnosis of hypothyroidism who are found to have an elevated thyrotropin measurement, consideration should be given to institution or adjustment of levothyroxine replacement. Factors such as the degree of clinical and biochemical hypothyroidism, active comorbidities, 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 thyrotropin?

■ **RECOMMENDATION**

The therapeutic goal of levothyroxine replacement in non-critically ill patients is long-term normalization of serum thyrotropin when steady-state thyroid hormone levels are achieved. We do not recommend titrating the levothyroxine dose to serum free thyroxine levels unless serum thyrotropin 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; for example, omission of doses of LT_4 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 pre-existing hypothyroidism develops a separate critical illness. The nonthyroidal illness syndrome (NTIS) (also known as the sick euthyroid syndrome or the low T_3 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 T_3 decreases, followed by declines in serum TSH and/or T_4, and then declines in FT_4 in some sicker patients (592,593). In current practice, these patients are not treated with TH replacement (see recommendation 22 regarding NTIS).

In contrast, patients with established hypothyroidism are maintained on TH when they become critically ill, even though they too may exhibit the physiologic changes of 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 TH deficiency, and TH 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. LT_4 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 PPIs and specialized tube feedings. If using intravenous LT_4, the equivalent intravenous dose is approximately 75%, assuming the enteral LT_4 dose had achieved euthyroidism.

It should be noted that increased LT_4 replacement therapy may lead to TSH normalization without normalization of T_3 (594), presumably due to accelerated metabolism of T_3. However, as the NTIS is considered adaptive, logic dictates that ''correction'' of the low T_3 may not be an appropriate goal of replacement, even for patients with a known history of hypothyroidism being maintained on LT_4. Indeed, using LT_3 for replacement is problematic because the appropriate target range for serum T_3 is not defined in this setting; furthermore, high doses of T_3 have been linked to adverse outcomes (595). High-quality randomized placebo controlled trials of various TH 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 nonthyroidal 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 TH (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 200–400 μg of levothyroxine may be given, with lower doses given for smaller or older patients and those with a history of coronary disease or arrhythmia. A daily replacement dose of 1.6 μg/kg body weight, reduced to 75% as long as it is 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 5–20 μg can be given, followed by a maintenance dose of 2.5–10 μg every 8 hours, with lower doses chosen for smaller or 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 TH 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 TH therapy should be instituted, or increased if a patient is already receiving treatment. LT_4 should be given initially. LT_3 can be given as well, though case series suggest that higher doses of LT_3 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 TH, 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 nonthyroidal 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 T_4 to T_3 conversion become relevant, and replacement with LT_3 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 TH replacement for myxedema coma should be LT_4 given intravenously. A loading dose of 200–400 μg of LT_4 may be given, with lower doses given for smaller or older patients and those with a history of coronary disease or arrhythmia. A daily replacement dose of 1.6 μg/kg body weight, reduced to 75% as long as it is 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 μg intravenous LT_4 daily showed normalization of TH 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 T_4 and T_3 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; for example, 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, FT_4 or T_4, and T_3 in patients being treated for myxedema coma could provide supportive evidence that the therapy is working and could ensure that very high levels of T_3 are avoided. In addition, checking the serum T_4 and T_3 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, LT_4 could be increased and/or LT_3 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 T_4 conversion to T_3 may be decreased in patients with myxedema coma, intravenous LT_3 may be given in addition to LT_4. High doses should be avoided given their association with mortality (595). A loading dose of 5–20 μg can be given, followed by a maintenance dose of 2.5–10 μg every 8 hours, with lower doses chosen for smaller or older patients and those with a history of coronary artery disease or arrhythmia. If intravenous therapy with LT_3 is initiated, there are no data addressing optimum duration of such therapy. However, it would seem reasonable to continue intravenous therapy with LT_3 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 LT_3 monotherapy administered at doses of either 25 or 50 μg daily in hypothyroid patients with serum TSH values in the range of 68–81 mIU/L lead to normalization of various cardiovascular, pulmonary, and metabolic parameters within a week (605). TSH values decreased significantly within the same time period, although less so than the TSH response to intravenous LT_4 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 TH 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 Triiodothyronine Concentrations in Hospitalized Patients

22a. In hospitalized adult patients exhibiting the "nonthyroidal 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 nonthyroidal 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 "nonthyroidal 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 nonthyroidal 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 TH binding, alteration in TH uptake by cells, decreased T_4 to T_3 conversion due to the effects of endogenous circulating cortisol, cytokines, free fatty acids, and various drugs on D1. There may also be increased T_3 catabolism due to changes in the deiodinases, namely D3, in peripheral tissues. All these effects lead to low circulating T_3 levels. As illness becomes more prolonged, superimposed upon these changes is central suppression of the hypothalamic pituitary axis, with decreases in circulating TSH and T_4.

While decreased T_4 to T_3 conversion has been posited as an etiologic cause of the NTIS, more recent data suggest that increased T_3 catabolism because of ectopically up-regulated D3 in tissues such as liver, skeletal muscle, and heart has a greater impact in lowering T_3 (26). Studies in animal models have linked D3 induction to hypoxia, with direct up-regulation of the D3 gene by hypoxia-inducible factor 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 THs 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 T_4 to T_3 conversion would be expected to increase the local supply of T_3, thus decreasing TRH and TSH production rates (627). An increase in D2-mediated T_4 to T_3 conversion would be expected to increase the supply of T_3 to important regulatory centers in the brain controlling the thyroid axis.

The extent to which central hypothyroidism, versus reduced D1 activity, and increased D3-mediated clearance in peripheral tissues cause 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 NTIS will not be possible without further studies of the effects of illness-related cytokine fluxes on TH 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 T_3 is observed, followed by decreases in serum T_4 and TSH if the clinical course does not improve. This stereotypic pattern, known as NTIS or alternatively ''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 TH replacement.

Data from RCTs 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 LT_3, and one study showed increased mortality with LT_4 therapy in patients with acute renal failure (629). On the other hand, lower doses of LT_3 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 TH replacement, and accept as dogma that NTIS is an adaptive process.

In order to evaluate whether hospitalized patients in the ICU with NTIS should be treated with LT_4 or LT_3, we first had to define which group of patients should be included. Given that our focus is adult patients in the ICU, 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 perioperative (cardiac surgery) LT_3 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 LT_3 therapy in this clinical setting (28,356,447, 624,631–636).

Kaptein *et al.* (447) have performed comprehensive reviews of this subject, published in 2009. They also performed a review of the postoperative literature in 2010 (632). They excluded studies that examined patients less than 18 years of age [except for Brent and Hershman (637)], studies of perioperative patients, studies with before and during study design, and studies of TH use for less than 24 hours. They also excluded studies for ''data not extractable or end-points not included'' as well (discussed later). Thus the results of seven RCTs (629,637–642), the most recent of which was published in 2004 were included. Five of the studies utilized LT_4 (629,637,639–641), and two utilized LT_3 (638,642) (see Table 9). PubMed search of the literature revealed no relevant studies published since the Kaptein review.

Therefore, recommendation 22b regarding the use of LT_3 in critically ill subjects is based on only two published studies identified by Kaptein and colleagues (447). Becker *et al.* (638) studied burn patients (14 controls, 14 treated) in 1982, with the finding that 200 μg oral LT_3 did not alter mortality (four 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 μg LT_3 or placebo daily orally for 7 days prior to coronary artery bypass surgery and continued therapy until discharge. T_3 levels were higher in the treated group before surgery and after (but were

Table 9. Characteristics of Randomized Controlled Trials Comparing ''Clinical Endpoints'' in Hospitalized Patients Treated with Either LT_3 or LT_4

Reference	*Treatment dosing*	*Patient population*	*Design*	*No. of patients randomized*
638	T_3: 200 μg/d Dosing: once daily	Burn patients	Parallel, blinded	28
637	T_4: 1.5 μg/kg Dosing: once daily	Mixed ICU patients	Parallel, unblinded	23
640	T_4: 100 μg/d Dosing: once daily	Cardiomyopathy	Parallel, blinded	20
639	T_4: 100 μg/d Dosing: once daily	Cardiomyopathy	Parallel, blinded	20
644	T_4: 150 μg/d Dosing: twice daily	Acute renal failure	Parallel, blinded	59
641	T_4: 50 μg/d Dosing: once daily	CHF III/IV	Parallel, unblinded	28
642	T_3: 125 μg/d versus placebo	Cardiac surgery patients	Parallel, blinded	80

CHF, congestive heart failure; ICU, intensive care unit.

similar during cardiopulmonary bypass). Inotropic requirements were decreased in the T_3 group. Length of ICU stay was decreased in the T_3 group. Three patients died in each group. Atrial fibrillation was not increased in the T_3 group. Morbidity and mortality were otherwise unaffected.

One notable study by Pingitore and colleagues (643) published in 2008 was excluded by the Kaptein *et al.* (447) analysis for ''data not extractable.'' The endpoints were hemodynamic and neurohormonal testing. This trial (10 control, 10 T_3 treated) employed intravenous infusion of LT_3 for 3 days such that levels were higher than normal on day 1, then normal. No adverse outcomes were reported with T_3. It should be noted that studies with LT_3 administration <24 hours were omitted from the analysis by Kaptein *et al.*, as were patients treated with LT_3 in the perioperative period (in subjects who may or may not have had NTIS). However, these studies are, nevertheless, cited by other authors to support the potential safety of short-term LT_3 replacement. For example, Acker *et al.* (644) studied patients with delayed graft function in cadaveric renal transplantation, finding the intravenous infusion of LT_3 (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.

De Groot's review (624) suggests that if LT_3 therapy is to be initiated, it should be at a ''replacement dose'' of approximately 50 μg/d in divided doses. This is much lower than used in the two trials previously mentioned (638,642). The review also suggests that T_3 be followed and adjusted such that it is ''at least low normal'' before the next scheduled dose. De Groot (624) also advocates starting LT_4, though no data for use of combination therapy in this situation could be identified. Interestingly, one *postmortem* study analyzing 31 patients that had died in the ICU and had been treated with 150 μg T_4 and 0.6 μg T_3/kg daily compared to 48 patients that had not been treated with THs, provided clear evidence for tissue specific regulation of tissue T_4 and T_3 concentrations in critical illness (645). Patients treated with T_4 and T_3 had approximately 1.5 times higher levels of serum and muscle T_3, whereas liver T_3 concentrations were more than 4 times higher in patients receiving T_4 and T_3 therapy. However, this study did not address any potential benefits of TH use because 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 T_3 alterations on cardiac output, contractility, vascular resistance, and blood pressure, as well as cholesterol metabolism (646). On a cellular level, similar to other tissues, T_3 has both genomic and nongenomic effects on the cardiac myocyte. However, cardiac cells may be more reliant on adequate serum T_3 levels for normal function based on data suggesting decreased transport of T_4 into the cardiac myocyte (647). The role of T_3 in cardiovascular disease is highlighted by NTIS in which the physiologic response to illnesses such as heart failure are characterized by a decrease in total and free T_3 with normal T_4 and TSH levels. NTIS is typically considered an adaptive response; however, there is continued discussion over whether LT_3 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.* (648) reported on the safety of short-term LT_3 infusion in 23 patients with advanced heart failure showing that administration of LT_3 (cumulative dose 0.15–2.7 μg/kg) was well tolerated with no significant change in heart rate, metabolic rate, or core temperature. In addition, the LT_3 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.* (643) reported a similar positive effect of LT_3 on cardiac function in 20 patients with dilated cardiomyopathy. At a starting dose of 20 $\mu g/m^2$, adjusted to obtain a normal serum T_3 level, LT_3 infusion for a 3-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 LT_3 therapy (643), but cardiovascular outcomes with longer-term therapy are needed. While these studies are encouraging (649), the question remains whether serum T_3 may be better considered as a marker of disease status rather than a focus of therapy. The recent study by D'Aloia *et al.* (650) highlights this consideration where short-term dobutamine therapy resulted in statistically improved cardiac status associated with reduced brain natriuretic peptide reduction and increased FT_3 levels.

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 preclinical 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

T_3 exerts its genomic effects via binding to its nuclear 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, TRα and TRβ, encoded by separate genes. TR mRNAs can be alternatively spliced; in humans, three main splice variants are found, namely TRα1, TRα2, and TRβ2. 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, TRβ is the prevalent isoform in the liver and pituitary, whereas TRα is predominant in the heart, brain, and the skeleton. Thyroid hormone analogs may have significantly greater affinity for TRβ than TRα, in the order of 22-fold greater for eprotirome (651), 10-fold greater for sobetirome (652), 14- to 15-fold greater for KB141 (653) and MB07344 (654), and 40-fold greater for GC-24 (655). The various TH analogs, their relative selectivity for the TRβ, and potential uses based on this selectivity are shown in Table 10.

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 T_3 excess can be isolated pharmacologically, while avoiding unwanted effects. For example, given the predominance of TRβ in the liver, it has been postulated that selective TRβ agonist drugs could be used to lower cholesterol without the adverse TRα-driven cardiac and skeletal effects that would be seen with pharmacologic T_3 administration. Animal studies using TRβ agonists have verified that this strategy is indeed possible (657–659). Furthermore, preclinical studies show that highly TRβ-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 T_3. For example, bindings studies suggest that TRIAC exhibits ~3.5-fold greater affinity for TRβ and ~1.5-fold greater affinity for TRα compared to T_3 (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 T_3 (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 TRα and TRβ with similar affinity (664). Studies of DITPA in animals have shown 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 postischemic cardiac function showed

TABLE 10. THE SELECTIVITY AND POTENTIAL USES OF THYROID HORMONE ANALOGS

Analog	*Selectivity for TRβ (compared with TRα)*	*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- to 3-fold greater	RTH
Tetrac	Metabolized to TRIAC	RTH
CO23	TRβ vs. TRα selectivity not seen in rodents	Effects on behavior (if TRα-selective)

DIPTA, 3,5-diiodothyropropionic acid; RTH, resistance to thyroid hormone; TRα, thyroid hormone receptor α; TRβ, thyroid hormone receptor β; TRIAC, 3,5,3′-triiodothyroacetic acid or tiratricol.

an increased incidence of arrhythmias during ischemia and reperfusion with the use of DITPA (667).

Discussion of the clinical literature

A number of TH 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 TRβ-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 TH 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 TRβ agonist that currently has an active investigational new drug status. A clinical trial started at Oregon Health Sciences University in the fall of 2012 (NCT01787578) in patients with X-linked adrenoleukodystrophy based on preclinical data indicating that T_3 or TRβ agonists up-regulate the gene *ABCD2*; up-regulation 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 LDL 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 FT_4 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 TH 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 TRα signaling, while minimizing the symptoms caused by deficient TRβ 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

RTH (OMIM identifier # 188570) (677) is a rare genetic disease characterized by increased serum levels of THs and inappropriately normal or increased TSH (678). RTH is caused by inactivating mutations in TRα (RTHα) or TRβ (RTHβ). Patients with RTHα have normal levels of TSH in combination with a low FT_4 and high T_3 and suffer from local hypothyroidism in tissues that predominantly express TRα (376,377). Patients with RTHβ have normal or elevated levels of TSH despite elevated levels of FT_4 and FT_3. Symptoms in these latter patients are due to a combination of low TH action in predominantly TRβ-expressing tissues and TH overexposure in TRα-expressing tissues (378,379).

The majority of RTH forms are caused by autosomal dominant mutations in the TRβ 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 TRβ have been described to date. These mutations may be associated with impaired ability to bind T_3, and/or may prevent the normal TR-mediated gene transactivation. The mutant TRβ/corepressor complexes remain bound to the T_3-responsive genes and transcriptional repression cannot be lifted by the presence of T_3. Thus, mutant TRβ molecules exhibit a ''dominant negative'' effect.

TRβ 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 T_4 and T_3. In effect, RTH patients exhibit unbalanced hormonal signaling due to the combination of defective TRβ

and otherwise normal TRα receptors exposed to supraphysiologic levels of TH. The result is a mix of hyperthyroid symptoms and signs arising from organs enriched with the TRα 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 TH analog with a preference for TRβ might be useful in treatment of RTH patients, since it would normalize TSH and lower TH production, while normalizing TH signaling directly in TRβ dominant tissues. Treatment with TRIAC, which has a higher affinity for TRβ than for TRα 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 β-blockers to minimize symptoms of hyperthyroidism arising from TRα dominant tissues such as tachycardia and tremor; in TRβ-dominant tissues, the excess TH is balanced for the most part by the relative insensitivity of the mutant TRβ. Quite often, RTH patients are erroneously diagnosed as thyrotoxic and treated with radioablation or thyroid surgery (684). In such cases, use of LT_4 therapy requires supraphysiological dosing if TRβ-dominant tissues are to be made ''euthyroid.'' However, this will potentially lead to hyperthyroidism in the TRα-dominant tissues (685). Thus, LT_4 can be combined with β-blockers to prevent TRα-related cardiac symptoms (380). Treatment must be individualized, and no target TH 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 LT_3 suppression test (Werner's test) as a diagnostic dynamic test to distinguish between RTH and TSH-producing adenomas, LT_3 is generally not considered part of therapy, although it has been employed as a treatment modality for children with RTH 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 LT_4 coupled with cardiac-selective β-blockers. Although not currently tested in humans, TRβ-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 T_3 may also optimize therapy. However, current exogenous therapies do not reproduce endogenous serum T_4 excursions or serum T_3 rhythms.

It has been clearly established that LT_4 therapy results in a higher serum T_4/T_3 ratio than is observed in the nonathyreotic state. It is not known whether there is a detrimental effect of this abnormal serum T_4/T_3 ratio. For example, because T_4 is a primary inhibitor of D2 activity, does excessive circulating T_4 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 T_3 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 subpopulations, is that the biologic activity of serum TSH is not always concordant with its measured concentrations. Of particular note, the questions 7a–7c raised by task force members, which relate to the significance of serum T_3 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 T_3 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 T_3 is not necessarily accompanied by a normal T_3 concentration in all tissues. The ability of tissue T_3 to mirror serum T_3 is dependent on the particular tissue's complement of deiodinases. Gene profiling can demonstrate the genomic actions of TH within particular tissues. However, commercially available tests to indicate tissue status in humans are not available.

If the premise that LT_4 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 3 months no longer showed maintenance of this benefit at 12 months. This is an important consideration given that TH therapy is generally lifelong. It is interesting that, assuming trials of combination therapy have been driven by a concern about low serum T_3 levels, the serum T_3 response has not been rigorously assessed in many trials, and restoration of serum T_3 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 TH signaling elements, or those with disproportionately lower serum T_3 levels while taking LT_4 monotherapy. If *N*-of-1 trials were being considered these might also logically be conducted in those with low or low-

normal serum T_3 concentrations. It is also possible that trials of once or twice daily LT_3 therapy added to LT_4 monotherapy have not had more positive outcomes because of the non-physiologic nature of the LT_3 dosing. A sustained release preparation, or even a preparation with a new delivery system that mimics the normal diurnal rhythm of serum T_4 and T_3, may be necessary in order to reveal a benefit. Large, prospective, long-term studies examining clinically significant outcomes are needed to clarify the optimal formulation or combination of formulations of TH 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 TH 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 for more precise quantitative instruments; they also help 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 TH 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 LT_4 therapy
3) Better understanding of maternal-fetal physiology during pregnancy with development of improved titration of LT_4 therapy in hypothyroid pregnant patients
4) Further studies of soft gel LT_4 capsules to determine their proper place in the therapeutic armamentarium
5) Further study, and improved standardization, of compounded formulations of LT_4 and/or LT_3
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 T_3 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 T_3 concentrations
9) Research into the relationship between serum T_3 and T_3 concentrations in specific tissues
10) Development of more accurate assays to measure serum concentrations of FT_3, total T_3, and FT_4
11) Development of a sustained release T_3 preparation that can then be prospectively tested in clinical trials (e.g., in combination with LT_4 in a physiologic ratio of about 14:1)
12) In the absence of the availability of a sustained release T_3 preparation, study of when, if ever, the use of LT_3 would be beneficial in selected patients with apparent decreased T_4 to T_3 conversion and disproportionately low serum T_3 levels
13) Long-term outcome research using thyroid extracts that includes documentation of the consequences of excursions in serum T_3 concentrations
14) Development of TH 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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Abbreviations Used

$3,5\text{-}T_2$ = 3,5-Diiodothyronine
AACE = American Association of Clinical Endocrinologists
ACE = Angiotensin-converting enzyme
ACP = American College of Physicians
AITD = Autoimmune thyroid disease
ATA = American Thyroid Association
AUC = Area under the curve
BMI = Body mass index
CAD = Coronary artery disease
CH = Congenital hypothyroidism
Cmax = Maximum concentration
D1 = Deiodinase type 1
D2 = Deiodinase type 2
D3 = Deiodinase type 3
DIO1 = Deiodinase type 1 gene
DIO2 = Deiodinase type 2 gene
DIO3 = Deiodinase type 3 gene
DITPA = 3,5-Diiodothyropropionic acid
ETA = European Thyroid Association
FDA = U.S. Food and Drug Administration
FT_3 = Free triiodothyronine
FT_4 = Free thyroxine
GH = Growth hormone
GHQ = General Health Questionnaire
GWAS = Genome-wide association studies
HDL = High-density lipoprotein
ICU = Intensive care unit
IRB = Institutional review board
LC/MS/MS = Liquid chromatography–tandem mass spectrometry
LDL = Low-density lipoprotein
LT_3 = Liothyronine

Abbreviations Used (Cont.)

LT_4 = Levothyroxine
MCT = Monocarboxylate transporter
NTIS = Nonthyroidal illness syndrome
OATP = Organic anion transporting polypeptide
OH = Overt hypothyroidism
PPI = Proton pump inhibitor
PTU = Propylthiouracil
RCR = Responsible conduct of research
RCT = Randomized controlled trial
rT_3 = Reverse triiodothyronine
RTH = Resistance to thyroid hormone
RTHα = Syndrome of resistance to thyroid hormone with mutation in TRα
RTHβ = Syndrome of resistance to thyroid hormone with mutation in TRβ
SCH = Subclinical hypothyroidism
SHBG = Sex hormone binding globulin
SNPs = Single nucleotide polymorphisms
SSRIs = Serotonin re-uptake inhibitors
T_3 = Triiodothyronine
T_4 = Thyroxine
TBG = Thyroxine binding globulin
TCA = Tricyclic antidepressant
TH = Thyroid hormone
TPOAb = Thyroid peroxidase antibodies
TR = Thyroid hormone receptor
TRH = Thyrotropin-releasing hormone
TRIAC = 3,5,3′-triiodothyroacetic acid
TRα = Thyroid hormone receptor-α
TRβ = Thyroid hormone receptor-β
TSH = Thyrotropin
USP = United States Pharmacopeia