

Treatment With Thyroid Hormone

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Thyroid hormone deficiency can have important repercussions. Treatment with thyroid hormone in replacement doses is essential in patients with hypothyroidism. In this review, we critically discuss the thyroid hormone formulations that are available and approaches to correct replacement therapy with thyroid hormone in primary and central hypothyroidism in different periods of life such as pregnancy, birth, infancy, childhood, and adolescence as well as in adult patients, the elderly, and in patients with comorbidities. Despite the frequent and long term use of L-T₄, several studies have documented frequent under- and overtreatment during replacement therapy in hypothyroid patients. We assess the factors determining L-T₄ requirements (sex, age, gender, menstrual status, body weight, and lean body mass), the major causes of failure to achieve optimal serum TSH levels in undertreated patients (poor patient compliance, timing of L-T₄ administration, interferences with absorption, gastrointestinal diseases, and drugs), and the adverse consequences of unintentional TSH suppression in overtreated patients. Opinions differ regarding the treatment of mild thyroid hormone deficiency, and we examine the recent evidence favoring treatment of this condition. New data suggesting that combined therapy with T₃ and T₄ could be indicated in some patients with hypothyroidism are assessed, and the indications for TSH suppression with L-T₄ in patients with euthyroid multinodular goiter and in those with differentiated thyroid cancer are reviewed. Lastly, we address the potential use of thyroid hormones or their analogs in obese patients and in severe cardiac diseases, dyslipidemia, and nonthyroidal illnesses. (*Endocrine Reviews* 35: 433–512, 2014)

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Abbreviations: AACE, American Association of Clinical Endocrinologists; AAP, American Academy of Pediatrics; AF, atrial fibrillation; APS, autoimmune polyglandular syndrome; ATA, American Thyroid Association; AUC, area under the curve; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CH, central hypothyroidism; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CoH, congenital hypothyroidism; D1, deiodinase type 1; D2, deiodinase type 2; D3, deiodinase type 3; DITPA, 3,5-diiodothyropropionic acid; DTC, differentiated thyroid cancer; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EndoSHyper, endogenous subclinical hyperthyroidism; ES, Endocrine Society; ETA, European Thyroid Association; ExoSHyper, exogenous subclinical hyperthyroidism; FT₄, free T₄; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; IQ, intelligence quotient; LDL, low-density lipoprotein; LV, left ventricular; MC, myxedema coma; MCT8, monocarboxylase transporter 8; MI, myocardial infarction; MNG, multinodular goiter; NHANES, National Health and Nutrition Survey; OR, odds ratio; PTC, papillary thyroid cancer; QOL, quality of life; RCT, randomized controlled trial; rhGH, recombinant GH; RR, relative risk; SHypo, subclinical hypothyroidism; SVR, systemic vascular resistance; TBG, T₄-binding globulin; T1DM, type 1 diabetes mellitus; Tg, thyroglobulin; THST, thyroid hormone TSH suppression therapy; TKI, tyrosine kinase inhibitor; TPOAb, thyroid peroxidase antibody; TR, thyroid hormone receptor; TRIAC, 3,5,3'-triiodo-thyroacetic acid.

ISSN Print 0163-769X ISSN Online 1945-7189

Printed in U.S.A.

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Received July 27, 2013. Accepted December 3, 2013.

First Published Online January 16, 2014

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I. Introduction

Replacement therapy with thyroid hormone is indicated as a lifelong treatment when the diagnosis of persistent thyroid hormone deficiency is confirmed (1–3). L-T₄ is considered to be the treatment of choice in hypothyroid patients and has long been used in TSH-suppressive doses in patients with nontoxic uninodular or multinodular goiter (MNG) and differentiated thyroid cancer (DTC) to improve their prognosis (4).

L-T₄ represents one of the most commonly administered drugs in the world, and its use has been increasing in the last several years (5, 6). In a report by the IMS Institute of Healthcare Informatics, L-T₄ was listed as the second most prescribed drug in the United States with 104.7 mil-

lion prescriptions in 2011 (IMS Institute for Healthcare Informatics) (7).

Adequacy of L-T₄ treatment is generally monitored by measurements of serum T₄ and TSH. Although management of L-T₄ therapy has been considered relatively straightforward, several studies in the past 2 decades have indicated aspects of previously unrecognized complexity despite the improvement in TSH and thyroid hormone assays (4, 8–11). Epidemiological studies have reported that inadequate thyroid hormone replacement is present in over a third of L-T₄-treated hypothyroid patients (12–14) despite frequent biochemical monitoring (15, 16). Under- or overtreatment with L-T₄ leads to subclinical hypo- or hyperthyroidism, respectively (9, 10). These conditions may induce adverse clinical consequences, especially in regard to specific periods of life (8–11).

Consequently, new guidelines have clarified recommendations for replacement treatment with L-T₄ in patients with persistent overt and subclinical hypothyroidism (SHypo) (3), including specific suggestions in pregnant women (17–19) and in children with congenital hypothyroidism (CoH) (20–22). And more precise guidelines have been formulated for the degrees of TSH-suppressive therapy, with L-T₄ indicated in patients with benign and malignant thyroid nodules (23–25).

Controversy persists whether L-T₄ monotherapy is adequate or optimal in all patients because some hypothyroid patients may remain symptomatic despite biochemical euthyroidism during treatment with L-T₄ alone (26). As a consequence, several studies have suggested a rationale and potential indication for combined treatment with L-T₄ and L-T₃ in selected hypothyroid patients (27–31). Recent commentaries have reviewed and evaluated the potential role, limits, and adverse effects of this combination treatment (26, 32).

A final important point related to thyroid hormone therapy is the potential usefulness of thyroid hormone analogs for treatment of heart dysfunction and metabolic disorders, opening a new scenario for pioneering indications or modulating applications of replacement therapy with thyroid hormone (33–35). Given the continuing controversies in the management of replacement therapy with thyroid hormone and its importance for clinical endocrinologists, cardiologists, gynecologists, and pediatricians, the aim of this review is to update advances in this treatment with all of its implications, limits, and adverse effects as well as potential future indications.

II. Methods

A. Identification of sources

We searched personal files, MEDLINE articles, meta-analyses, and references of relevant articles and textbooks

27 published from 1968 to 2013, as well as citations from recently published international guidelines. Although the primary focus was on articles in English, selected relevant translated articles were also included. Some pre-1968 reports of studies were also included absent more recent information on a given issue. The following search terms were used: L-thyroxine, L-triiodothyronine, thyroid hormone analogs, hypothyroidism, subclinical thyroid disease, replacement therapy, thyroid hormone TSH suppression therapy (TSHT), pregnancy, children, adolescents, elderly, CoH, central hypothyroidism (CH), and myxedema coma (MC).

B. Methods of evaluation

A critical assessment of the literature was performed. The 2 authors agreed on criteria for the inclusion or exclusion of the studies considered. Preference was given to high-quality papers, randomized controlled trials (RCTs), longitudinal trials, and studies that appeared to have been performed with correct statistical analysis and accurate methods. When identified, shortcomings or limitations in study design or execution are described.

III. Hypothyroidism

A. Definition

Hypothyroidism is a pathological condition in which there is an insufficient production of thyroid hormones. Pri-

mary hypothyroidism caused by underactivity of the thyroid gland accounts for perhaps 99% of cases of hypothyroidism (9, 10, 36). Secondary hypothyroidism, also known as CH, is due to insufficient stimulation of a normal thyroid gland due to a deficiency in TSH as a result of hypothalamic or pituitary disease (37, 38). CH is characterized by low thyroid hormone levels and inappropriately low-normal or slightly elevated serum TSH. It is estimated that less than 1% of cases of hypothyroidism are due to TSH deficiency.

Hypothyroidism can be further categorized on the basis of its time of onset, eg, congenital or acquired, and on the basis of its severity, as in overt, subclinical, and mild disease (Table 1).

Traditionally, the term myxedema is reserved for severe and/or complicated thyroid hormone deficiency in adult patients; the term is also used to indicate a nonpitting edema caused by the accumulation of glycosaminoglycans in sc and interstitial tissues (3, 39, 40). On the other hand, cretinism refers to the complex severe syndrome of thyroid hormone deficiency (mental retardation, short stature, facial deformities, deafness, etc.) occurring in untreated CoH (41).

Overt hypothyroidism is a clinical condition in which TSH is increased and free thyroid hormones (especially free T_4 [FT₄]) are low (36). SHypo is present when TSH is above the upper limit of the normal reference range and free thyroid hormones are within their reference range (9, 10). Patients with SHypo are often classified into 2 groups:

Table 1. Definition of Primary and Secondary Hypothyroidism According to Age and Physiological Conditions

| Condition | Definition |
|---|--|
| In adult patients | |
| Primary overt hypothyroidism | TSH >10 mU/L with low FT ₄ concentration |
| Severe hypothyroidism | TSH >10 mU/L with low FT ₄ and FT ₃ concentrations |
| SHypo | |
| Severe SHypo | TSH levels ≥10 mU/L with normal FT ₄ concentrations |
| Mild SHypo | TSH levels 4.5–9.9 mU/L with normal FT ₄ concentrations |
| Mild SHypo in elderly patients | TSH levels >7.0 mU/L with normal FT ₄ concentrations |
| In CH | Low serum TSH and low thyroid hormones |
| In pregnant women | |
| Overt hypothyroidism | Serum TSH >2.5 mU/L with decreased FT ₄ concentrations during the first trimester of pregnancy |
| | Serum TSH >3 mU/L with decreased FT ₄ concentrations during the second and third trimester of pregnancy |
| | Serum TSH >10 mU/L irrespective of FT ₄ concentrations |
| SHypo | Serum TSH 2.5–10 mU/L with normal FT ₄ concentrations |
| Maternal isolated hypothyroxinemia | Normal TSH concentration with FT ₄ concentrations in the lower 5th or 10th percentile of the reference range. |
| In CoH | |
| Suspicious CoH at first screening program | T ₄ below the 10th percentile and/or TSH >30 mU/L |
| Confirmatory serum thyroid testing | |
| Primary hypothyroidism | TSH level >9 mU/L and free T ₄ <0.6 ng/dL |
| SHypo | TSH level >9 mU/L and normal free T ₄ (0.9–2.3 ng/dL) |
| CoH | TSH level <9 mU/L and free T ₄ <0.6 ng/dL |
| Persistent hyperthyrotropinemia | Moderate TSH increase (5–10 mU/L) during follow-up |
| Transient CoH | Normal thyroid function and normal TSH after L-T ₄ withdrawal and during the subsequent follow-up |

those with mild SHypo in whom TSH is mildly increased (TSH 4.5–9.9 mU/L) and those with a more severe dysfunction when TSH is ≥ 10 mU/L (9, 10).

In the past few years, the definition of hypothyroidism and the target serum TSH for treatment of thyroid hormone deficiency have been modified by the results of assessments of normal thyroid function in important population-based studies (12, 42, 43) and by the opinion of experts regarding the upper limit of the normal serum TSH concentration (44–47). The National Health and Nutrition Survey (NHANES) III, a population-based study of a disease-free population in the United States, indicated that 95% of adult subjects have a serum TSH concentration within the range of 0.45 to 4.12 mU/L, after the exclusion of subjects with a personal or family history of thyroid disease and/or positive thyroid autoantibodies (42). However, TSH values did not have a Gaussian distribution because the curve was skewed by individuals with occult autoimmune thyroid dysfunction despite negative thyroid peroxidase antibodies (TPOAbs) and the inclusion of elderly patients (42). Similar findings were reported by the more recent Hanford Thyroid Disease Study in a cohort without evidence of thyroid disease, negative thyroid autoantibodies, and normal thyroid ultrasound examination (43). On the contrary, the National Academy of Clinical Biochemists in the United States indicates that 95% of individuals without evidence of thyroid disease will have TSH concentrations below 2.5 mU/L (46). This last opinion is supported by a recent meta-analysis that offered evidence for the association of high-normal serum TSH with negative cardiovascular and metabolic effects (48). This meta-analysis indicates that there is an increased risk of adverse cardiovascular outcomes (odds ratio [OR] = 1.21; 95% confidence interval [CI], 1.15–1.27) and of adverse metabolic outcomes (OR = 1.37; 95% CI, 1.27–1.48) in individuals with TSH levels in the upper part of the reference range than in subjects with TSH levels in the lower part of the reference range.

To further complicate the issue of what constitutes the normal TSH reference range, epidemiological studies have emphasized that age, ethnicity, body mass index (BMI), iodine intake, genetic and environmental factors, and some particular physiological and pathological conditions (pregnancy or illness) may also change serum TSH values (49–55). Genetic variants in the phosphodiesterase 8B gene and in the TSH receptor may also influence the set-point of the hypothalamic-pituitary-thyroid axis (56–58).

Serum TSH level is higher in white populations than in black ones, which suggests a genetic and ethnic/race influence (49). Several studies have indicated an age effect, with the 97.5th percentile of serum TSH noted to increase

by 0.3 mU/L every 10 years after the age of 30 to 39 years (49–51).

The reanalysis of NHANES III data 5 years later showed that the upper limit of normal serum TSH at the 97.5th percentile was approximately 3.5 mU/L in individuals 20 to 29 years old, 4.5 mU/L in people 50 to 59 years old, 5.9 mU/L in elderly subjects 70 to 79 years old, and 7.5 mU/L in those at 80 years and older (51). Therefore, it seems conceivable that a slightly increased serum TSH might not always reflect mild thyroid hormone deficiency in healthy elderly subjects because the distribution of serum TSH shifts to higher concentrations with age due to a presumed change in the set-point of the hypothalamic-pituitary-thyroid axis with aging (47, 59). Consequently, the diagnosis of SHypo in elderly patients should be considered only when serum TSH is above a cutoff limit for age, which will be higher in older subjects, whereas serum free and total T_4 will be by definition within their reference range. Moreover, age-adjusted serum TSH levels should be considered during L- T_4 replacement therapy (3, 10).

BMI may also influence serum TSH levels. TSH is higher in overweight and obese individuals than in lean subjects. This appears to be an effect of the hormone, leptin, produced by adipocytes, which acts to stimulate release of TRH by the paraventricular nucleus of the hypothalamus (52, 60). The altered thyroid hormone pattern in obese patients is reversible with weight loss, suggesting that the mild increased serum TSH level is not indicative of SHypo in obese patients, especially when thyroid hormones are in their reference range and thyroid autoantibodies are negative (52).

During pregnancy, the thyroid gland increases its size by about 10% in iodine-replete countries and by 20% to 40% in the presence of iodine deficiency. The production of T_4 and T_3 is increased by 50%, and the daily iodine requirement is increased by 50% (61). The TSH normal reference range in pregnancy is influenced by high T_4 -binding globulin (TBG), estrogens, human chorionic gonadotropin levels, increased iodine clearance, and enhanced type III 5-deiodinase activity of the placenta (61). Recent guidelines have been updated to reflect recent data bearing on establishing a correct diagnosis of thyroid hormone deficiency in pregnancy (17–19). According to these guidelines, the upper limit for TSH should be 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimester (17–19).

Consequently, hypothyroidism in pregnancy is defined as an elevated serum TSH > 2.5 to 3 mU/L with a decreased serum FT_4 concentration. Moreover, women with TSH levels of 10 mU/L or higher should be considered as having overt hypothyroidism, irrespective of their FT_4 levels (18). On the basis of these criteria, SHypo in pregnant women

is defined as a serum TSH between 2.5 and 10 mU/L with a normal FT₄ concentration (18). Isolated hypothyroxinemia is defined as a normal maternal TSH concentration in conjunction with FT₄ concentrations in the lower 5th or 10th percentile of the reference range (18, 19).

CoH is a condition of thyroid hormone deficiency diagnosed at birth (20–22). Primary CoH is defined by a low FT₄ or total T₄ concentration and elevated serum TSH concentration, whereas the diagnosis of SHypo can be made as in adults, when TSH is increased and total and FT₄ is normal (62). Infants with a low serum total T₄ and normal TSH concentrations may have CH, hypothalamic immaturity, TBG deficiency, or maternal hyperthyroidism (62). A repeated serum FT₄ with measurement by the equilibrium dialysis method is recommended to confirm a diagnosis of CH (62, 63). On occasion, a delayed TSH rise may be seen and is defined as a normal TSH level with a low T₄ level at an initial screening for CoH, but a persistently low T₄ level and an elevated TSH level at the subsequent screening evaluation (62, 63). This condition, which is frequent in pre-term infants, low-birth-weight infants and sick full-term newborns, may reflect an altered hypothalamic-pituitary-thyroid axis secondary to immaturity (64).

Finally, the entity of consumptive hypothyroidism refers to a rare condition that may occur in patients with large hepatic hemangiomas and other tumors in which type 3 iodothyronine deiodinase is expressed, resulting in accelerated degradation of T₄ and T₃ (64).

In conclusion, the definition of hypothyroidism has changed somewhat over the past several years, with def-

inition of previously unrecognized entities such as sub-clinical, mild hypothyroidism, isolated hypothyroxinemia, and delayed TSH rise. The TSH and FT₄ reference limits defining these conditions should take into account age, sex, race, BMI, iodine intake, method-specific variations in the assay assessments, and physiological and pathological conditions. Different TSH cutoff levels should be used to define and treat hypothyroidism in children with CoH, in pregnant women, in elderly patients, and in patients with comorbidities.

The recent American Thyroid Association (ATA) guidelines suggest that when upper and lower values of third-generation TSH assays are not available, the TSH normal reference range should be 0.45 to 4.12 mU/L based on the NHANES III reference population (3).

B. Etiology

1. Transient and persistent adult hypothyroidism

Transient hypothyroidism is defined as a period of reduced thyroid function with elevated TSH, which is followed by recovery to a euthyroid state (9, 10). The major causes of acquired transient hypothyroidism are listed in Table 2. Transient causes of a TSH increase in adults are frequently due to viral or autoimmune thyroiditis, drugs that interfere with thyroid function, or a toxic injury affecting the thyroid gland.

The term persistent subclinical and overt hypothyroidism is defined by the presence of a permanent reduced secretion of thyroid hormones by the thyroid gland (9, 10,

Table 2. Etiology of Congenital and Acquired Transient Hypothyroidism

| Condition | Causes |
|--|--|
| Transient primary hypothyroidism in adults | Transient hypothyroidism following subacute, painless, or postpartum thyroiditis Drugs impairing thyroid function Chemotherapy in patients with lymphoma and women with breast cancer Toxic injury: pesticides, herbicides, industrial chemicals, and naturally occurring environmental chemicals |
| Transient CH in adults | Administration of antithyroid drugs After withdrawal of thyroid hormone therapy in euthyroid patients Drugs that inhibit TSH secretion: glucocorticoid, dopamine, cocaine, bexarotene Nonthyroidal illnesses Major surgery Bone marrow transplantation Severe trauma Infections Depressive disorders Anorexia nervosa Malnutrition |
| Transient CoH | Maternal or neonatal excess iodine exposure Maternal or neonatal mild iodine deficiency Maternal treatment of hyperthyroidism with anti-thyroid drugs Maternal transfer of TR-blocking antibodies Heterozygous thyroid oxidase (<i>THOX2</i>) and <i>DUOXA2</i> mutations Congenital hepatic hemangioma/ hemangioendothelioma |

36). The major causes of acquired persistent hypothyroidism are listed in Table 3.

Iodine deficiency is the single most common cause of persistent hypothyroidism in the world (65, 66). Hashimoto's thyroiditis, an autoimmune disease often able to progressively destroy the thyroid gland, represents the most common cause of acquired subclinical or overt hypothyroidism in adults in areas of iodine sufficiency (9, 10, 36). Its incidence is about 7-fold in women with an increased risk of development during the middle years of life (9, 10, 36). The frequency of Hashimoto's thyroiditis increases with age and is more common in people with a familial or personal history of other autoimmune endocrine or nonendocrine disorders (9, 10, 36). Hashimoto's thyroiditis may be associated with autoimmune polyglandular syndrome (APS) (67). Autoimmune thyroiditis is present in about 10% to 15% of cases with type 1 APS, and it is caused by mutations in the autoimmune regulator gene (*AIRE*), resulting in production of defective autoimmune regulator protein (67); it may be associated with hypoparathyroidism, Addison's disease, and mucocutaneous candidiasis (67). Type 2 APS, usually known as Schmidt's syndrome, is characterized by Addison's disease, autoimmune thyroiditis, and type 1 diabetes (67). Hypothyroidism may spontaneously develop in 5% to 20% of patients with

Graves' disease (68). Treatment with radioiodine for hyperthyroidism may induce thyroid hormone deficiency ultimately in about 82% of patients with Graves' disease over a 25-year period (69, 70). A lower percentage of hypothyroidism has been reported in patients with autonomous thyroid nodules treated with radioiodine with a progressive development of clinical hypothyroidism or SHypo in 60% of patients with toxic adenoma after 20 years (71) and in 64% of patients with toxic multinodular goiter after 24 years (72). Acquired hypothyroidism develops after total and partial thyroidectomy (73, 74), external radiotherapy of the head and neck (75), and radiation release from nuclear accidents (76) and in about 20% to 25% of patients treated for malignancy with [¹³¹I]meta-iodobenzylguanidine (77) or with monoclonal antibodies radiolabeled with ¹³¹I (78).

Several drugs (iodine-containing compounds, lithium carbonate, cytokines, tyrosine kinase inhibitors (TKIs), amiodarone, aminoglutethimide, ethionamide, sulfonamides, sulfonylureas, and thalidomide) can induce persistent subclinical or overt hypothyroidism especially in patients with preexisting thyroid autoimmunity (79).

Infiltrative or infectious disorders (amyloidosis, scleroderma, hemochromatosis and cystinosis, AIDS, and Kaposi's sarcoma) and inflammatory or infiltrative thyroid

Table 3. Etiology of Persistent Congenital and Acquired Primary Hypothyroidism

| Condition | Causes |
|---|--|
| Persistent primary hypothyroidism in adults | Severe iodine deficiency Chronic autoimmune thyroiditis Non-autoimmune thyroiditis Partial or total thyroidectomy and/or neck surgery Radioactive iodine therapy for treatment of hyperthyroidism External radiotherapy of the head and neck in patients with Hodgkin's lymphoma, leukemia, aplastic anemia, brain tumors, or bone marrow transplantation Radiation release from nuclear accidents Treatment with ¹³¹ I meta-iodobenzylguanidine or with ¹³¹ I-radiolabeled monoclonal antibodies Infiltrative disorders of the thyroid gland (amyloidosis, sarcoidosis, hemochromatosis, Riedel's thyroiditis, cystinosis, AIDS, primary thyroid lymphoma) Drugs impairing thyroid function in patients with autoimmune thyroiditis (iodine excess, iodine-containing medications such as amiodarone and radiographic contrast agents, lithium carbonate, cytokines (especially interferon- α)) Inadequate replacement therapy Toxic substances and industrial and environmental agents Adult onset of partial defect of hormonogenesis |
| Persistent primary congenital hypothyroidism | Thyroid dysgenesis (athyreosis, hemiagenesis, thyroid ectopia, thyroid hypoplasia) Thyroid dyshormonogenesis: sodium-iodide symporter (trapping) defect, thyroid peroxidase defect, hydrogen peroxide generation or maturation defects, Tg synthesis defect, deiodinase defect Resistance to TSH binding or signaling TSH receptor defect G protein defect |
| Familial infantile hypothyroidism | Dyshormonogenesis Generalized resistance to thyroid hormone |
| Acquired juvenile and adolescent hypothyroidism | Iodine deficiency Autoimmune thyroiditis External irradiation of the neck Thyroidectomy |

Table 4. Etiology of Persistent Congenital and Acquired CH

| Condition | Causes |
|--------------------------|--|
| Persistent CH in adults | Hypothalamic or suprasellar mass (germinoma, glioma and meningioma, craniopharyngioma, etc) Pituitary macroadenoma Iatrogenic causes: surgery, irradiation, drugs, head trauma Infiltrative disorders causing hypothalamic dysfunction (sarcoidosis, hemochromatosis, cell hystiocytosis, Langerhans' cell) Immunological disorders: lymphocytic hypophysitis Pituitary apoplexy (including Sheehan syndrome) Infectious disorders: tuberculosis, syphilis, mycoses Empty sella Metastases |
| Persistent congenital CH | Isolated TSH deficiency (synthesis defect or hypoactivity) Congenital hypopituitarism (multiple pituitary hormone deficiencies) |

diseases (Riedel's thyroiditis, subacute, postpartum, and painless thyroiditis) may also induce persistent subclinical and overt hypothyroidism (9, 10, 36). Synthetic and natural chemicals and industrial agents (pesticides, herbicides, biphenyls, and resorcinol) may increase the risk of developing hypothyroidism (80).

CH can be due to pituitary gland adenomas, empty sella, pituitary surgery, radiotherapy, extrapituitary tumors, or inflammatory and infiltrative disorders of the pituitary gland (81) (Table 4).

Some special populations are at higher risk of developing hypothyroidism (Table 5), such as postpartum women and individuals with a personal and/or family history of autoimmune thyroid disorders, autoimmune endocrine conditions (type 1 diabetes mellitus, adrenal insufficiency, ovarian failure, etc), or nonendocrine autoimmune disorders (celiac disease, vitiligo, pernicious anemia, Sjogren syndrome, multiple sclerosis, primary pulmonary hypertension, etc) (9, 10, 36). Subjects with Down's and Turner syndromes are at increased risk of developing thyroid hormone deficiency (9, 10, 36). Inexplicably, subjects with a history of having given up smoking are at an increased risk of hypothyroidism (82).

2. Transient and persistent CoH

CoH can be classified as permanent and transient. Transient CoH refers to a temporary thyroid hormone deficiency discovered at birth with subsequent recovery of thyroid function (41, 62). The incidence of transient CoH

Table 5. Patients at High Risk of Developing Hypothyroidism

| High-Risk Patients |
|--|
| Individuals with a personal or family history of autoimmune thyroid disorders Associated autoimmune endocrine conditions (T1DM, adrenal insufficiency, ovarian failure, etc) Associated nonendocrine autoimmune disorders (celiac disease, vitiligo, pernicious anemia, Sjogren syndrome, multiple sclerosis, primary pulmonary hypertension, etc) Postpartum women Underlying thyroid, pituitary, or hypothalamic disorders Previous treatment that can destroy thyroid, pituitary, or hypothalamic tissue Previous head and neck external radiation therapy Down's and Turner syndromes Subjects with a history of having given up smoking Patients submitted to bone marrow transplantation Smokers |

is increased in Europe (1 in 100) compared with the United States and frequently occurs in preterm infants born in iodine-deficient areas (41). Frequent causes of transient CoH are maternal thyroid autoantibodies, which can cross the placenta and block the TSH receptor, fetal exposure to maternal antithyroid drugs, and maternal or neonatal iodine exposure (41) (Table 2). Rare congenital liver hemangiomas that produce large amounts of type 3 iodothyronine deiodinase may induce a consumptive hypothyroidism for which large doses of L-T₄ are required (41). Mutations in dual oxidase 2 (*DUOX2*) can be responsible for transient or permanent CoH (41).

Permanent CoH is defined as persistent thyroid hormone deficiency that requires life-long treatment. It can be further classified into primary hypothyroidism caused by thyroid gland disease and secondary or CH due to a congenital TSH deficiency. Permanent primary hypothyroidism may be caused by a defect in thyroid gland development (thyroid dysgenesis) or a defect in thyroid hormone production (dys hormonogenesis) (Table 3) (41, 62). Thyroid dysgenesis (thyroid ectopy, athyreosis, and thyroid hypoplasia) accounts for about 85% of cases of permanent primary CH, with thyroid ectopy being the most common, accounting for approximately two-thirds of thyroid dysgenesis (41, 62). Some gene mutations may be implicated in the development of thyroid dysgenesis, including *PAX8*, *NKX2-1*, and *FOXE-1* (41, 62).

Thyroid dys hormonogenesis accounts for about 10% to 15% of cases of permanent CH, leading to goitrous hypothyroidism (41, 62). These hereditary defects are autosomal recessive and include mutations in the genes coding for the sodium-iodide symporter, TPO, hydrogen peroxide generation (thyroid oxidase and dual oxidase), transcription factors, thyroglobulin (Tg), and iodoty-

rosine deiodinase. CH may be associated with other congenital malformations leading to syndromic forms of CH such as Pendred, Bamford-Lazarus, and Kocher-Debrè-Semelaigne syndromes (41, 62). Pendred syndrome is a genetic syndrome characterized by a defect in the transmembrane protein pendrin, which leads to impaired iodine organification. This syndrome is defined by the association of hypothyroidism, goiter, and deafness. Bamford-Lazarus syndrome is a genetic condition that results in thyroid dysgenesis and is due to recessive mutations in forkhead/winged-helix domain transcription factor *FKLH15* or *TTF2*. It is characterized by hypothyroidism, cleft palate, and spiky hair. Kocher-Debrè-Semelaigne syndrome is characterized by myopathy and hypothyroidism associated with pseudohypertrophy in infancy or childhood. Rarely, a homozygous mutation in the human iodotyrosine deiodinase gene (*DHEAL1*) may lead to CH and goiter.

Permanent secondary CH is usually caused by a mutation of the *TSH β* subunit gene or may be associated with congenital hypopituitarism (Table 4). Some mutations in genes regulating pituitary gland development may be responsible for familial hypopituitarism (81). Mutations in transcription factor genes involved in pituitary gland development or function (*HESX1*, *LHX3*, *LHX4*, *PHF6*, *PITX1*, *PITX2*, *OTX2*, *SOX2*, *SOX3*, *PROX1*, and *POU1F1*) have been reported. Peripheral CH is defined as a defect in thyroid hormone transport, metabolism, or action (Table 6). Uncommon causes of peripheral CH include defects in thyroid hormone transport (mutations in the gene for monocarboxylase transporter 8 [MCT8]), metabolism (selenocysteine insertion sequence-binding protein 2), or resistance to thyroid hormone action (mutations in the thyroid hormone receptor [TR]).

A mutation in a gene encoding MCT8 is a rare cause of X-linked hypothyroidism with mental retardation and neurological abnormalities (Allan-Herndon-Dudley syndrome) (83).

Peripheral resistance to thyroid hormone is caused by a mutation in the gene encoding for TR β in 90% of cases (84). These patients are usually euthyroid with elevated thyroid hormones without suppression of TSH; however,

hypothyroidism has been reported in some cases. Some patients with an inactivating mutation in TR α 1 have been reported; these patients had abnormal thyroid function tests (low FT₄, high T₃, and normal TSH levels), with a phenotype characterized by mildly delayed cognitive development, growth retardation, delayed bone development, and constipation (85, 86). Treatment with L-T₄ improved certain features of this phenotype, although the impairment in cognitive and motor function did not improve (87).

3. Hypothyroidism during infancy, childhood, and adolescence

Infantile hypothyroidism is defined by the appearance of hypothyroid symptoms after 6 months of age in infants with CH that are not detected by screening (88, 89). Ectopic thyroid dysgenesis, thyroid dyshormonogenesis, and generalized resistance to thyroid hormone action represent the most frequent causes of these late-onset congenital causes of hypothyroidism (88, 89). The clinical presentation is similar to that of infants with CH, and the intellectual and neuropsychological impairment depends on the age of the onset of hypothyroidism and its duration (Table 7).

Acquired juvenile hypothyroidism is defined by the onset of hypothyroidism after 3 years of age (88, 89). The appearance of thyroid hormone deficiency in this period of the life is not associated with a permanent impairment of the central nervous system (Table 7).

Acquired hypothyroidism during adolescence is usually a less severe form of thyroid hormone deficiency (88, 89) (Table 7). Acquired hypothyroidism may develop after external irradiation or bone marrow transplantations to treat tumors or primary immunodeficiency during infancy and adolescence. The incidence of autoimmune hypothyroidism during adolescence is approximately 1% to 2% and may occur in association with other autoimmune diseases, such as type 1 diabetes mellitus, alopecia, vitiligo, or Addison's disease or in association with other disorders such as Down's syndrome, Turner syndrome, cystinosis, and thalassemia. Children whose family members have autoimmune thyroid diseases are at increased risk of autoimmune hypothyroidism.

C. Epidemiology

Hypothyroidism is one of the most common endocrine disorders. The prevalence of clinical hypothyroidism in adults is 1.9% in women and 0.1% in men (90) with an annual incidence of 0.4% in women and 0.06% in men (91). Its prevalence is increased in men and women older than 60 years of age, being 0.5% to 5.0% (92). The prevalence of SHypo is about 3% to 10% in iodine-replete population (8–10, 90, 91). This prevalence increases to

Table 6. Causes of Persistent Peripheral Hypothyroidism

| Cause |
|---|
| Resistance to thyroid hormone |
| Mutation in the gene encoding for TR β in 90% of cases |
| Inactivating mutation in TR α 1 (rare cases) |
| Thyroid hormone transport defect (MCT8, Allan-Herndon-Dudley syndrome) |
| Thyroid hormone metabolism defect (selenocysteine insertion sequence binding protein) |

Table 7. Symptoms and Signs of Primary and CH in Different Periods of the Life

| Condition | Symptoms and Signs |
|---|--|
| Primary overt hypothyroidism In young and middle-aged patients | Fatigue Weight gain Dry skin and cold intolerance Slow thinking Puffy eyes Coarseness or loss of hair Goiter Constipation Cold intolerance Hoarseness Muscle weakness and cramps Delayed relaxation of deep tendon reflexes Memory impairment Decreased concentration Neurocognitive deficits Irregular or heavy menses Infertility Myalgias Hyperlipidemia Bradycardia Hypothermia CHD |
| In elderly patients | Mixedema in severe hypothyroidism Memory and mental impairment Dementia Anemia Depression Heart failure CHD |
| Neonatal appearance | Prolonged icterus Edema of the eyelids, hands, and feet Hypotonia Inactivity Gestation >42 wk Birth weight >4 kg Poor feeding Hypothermia Abdominal distention Open posterior fontanelle (>5 mm) |
| During the first month of age | Respiratory distress Failure to gain weight, poor sucking ability Decreased stool frequency |
| During the first 3 mo of age | Decreased activity and lethargy Umbilical hernia Dry skin with carotenemia Macroglossia Infrequent and hard stools Generalized swelling or myxedema |
| Between 6 mo and 3 y of age | Hoarse cry Deceleration of linear growth Coarse facial features Dry skin with carotenemia Hoarse cry and large tongue Umbilical hernia |
| In childhood | Muscular pseudohypertrophy Deceleration of linear growth with or without short stature Delayed eruption of teeth and in shedding of primary teeth Skeletal retardation Muscle weakness Muscular pseudohypertrophy |

(Continued)

Table 7. Continued

| Condition | Symptoms and Signs |
|--------------------|---|
| During adolescence | Infrequent and hard stools |
| | Dry skin with carotenemia |
| | Precocious sexual development with incomplete sexual maturation |
| | Isolated menarche |
| | Hyperprolactinaemia and galactorrhea |
| | Changes in mental and physical performance |
| | Enlargement of the sella turcica and the pituitary gland |
| | Generalized swelling or mixedema |
| | Delayed onset of puberty |
| | Deceleration of linear growth with or without short stature |
| | Delayed eruption of permanent teeth |
| | Infrequent and hard stools |
| | Dry skin with carotenemia |
| CH | Galactorrhea (girls) |
| | Generalized swelling or myxedema |
| | Mild-moderate symptoms of hypothyroidism |
| | Signs and symptoms of other pituitary deficits |
| | Manifestations of concomitant hypothalamic-pituitary disease |

about 10% in women older than 55 to 60 years of age and rises further to 5% to 20% in men and women older than 60 years of age (8–10, 12).

This wide range of prevalence of hypothyroidism reflects the heterogeneity in race, age, sex, BMI, and dietary iodine intake among different populations and the different TSH cutoff values used for the definition of SHypo in different studies (9, 10). About 75% of patients with SHypo have mild thyroid deficiency (TSH \leq 10 mU/L) (9, 10). Patients with SHypo may progress to overt disease, with the rate and frequency of progression affected by iodine intake, sex, the underlying cause of thyroid hormone deficiency, basal TSH, FT₄ levels, and the patient's age (9, 10). A serum TSH above 2.5 mU/L and positive thyroid autoantibodies were predictors of long-term risk of hypothyroidism in some longitudinal studies (89, 93–95). The annual rate of progression to overt disease is particularly increased (4.3%) in women with elevated serum TSH and antithyroid antibodies (9, 10). Other factors associated with an increased risk of progression to overt hypothyroidism include high iodine intake, a greater increase in serum TSH ($>$ 10 mU/L), positive thyroid autoantibodies, low-normal FT₄ levels, and adult age (93–96).

The incidence of overt hypothyroidism in pregnant women is approximately 0.3% to 0.5%, whereas the incidence of SHypo is approximately 2% to 3% (9, 10, 97). Worldwide iodine deficiency is the main cause of hypothyroidism in pregnancy (65). Chronic autoimmune thyroiditis represents the most frequent cause of thyroid hormone deficiency in pregnant women living in iodine-sufficient areas. Thyroid autoantibodies are positive in 5% to 15% of women during pregnancy. In a prospective population study on 9471 pregnant women, autoimmune

thyroiditis was found in 55% of patients with SHypo and 80% of those with overt disease (98).

D. Diagnosis

1. In adult patients

Overt hypothyroidism is a clinical condition and can be suspected in the presence of specific symptoms of thyroid hormone deficiency (Table 7) (99). However, the onset of clinical symptoms in hypothyroid patients may be influenced by the severity of the disease, duration, age, and the individual sensitivity to thyroid hormone deficiency (9). Elderly patients with thyroid hormone deficiency may be minimally or completely asymptomatic (100, 101).

In symptomatic patients, the onset of symptoms may be attributed to the aging process or concomitant diseases (9). Moreover, atypical clinical presentations of hypothyroidism are prevalent in elderly subjects (Table 7) (102–105). Pericardial and pleural effusion, hypothermia, and coma may develop in patients with more severe disease (103–107) (Table 7).

Although several rating scales have been proposed for the diagnosis of hypothyroidism and for the assessment of the severity of specific symptoms (108–110), it is difficult to diagnose thyroid hormone deficiency on the basis of clinical symptoms alone because none of the symptoms or signs of hypothyroidism is sufficiently sensitive or specific to distinguish euthyroid subjects from patients with mild thyroid hormone deficiency (99). The Nijmegen Biomedical Study, which assessed the relationship between fatigue and serum TSH, FT₄, and TPOAbs in 5897 participants, showed that subjects with a history of thyroid disease experienced more fatigue than the general population de-

spite the normal TSH and FT₄ values (111). In the Colorado study, the positive predictive value of individual hypothyroid symptoms was only 8% to 12% (97). However, this study showed that patients who report many or newly developed symptoms are most likely to have thyroid hormone deficiency, although absence of symptoms does not exclude the diagnosis of thyroid hormone deficiency. As a result, the presence of specific and suggestive symptoms may be useful only to select patients who need thyroid function testing, with the diagnosis of hypothyroidism in adults made on the basis of the biochemical test results.

Hypercholesterolemia, hypertriglyceridemia, hyperprolactinemia, hyperhomocysteinemia, hyponatremia, anemia, and/or elevated creatine phosphokinase levels may raise suspicion of hypothyroidism sufficiently to warrant thyroid function testing (36, 112).

Primary hypothyroidism is the major cause of hypothyroidism, and serum TSH measurement is the most sensitive and specific test in the presence of an intact pituitary-hypothalamic axis, with immunometric assays for TSH having a 99% sensitivity and specificity (36). Serum TSH is the first-line diagnostic test for the identification of thyroid hormone deficiency, even in patients with mild thyroid hormone deficiency (9, 10, 36, 113). Elevated serum TSH and decreased FT₄ levels represent the classical combination indicating primary hypothyroidism. Serum FT₄ RIA and serum FT₄ index are adequate but less sensitive methods to detect hypothyroidism, especially SHypo (9, 10, 36). In fact, FT₄ levels are in the lower-normal reference range in patients with SHypo and are associated with raised TSH values; thus, the rising TSH in this condition is based on the sensitivity of the hypothalamic pituitary thyroid axis to the slight decreases from baseline normal T₄ levels to the low-normal range.

Serum FT₃ evaluation is only marginally useful in diagnosing hypothyroidism and may achieve low serum levels only in severe hypothyroidism. Significant decreases in FT₃ levels are not seen until patients are in an advanced state of thyroid hormone deficiency due to the compensatory increase in hepatic T₄ to T₃ conversion and to residual thyroidal T₃ secretion (36). Recent data have shown that a single evaluation of thyroid-function tests and biological variation in thyroid test results may severely limit the diagnosis of true persistent SHypo, supporting the need for a periodic follow-up without treatment before diagnosing this disorder in presence of mild TSH increase (114). Serum TSH concentration should be reevaluated after 3 to 6 months in the event of slightly increased values to exclude a laboratory error or a transient TSH increase due to temporary thyroiditis recovery from systemic illness or drugs (9, 10). Transient causes of increased serum

TSH should be excluded before commitment of patients to a lifetime of T₄ replacement therapy. A laboratory pattern indistinguishable from SHypo may be rarely seen in patients with TSH receptor mutations causing mild TSH resistance. These subjects usually relate a family history of raised serum TSH concentrations but an absence of personal or familial history of thyroid autoimmunity. Pituitary resistance to thyroid hormones and thyrotropin secreting pituitary adenoma may be associated with increased serum TSH; however, both of these conditions are characterized by raised serum free thyroid hormone levels.

Although TSH is the first-line test to perform when hypothyroidism is suspected, measurement of thyroid hormones can provide additional information as to the cause of the hypothyroidism and is necessary to achieve a correct diagnosis before replacement therapy is initiated. Consequently, serum TSH assay alone may be insufficiently sensitive for the diagnosis of 1) patients with CH due to hypothalamic or pituitary disorders, 2) subjects recovering from nonthyroidal illnesses, 3) administration of some drugs that can suppress TSH, 4) overweight and obese subjects, 5) short-term withdrawal of thyroid hormone therapy in euthyroid subjects, 6) presence of heterophilic antibodies against mouse proteins in some immunoassays that may falsely raise serum TSH, and 7) patients with untreated adrenal insufficiency.

The concomitant presence of other disorders and/or nonthyroidal illnesses may severely limit the diagnosis of hypothyroidism in the elderly. Elderly patients with raised serum TSH are hypothyroid only after excluding the administration of drugs that can interfere with thyroid function or the state of recovery from severe illness. Some drugs may interfere with TSH synthesis and secretion; glucocorticoids, dopamine, and dopamine agonists (bromocriptine and cabergoline), somatostatin analogs (octreotide), dobutamine, and retinoids may all suppress TSH at the level of the hypothalamus or pituitary (115). Moreover, metformin can lower serum TSH and was shown to do so in one small study in type 2 persons with diabetes who also had hypothyroidism (116) and in euthyroid patients with higher baseline TSH levels independent of the presence of positive TPOAb (117).

During the recovery phase from nonthyroidal illness, serum TSH levels may be increased to levels above normal, although generally no higher than 20 mU/L (118).

About 90% of patients with Hashimoto's thyroiditis have detectable anti-TPO and anti-Tg antibodies. The evaluation of thyroid antibody titers (which include anti-Tg antibodies, antimicrosomal/TPOAbs, and anti-TSH receptor antibodies) is useful to confirm the diagnosis of autoimmune hypothyroidism and predict the subsequent development of overt hypothyroidism in patients with

mild disease, in pregnant women, in the postpartum period, in the presence of other autoimmune disease, and during treatment with drugs such as lithium, interferon- α , and amiodarone or exposure to excessive amounts of iodine.

The hypoechoogenicity of the thyroid gland at the ultrasound evaluation may allow clinicians to identify individuals with autoimmune thyroiditis (9). The ultrasonographic pattern typical of autoimmune thyroiditis may be useful to provide a correct diagnosis in about 10% of patients with no detectable thyroid autoantibodies (9).

CH can be suspected in the presence of specific symptoms of thyroid hormone deficiency in patients with clinical findings of other pituitary hormone deficiency or in the presence of a history of pituitary gland tumors and surgery or pituitary inflammatory and infiltrative disorders (38, 81). TSH measurement is of little value in guiding management in CH because the deficiency in central disease is due to the low levels of TSH. Instead, SHBG, ankle reflex relaxation time, heart rate, and Doppler echocardiography may be useful surrogate peripheral tissue parameters to assess the restoration of euthyroidism during treatment with thyroid hormone (81). Although potentially useful to guide replacement hormone dosage, none of these tissue parameters is sufficiently sensitive or specific for actual diagnosis.

2. Diagnosis of hypothyroidism in pregnancy

The diagnosis of thyroid hormone deficiency in pregnancy can be difficult. Serum TSH decreases in the first trimester of pregnancy secondary to the physiological increase in human chorionic gonadotropin and the resultant stimulation of thyroid hormone release. The use of a normal reference range for nonpregnant women did not identify 10.4% of women with thyroid dysfunction in the first trimester and 6.7% in the second trimester (119). Therefore, the current guidelines suggest considering a trimester-specific reference range for both TSH and thyroid hormones during pregnancy (17–19). If trimester-specific reference ranges for TSH are not available in the laboratory, the following reference ranges are recommended: 0.1 to 2.5 mU/L in the first trimester, 0.2 to 3.0 mU/L in the second trimester, and 0.3 to 3.0 mU/L in the third trimester (17–19).

The ATA guidelines (18) defined maternal hypothyroxinemia as low FT₄ concentrations (<5th or <10th percentile) with normal TSH levels. Moreover, the recently updated guidelines have recommended being prudent in interpreting serum FT₄ levels during pregnancy. They have suggested the use of a trimester-specific FT₄ reference range, which should be method specific (19). Serum FT₄ concentrations decrease with progression of gestation,

and their interpretation is complicated by the increased TBG levels and the decreased albumin concentrations. These changes may affect and limit the validity of the FT₄ measurement by immunoassay methods during pregnancy. In addition, there are large method-dependent variations in FT₄ assessments during pregnancy, and therefore, incorrect abnormal FT₄ levels can be detected with the different FT₄ assays in the laboratories. The best recognized technique for FT₄ measurement in pregnancy is the separation of the free hormone from binding globulins by equilibrium dialysis or ultrafiltration of serum, followed by thyroid hormone measurement by either RIA or liquid chromatography tandem mass spectrometry (120). However, this latter method is expensive. As an alternative, the recent Endocrine Society (ES) guidelines recommend the use of the FT₄ index or the total T₄ adjusted for pregnancy to estimate FT₄ values in pregnancy (19). According to these suggestions, total T₄ should be adjusted by a factor of 1.5 in pregnancy. The FT₄ index should be measured as total T₄ mathematically corrected for TBG (19).

3. Diagnosis of CoH

Infants with CoH can be detected by newborn screening programs. Congenital hypothyroidism meets the published accepted criteria for a mass population screening because of the following points: 1) the disorder is infrequent (the incidence in Europe is 1 in 2708 births and in the United States was 1 in 2372 in 2002), 2) the clinical diagnosis is made in only 10% of cases within the first month of life, 3) the delay or lack of diagnosis may induce severe mental retardation, 4) the cost to benefit ratio is favorable because it is a preventable disorder with an effective method of screening, and 5) an effective therapy (with L-T₄) is available. The first newborn screening program was introduced in Canada in the late 1970s, and now this screening is available for all newborns in most developed countries (United States, Europe, Australia, and Japan) (121, 122). Changes in recent clinical screening practices (reduction of TSH cutoff) and assay techniques (from a radiochemical-based assay to fluoroimmunoassay or chemiluminescence for determining both TSH and T₄ in dried blood spots) have allowed detection of milder cases of CoH. The typical screening test for CoH is performed by heel-prick blood that is spotted on special filter paper cards. It is usually collected between 2 and 4 days after birth on cord blood. Earlier collection may lead to a false-positive result due to the physiological postnatal rise in serum TSH.

Some screening programs use a primary T₄ test with a follow-up TSH test in infants with a serum T₄ below the cutoff value; this strategy helps detect cases with primary

and secondary hypothyroidism and infants with delayed TSH rise (123). Some other screening programs perform an initial TSH test that has the advantages of detecting infants with mild or SHypo. Simultaneous T_4 and TSH measurement appears to represent the best strategy, although it is more expensive and used in a minority of screening centers (124).

With the more sensitive TSH assays currently in use, the new TSH cutoff has declined from 40 to 50 mU/L to serum values of 20 to 30 mU/L (corresponding to 10–15 mU/L in whole blood). However, age-specific normal reference values for TSH and FT_4 should be considered to establish specific cutoff levels. Diagnosis and treatment should not be based on screening test results alone. Generally, if the screening T_4 is below the 10th percentile and/or the TSH is greater than 30 mU/L, an infant is recalled for confirmatory serum testing (41, 62) (Table 1). The confirmatory serum tests may be a TSH and free T_4 or a total T_4 combined with some measures of binding proteins such as a T_3 resin uptake. These tests can be performed after 1 or 2 weeks of life when the upper limit of serum TSH is approximately 10 mU/L and FT_4 in the range of 10 to 26 pmol/L (41, 62) (Table 1). A routine second screening test at 2 to 6 weeks of age may help diagnose a delayed TSH rise in preterm and acutely ill term infants who may not have an elevated serum TSH at the first screening test (41, 62). It is important to establish the etiology of the hypothyroidism for the future management of children with CoH diagnosed at birth. In most cases, the underlying defect in thyroid function may be uncovered with a thyroid radionuclide uptake and scan, thyroid ultrasonography, serum Tg measurement, thyroid autoantibodies, and urinary iodine measurement (62). ^{123}I or sodium pertechnetate 99m ($\text{Tc}99\text{m}$) rather than ^{131}I should be used in neonates to avoid a high dose of radioactivity in the thyroid and total body. Radionuclide uptake and scan may identify thyroid aplasia, hypoplasia (decreased uptake, small gland in a eutopic location), or an ectopic gland. Infants with absent uptake should be further evaluated by thyroid ultrasonography. A large gland or goiter with increased uptake suggests dyshormonogenesis. A perchlorate discharge test may be helpful in the identification of defective oxidation and organification. Genetic counseling is necessary in familial forms of CoH to diagnose the specific gene mutation. In the absence of a screening program, the diagnosis of CoH will be made after the onset of clinical manifestations (Table 7). Clinical manifestations usually depend on the severity of the thyroid hormone deficiency and may progressively develop after birth. Neurological abnormalities and genitourinary and cardiac congenital malformations should be investigated in infants with CoH.

To summarize the issue of diagnosis, although hypothyroidism can be suspected by the onset of specific symptoms of thyroid hormone deficiency, it should be specifically confirmed on the basis of results of thyroid function tests. The diagnosis of hypothyroidism can be difficult in children with CoH, in CH, in elderly patients, in pregnant women, in subjects with comorbidities or in those receiving drugs that can interfere with thyroid function. Peripheral parameters of thyroid hormone action may help to diagnose CH.

IV. Treatment With Thyroid Hormone

A. Brief historical overview of T_4 treatment for hypothyroidism

A thyroid hormone preparation for the treatment of hypothyroidism was first administered by Dr George Murray in 1891 by the im injection of sheep thyroid extract into a patient with myxedema. In just a few years thereafter, preparations of thyroid extracts were administered by mouth (125). In 1914, Edward Kendall isolated and crystallized the active substance in the thyroid that he initially named thyroxin, and it was Harrington who established its crystalline structure in 1926 (126). Desiccated thyroid, made from animal thyroid glands, remained the main form of therapy until about 1960 (126). This extract contains a combination of T_4 and T_3 in a ratio 2- to 3-fold higher than that found in human thyroid. The development of the sodium salt of L- T_4 in the 1950s provided the compound that today is the basis for the therapy of hypothyroidism. Simultaneous publications in 1952 by Gross and Pitt-Rivers in the United Kingdom and by Roche, Lissitsky, and Michel in France, reported the discovery of T_3 (126). Almost 20 years later in 1970, Braverman, Sterling, and Ingbar demonstrated that circulating T_3 is largely derived from T_4 deiodination in extrathyroidal tissues by detecting T_3 in the serum of athyreotic patients receiving L- T_4 (127). Synthetic preparations of L- T_3 were available in 1956, whereas synthetic preparations of L- T_4 became accessible in 1958. Until 1962, the U.S. Food and Drug Administration (FDA) in the United States did not require a new drug application for L- T_4 , based on the belief that it was not a new drug. Replacement doses of L- T_4 were higher in 1960 (about 200–400 μg daily) compared with the doses recommended today; the poorly sensitive hormone assays in the past did not allow clinicians to distinguish between low-normal and suppressed TSH levels (9). Total T_4 and FT_4 levels were frequently increased at that time in patients being treated with L- T_4 (9). The more highly sensitive TSH assay became available in 1980, and by the early 1990s, the first studies showed the

negative effects of TSH suppression on the heart, liver, and bone (9). Between the years 1990 and 2000, the first double-blind controlled studies evaluated the effects of L-T₄ in patients with SHypo (9). In 1970, Smith et al (128) published the first double-blind crossover study to assess the effects of combination therapy with T₃ and T₄ in patients with hypothyroidism.

A. Feedback regulation of thyroid secretion

Thyroid hormones are produced by the thyroid gland through the iodination of tyrosine residues in the glycoprotein Tg. The anterior pituitary releases TSH in response to TRH, which is secreted by hypothalamus (129). TSH acts directly on the TSH receptor expressed on the thyroid follicular cell membrane. TSH regulates iodide uptake mediated by the sodium/iodide symporter and stimulates thyroid hormone synthesis and secretion (26, 129). The thyroid gland secretes both T₄ and T₃, which exert a negative feedback on TRH and TSH secretion. TSH secretion by the pituitary gland is the result of a complex feedback interaction between central hypothalamic TRH control and thyroidal production of thyroid hormones to the periphery. This negative feedback loop maintains levels of the circulating thyroid hormones and TSH in a physiological inverse relationship that defines the hypothalamic-pituitary-thyroid axis set-point, which is genetically determined and variable among individuals (130). The set-point for TSH secretion depends on both circulating serum T₃ and intracellular pituitary T₃. It may be influenced by environmental factors, iodine intake, age, and systemic illness as the organism autoregulates deiodinase activity and the resultant conversion of T₄ to T₃ (26).

More than 99% of circulating thyroid hormones are bound to plasma proteins TBG, T₄-binding prealbumin (transthyretin), and albumin. The higher affinity of both TBG and T₄-binding prealbumin for T₄ vs T₃ partially explains the higher serum T₄ levels and its slower metabolic clearance and longer half-life compared with T₃. Only the unbound or free thyroid hormone concentration is metabolically active.

The availability of T₃ at the tissue level is regulated by 3 deiodinase isoforms termed deiodinase type 1 (D1), type 2 (D2), and type 3 (D3) (131, 132). D1 is expressed mainly in the thyroid gland, liver, and kidney, where it converts T₄ to T₃ and thus contributes significantly to the pool of circulating T₃. D3 protects tissues from thyroid hormone excess by decreasing local T₃ concentrations (131, 132). D2 catalyzes 5'-deiodination and converts T₄ to T₃; it is present in the brain, pituitary gland, skeletal muscle, brown adipose tissue, thyroid gland, osteoblasts, aortic smooth muscle cells, and the human heart (131, 132). T₄

is synthesized and secreted exclusively by the thyroid gland, whereas the major source of human extrathyroid-produced T₃ in the euthyroid state is derived by D2 activity (133). The major role of D2 is to control the intracellular T₃ concentration to protect tissues from the detrimental effects of hypothyroidism (131–133).

The efficiency of conversion of T₄ to T₃ by D2 increases as the serum T₄ decreases (26). Consequently, in the presence of a low level of T₄ or in case of a hypothyroid state, D2 expression and activity are increased and can generate a proportionately greater quantity of plasma T₃ (26).

C. Thyroid hormone formulations: pharmacokinetics and pharmacodynamics

Thyroid hormone preparations available for therapy fit into 2 categories: natural hormonal preparations derived from animal thyroid and synthetic preparations.

1. Thyroid extracts (thyroid USP)

Natural preparations include desiccated thyroid and Tg. Desiccated thyroid products (dried and powdered) are derived from the thyroid glands of domesticated animals that are used for food by man (either beef, hog, or sheep), and Tg is derived from the thyroid glands of the hog. The content of thyroid hormone and the ratio of T₄ to T₃ may vary in desiccated thyroid preparations, depending on the brand employed and whether it is of porcine or bovine origin. Desiccated thyroid contains approximately 80% T₄ and 20% T₃ as well as other iodinated compounds (eg, diiodotyrosine and monoiodotyrosine). Absorption studies indicate that the bioavailability of T₃ in desiccated thyroid is comparable to that of orally administered synthetic T₃.

The most commonly used form of desiccated thyroid, known as Armour Thyroid, is of porcine origin and may be viewed as a mixture of T₃ and T₄ (1 grain, about 60 mg desiccated pig thyroid extract is approximately equivalent to 88 μg L-T₄) (134). Other commercial preparations derived from animal thyroid extracts are Prothyroid, Novothyral, Thyreotom, Thyrolar-3, and Diotroxin.

Some formulations of thyroid extracts have a characteristic odor and may be antigenic being an animal protein-derived product. A recent randomized, double-blind, crossover study has assessed the efficacy of desiccated thyroid treatment vs L-T₄ in 70 patients (age 18–65 years) with primary hypothyroidism who were on a stable L-T₄ dosage for 6 months (134). The authors evaluated symptoms, cognitive function, and the quality of life (QOL). The results have shown that although the treatment with desiccated thyroid hormone did not improve the QOL; 48.6% of these patients preferred this therapy vs L-T₄ because it was associated with weight loss (134).

The inappropriate use of thyroid extracts in euthyroid and hypothyroid patients can result in thyrotoxic symptoms and severe adverse effects (135). Some cases of thyroid storm have been reported during the inappropriate use of thyroid hormone extracts (136). The recent American Association of Clinical Endocrinologists (AACE) and ATA guidelines advise that there is no evidence to support using desiccated thyroid hormone in preference to synthetic L-T₄ monotherapy and advise that desiccated thyroid hormone not be used for treatment of hypothyroidism particularly due to content of a nonphysiological proportion of T₃ (3) (recommendation 22.4).

2. Levothyroxine

L-T₄ represents the first-line treatment in patients with hypothyroidism. Although plasma T₄ reaches a peak concentration 2 to 4 hours after oral administration, a once-daily dose of L-T₄ each morning provides stable and relatively constant blood levels of T₄ because of its long half-life (about 7 days) (26). The absorption of oral L-T₄ takes place through the intestinal mucosa within the first 90 minutes after tablet ingestion with 21% absorbed in the duodenum, 45% in the upper jejunum, and 34% in the lower jejunum and ileum (137–139). Absorption is incomplete because only 70% to 80% of the administered dose is absorbed. Normal gastric acid secretion is important for the subsequent intestinal absorption of thyroxine (140–142). T₄ absorption is increased by fasting and decreased in malabsorption syndromes and by certain foods and drugs (143, 144). Thyroid hormones are metabolized by the liver and mainly eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged. Approximately 20% of T₄ is eliminated in the stool. Physiological amounts of T₃ are generated by the monodeiodination of T₄ in target tissues, thereby maintaining normal serum T₃ levels in patients receiving L-T₄ monotherapy. With an appropriate individual dosage adjustment, treatment with L-T₄ is generally considered safe and well tolerated, and its use is commonly associated with good patient compliance (9, 10, 26). In several countries, L-T₄ is available in tablets with different dosage strengths of 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 μg. These multiple various tablets allow clinicians to obtain a correct titration for individualized dosing.

3. Different T₄ formulations: branded vs generic preparations

Several different branded and generic formulations of L-T₄ are commercially available. As a result, 10 to 12 million Americans affected by hypothyroidism are treated with different formulations of L-T₄. The FDA issued standards for L-T₄ bioequivalence and established that only L-T₄ preparations that meet these standards may have the

same clinical effect and safety profile as the reference product to which they are compared (145–148). In 1997, the FDA changed the process for approving L-T₄ preparations after receiving 58 adverse drug event reports over a 7-year period. However, since 1997, whether or not different L-T₄ preparations can be substituted has been a matter of great controversy (149–151). Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives with a similar record of safety and efficacy. Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action. Bioequivalence, in turn, establishes therapeutic equivalence and, therefore, the interchangeability of 2 similar products. Therapeutic equivalence permits substitution of one drug for another with the expectation of similar clinical effects with the expectation that strict follow-up testing would not be required.

The FDA approves a generic substitute only if it has been proven to be identical or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. The FDA requires that the 90% CIs of the generic's pharmacokinetic properties fall within the 80% to 125% range of that of the brand. In 2004, the FDA determined bioequivalence of L-T₄ formulations on the basis of 2 pharmacokinetic parameters (the area under the curve [AUC] and the maximum T₄ concentration) in euthyroid adult volunteers who received a supraphysiological dose (600 μg) of the L-T₄ formulation. The analysis of data provided to the FDA indicated that the reference L-T₄ preparations (Unithroid, Levoxyl, Synthroid, or Levothyroid) were comparable because the 90% CIs of the difference in AUC and maximum T₄ concentration fell between 80% and 125% of the reference formulation. Therefore, these products were considered therapeutically equivalent and interchangeable, and the FDA approved generic substitution for L-T₄ (146). The designation AB was used for interchangeable products meeting a positive standard for bioequivalence, whereas products not meeting the standard were rated as BX. However, the latter method of determining bioequivalence by the FDA has been consistently criticized by professional societies of endocrinologists, including the ES, the AACE, and the ATA. The physicians expressed concern that potential harm could come to patients being either overtreated or undertreated when nonbioequivalent preparations of L-T₄ were interchanged. Clinical data were collected to demonstrate this issue in 2007 in a pharmacovigilance study that reported adverse events that were related to interchanges of L-T₄ preparations (151). The results of this survey sus-

tained the opinion that although L-T₄ products were ostensibly standardized, there existed subtle differences between various brand and generic L-T₄ products because the methodology to determine interchangeability was faulty and that the various preparations could not necessarily be considered therapeutically equivalent (152). Presumably, the pharmacokinetic method used by the FDA to assess bioequivalence was too insensitive to assess therapeutic equivalence for L-T₄ (152, 153), with the major criticism being that pharmacodynamic considerations such as serum TSH levels accompanying administration of the various L-T₄ preparations were not assessed.

In a pharmacokinetic study of 36 normal volunteers, Blakesley et al (154) demonstrated that using current FDA methodology, a difference of 25% to 33% of the administered L-T₄ dose might not be detected, and even after correction for baseline endogenous T₄ levels, a difference of 12.5% would not be identified. Based upon these observations, it was conceivable that the pharmacokinetic criteria that have been used by the FDA to assess the bioequivalence of L-T₄ products might not distinguish dose differences of up to 33% (eg, 400 vs 600 μg) and doses that differ by 12.5% (eg, 400 vs 450 μg). A log-linear relationship exists between the serum concentrations of T₄ and TSH such that small changes in the serum FT₄ concentration are associated with much larger changes in the TSH level (155). As a result, L-T₄ is a drug with a narrow therapeutic index or toxic-to-therapeutic ratio with the potential of significant clinical consequences with minor degrees of excessive or inadequate dosage (26). Variability in dosage due to poor interchangeability was considered potentially especially dangerous in vulnerable populations of patients who require precise dose titration such as children, patients with thyroid cancer, pregnant women, elderly patients, and patients with heart or bone disease (9, 10). If these concerns regarding noninterchangeability were valid, even switching L-T₄ preparations with a 12.5-μg difference could produce clinically relevant effects due to iatrogenic subclinical hyperthyroidism and hypothyroidism (9, 10). However, despite widespread concern about the validity of the current FDA methodology for determining L-T₄ bioequivalence, there are few prospective RCTs that support that criticism (156–159). The few available data extant today are conflicting and controversial and often marred by their own methodological flaws.

It is conceivable that improved manufacturing techniques resulting in products of more uniform potency and content have assuaged many of these earlier concerns. In a 5-year retrospective study of children with CoH, the use of generic L-T₄ treatment appeared to result in better control of their hypothyroidism than the branded comparator

product, Synthroid (160). On the other hand, the opposite result was noted in another recent prospective randomized crossover study that evaluated the bioequivalence of a brand-name L-T₄ (Synthroid) vs an AB-rated generic formulation (Sandoz) in children with severe hypothyroidism (161). The patients received 8 weeks of one L-T₄ formulation followed by 8 weeks of the other. The results suggested that Synthroid and the AB-rated generic L-T₄ are not bioequivalent for patients with severe hypothyroidism due to CoH (161). Reasons for the discrepancy between these two studies have not been proposed.

There are numerous different branded formulations of L-T₄ that are available in the world. They include Eltroxin, Euthyrox, Letrox, Levaxin, L-T₄, Thyrax, and Thyrax Duotab in Europe; Thyrox in South Asia; Eutirox, Synthroid, and Tirosint in Europe and North and South America; and Thyrolar in Bangladesh (148). Given the above concerns and considerations regarding true bioequivalence or interchangeability of different preparations, patients and physicians who are not thyroid specialists should be aware of the possible consequences of a change in L-T₄ dosage or commercial formulation to avoid potential adverse events (150, 162). Patients should be instructed to avoid switching between branded L-T₄ products and should consult their physician should any related adverse effects be suspected. Moreover, should there occur a switch in the T₄ product, thyroid function testing should be repeated within 4 to 8 weeks and dosage retitrated to achieve the therapeutic target (serum TSH level) with the new preparation.

In conclusion, until it is certain that the degree of any differences in branded L-T₄ preparations has little clinical significance, the available literature supports a prudent approach to interchange or substitution of L-T₄ formulations in certain clinical situations, including severe hypothyroidism, children, pregnant women, the elderly, and patients with major comorbidities.

4. Liothyronine

In individuals with normal thyroid function, the major surge of circulating T₃ arises from the 5'-deiodination of T₄ in the liver and other peripheral tissues (133). T₃ is the most active thyroid hormone because its affinity for the nuclear receptor is 10- to 20-fold that of T₄ (131, 132). The ratio of T₄ to T₃ in the human thyroid gland is approximately 15:1 (26). L-T₃ tablets are commercially available in the United States as Cytomel, a synthetic form of the sodium salt available in the United States and Europe in 3 dosage strengths of 5, 12.5, and 25 μg. Most authorities discourage the routine use of L-T₃-containing preparations for thyroid hormone replacement therapy because T₃ has a relatively short half-life and the available

formulations of L-T₃ are rapidly absorbed, resulting in wide nonphysiological fluctuations in serum T₃ levels (3, 26, 32). Typically after T₃ administration, supraphysiological serum T₃ concentrations were maintained for several hours followed by a rapid decline (26).

A recent clinical trial of T₃ therapy for hypothyroid patients by Celi et al (27) has aroused new interest in re-examining the role for T₃ replacement therapy. These authors performed a randomized double-blind crossover study in 10 thyroidectomized patients. Steady-state pharmacodynamic equivalence of T₃ with T₄ was achieved by completely substituting L-T₄ with L-T₃, using a thrice-daily regimen of T₃ in an approximate ratio of 1:3 designed to obtain a target serum TSH of 0.5 to 1.5 mU/L (27). The assessment of the dynamic pituitary response to escalating doses in a TRH stimulation test showed that this T₃ ratio obtained a near-identical degree of pituitary euthyroidism compared with equivalent doses of L-T₄ (163). Patients receiving T₃ achieved reduced body weight and an improved lipid profile after 6 weeks of treatment with T₃ with no significant adverse effects on cardiac function, insulin sensitivity, or QOL (164). Additional prospective double-blind randomized and controlled larger studies will be necessary to determine whether potential beneficial effects of L-T₃ therapy may be achieved without accompanying adverse effects.

Currently, the clinical use of L-T₃ as monotherapy is quite limited. L-T₃ generally is reserved for use as a second-line drug with specific indications for conditions such as MC or as short-term therapy in patients with DTC when L-T₄ therapy is being withdrawn or restarted in preparation for radioiodine therapy. The rationale for the latter brief interval of T₃ therapy is to reduce the duration of hypothyroidism and its associated symptoms and improve the QOL of patients with DTC undergoing radioiodine therapy (26).

5. Preparations containing both L-T₃ and L-T₄

Some commercially available tablets are available throughout the world of mixtures of synthetic L-T₃ and L-T₄ doses in various ratios of content. However, such fixed-combination products do not allow personalization of dosing to attempt to provide the most physiological ratio of the two hormones for the treatment of hypothyroid patients.

6. Liquid thyroid hormone preparations

Recently, oral soft gelatin capsules (TIROSINT; L-T₄ sodium capsules), containing L-T₄ dissolved in inactive ingredients gelatin, glycerin, and water have become available in the United States. This new formulation is therapeutically equivalent with the same preparation in a tablet

formulation by pharmacokinetic analysis (165). The same commercial formulation is also available in Europe in an oral liquid formulation of either L-T₃ or L-T₄ that can be administered as drops and have been shown to be bioequivalent to tablets of the two hormones (166). Some studies have suggested a different dissolution and absorption profile of these liquid formulations compared with solid formulations. Initial studies have suggested their potential utility in patients affected by changes in gastric pH such as those with chronic gastritis or lactose intolerance or those receiving histamine H₂ receptor blockers and proton pump inhibitors (167–169). This liquid L-T₄ preparation may allow 100% absorption from the gastrointestinal (GI) tract with relatively immediate dissolution apparently relatively unaffected by pH (169).

V. Replacement Therapy With L-T₄ in Hypothyroid Patients

A. Treatment of primary hypothyroidism

1. Overt hypothyroidism: evidence for treatment

Although the normal thyroid gland secretes both T₄ and T₃, currently, only L-T₄ is recommended as a replacement therapy for hypothyroidism. Guidelines from all professional societies, including the European Thyroid Association (ETA), the ATA, the AACE, and the ES recommend L-T₄ monotherapy as the treatment of choice for all patients with persistent overt hypothyroidism (1–3, 17–21, 32). Patients with hypothyroidism should be treated to prevent the risk of progression to a more severe disease and to avoid the risk of adverse cardiovascular events. The goal of replacement therapy in hypothyroid patients is to restore biochemical and clinical euthyroidism. Treatment with L-T₄ is generally considered safe and well tolerated. It is important to normalize the serum TSH during replacement doses of L-T₄ because a high-normal and undetectable low-normal serum TSH have been associated with an increased cardiovascular risk (9, 10, 47, 48).

Replacement treatment with L-T₄ to achieve a target TSH level should be individualized in patients with hypothyroidism, and the desired TSH level may vary in different patient populations. In the NHANES III disease-free population, 86.7% of young people from 20 to 29 years of age had TSH concentrations in the category of 0.4 to 2.5 mIU/L and only 2.5% had TSH values greater than 4.5 mIU/L (51). Therefore, in our opinion, the target TSH level with replacement therapy should be from 1 to 2.5 mIU/L in young patients, although data supporting a target TSH in this range in hypothyroid young patient are lacking. An

age-adjusted serum TSH should be targeted in middle-aged and elderly patients (9, 10, 47, 48).

A double-blind, randomized clinical study with a crossover design has shown that the target TSH for treatment of primary hypothyroidism in the lower part of the reference range does not improve the persistence of symptoms or optimize the QOL in middle-aged and elderly patients with primary hypothyroidism (170).

After establishing appropriate initial dosage, TSH concentrations should be reassessed every 6 to 12 months to ensure that they remain within the normal range (9, 10).

Untreated overt hypothyroidism can lead to an increased risk of atherosclerosis, coronary heart disease (CHD), heart failure (HF), pericardial and pleural effusion, and ventricular arrhythmias because thyroid hormone has profound effects on the vascular system, cardiac function, and lipid profiles (171–175). Overtly hypothyroid patients may have elevated levels of serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, apolipoprotein B, lipoprotein(a), and triglycerides, which are reversible with L-T₄ therapy (9, 10, 175, 176). Postmortem studies in patients with hypothyroidism have documented the link between atherosclerosis and thyroid hormone deficiency (175).

One meta-analysis involved a pooled examination of 17 417 individuals with overt hypothyroidism to assess mortality risk (177). Although the results of this analysis did not show an increased mortality in patients with hypothyroidism compared with the control group, the authors concluded that the available studies are not adequately designed to determine whether hypothyroidism contributes to mortality. In fact, many patients were treated with L-T₄ during the follow-up interval, thereby potentially affecting the study results. The authors of this meta-analysis estimated that a Cox regression analysis would require a study population of 900 cases to detect a 20% increase in mortality. As a consequence, most of the studies extant could be considered underpowered to assess the cardiovascular and total mortality in overt hypothyroidism (177).

Treatment with L-T₄ will prevent progression of hypothyroidism to a more profoundly hypothyroid state (myxedema) and may improve symptoms, QOL, and the risk of cardiovascular complications (9, 10, 36). Normalization of a variety of clinical and metabolic end points (heart rate, systolic and diastolic function, diastolic blood pressure [BP], systemic vascular resistance [SVR], arterial stiffness, serum cholesterol levels, serum creatine kinase, or other muscle or hepatic enzymes, sleep pattern, menstrual cycle abnormalities, fertility, etc) have been documented when a euthyroid state is reached during optimal replacement therapy with L-T₄ (36, 173–175).

During pregnancy, hypothyroidism should be treated to avoid adverse obstetric outcomes and the impaired neuropsychological development that may occur in the offspring of untreated women (17–19, 178).

After delivery of an infant with CH, treatment should be treated with optimal doses as soon as possible to avoid the risk of an adverse neurological outcome (20–22).

2. Subclinical hypothyroidism

a. Evidence for treatment. Patients with SHypo have a significantly increased risk of progression to overt hypothyroidism, are more frequently symptomatic, and may have an increased risk of HF and CHD events and mortality (9, 10). The serum TSH concentration represents the most important predictive factor of progression to overt hypothyroidism. In the study by Díez et al (93), TSH levels greater than 10 to 15 mU/L were associated with a hazard ratio (HR) of 9.69 for the development of overt disease; this risk increased even more (HR, 27.9) when serum TSH was 15 to 19.9 mU/L.

Although the degree of cardiovascular risk associated with SHypo remains controversial, some clarity may be gleaned from the various meta-analyses that have critically evaluated the results of all of the available prospective studies (179–183) (Table 8). A modest increased risk of CHD and mortality was reported in 3 of these analyses (181–183), although heterogeneous results were found among the selected epidemiological studies. The risk of CHD increased with the severity of thyroid hormone deficiency and was even higher when TSH values were above 10 mU/L (182, 183). Furthermore, as assessed in 2 meta-analyses, the risk of all-cause mortality (181) and mortality from CHD (183) were particularly increased in patients with comorbid conditions. However, the prospective studies that were included in these analyses differ in respect to several important points: 1) the inclusion of individuals who varied in terms of age, sex, race/ethnicity, and lifestyle; 2) the duration of follow-up; 3) cutoff values of TSH levels considered to define SHypo; 4) the methods employed to assess the risk of CHD; and 5) confounding factors used for adjustment of cardiovascular risk. The validity of these meta-analyses to accurately assess the risk of CHD events and mortality in patients with SHypo is limited or precluded by these important limits and the lack of individual participant data from the selected cohort studies.

A recent meta-analysis assessed the risk of CHD events, CHD mortality, and total mortality from an evaluation of the data derived from 55 287 participants from 11 prospective studies on SHypo from United States, Europe, Australia, Brazil, and Japan (184). The risk of CHD events and CHD deaths was examined in 25 977 participants

Table 8. Summary of Meta-analyses Assessing the Risk of Coronary Artery Disease Events, Cardiovascular Mortality, and Total Mortality in Patients With SHypo

| Study | Ref. | Year | Studies Included | TSH, mU/L | RR or HR ^a |
|----------------------------|------|------|------------------|-----------|-----------------------|
| CHD events | | | | | |
| Singh et al | 180 | 2008 | 3 | | RR 1.18 (1.02–1.37) |
| Razvi et al ^b | 182 | 2008 | 6 | | HR 1.27 (0.95–1.22) |
| Ochs et al ^c | 183 | 2008 | 10 | | HR 1.20 (0.97–1.49) |
| Rodondi et al ^d | 184 | 2010 | 7 | | HR 1.18 (0.99–1.42) |
| | | | | 10–19.9 | HR 1.89 (1.28–2.80) |
| | | | | 7.0–9.9 | HR 1.17 (0.96–1.43) |
| HF events | | | | | |
| Gencer et al ^e | 188 | 2012 | 6 | <10 | HR 1.65 (0.84–3.23) |
| | | | | >10 | HR 1.86 (1.27–2.72) |
| Cardiovascular mortality | | | | | |
| Razvi et al | 182 | 2008 | 8 | | HR 1.09 (0.84–1.41) |
| Ochs et al | 183 | 2008 | 8 | | HR 1.18 (0.98–1.42) |
| Rodondi et al ^f | 184 | 2010 | 10 | | HR 1.14 (0.9–1.32) |
| | | | | 10–19.9 | 1.58 (1.10–2.27) |
| | | | | 7.0–9.9 | 1.42 (1.03–1.95) |
| Total mortality | | | | | |
| Singh et al | 180 | 2008 | 3 | | RR 1.15 (0.99–1.25) |
| Haentjens et al | 181 | 2008 | 9 | | HR 1.22 (0.96–1.57) |
| Ochs et al | 183 | 2008 | 6 | | RR 1.12 (0.99–1.26) |
| Rotondi et al ^g | 184 | 2010 | 11 | | HR 1.09 (0.96–1.24) |

^a 95% CIs are shown in parentheses.

^b The risk of CHD was significantly increased in subjects 65 years of age or younger but not in those 65 or older. The risk was statistically significant only in women in the meta-analysis by Razvi et al.

^c Risk estimates were lower when higher-quality studies were pooled (RR, 1.02–1.08).

^d The subgroup analysis revealed no evidence of greater risks of CHD events among pooled participants over 80 years of age.

^e The risk of HF persisted after excluding patients with preexisting HF or AF. Among older participants (>80 years old), the risk of HF events was not increased. The risk of HF was increased after excluding participants using thyroid medications (mainly T₄ replacement) at baseline and during periods of follow-up.

^f The subgroup analysis revealed no evidence of greater risks of CHD mortality among pooled participants over 80 years of age.

^g The subgroup analysis revealed no evidence of greater risks of total mortality among pooled participants over 80 years of age.

from 7 cohorts, analyzed with respect to age, sex race, TSH concentrations, and preexisting cardiovascular disease. The severity of SHypo was stratified according to 3 categories of TSH concentration: 4.5 to 6.9, 7.0 to 9.9, and 10.0 to 19.9 mU/L. Separate Cox proportional hazard models were used to assess the relationship between SHypo and CHD events and mortality for each cohort. The risk of CHD events and mortality from CHD increased with higher TSH concentrations. In age- and sex-adjusted analyses, the HR for CHD events was 1.00 (95% CI, 0.86–1.18) for a TSH level of 4.5 to 6.9 mU/L, 1.17 (95% CI, 0.96–1.43) for a TSH level of 7.0 to 9.9 mU/L, and 1.89 (95% CI, 1.28–2.80) for a TSH level of 10 to 19.9 mU/L ($n = 70$ events per 235; 38.4 per 1000 person-years; $P < .001$ for trend). The resulting HRs for CHD mortality were 1.09 (95% CI, 0.91–1.30), 1.42 (95% CI, 1.03–1.95), and 1.58 (95% CI, 1.10–2.27, $n = 28$ deaths per 333; 7.7 per 1000 person-years; $P = .005$ for trend). Total mortality was not increased among participants with SHypo, and the results were similar after further adjustment for traditional cardiovascular risk factors. Risks did not significantly differ by age, sex, or preexisting car-

diovascular disease. This analysis demonstrates a significant trend of increased risk of both CHD events and mortality at higher serum TSH concentrations, particularly in participants with a TSH level of 10 mU/L or greater (184).

Other studies indicate that SHypo may worsen cardiovascular hemodynamics and lead to HF (173, 185), with an increased incidence of HF observed in patients with TSH concentrations of more than 7 to 10 mU/L (104, 186, 187). A recent meta-analysis performed a pooled analysis of individual participant data using all the available prospective cohorts with thyroid function tests and subsequent follow-up of HF events (188) (Table 8). The pooled analysis was stratified according to age, sex, gender, race, TSH levels, and preexisting cardiovascular disease and HF, thereby accounting for the heterogeneity inherent in the available cohort studies related to the risk of HF events. SHypo was defined as a TSH of 4.5 to 19.9 mU/L with normal reference range thyroid hormone levels. There were 25 390 participants in this individual data analysis that included 2068 subjects with SHypo from 6 prospective cohorts from the United States and Europe. The risk of HF events was related to higher TSH levels with

a statistically significantly increased risk among those with TSH above 10.0 mU/L (HR, 1.86; 95% CI, 1.27–2.72). The increased risk of HF in adults persisted after excluding those with preexisting HF or atrial fibrillation (AF). Further adjustments for cardiovascular risk factors and other potentially confounding risk factors for HF did not significantly change the association with HF events. Among older participants (>80 years old), the risk of HF events was not increased. The risk of HF was increased after excluding participants using thyroid medications (mainly T₄ replacement) at baseline and during periods of follow-up (188).

In our view, these two important meta-analyses (184, 188) provide sufficient evidence to justify the treatment of patients with SHypo having a serum TSH level above 10 mU/L to reduce the risk of CHD and HF, and L-T₄ monotherapy has been recommended for such patients (3) (recommendation 15, grade B). Data in the available literature results are considered sufficient for this recommendation with the belief that treatment of this condition may avoid the risk of progression of CHD and cardiovascular risk (3, 10).

b. Benefit of treatment with replacement doses of L-T₄. Various placebo-controlled studies have assessed the effects of L-T₄ replacement therapy on symptoms and signs in patients with SHypo. The results of these studies have been often conflicting (9, 10). A comparative analysis of these studies is difficult because they enrolled heterogeneous patients in terms of the causes of hypothyroidism, age, severity of thyroid hormone deficiency, duration of replacement therapy, and L-T₄ dose, and in addition, employed differing scoring systems to assess the symptomatic response to treatment (9, 10). However, despite these limitations, it is reasonable to conclude that there are beneficial effects of L-T₄ treatment on mood, cognition, and symptoms in patients with SHypo that are most apparent in patients with serum TSH greater than 10 mU/L (9, 10).

The link between SHypo and lipid values is also somewhat controversial (189). Contradictory results have been published in regard to whether there are significant differences in levels of serum total cholesterol, LDL-cholesterol, high-density lipoprotein cholesterol, or triglycerides between euthyroid control subjects and patients with SHypo, especially in patients with a mild increase in TSH (189). Eight placebo-controlled randomized clinical trials have examined the effects of replacement L-T₄ therapy on serum lipids in SHypo (9, 10). L-T₄ did not reduce total cholesterol in 4 studies but had a beneficial effect in the other 4 studies with the more evident improvement in lipid profile observed in patients with TSH above 10 mU/L (9, 10). In a meta-analysis of 13 studies on 200 patients with

thyroid hormone deficiency, the beneficial effects of replacement therapy with L-T₄ on lipid levels were proportional to both the severity of hypothyroidism and the magnitude of the elevation in lipid levels (112). Patients who had higher baseline serum lipid values showed a greater reduction in serum lipid concentrations after thyroid hormone treatment (112).

No clinical trial has assessed the benefit of replacement doses of L-T₄ on the frequency of CHD and HF events, but a survival benefit was associated with L-T₄ therapy in some studies (190, 191).

In the reanalysis of the Wickham survey on 97 individuals (mean age, 49 years), during a 20-year follow-up, all-cause mortality was significantly lower in L-T₄-treated patients with SHypo than in untreated individuals after adjusting for age, gender, and cholesterol levels (190). Further adjustment for other risk factors for ischemic heart disease did not change the results with an HR of 0.22 (0.06–0.81; *P* < .02). Moreover, L-T₄ treatment was noted to be associated with lower all-cause mortality in patients with moderate hypothyroidism (191), and the risk of HF events was significantly lower in L-T₄-treated patients with TSH >10 mU/L in the Cardiovascular Heart Study (187).

In summary, the evidence appears substantive for a beneficial effect of L-T₄ replacement therapy in patients with TSH >10 mU/L that could serve to reduce progression of cardiovascular risk. Despite the lack of definitive long-term studies on the outcome of mild to moderate hypothyroidism with and without replacement therapy, recommendations for treatment of these patients recently have been formulated (3). Prospective randomized clinical trials will be necessary to assess the beneficial effects of L-T₄ in patients with SHypo and establish a guideline for the optimal TSH cutoff level that would indicate the value of replacement therapy that would provide improved symptoms, QOL, and cardiovascular morbidity and mortality. For the longer-term follow-up of these patients, it should be mentioned that those patients with serum TSH above 10 mU/L are more likely to progress to overt hypothyroidism with time and need to be monitored with increases in L-T₄ dosage as required.

3. Management of patients with minimally increased serum TSH

a. Evidence in favor of treatment. Whether or not to treat patients with mild SHypo remains controversial, in part because of differing opinions on what constitutes the TSH reference range and therefore what constitutes an increase in serum TSH. However, having considered a given value as slightly elevated and instituted T₄ treatment, the rate of TSH normalization is faster in patients who have a lesser

degree of serum TSH elevation (TSH values <4 – 8 mU/L). This is especially true in patients with negative antithyroid antibody titers, suggesting that patients with a mild TSH increase and nonautoimmune thyroiditis may frequently have transient TSH elevation (9, 10). Some justification for treatment may be inferred from the presence of elevated serum lipids, which is more likely to be seen in patients with SHypo and serum TSH of >10 mU/L, in smokers, and in insulin-resistant patients (9, 10). However, an argument against treatment may be made based upon 2 recent meta-analyses indicating that mild SHypo was not associated with an increased risk of CHD and HF events (184, 188).

Although these 2 important meta-analyses provide evidence for treating particularly those patients with SHypo with serum TSH >10 mU/L, limitations inherent in the studies reported deserve mention. These include 1) inclusion of a study population that was predominantly white with the exception of 2 studies from Japan and Brazil; 2) the lack of follow-up data on thyroid function, which was assessed only at baseline evaluation, thereby precluding assessment of each individual's response to treatment and either progression, stabilization, or regression of the SHypo; and 3) the lack of FT₃ assessment in most cohorts, which would prove useful to exclude other causes of increased TSH levels, eg, as in elderly subjects.

b. Effects of treatment with replacement doses of L-T₄. Reports of the effects of L-T₄ treatment of SHypo on lipid profile, specific symptoms of hypothyroidism, or cognitive and neuropsychiatric symptoms have been conflicting, indicating either benefit or lack of benefit (9, 10). However, there is evidence in some placebo-controlled studies of potential improvement of cardiovascular hemodynamics and cardiovascular risk factors with L-T₄ therapy in patients with TSH <10 mU/L (192). Mild SHypo may be associated with a greater cardiovascular risk in young and middle-aged people (192, 193).

Recently, Razvi and co-workers (193) examined the outcomes of treated individuals with mild SHypo (serum TSH of 5.01–10.0 mU/L) by analyzing data from the United Kingdom General Practitioner Research Database. All analyses were stratified according to subsequent L-T₄ treatment for younger (40–70 years) vs older (<70 years) patients. For a median follow-up period of 7.6 years, 52.8% of younger and 49.9% of older patients with mild SHypo were treated with a median L-T₄ dosage of L-T₄ of 75 μ g/d (range, 12.5–175 μ g/d). This analysis indicated that treatment of mild SHypo with L-T₄ was associated with better outcomes in younger (<70 years) people with respect to incident fatal and nonfatal ischemic heart disease events and mortality (193).

On the other hand, treatment of older people with SHypo was not associated with similar benefits. After adjustment for baseline cardiovascular risk factors, age, sex, baseline serum TSH levels, and L-T₄ use, the number of incident ischemic heart disease events was lower in the L-T₄-treated younger group (adjusted HR, 0.61; 95% CI, 0.39–0.95) (193). All-cause mortality was lower in the treated younger group (multivariate-adjusted HR, 0.36; 95% CI, 0.19–0.66), primarily because of a reduction in circulatory and cancer-related deaths (193). Incident cerebrovascular disease events were unchanged, and incident AF was not related to L-T₄ exposure (193). This study clearly demonstrated the benefit of replacement therapy in young patients with mild TSH increase; however, its major limit is the retrospective design.

Therefore, although some studies have demonstrated the potential beneficial effects of L-T₄ therapy to improve cardiovascular risk patients with mild SHypo, large randomized controlled studies will be required to assess the importance of this treatment in the presence of minimal TSH elevation. It has been estimated that an appropriately powered RCT of L-T₄ therapy in 40- to 70-year-old people with SHypo will require the recruitment of about 1450 individuals.

The Thyroid Hormone Replacement for Subclinical Hypothyroidism trial (TRUST), a multicenter double-blind placebo-controlled randomized trial is recruiting 3000 older adults with hope of clarifying the effects of thyroid hormone replacement therapy in untreated older adults with SHypo (194). Moreover, the Institute for Evidence-based Medicine in Old Age (IEMO), started the 80-plus Thyroid Trial Collaboration, a multicenter trial on participants aged 80 years and older, to evaluate the effect of treatment with L-T₄ on several endpoints (cardiovascular disease and mortality, cognitive and physical function, and QOL) in elderly subjects (195).

c. Recommendations for treatment. Patients with SHypo and new onset of symptoms or depression, goiter, or cardiovascular risk factors (eg, hypertension, hypercholesterolemia, insulin resistance or diabetes, kidney failure, or isolated diastolic dysfunction) might benefit from L-T₄ treatment (9, 10). Moreover, treatment of mild SHypo may be indicated in patients with positive antithyroid antibody tests and a progressively rising TSH level to avoid worsening thyroid function (9, 10). On the other hand, the SHypo may be transient in some patients with an initial slightly increased TSH level that returns to well within the reference range with further follow-up. In such patients, serum TSH concentrations could be assessed at yearly intervals to avoid the risk associated with unnecessary treatment (9, 10). If a therapeutic trial is implemented, replace-

ment therapy should be stopped in the absence of a clear beneficial effect or with development of an undetectable TSH with low doses of L-T₄. Young patients with serum TSH concentrations from 3 to 4.5 mU/L should be monitored with periodic thyroid function tests, particularly if they have positive TPOAbs (9, 10, 47).

B. Determinants of L-T₄ requirements and starting dose of L-T₄

Although achieving optimal L-T₄ replacement may seem a rather straightforward task, consistently reaching the target TSH may be rendered problematic due to a variety of factors including the cause and severity of hypothyroidism, sex, age, gender, menstrual status, body weight, lean body mass and body surface area, comorbidities, pathological or physiological conditions, drugs, and adherence to therapy (Table 9).

The dose requirement of L-T₄ is higher in infants and children (20, 21) and is usually higher in younger compared with elderly patients. In some studies, elderly patients required lower doses of L-T₄ than younger patients with an age-related decline in L-T₄ dose in men compared with women (196–198). The dose requirement of L-T₄ also seems to be associated with hormonal status, with lower doses required in postmenopausal women compared with premenopausal women (198). A study on 50 patients after thyroidectomy found that the weight-based L-T₄ dosage required to normalize TSH was 1.7 μg/kg in both sexes; however, premenopausal women appeared to need a greater dosage than both postmenopausal women and men (196). However, in contrast to these studies (196, 198), in another study, hormonal status in women did not

significantly affect L-T₄ requirement because replacement doses did not differ between premenopausal and postmenopausal women (199). Moreover, men had a lower requirement than premenopausal women (199).

Gender-based differences in L-T₄ dosage became apparent only when the degree of overweight was included in the analysis (199).

Body weight is directly related to L-T₄ dose (200, 201). Moreover, it has been reported that the most appropriate replacement therapy dosage correlates best with lean body mass rather than total body weight, suggesting that adipose tissue is less metabolically responsive to L-T₄ than the muscle compartment (202–204). A large retrospective study in euthyroid patients (without serious chronic conditions or confounding medications) who were receiving L-T₄ replacement therapy for primary hypothyroidism suggests that age-gender differences in doses of L-T₄ may be secondary to differences in body weight, lean body mass, and ideal body weight (199). In this study, multivariate analysis indicated that body weight and body composition, but not age, influenced the L-T₄ requirement (199). These data suggest that the age-related decrease in L-T₄ requirement is mediated by alterations in body weight and body composition (199).

Most clinicians initiating L-T₄ therapy will base dose selection on body weight (200).

Usually body weight is considered a good indicator for calculating an appropriate starting dose of L-T₄. Most patients are well treated with a narrow dose window that varies according to body weight from 1.6 to 1.8 μg/kg/d for replacement therapy in young and middle-aged pa-

Table 9. Determinants of L-T₄ Requirements

| Determinant | Dosage Requirements |
|----------------------------|--|
| Etiology of hypothyroidism | Larger doses are required in athyreotic patients compared with patients with residual thyroid function (thyroidectomized patients vs autoimmune hypothyroidism and radioiodine-ablated patients) |
| Severity of hypothyroidism | Lower doses are required in patients with CH Larger doses are required in patients with overt hypothyroidism compared with mild and subclinical disease |
| Age | Decrease in L-T ₄ requirement with advancing age |
| Gender | Men have a lower requirement than premenopausal women |
| Adherence to therapy | Variable adherence may falsely suggest an increased requirement of L-T ₄ |
| Body weight | Good parameter to start L-T ₄ therapy |
| Lean body mass | Better parameter to assess L-T ₄ requirement |
| Ideal body weight | Best parameter to assess L-T ₄ requirement |
| Deiodinase activity | Reduced activity in elderly patients, obese patients, some chronic and acute illnesses, important surgery procedures |
| Deiodinase polymorphisms | Increased activity in tumors that express D3 (hemangiomas, vascular tumors) |
| Pregnancy | Increment in dosage |
| Interferences | 30%–50% increment in dosage |
| Food and beverage | Increment or decrement in dosage |
| Herbal remedies | |
| Drugs | |

tients with primary hypothyroidism and 2.0 to 2.5 $\mu\text{g}/\text{kg}/\text{d}$ when suppressive doses of L-T_4 are desired (199).

However, severely obese individuals may need higher L-T_4 -suppressive or replacement doses than normal-weight individuals due to the impaired L-T_4 pharmacokinetic parameters (higher plasma volume and/or to delayed GI-L-T_4 absorption) and their altered T_4 to T_3 conversion (205).

The etiology and severity of hypothyroidism may affect the L-T_4 dosage. The amount of residual functional thyroid tissue may contribute to the T_4 production and affect the replacement dose of L-T_4 (201, 206, 207). Higher doses of L-T_4 generally are required in thyroidectomized patients compared with patients with autoimmune hypothyroidism or after radioiodine thyroid ablation for Graves' disease (208–210). Patients with SHypo require lower doses of L-T_4 than patients with overt disease (9, 10). One randomized control trial evaluated the efficacy of selecting T_4 doses on the basis of the initial levels of serum TSH (25 μg for TSH 4.0–8.0 mU/L, 50 μg for TSH 8–12 mU/L, and 75 μg for TSH >12 mU/L) and reported that only minimal adjustments were required after this initial dose selection to achieve euthyroidism, according to their criteria for optimizing TSH on L-T_4 replacement therapy (211). Not surprisingly, this study suggested that doses of 25 to 75 μg daily are usually sufficient for achieving euthyroid levels in patients with mild hypothyroidism and that larger doses are usually required in patients with more severe disease. This study suggests that it might be useful to start treating SHypo with low doses of L-T_4 to normalize the serum TSH with the minimal amount of L-T_4 to avoid overtreatment.

Lower doses tend to be required in patients with CH (81); the estimated starting dosage of L-T_4 is 1.3 $\mu\text{g}/\text{kg}/\text{d}$ (212).

Optimal management of L-T_4 replacement treatment should take into account conditions increasing the L-T_4 requirement (eg, pregnancy, glomerular disease, malabsorption, drugs interfering with L-T_4 absorption, increased metabolism, or deiodinase activity) or those conditions that may decrease the L-T_4 dose (weight loss, withdrawal of drugs interfering with L-T_4 , and atrial arrhythmias).

Higher doses of L-T_4 are needed in pregnant women. The L-T_4 dose often needs to be incremented by 4 to 6 weeks gestation and may require a 30% to 50% increment in dosage over that taken in the nonpregnant state (17–19). Overt hypothyroidism discovered during pregnancy should be corrected as soon as possible with a full starting dose of L-T_4 of about 2.0 to 2.4 $\mu\text{g}/\text{kg}/\text{d}$ (17–19). It has been recommended that a 2-tablet per week increase in L-T_4 dosage be initiated as soon as pregnancy is confirmed

to significantly reduce the risk of maternal hypothyroidism during the first trimester and mimic normal physiology (213).

The increased L-T_4 dosage in hypothyroid pregnant women often depends on the etiology of hypothyroidism. In one retrospective study, the average baseline L-T_4 dose for patients with primary hypothyroidism was 92.5 ± 32.0 , 140.4 ± 62.4 , and 153.2 ± 30.3 μg daily, respectively, for patients with primary hypothyroidism, in patients with hypothyroidism resulting from treated Graves' disease or goiter, and in patients with thyroid cancer (214). The cumulative increase from baseline L-T_4 dosage was 13% in the first trimester, 26% in the second trimester, and 26% in the third trimester ($P < .001$) (214).

Patients with nephrotic syndrome and other severe illnesses may have an altered clearance of L-T_4 and require a higher dose (215, 216). GI diseases may reduce L-T_4 absorption (142). Some drugs or medications may alter L-T_4 absorption, T_4 binding, or thyroid hormone metabolism or affect T_4 to T_3 conversion (79). Patients with D2 polymorphism (threonine 92 alanine) may also need higher doses of L-T_4 to restore euthyroidism (217). Rare tumors that express D3 such as hemangiomas and vascular tumors may increase the L-T_4 requirement (64).

An RCT has shown that a full dose of L-T_4 can be started in adult patients without significant comorbidities (218). In this study, patients were randomized into 2 groups who either started L-T_4 therapy with a full replacement dose (1.6 $\mu\text{g}/\text{kg}/\text{d}$) or with a low L-T_4 dose that was progressively increased every 4 weeks. After 12 and 24 weeks, the authors did not observe any cardiac symptoms or acute cardiovascular events (218). This approach with an initial full replacement dose was deemed safe and more rapidly effective in reversing symptoms of hypothyroidism than the traditional approach of gradually increasing L-T_4 dosage (218).

However, in some conditions, it is not advisable to start a full L-T_4 dosage.

It is considered prudent in patients older than 50 to 60 years without evidence of CHD to start replacement with doses of 25 to 50 $\mu\text{g}/\text{d}$; this dosage should be titrated gradually with a progressive increase every 2 to 3 weeks until euthyroidism is reached (173, 175). In patients with severe ischemic heart disease and in very old patients with severe hypothyroidism, the recommended starting dose should be even lower, with 12.5 $\mu\text{g}/\text{d}$ with a progressive increase of 12.5 $\mu\text{g}/\text{d}$ every 4 to 6 weeks (173, 175). Some patients may need coronary revascularization to tolerate the dosage of L-T_4 required to achieve euthyroidism because a full replacement dose of L-T_4 may trigger severe angina, myocardial infarction (MI), and arrhythmias in patients with asymptomatic underlying ischemic heart dis-

ease (219). Emergency coronary artery bypass grafting in patients with unstable angina or left main coronary artery occlusion may be safely performed while the patient is still moderately to severely hypothyroid (173, 175).

On theoretical grounds, an exacerbation of adrenal insufficiency may occur when starting full replacement therapy with L-T₄ in patients with central or autoimmune unsuspected adrenal disease. Although it rarely occurs, patients at risk should be treated with clinically appropriate doses of hydrocortisone until adrenal insufficiency is ruled out (220, 221).

For the newborn, the American Academy of Pediatrics and the European Society of Pediatric Endocrinology recommend a dose of 10 to 15 $\mu\text{g}/\text{kg}/\text{d}$ (about 37.5–50 $\mu\text{g}/\text{d}$) (20, 21). This dosage permits prompt FT₄ and TSH normalization without adverse effects on growth and skeletal maturation (20, 21). The discovery of CH in utero is rare; however, when confirmed or strongly suspected, it can be managed with intra-amniotic injections of L-T₄. Alternatively, treatment of infants in the first 2 to 4 weeks of life avoids the potential risks associated with treatment in utero and is associated with an excellent prognosis.

In conclusion, different conditions may affect the L-T₄ requirement. The starting doses of L-T₄ will vary depending upon the cause and severity of hypothyroidism, patient age and sex, BMI, and any underlying physiological or pathological conditions (pregnancy, CoH, and comorbidities) (Table 10).

C. Follow-up and target serum TSH in patients receiving replacement therapy with L-T₄

TSH is the most sensitive indicator of adequacy of L-T₄ therapy during treatment with replacement doses in hypothyroid patients (222). TSH levels will decline within a month after starting L-T₄ therapy. Dose adjustments are usually guided by serum TSH determinations every 4 to 8

weeks to give sufficient time to reset the pituitary gland between dosage changes (3). Changes of about 12.5 to 25 $\mu\text{g}/\text{d}$ are initially made, but even smaller changes may be necessary to achieve the desired TSH levels. In patients with primary hypothyroidism, TSH levels should be normalized to a target level within the reference range, considering the age of patients and concomitant physiological or pathological conditions (3, 9, 10). Periodic follow-up evaluations with repeated TSH testing at 6- and 12-month intervals are appropriate in patients with stable euthyroidism during L-T₄ therapy.

Thyroid hormone requirements are increased in pregnancy and return to the prepregnancy range after delivery when the dose of L-T₄ should be reduced (17–19). More frequent evaluations of thyroid function are necessary in pregnant patients and in patients receiving drugs that can interfere with thyroid function, those with malabsorption, and/or those losing or increasing their body weight. Dosage adjustments are necessary when medications influencing absorption, plasma binding, or metabolism are either added or discontinued. In addition to the TSH level, adequacy of therapy is mostly reflected by the combination of measurements of FT₄ and FT₃ levels. The assessment of serum FT₄ targeting the mid reference range should be considered when monitoring L-T₄ therapy. However, FT₃ levels may remain in the low-normal reference range in a significant subset of thyroidectomized patients receiving replacement doses of L-T₄ (28–30).

In patients with CoH, adequate L-T₄ replacement therapy is necessary during the first 2 to 3 years of life to optimize the likelihood of normal brain development (20–22). It is important to emphasize that the target level of serum TSH in patients with CoH should be <5 mU/L (optimal values, 0.5–2.0 mU/L) with a serum FT₄ or total T₄ in the upper limit of the normal range. During the first

Table 10. Starting L-T₄ Dose According to the Age of the Patients and Physiological and Pathological Conditions

| Age/Condition | Starting L-T ₄ Dose |
|---|--|
| Adults with primary hypothyroidism | 1.6–1.8 $\mu\text{g}/\text{kg}/\text{d}$ for replacement doses 2.0–2.5 $\mu\text{g}/\text{kg}/\text{d}$ for TSH suppressive doses of L-T ₄ |
| Elderly patients | 25–50 $\mu\text{g}/\text{d}$ with 25–50 $\mu\text{g}/\text{d}$ incremental dose every 3–4 wk |
| Very elderly patients | 12.5–25 $\mu\text{g}/\text{d}$ with 12.5–25 $\mu\text{g}/\text{d}$ incremental dose every 3–4 wk |
| Patients with CHD | 12.5 $\mu\text{g}/\text{d}$ with 12.5 $\mu\text{g}/\text{d}$ incremental dose every 3–4 wk |
| Pregnancy | 30–50% increment in dosage (~2.0–2.4 $\mu\text{g}/\text{kg}/\text{d}$) |
| Congenital hypothyroidism | 10–15 $\mu\text{g}/\text{kg}/\text{d}$ (~37.5–50 $\mu\text{g}/\text{d}$) |
| Hypothyroidism during the first 6 mo of age | 8–10 $\mu\text{g}/\text{kg}/\text{d}$ (~25–37.5 $\mu\text{g}/\text{d}$) |
| Hypothyroidism after 6 mo of age | |
| 6–12 mo | 6–8 $\mu\text{g}/\text{kg}/\text{d}$ (~50–75 $\mu\text{g}/\text{d}$) |
| 1–5 y | 5–6 $\mu\text{g}/\text{kg}/\text{d}$ (~75–100 $\mu\text{g}/\text{d}$) |
| 6–12 y | 4–5 $\mu\text{g}/\text{kg}/\text{d}$ (~75–125 $\mu\text{g}/\text{d}$) |
| 12 y to adults | 1–3 $\mu\text{g}/\text{kg}/\text{d}$ (~100–200 $\mu\text{g}/\text{d}$) |
| Infantile CH | 8–10 $\mu\text{g}/\text{kg}/\text{d}$ (~25–37.5 $\mu\text{g}/\text{d}$) |
| Juvenile and adult CH | 1.3 $\mu\text{g}/\text{kg}/\text{d}$ |

Table 11. Target Serum TSH Values According to the Age of the Patients and Physiological Conditions During L-T₄ Therapy

| Age/Condition | Target Serum TSH, mU/L |
|---------------------------|---|
| Preconception | Lower quartile of the reference range, <1.2 |
| Pregnancy (1st trimester) | <2–2.5 |
| Children with CoH | <5 (optimal values (0.5–2.0) with a serum FT ₄ or total T ₄ in the upper limit of the normal range during the first year of life) |
| Young patients | 1–2.5 |
| Middle-aged patients | 1.5–3 |
| Elderly patients | |
| ≤65 y | >4.5 |
| 60–70 y | >6.0 |
| 70–80 y | >7.0–8 |
| CH | Serum FT ₄ levels in the upper half of the normal range |
| Thyroid cancer | Risk-related TSH target |

year of life, the target value of serum total T₄ and FT₄ should be 130 to 260 nmol/L (10–16 μg/dL) and 18 to 30 pmol/L (1.4–2.3 ng/dL), respectively (20–22). Thereafter, FT₄ should be at the upper half of the reference range for age (Table 11).

In summary, the ideal target serum TSH during L-T₄ replacement therapy should be targeted and achieved with consideration of the age of the patients, the cause of hypothyroidism, and any underlying physiological or pathological conditions (3, 9, 10) (Table 11). The follow-up of patients with primary hypothyroidism is shown in Table 12.

D. Drugs interfering with L-T₄ administration

A large number of drugs may affect thyroid function and/or may interfere with the L-T₄ requirement by interfering with absorption of L-T₄ or by other mechanisms (79, 223). Appreciation of the large number of such drugs and their mechanisms of action have been growing in recent years (Table 13). An increased dose of L-T₄ is required in hypothyroid patients receiving these drugs during replacement therapy to maintain euthyroidism.

1. Drugs affecting thyroidal synthesis of T₄ or T₃

Some drugs may induce hypothyroidism and may further aggravate thyroid function in patients with a previous diagnosis of thyroid hormone deficiency. This phenomenon may serve as a rationale for initiation of L-T₄ therapy when hypothyroidism (or perhaps SHypo) is diagnosed. In patients receiving drugs known to potentially alter thyroid function, periodic monitoring of thyroid function tests should be performed, and an increase in L-T₄ doses is usually necessary in patients with a previous diagnosis of hypothyroidism.

a. Lithium. Lithium carbonate is an effective treatment for bipolar disorders. Long-term lithium treatment may lead to goiter in about 50% of cases and may induce subclinical (34%) or overt (15%) hypothyroidism (224). A review of 4681 patients treated with lithium reported a prevalence of hypothyroidism between 3.4% and 23% (225). The mechanism involved in lithium-induced hypothyroidism is due to the inhibition of both thyroid hormone synthesis and release, a cytotoxic effect, and an increased thyroid autoimmunity. The risk of hypothyroidism in patients treated with lithium is increased in the presence of thyroid

Table 12. Follow-Up of Adult Patients With Primary Hypothyroidism and CH

| | Evaluation |
|-----------|--|
| Baseline | Clinical examination, FT ₄ , TSH, TPOAb, anti-Tg antibodies, thyroid ultrasound ECG and Doppler echocardiography in severe hypothyroidism Assessment of autoimmune endocrine disease in patients with suspected APS |
| Follow-up | TSH and FT ₄ 2 mo after starting L-T ₄ 4 wk after every dose adjustment Every 6 mo during the first year Annually in patients with stable TSH values during replacement L-T ₄ therapy Annual thyroid ultrasound in patients with nodular goiter ECG and Doppler echocardiography every month in patients with CHD, arrhythmias, and pericardial-pleural effusion. |

Table 13. Drugs Interfering With L-T₄ Administration**Drug Effect**

| |
|--|
| Drugs that influence thyroid hormone synthesis and release and thyroid autoimmunity |
| Reduction of TH synthesis: lithium, flavonoids, resorcinol, aminoglutetamide, thionamides, thiocyanate |
| Inhibition of iodine uptake: lithium, ethionamide, amiodarone |
| Organification of iodine: amiodarone, sulfonamides, lithium, ketoconazole |
| Cytotoxic effect: lithium, cytokines tyrosine kinase inhibitors |
| Alteration of thyroid autoimmunity: lithium, cytokines, amiodarone, tyrosine kinase inhibitors |
| Drugs altering T ₄ metabolism |
| Drugs that increase serum TBG concentration |
| Estrogens |
| Tamoxifen |
| Raloxifene |
| Heroin |
| Methadone |
| Mitotane |
| Fluorouracil |
| Capecitabine |
| Clofibrate |
| Drugs that decreases serum TBG concentration |
| Androgens |
| Anabolic steroids (danazol) |
| Slow-release nicotinic acids |
| Glucocorticoids |
| Displacement from protein binding sites |
| Salicylates (>2 g/d) and salsalate (1.5–3 g/d) |
| Drugs and food affecting L-T ₄ absorption |
| Cholestyramine |
| Colestipol |
| Aluminum hydroxide |
| Antacids |
| Ferrous sulfate |
| Sucralfate |
| Laxatives |
| Calcium carbonate |
| Proton pump inhibitors and H ₂ blockers |
| Lovastatin |
| Bile acid sequestrants |
| Activated charcoal |
| Anion-exchange resins |
| Drugs affecting thyroid hormone metabolism (increase L-T ₄ requirements) |
| Amiodarone |
| Phenobarbital |
| Rifampicin |
| Phenytoin |
| Carbamazepine |
| Tyrosine kinase inhibitors |
| Sertraline |
| Drugs affecting deiodinase activity |
| Amiodarone |
| Glucocorticoids |
| β-Blocking drugs |
| Propylthiouracil |
| Drugs affecting TSH secretion |
| Dopamine and dopamine agonists |
| Somatostatin analogs |
| Dobutamine |
| Amphetamine |
| Bexarotene |
| GH |
| Bromocriptine |
| Peripheral antagonists of thyroid hormone |
| L-Carnitine |

autoantibodies (50%), female gender (female to male, 5:1), older age, and a prolonged duration of treatment (more than 2 years) (225, 226).

As a consequence, thyroid function and the presence of thyroid autoantibodies should be evaluated before starting lithium therapy and every 6 months thereafter as long as treatment is continued. Once patients develop hypothyroidism and L-T₄ therapy is initiated, lithium treatment may be continued.

b. Amiodarone and other iodinated drugs. Amiodarone is a benzofuran-derived, iodine-rich antiarrhythmic agent used for the treatment of atrial and ventricular arrhythmias (227). A daily dose of 200 to 600 mg of amiodarone provides approximately 7 to 21 mg iodine. This is an extraordinary iodine load relative to the average daily requirement for iodine of 150 μg. Because of this iodine excess, amiodarone may induce hypothyroidism in about 5% to 15% of patients with the highest risk during the first 18 months of treatment, particularly in certain populations including patients living in iodine-sufficient areas, women, the elderly, and patients with positive thyroid antibodies (227, 228). No clear correlation has been demonstrated between the onset of hypothyroidism and the cumulative dose of amiodarone and/or the duration of treatment. The pathogenesis of amiodarone-induced hypothyroidism is related to the inability of the thyroid gland to escape from the acute Wolff-Chaikoff effect after an iodine load in patients with preexisting Hashimoto's thyroiditis (227, 228). Chronic amiodarone therapy may also decrease T₄ deiodinase activity, resulting in a 150% increase in rT₃ and a 15% to 20% reduction in FT₃ (227, 228). Amiodarone also inhibits T₄ transport in the liver, decreasing T₄ metabolism and resulting in a 20% to 40% increase in serum T₄ and FT₄ (227, 228). A transient 20% to 50% increase in TSH levels is observed during the first 3 months of treatment with amiodarone. The increases in total and FT₄ and rT₃ usually occur during the first months of administration in euthyroid subjects.

Optimal management of the patient treated with amiodarone would include a baseline assessment of thyroid function before initiating therapy with repeat follow-up measurements of TSH and FT₄ after the first 3 months of treatment and every 3 months thereafter. If and when hypothyroidism does develop, initiation of L-T₄ therapy may also have a beneficial effect on the underlying heart disease (228). However, it is advisable to titrate the L-T₄ replacement therapy to maintain the TSH values at the upper limit of the normal reference range in view of the likelihood of severe underlying heart disease in these patients. Discontinuing L-T₄ after 6 to 12 months can be considered to reassess thyroid function, and spontaneous remission of

hypothyroidism may be seen in about 60% of the patients who had no antecedent or underlying thyroid disease. Many other iodine-containing compounds may affect thyroid function such as saturated solution of potassium iodine (amount of iodine, 38 mg/drop), Lugol's iodine (6.3 mg/drop), povidone iodine (10 mg/mL), iopanoic acid (333 mg/tablet), ipodate sodium (308 mg/capsule), and various iv radiographic contrast agents (~140–380 mg/mL).

c. Cytokines. Thyroid dysfunction due to increased thyroid autoimmunity may develop in patients receiving long-term treatment with cytokines for their cytotoxic effects. The administration of interferon (α and β), interleukins, and granulocyte macrophage colony-stimulating factor has been associated with hypothyroidism and the development of thyroid autoimmunity (9). Important risk factors for the development of hypothyroidism in patients treated with cytokines include female gender, prolonged duration of treatment, advanced age, and preexistent thyroid autoimmunity (9). Interferon- α is a human recombinant cytokine used in the treatment of breast cancer, Kaposi's sarcoma, chronic hepatitis, and leukemia; its use is associated with the development of thyroid antibodies in 20% of patients who were previously antibody negative (229). Persistent hypothyroidism may develop in about 30% to 40% of patients with positive antithyroid antibodies before treatment (230). There may be an even greater risk of hypothyroidism with coadministration of interferon- α with ribavirin in patients with hepatitis C virus-positive hepatitis, or with IL-2 in the treatment of some tumors (229–231). The mechanism of onset of thyroid autoimmunity by interferon- γ appears related to increases in the expression of cell surface major histocompatibility complex class II molecules (232, 233). IL-1 and TNF- α are known to inhibit both iodine organification and thyroid hormone release. Treatment with IL-2 is associated with transient painless thyroiditis in about 20% of patients (233). Granulocyte macrophage colony-stimulating factor may induce hypothyroidism in about 10% of patients (233).

Pretreatment screening is recommended for all patients to be treated with cytokines. The development of thyroid autoantibodies and the onset of hypothyroidism are not contraindications to continuing therapy with cytokines (233), but L-T₄ therapy should be started as soon as hypothyroidism is documented (233).

d. Tyrosine kinase inhibitors. TKIs are antineoplastic agents indicated in the treatment of some metastatic tumors, including thyroid cancer (234, 235). Hypothyroidism is a well-recognized side effect of these agents. Several mech-

anisms have been proposed to explain the development of hypothyroidism: 1) the inhibition of thyroid iodine uptake (236), 2) the inhibition of thyroid peroxidase (237), 3) a toxic effect with development of painless destructive thyroiditis (238, 239), 4) the inhibition of thyroidal vascularization leading to thyroid atrophy (240–242), or 5) an increase in D3 activity (243). Sunitinib has been associated with hypothyroidism in 14% to 85% of patients, ranging from transient increases in TSH to persistent hypothyroidism (242).

Sorafenib has been associated with TSH elevations in about 18% of patients with metastatic renal cell carcinoma and in 33% of patients with thyroid carcinoma (243–255). Moreover, a peripheral effect is suggested by the development of thyroid function abnormalities during treatment with second-generation TKIs (imatinib, motesanib, nilotinib, and dasatinib) in athyreotic patients (246–248). Imatinib and sorafenib also may increase hepatic metabolism of thyroid hormone.

An increase in dosage of L-T₄ may be necessary in athyreotic patients who are treated with TKIs; therefore, a careful follow-up is necessary during treatment with these drugs (248). Anesthesiologists should be aware of the effects of TKIs on thyroid hormone metabolism that could prove serious in the perioperative period in view of reports of MC or severe hypothyroidism (249).

e. Other drugs. Resorcinol may induce hypothyroidism by inhibition of TPO and the associated reduction of thyroid hormone synthesis. Clinical case reports of patients undergoing resorcinol therapy for dermatological indications reveal thyroid side effects after administration of copious amounts of resorcinol (greater than 34 mg/kg/d) for several months or years (250). Thalidomide may increase the risk of hypothyroidism by a mechanism still unknown (251). SHypo developed in about 20% of patients with multiple myeloma receiving thalidomide in association with chemotherapy. Some nutraceuticals and dietary supplements may induce hypothyroidism (252, 253). In patients taking L-T₄, soy protein supplements may increase the need for L-T₄ by reducing GI absorption (254). Flavonoids are present in plants, beverages, vegetables, and fruits or in many dietary supplements, and soy isoflavonoid has estrogenic activity. The published literature provides evidence that these drugs may have antithyroid effects by inhibiting thyroid peroxidase and deiodinase activity when administered per os (255, 256). On the contrary, soy isoflavones have very little significant effect on L-T₄ requirement during exposure to vaginal epithelium or endometrium (257). Results of a recent study indicated that chronic administration of pure genistein gly-

cone (54 mg/d) does not affect thyroid function in postmenopausal women after 3 years of treatment (258).

2. Drugs interfering with thyroid hormone transport

a. Estrogens, androgens, antiandrogens, and selective estrogen receptor modulators. Some drugs, including estrogens, androgens, antiandrogens, selective estrogen receptor modulators, corticosteroids, and 5-fluorouracil, may interfere with transport of thyroid hormones by altering the synthesis and/or glycidic composition of TBG (223, 259) and induce changes in circulating levels of total T_4 and total T_3 . Oral estrogens increase TBG concentrations by augmenting its sialylation and thereby decreasing its clearance rate and raising its serum concentration. Serum TBG is elevated by about 30% to 50% and serum total T_4 by 20% to 35% with use of the commonly employed dosages of 10 to 100 μg of ethinyl estradiol or 0.3 to 2.5 mg of conjugated estrogens (Premarin) (223, 259). As a consequence, an adjustment of $L\text{-}T_4$ dosage may be necessary in hypothyroid patients also taking these agents. The antiestrogen tamoxifen has only a slight effect on serum TBG concentration (223). On the contrary, androgens reduce sialylation or synthesis of TBG, thereby decreasing circulating levels of total T_4 and total T_3 while increasing FT_4 and T_3 and perhaps requiring a reduction of $L\text{-}T_4$ dosage (223). This effect does not occur in the case of transdermal preparations of estrogens or androgens because of the absence of the first passage of the drug to the liver.

b. Salicylate, clofibrate, furosemide, and heparin. Salicylates in doses >20 g/d inhibit the binding of thyroid hormones to TBG and transthyretin, decreasing the total T_4 concentration by about 20% to 30% without affecting FT_4 . Clofibrate, heroin/methadone, and mitotane also may cause a decrease in serum TBG concentration.

Large iv doses of furosemide (more than 80 mg) may induce a transient increase in serum FT_4 and a decrease in serum total T_4 concentrations by inhibiting the T_4 binding to its carrier proteins (260). Heparin in standard sc doses (5000 U) may inhibit protein binding of T_4 because of its ability to activate lipoprotein lipase. Heparin administration results in a false elevation in the concentration of unbound (free) T_4 in the plasma, particularly when measured by equilibrium dialysis (261). Some medications that increase T_4 and T_3 in vivo may result in an underestimate of free hormone as measured by many hospital or commercial laboratories.

Total serum T_4 corrected for alterations in TBG concentration will provide a more sensitive estimation of T_4 concentration than most popular current methods of free hormone estimation (262).

3. Drugs interfering with $L\text{-}T_4$ metabolism

Some drugs may interfere with TSH, FT_3 , and FT_4 evaluation in patients receiving replacement doses of $L\text{-}T_4$.

a. Antiepileptic drugs. Phenytoin, carbamazepine, hydantoins, phenobarbital, and ritonavir may cause a 20% to 40% decrease in serum total and FT_4 concentration and a smaller reduction in serum total and FT_3 (223, 263). These drugs affect liver cytochrome P450, resulting in an increase in the metabolic clearance and hepatic metabolism of T_4 .

Sertraline lowers serum T_4 concentrations and raises serum TSH. Although the mechanism by which sertraline may affect thyroid function is uncertain, some authors have reported that this drug may increase the clearance of T_4 . An increased dose of $L\text{-}T_4$ is necessary in patients with hypothyroidism treated with $L\text{-}T_4$ who have elevated serum TSH during treatment with sertraline (264).

b. Other drugs. Rifampicin has similar effects to those of the latter agents mediated via an important effect on hepatic mixed-function oxygenase (79). Aminoglutethimide, lithium, methimazole, propylthiouracil, sulfonamides, tolbutamide, propranolol >160 mg/d, and dexamethasone ≥ 4 mg/d may decrease 5'-deiodinase activity (79, 223).

VI. Management of Persistent TSH Elevation in Patients on High-Dose $L\text{-}T_4$ Replacement Therapy

Some patients may have persistently high serum TSH and low T_4 values despite the administration of apparently adequate doses of $L\text{-}T_4$. In this circumstance, a number of possible interfering factors should be considered and excluded, especially when the prescribed $L\text{-}T_4$ doses exceed the theoretical daily dose calculated according to body weight. The following factors should be investigated: 1) poor patient compliance; 2) inadequate or incorrect $L\text{-}T_4$ dosage and/or administration; 3) increased turnover or excretion of $L\text{-}T_4$ related to drugs administered for concomitant illnesses; 4) heterophile antibody interference with the laboratory test (commonly including antimouse antibodies, rheumatoid factor, and autoimmune anti-TSH antibodies) that may cause a falsely elevated serum TSH; 5) $L\text{-}T_4$ malabsorption due to the coexistence of celiac disease, autoimmune gastritis, or administration of drugs that may interfere with $L\text{-}T_4$ absorption (eg, calcium, iron, and H₂-blockers); 6) coexistence with thyroid hormone resistance; and 7) coexistence with adrenal insufficiency, which may induce a TSH elevation reversible with glucocorticoid replacement.

A. Timing of L-T₄ administration

The timing of L-T₄ administration has an important impact on absorption. Awareness of common interferences with L-T₄ absorption such as food is important to achieve the desired stable TSH level. Optimal absorption of L-T₄ occurs with fasting, whereas a reduction of as much as 40% to 80% may be observed during food and drink administration (253, 254).

1. Morning vs evening administration

Some studies have evaluated the efficacy of bedtime dosing of L-T₄ (265–269). In a small nonrandomized study involving 11 hypothyroid patients who had been receiving a stable dose of L-T₄ each morning, a decrease in mean TSH and an increase in FT₄ levels was noted after bedtime administration of L-T₄ compared with the same L-T₄ dose taken in the morning (267). In a subsequent randomized double-blind crossover trial, the same investigators reported that bedtime administration was associated with a mean TSH decrease of 1.25 mU/L, a mean FT₄ increase of 0.07 ng/dL, and a total T₃ increase of 6.5 ng/dL (268). However, no improvement in QOL, lipid profile, and BP was observed with the bedtime regimen (268). Likewise, a randomized trial of 77 patients with newly diagnosed hypothyroidism found no difference in clinical symptoms, QOL, and lipid profile between L-T₄ administration a half an hour before breakfast or 2 hours after an evening meal (269). Bedtime administration did not significantly improve TSH levels in a retrospective study on 15 elderly subjects (265). And 65 patients in a crossover design of a 3- to 8-week regimen were randomized in an examination of the difference in receiving L-T₄ in either a fasting state, at bedtime, or with breakfast (266). In this study, serum TSH levels were lower during L-T₄ administration in the fasting state than during nonfasting conditions. A nonfasting regimen of L-T₄ administration (at bedtime and with breakfast) was associated with higher and more variable TSH concentrations (266).

In a recent prospective, randomized, open-label, crossover study of 45 patients with primary hypothyroidism, L-T₄ administration during a fasting state was compared with administration during breakfast. This study confirmed previous findings because serum TSH level was higher during L-T₄ administration with breakfast than during fasting (2.89 vs 1.9 mU/L, $P = .028$) (270).

2. Daily vs weekly administration

In a randomized crossover study on 12 hypothyroid patients, a once-weekly administration of L-T₄ was effective and well-tolerated. However, TSH levels were increased during the weekly regimen compared with those obtained during the daily dose regimen, suggesting the

necessity for a higher L-T₄ dosage to maintain euthyroidism during the once-weekly regimen (271). In another small single-blind randomized controlled crossover study, twice-weekly L-T₄ administration was able to achieve acceptable biochemical control in elderly patients with primary hypothyroidism (272).

In conclusion, there are conflicting data on the importance of the timing of L-T₄ administration. These varied results may reflect heterogeneity in the causes of hypothyroidism, differences in the patients studied (newly diagnosed vs patients on a stable dose of L-T₄), failure to account for confounders (drugs, etc.), and eating habits relative to drug administration. L-T₄ is generally taken in the morning 30 to 60 minutes before breakfast. The patient should be fasting to minimize or avoid interference with L-T₄ absorption. Traditionally, most patients are compliant with taking their daily dose of L-T₄ in the morning during the fasting state, which has been demonstrated to be the easiest and the best means of administration. Taking L-T₄ 1 hour before breakfast results in lower TSH values compared with taking the medication only 30 minutes before breakfast (266). However, bedtime dosing or L-T₄ administration with breakfast could be useful as an alternative strategy in patients who have difficulty taking their L-T₄ dose regularly in the morning before breakfast.

Noncompliant patients who have problems taking once-daily L-T₄ may engage in a trial regimen of taking their entire L-T₄ dose once weekly or half the dose twice weekly (273). However, this approach should be avoided in patients with underlying heart disease because of the potential exacerbation of CHD and arrhythmias due to the transient supraphysiological hormone concentrations achieved in the first 1 or 2 days. Crushed L-T₄ tablets suspended in water should be given through a nasogastric tube to patients receiving enteral feeding. For optimal absorption, feeding should be interrupted with doses given as long as possible or at least 1 hour before resuming feeding. A weekly im injection of L-T₄ may be a useful therapeutic approach in obtaining biochemical and clinical euthyroidism in patients with persistently increased serum TSH despite high doses of L-T₄ replacement therapy (274).

3. Intravenous thyroid hormone therapy

The option of administering iv L-T₄ solution is not universally available; it should be considered when oral administration cannot be used in patients with severe hypothyroidism (275). Because approximately 70% of an orally administered dose of T₄ is absorbed, individuals unable to ingest L-T₄ should initially receive 70% or less of their usual dose iv.

Patients taking lifelong T₄ replacement therapy will potentially suffer an interruption of that treatment when hos-

pitalized, especially when they are to undergo a surgical procedure and are not able to intake anything by mouth, including medications. A delay of 24 to 36 hours in T_4 ingestion will not be associated with any significant physiological alterations, but the patient who is NPO (nilim per os) for several days is best managed by the administration of parenteral $L-T_4$, preferably by the iv route. For example, prolonged periods of rest or inactivity of the GI tract are common after intra-abdominal procedures, especially when intestinal resection has been performed. For maintenance of euthyroidism in these and other surgical patients, both $L-T_4$ and T_3 are widely available in iv preparations.

The iv dose is typically administered once daily as a bolus injection. Adjunctive iv administration of T_3 has been advocated by some for the treatment of MC, but otherwise its use has little application for hospitalized hypothyroid patients. Because 90% to 100% of orally administered T_3 is absorbed, the iv dose would not need to be reduced. Adequacy of iv T_4 dosage can be monitored in the usual manner with measurements of serum TSH and FT_4 .

B. Poor patient compliance

One daily dose of $L-T_4$ accounts for 14% of the total weekly dose. Therefore, a missed dose of $L-T_4$ may affect FT_4 and TSH levels over several weeks due to the long half-life of $L-T_4$.

High serum TSH with normal (or even high) FT_4 levels may be observed in poorly compliant patients, typically after missing several doses over time but then taking the $L-T_4$ shortly before their follow-up thyroid function blood tests. The prevalence of noncompliant hypothyroid patients has been reported to be between 30% and 80% (276–278) despite the simplicity of $L-T_4$ replacement therapy and its once-daily oral administration.

Some of the following factors may play a role in poor adherence to $L-T_4$ therapy: 1) patients could have poor adherence to $L-T_4$ therapy because they may not be satisfied with the sense of well-being achieved during the initial period of replacement therapy; 2) the cost of the medication may be an important economic consideration in some countries; and 3) patients may be intolerant of side effects related to a sudden increase in metabolism induced by $L-T_4$ therapy, especially if the initially selected dosage is TSH-suppressive.

In one study that assessed compliance in some chronic illnesses (ie, hypothyroidism, hypertension, diabetes mellitus, hypercholesterolemia, or osteoporosis), only about 68% of hypothyroid patients had good adherence to $L-T_4$ therapy (276). In this study, the noncompliance rate in hypothyroid patients was similar to that in other chronic

disorders requiring more complex treatment regimens and more frequent or more complex monitoring (276). The poor compliance rate reached a surprisingly high 82% in one study of 100 patients from public hospitals in Campinas and Rio de Janeiro, who presented with persistently elevated TSH levels irrespective of efforts to increase their $L-T_4$ dose (277). Sixty-two percent of these patients had a poor adherence, including forgetting or neglecting to take their pills in 62%, complaints of intolerance or side effects in 12%, and financial stress in 8% (277). Interestingly, about 18% of these patients had serum T_4 levels in the hyperthyroid range after 1 month of ostensibly appropriate $L-T_4$ dosage (277). Improvement in adherence to $L-T_4$ therapy is usually observed with increasing age, and adherence levels of 80% or better are seen in patients aged 60 years or older (276). On the contrary, the worst medication compliance is seen in adolescents (276).

Irrespective of our awareness of the frequency of non-compliance, it is often difficult to exclude it as the explanation for a persistently elevated serum TSH. Some of the usual measures for assessing compliance include pill counting, counseling methods, interviewing, and laboratory tests to estimate $L-T_4$ absorption. In an RCT to assess the impact of education on $L-T_4$ adherence, a booklet about $L-T_4$ medication was distributed to the patients, but no improvement in compliance was observed (278). Rather than educational materials, it appears that it is the doctor-patient relationship that plays a key role in achieving adherence to the medication regimen. Adherence to treatment may be improved with simple questions to the patient about their difficulties in taking $L-T_4$ medication, by better understanding of psychosocial factors that may impact compliance, or by a discussion of the patient's concerns about potential side effects.

The patient's primary-care physician or relatives could be enlisted to pay special vigilance to the patient's pattern of $L-T_4$ ingestion and help with those noncompliant patients who may have psychological or psychiatric disorders. Such an approach to surveillance has been recommended by psychiatrists for patients presenting the psychopathological features of a Munchhausen syndrome or factitious disorder (279). Patients who falsely insist that they are being compliant but have thyroid function tests indicating otherwise (pseudomalabsorption) may be investigated further with parenteral infusion of $L-T_4$ (280). Such assessments may include administration of a single large dose of T_4 , ie, 1000 μg given in the morning after fasting overnight with serial blood sampling for thyroid function tests at 2, 4, and 6 hours after $L-T_4$ administration (281). Published data suggest that a serum FT_4 peak at 2 hours rising above the upper limit of the normal range (more than 25 pmol/L) with an increment of more than 20

pmol/L suggests poor adherence to treatment, or pseudomalabsorption in most cases (281–285), but unfortunately, there are no well-established standards for this test. Although a dose of 1000 μg of L-T₄ is traditionally used to exclude pseudomalabsorption, some authors have proposed that it would be more prudent to consider a 500- μg dose of L-T₄ to avoid side effects. A radioisotope-labeled L-T₄ (double-labeled T₄) tracer technique may be used to assess T₄ absorption more accurately, but this technique is not generally available for routine clinical practice (135).

C. Interference with absorption of L-T₄

1. Food and beverages

The fraction or degree of L-T₄ absorption and its consistency are important factors that will determine dosage of replacement L-T₄ therapy. Food, juices, milk, coffee, soy products, calcium, iron, multivitamin supplements, higher fiber intake, and a variety of drugs may influence the absorption of L-T₄ (254, 286–289). The ingestion of food is associated with both delayed and reduced L-T₄ absorption. Coffee, especially espresso coffee, impairs L-T₄ absorption; it may interact with T₄ tablets and keep T₄ within the intestinal lumen, making it less available for absorption (287). Dietary fiber and soy products appear to have a small but still significant effect on L-T₄ absorption (254, 288). Grapefruit juice and probably other citric fruits may also impair L-T₄ absorption (289). A recent study by Vita et al (168) suggests that the problem of coffee interference might be overcome by using a soft gel capsule preparation containing T₄ dissolved in glycerine to presumably facilitate more rapid absorption. Patients with impaired acid secretion and potential T₄ malabsorption might benefit from this new L-thyroxine preparation.

2. Drugs

Gastric acidity is important for L-T₄ absorption (140, 141). The variability of gastric acid production contributes to the individual variability observed in daily L-T₄ requirement (140).

Some medications (iron supplements, calcium carbonate citrate and acetate, laxatives, cholestyramine, other resins like kayexalate or colestipol, lovastatin, sucralfate, aluminum, magnesium, orlistat, and raloxifene) may interfere with L-T₄ absorption by altering gastric pH or by direct sequestration of L-T₄ into an insoluble complex (290–298). Moreover, antacids such as proton pump inhibitors and H₂ receptor antagonists may decrease intestinal absorption of L-T₄ by increasing gastric pH (142, 299, 300).

To counteract these inhibitory effects on absorption, calcium and iron supplements should not be taken until 3

to 4 hours after L-T₄ is taken. Moreover, the dose of L-T₄ may need to be increased by 20% to 30% in patients taking these drugs, and stability of dosage control will be affected whenever the regimen of the other drugs is altered.

3. GI diseases

Failure to respond appropriately to higher doses of L-T₄ in compliant patients suggests malabsorption due to a known or occult GI disorder that may require further investigation. Celiac disease is a condition resulting in intolerance to dietary gluten and related proteins; it may be associated with severe symptoms of steatorrhea and weight loss. Celiac disease affects mainly the jejunum and proximal ileum, which are both sites involved in L-T₄ absorption (301). Primary hypothyroidism due to autoimmune disease and celiac disease-related malabsorption may be closely associated on an autoimmune basis (301, 302), and coexistent hypothyroidism is commonly detected in patients with newly diagnosed celiac disease. The prevalence of celiac disease in autoimmune hypothyroidism has been reported to be between 2% and 5% of cases (301), whereas the prevalence of autoimmune hypothyroidism in patients with celiac disease has been reported to be as high as 30% (302). The diagnosis of celiac disorder is easily confirmed by the combination of clinical features and positive serological testing. In the last few years, serological screening with IgA, antiendomysial antibodies that have a high sensitivity (85%–98%) and specificity (97%–100%) and tissue transglutaminase (sensitivity of 95%–98% and specificity of 94%–95%) have substituted for the lesser sensitive measurement of antigliadin antibodies. However, the diagnosis of celiac disease can be missed in some selected cases of IGA deficiency and/or in the presence of atypical or subclinical manifestation of this disorder. Atypical celiac disease accounts for more than half of all cases; it may be characterized by anemia, osteoporosis and subfertility, and may be discovered as a result of investigation done after noting L-T₄ malabsorption (302). The diagnosis of celiac disease is confirmed with observation of the classic findings on endoscopic small bowel biopsy; after implementation of a gluten-free diet, L-T₄ absorption usually will improve (303, 304).

Lactose intolerance is another frequent cause of malabsorption (305). Intestinal infections and small intestinal bacterial overgrowth may develop in hypothyroid patients due to the decreased GI motility and slower oro-cecal transit seen before restoration of euthyroidism (306). Lactose intolerance may be associated with malabsorption syndrome, abdominal pain, flatulence, diarrhea, and weight loss (306).

The normal acid environment in the stomach is necessary for L-T₄ absorption. Therefore, *Helicobacter pylori*

infection and atrophic gastritis may affect L-T₄ absorption due to the severe hypochlorhydria and the increased ammonia production (142). Performance of a ¹⁴C urea breath test and serological tests for *H. pylori* antibodies performed on blood or saliva (although the sensitivity of salivary antibody tests is low) and in stool specimens by PCR should be considered in patients with L-T₄ malabsorption in whom *H. pylori* infection is suspected.

Autoimmune gastritis is an autoimmune disorder characterized by the presence of circulating antiparietal cell antibodies; it is frequently associated with Hashimoto's thyroiditis (307–309). This autoimmune gastric disease may lead to atrophic gastritis with a reduced number and function of oxyntic glands and a consequent reduction of gastric acidity with impaired L-T₄ absorption. In one study by Centanni et al (142), patients with atrophic gastritis required an increase of 27% in their L-T₄ dose, whereas patients with *H. pylori* nonatrophic gastritis required an increase of 22% in their dose. And patients with both *H. pylori* and atrophic gastritis needed a 34% higher doses of T₄.

Patients with positive tests for *H. pylori* should have thyroid function retested after treatment of their infection to avoid overtreatment with L-T₄ when they are cured (310).

Certain parasitic disorders may be an important cause of malabsorption. There is a report of a patient with severe hypothyroidism caused by intestinal giardiasis (311).

Bariatric surgery and all operations that reduce the GI absorptive surface may also impair L-T₄ absorption (312–316). Previous GI surgery (jejunostomy, jejunoleal bypass, and short bowel syndrome) may be other causes of L-T₄ malabsorption. L-T₄ malabsorption is observed in patients with cirrhosis, obstructive liver disease, or pancreatic insufficiency (16).

An absorption test with 1000 to 2000 μg of L-T₄ should be performed in patients suspected of having malabsorption. The most frequent conditions associated with L-T₄ malabsorption are summarized in Table 14.

Table 14. Frequent GI Conditions Associated With L-T₄ Malabsorption

GI Condition

| |
|--|
| Celiac disease |
| Lactose intolerance |
| Atrophic gastritis |
| <i>H. pylori</i> infection |
| Intestinal infections and small intestinal bacterial overgrowth |
| Liver diseases: cirrhosis, obstructive liver disease |
| Pancreatic diseases |
| Pancreatic insufficiency |
| Previous gastrointestinal surgery, jejunostomy, jejunoleal bypass, short bowel |

VII. Potential Adverse Effects During L-T₄ Therapy

Overtreatment or excessive L-T₄ dosage, has been reported in about 30% to 50% of patients treated with L-T₄ in the United States, England, and Scotland (12–14). A higher prevalence of over-replacement therapy has been observed in those receiving higher doses of L-T₄ (13), in elderly individuals, and in patients with low body weight or with diabetes (14).

A. Adverse effects of TSH suppression

Young patients with endogenous subclinical hyperthyroidism (EndoSHyper) and those with exogenous subclinical hyperthyroidism (ExoSHyper) and undetectable serum TSH levels during long-term therapy may have symptoms and signs of thyroid hormone excess (317–319). The hypermetabolic state associated with undetectable serum TSH can impair psychological, social, and physical QOL and may be associated with the development of some important cardiovascular risk factors (increased heart rate and enhanced risk of atrial arrhythmias, increased left ventricular [L] mass, and diastolic dysfunction) in ExoSHyper and EndoSHyper (9, 10, 317–320). Elderly patients may be asymptomatic for specific symptoms of thyroid hormone excess compared with younger patients. EndoSHyper is not associated with an increased risk of depression and anxiety in patients aged over 65 years (321). However, a recent review of 23 studies supports the evidence that there is an association between EndoSHyper and cognitive impairment, although the mechanism of this association remains unclear (322).

B. Cardiovascular risk and TSH suppression

ExoSHyper may lead to adverse cardiovascular and skeletal effects in the elderly. Some prospective studies have reported a 2 to 3-fold higher risk of AF in patients over 60 years of age affected by ExoSHyper (323) or EndoSHyper (323–325) compared with euthyroid controls. Two recent meta-analyses have linked SHyper with incident AF and an increased risk of HF and CHD and mortality, mainly in patients with endogenous TSH <0.1 mU/L (188, 326). A pooled analysis of individual participant data (648 participants) with EndoSHyper from 6 prospective cohorts indicated that the HR for HF events in age- and gender-adjusted analyses was 1.46 (95% CI, 0.94–2.27) compared with euthyroid subjects during a median follow-up of 10.4 years. The HR in patients with undetectable serum TSH was 1.94 (95% CI, 1.01–3.72) (188). The incidence of HF is increased further in elderly patients (mean age 75.3 years) with a high risk of cardiovascular disease (104). There are conflicting data on the

risk of stroke in patients with EndoSHyper (184, 327, 328). The incidence of stroke was increased in patients with EndoSHyper in a population-based prospective study conducted in Denmark on 609 subjects from a general practice aged 50 years or above with normal LV function (HR was 3.39; 95% CI, 1.15–10.00; $P = .027$) after adjusting for sex, age, and AF (328). Likewise, an increased mortality from circulatory diseases (both cardiovascular and cerebrovascular) was associated with a low TSH in a 10-year follow-up study of 1191 subjects aged over 60 years with EndoSHyper (327).

There are differing results in studies assessing the risk of total and cardiovascular mortality in patients with ExoSHyper. A prospective cohort study evaluated the mortality among elderly women (>65 years of age), receiving long-term thyroid hormone therapy (15.8 years) (329). In multivariate analysis, the mortality was similar among users of thyroid hormone compared with nonusers (HR, 1.11; 95% CI, 0.98–1.24; $P = .09$). In this study, only a history of previous hyperthyroidism was associated with a small increase in all-cause and cardiovascular mortality (329). On the contrary, the Thyroid Epidemiology Audit and Research Study (TEARS), a population-based study performed in Tayside, Scotland, reported that elderly patients (mean age 61.6 years) with suppressed serum TSH (≤ 0.03 mU/L) during L-T₄ replacement therapy (median follow-up of 4.5 years) had an increased risk of cardiovascular disease, dysrhythmias, and fractures when compared with patients with a serum TSH within the laboratory reference range (330). The risk of these outcomes was not increased in patients with a low but not suppressed TSH (0.04–0.4 mU/L) (330). For all endpoints, there was an increased risk with older age after adjusting for sex, history of a previous thyroid condition and cardiovascular disease, socioeconomic status, and presence of diabetes (330).

A recent meta-analysis provided evidence that EndoSHyper may increase cardiovascular mortality, particularly in patients with undetectable serum TSH (326). In age- and sex-adjusted analyses, EndoSHyper was associated with increased total mortality (HR, 1.24; 95% CI, 1.06–1.46) and mortality due to cardiovascular disease (HR, 1.29; 95% CI, 1.02–1.62), especially in the presence of a TSH level < 0.10 mU/L (326).

It remains to be established whether or not ExoSHyper and EndoSHyper exert the same adverse effects because T₃ levels are higher in patients with EndoSHyper, whereas FT₄ concentrations are often elevated in many patients undergoing L-T₄-suppressive therapy with a greater T₄ to T₃ ratio than in patients with EndoSHyper (28–30).

However, all of the above referenced data suggest that suppressed serum TSH may have harmful cardiovascular effects in elderly patients. Therefore, excessive L-T₄ ther-

apy should be avoided in this age group, consistent with recent AACE and ATA guidelines (3).

C. Fracture risk and TSH suppression

Overt hyperthyroidism is an important risk factor for osteoporosis and fractures (331). Four meta-analyses suggest that postmenopausal patients are at risk of bone loss during TSH suppression (332–335). Several studies have evaluated whether ExoSHyper increases the risk of fractures. Women with a history of thyroid cancer appeared to have their first fracture earlier ($P < .01$) than women without thyroid disease (336). A prospective population-based study in patients receiving L-T₄ prescriptions reported an increased risk of fracture in postmenopausal women with a history of hyperthyroidism (337). A 3-fold increased risk of hip fracture and a 4-fold increased risk of vertebral fracture was found in a prospective study by Bauer et al (338) of 686 women older than 65 years with ExoSHyper and a serum TSH level ≤ 0.1 mU/L who were compared with women with normal serum TSH levels. The risk of fractures was also increased in women receiving L-T₄ doses that maintained serum TSH in the range of 0.1 to 0.5 mU/L (338).

A suppressed serum TSH (≤ 0.03 mU/L) was associated with a doubled risk of osteoporotic fracture in postmenopausal women (mean age 60.3 years) in a recent population-based study of patients taking L-T₄ therapy (330). Patients with a serum TSH below the reference range, but not fully suppressed (0.04–0.4 mU/L), had no increased risk of fractures. However, data on FT₄ or T₃ levels were not reported in these studies (330, 338).

A retrospective cohort study of 213 511 L-T₄ users with a nested case-control design was performed in Ontario, Canada, on the available data from the population health database. Residents 70 to 105 years old receiving at least 1 prescription for L-T₄ were selected (339). This population-based study found a strong dose-response relation between current use of L-T₄ and the risk of fracture. A significant correlation was found in both sexes between current L-T₄ use and increased risk of fracture among older people (>70 years) (339). The risk of fractures remained higher even among those who discontinued L-T₄ within 6 months (339). Although thyroid function tests were not performed in this study, a strong correlation was observed between L-T₄ dose and the risk of fracture. Higher doses of L-T₄ were associated with a 2 to 3-fold increased risk of fractures compared with lower doses (339). These findings were confirmed in a recent study in which an increase in risk of femur fracture was found in men aged over 65 years with EndoSHyper (340). In this prospective cohort of U.S. community-dwelling adults, Lee and co-workers (340) followed 5567 people, 65 years or older, for a median of 13 years and showed that the incidence of hip fracture was

Table 15. Consequences of Over- and Undertreatment With L-T₄

| Potential Consequences of Overtreatment With L-T ₄ | Potential Consequences of Undertreatment with L-T ₄ |
|---|--|
| Symptoms of hyperthyroidism | Symptoms of hypothyroidism |
| Accelerated bone loss | Elevated total cholesterol and LDL-cholesterol |
| Fractures | Impaired cognition |
| AF | Increased diastolic BP |
| HF | Increased body weight |
| CHD events | Increased risk of CHD events and mortality |
| | Increased risk of HF |

higher in men (but not women) with SHyper compared with euthyroid controls (HR, 4.91; 95% CI, 1.13–21.27). After excluding those with a baseline use of thyroid-altering medications, men with EndoSHyper had a higher HR of 4.91 for hip fractures (95% CI, 1.13–21.27). No clear association between subclinical dysfunction and fracture was observed in women in this study (340).

Thus, it appears that current evidence supports the association of suppressed serum TSH during L-T₄ therapy and an increase risk of fractures, especially in certain patients including those receiving excessive therapy after previous treatment of hyperthyroidism, the elderly, postmenopausal women, and people with risk factors for osteoporosis. Treatment with L-T₄ should be carefully monitored in patients at a higher risk of bone fracture. Lower doses of replacement L-T₄ therapy should be used in postmenopausal women and in the presence of risk factors for bone fractures.

D. Adverse effects of increased serum FT₄ during L-T₄ therapy

Patients receiving replacement L-T₄ therapy usually have serum FT₄ values at the upper limit of the reference range compared with euthyroid subjects. Significantly higher serum FT₄ levels have been reported after total thyroidectomy in patients receiving L-T₄ treatment compared with their prethyroidectomy levels, especially during TSH suppression as would be expected (28).

Some studies have shown adverse effects of high FT₄ values on prognosis, risk of AF, cardiovascular events, dementia, and frailty in elderly patients (341–343). Moreover, an increased cardiovascular mortality was found in those >85 years of age (101, 344). The data described above suggest that TSH suppression and high FT₄ levels should be avoided in elderly patients receiving long-term TSH-suppression therapy, independent of the serum TSH value (Table 15).

VIII. Combined Treatment With L-T₄ Plus Liothyronine in Hypothyroid Patients

A. Persistence of symptoms in hypothyroid patients with normal serum TSH during L-T₄ therapy

About 15% of patients treated with L-T₄ do not reach clinical euthyroidism and continue to complain of psychological impairment, weight gain, depression, and persistence of symptoms of thyroid hormone deficiency despite biochemical euthyroidism demonstrated by normal serum TSH levels. Three large community-based studies from the United Kingdom (345), The Netherlands (346), and Norway (347) concluded that successful treatment of hypothyroidism is associated with only a partial recovery of neurocognitive improvement and psychological well-being, suggesting that replacement treatment with L-T₄ might not be fully adequate for optimal brain function. Vitality and mental health were significantly lower in patients receiving L-T₄ than in the general population in the study by Wekking et al (346) on 141 patients with compensated hypothyroidism. Similarly, in the large community-based survey on 381 patients by Saravanan et al (345), 26% of the patients with normal thyroid function on L-T₄ monotherapy scored significantly worse than did euthyroid matched controls on measures of well-being (General Health Questionnaire, 32.3% vs 25.6%) and hypothyroid symptoms (47% vs 35%). Furthermore, the HUNT 2 study on 1546 women ≥40 years of age who were receiving L-T₄ therapy observed higher depression and anxiety scores in comparison with 18 137 subjects without thyroid disease and who were not treated with T₄ (depression 18.4% vs 13.0%, *P* < .001; anxiety, 23.4% vs 18.7%, *P* < .001) (347).

However, traditional subjective procedures that assess symptoms and QOL are not reliable markers for the evaluation of the peripheral effects of thyroid hormone, and these parameters are not sensitive enough in detecting slight thyroid hormone deficiency or excess (100, 111, 170).

Some cardiovascular risk factors (such as lipid parameters, endothelial function, BMI, adiposity, and diastolic hypertension) may not be completely normalized after replacement therapy (348–355), leading to an increased morbidity for circulatory diseases and ischemic heart disease despite apparently adequate treatment with L-T₄ (356).

B. The effects of low-normal serum TSH during L-T₄ therapy

There are conflicting results on the potential improvement in QOL when the T₄ dosage is titrated until serum TSH is in the lower part of the reference range in patients

with primary hypothyroidism (155, 170). Small increases in L-T₄ dosage that approach TSH suppression may improve resting energy expenditure and reduce fat mass in hypothyroid patients (357). The effect is due to a significantly higher relative increase in resting energy expenditure as was observed in a prospective 12-month study in hypothyroid patients whose TSH level was maintained in the low-normal TSH range (0.4–2.0 mU/L) during L-T₄ therapy compared with a subgroup maintained within a high-normal TSH range (2.0–4.0 mU/L) (357). However, in this study, no significant differences were observed between the 2 groups of patients in other clinical variables (lipid profile, body composition, or bone mineral density [BMD]) (357).

Chemical or laboratory markers may be more sensitive indicators of thyroid hormone effect than the patients' complaints. For example, changes in T₄ dosage did not produce significant changes in hypothyroid symptoms, well-being, or QOL in a double-blind, RCT with a cross-over design of 56 subjects with primary hypothyroidism, although the levels of SHBG, alkaline phosphatase, and deoxyypyridinoline were higher and total cholesterol levels were lower during higher doses of L-T₄ compared with lower doses (358). Contrary to treatment with a combination of L-T₃ plus L-T₄ or to baseline levels in control healthy subjects, monotherapy with L-T₄ is usually associated with higher FT₄ levels and a higher T₄ to T₃ ratio, especially in hypothyroid patients receiving TSH replacement doses of L-T₄ (359–361).

Supraphysiological doses of L-T₄ are able to suppress serum TSH due to stimulation of D2 activity in the hypothalamus and pituitary. On the other hand, with a dose of exogenous L-T₄ that suppresses serum TSH, there is inhibition of T₃ secretion by the thyroid gland and reduced peripheral D2 activity with decreased conversion of T₄ to T₃. Therefore, the increased sensitivity of the pituitary/hypothalamic feedback mechanism to serum T₄ may explain why suppressive doses of L-T₄ can be associated with low T₃ levels and high T₄ levels (26, 362, 363). Current guidelines and recommendations suggest avoiding low or suppressed serum TSH during replacement L-T₄ therapy on the basis of the absence of beneficial effects and the risk of adverse effects on bone and heart (3).

C. L-T₄ therapy in thyroidectomized patients

Intracellular T₃ levels do not necessarily reflect similar levels in the circulation. Thus, the important moiety is primarily intracellular T₃, and normal plasma T₃ levels do not indicate that T₃ is also normal in the peripheral tissues. Administration of T₄ (in doses ranging from 0.2–0.8 μg/100 g body weight per day) was unable to normalize T₄ and T₃ in all tissues of thyroidectomized rats (364). In the

latter study, the L-T₄ dose needed to normalize thyroid hormone concentrations was different in each tissue, and only combined treatment with L-T₄ and L-T₃ was able to ensure euthyroidism and normalize both plasma and tissue T₄ and T₃ concentrations (364). Although this experimental observation cannot be extrapolated to humans without the usual caveats, some studies have reported that low serum FT₃ and significantly higher serum FT₄ levels can be observed in thyroidectomized patients receiving L-T₄ replacement therapy (28–30). For example, in a prospective study of 50 patients aged 18 to 65 years who were scheduled for total thyroidectomy, T₃ levels were lower during replacement doses of L-T₄ compared with their prethyroidectomy levels (28). Similar findings were reported in a recent retrospective study on 135 patients with thyroid cancer (30). In this study, higher serum FT₄ levels were observed after total thyroidectomy compared with those noted before surgery; moreover, serum FT₃ levels were significantly lower when serum TSH levels were in the normal reference range (0.3–3 mU/L) (30). In both of these studies, post-thyroidectomy serum T₃ levels were equivalent to the pre-thyroidectomy values only when serum TSH was suppressed (28, 30).

In a recent large cross-sectional study of 1880 athyretic patients on L-T₄ treatment, serum T₃ levels were significantly lower, although still within the normal reference range, compared with the levels observed in 3875 matched euthyroid controls (29). TSH was normalized during L-T₄ therapy (0.4–4.0 μU/L), but FT₄ levels were above the normal limit of the reference range in 72% of the patients, whereas T₃ levels were below the normal limits in 15.2% and the FT₄ to FT₃ ratio was higher than the normal range in 29.6% of patients. The FT₄ to FT₃ ratio increased with an increasing L-T₄ dose, and the widely variable ratio observed in this study indicates great heterogeneity of peripheral T₃ production in thyroidectomized individuals (29). These data support the concept that the lack of the normal 20% thyroidal T₃ secretion in thyroidectomized subjects might not be compensated by an increased peripheral deiodination of T₄. Higher serum T₄ levels are necessary in thyroidectomized patients to achieve normal serum T₃ concentrations and compensate for the absence of T₃ secretion by the thyroid gland. Therefore, in thyroidectomized patients who are persistently symptomatic during L-T₄ replacement therapy, it is important to evaluate whether the normalization of serum TSH is also associated with both normal FT₃ and FT₄ levels (27).

All of these observations suggest that TSH is not a perfect marker of peripheral tissue euthyroidism in thyroidectomized patients and that in these patients there may be a wide tissue heterogeneity in T₃ production (27).

D. Polymorphisms in the genes of the deiodinases

Deiodinase activities are specifically regulated in tissues. This fact may have important consequences for the peripheral effects of thyroid hormone and for the set-points of feedback regulation (27). Polymorphisms in the genes of deiodinases and in thyroid hormone transporters may influence tissue T_3 availability (365–367). The normal brain contains an efficient D2 activity that serves to maintain constant T_3 concentrations (368). Defects in the D2 pathway might be responsible for a reduced T_3 in the brain or in other tissues and may explain the persistence of hypothyroid symptoms in some patients receiving L- T_4 (368). A common Thr92AlaD2 polymorphism has resulted in some studies in tissue T_3 insufficiency (368). The Thr92Ala polymorphism has been associated with a number of conditions including variation in the hypothalamic-pituitary-thyroid axis, altered bone turnover, insulin resistance, increased BMI, mental retardation, osteoarthritis, and bipolar disorder (365–375). Moreover, a recent meta-analysis including 11 033 individuals showed that the homozygous form of the D2 Thr92Ala polymorphism is associated with an increased risk of type 2 diabetes (376).

The presence of the D2 Thr92Ala polymorphism was associated with the need for higher L- T_4 doses to normalize serum TSH in 191 consecutive thyroid cancer patients, previously treated with near-total thyroidectomy and radioiodine ablation (217). On the contrary, the same polymorphism was not associated with a requirement for higher L- T_4 doses to normalize serum TSH levels in patients with autoimmune hypothyroidism (377). Appelhof et al (378) reported that 2 polymorphisms in the D2 gene (the D2 ORFa-Gly3Asp and D2 Thr92Ala polymorphisms) were not determinant for differences in well-being, neurocognitive function, or preference for T_4/T_3 combination therapy in 141 patients with primary autoimmune hypothyroidism. The Weston Area T_4/T_3 (WATTS) study of 552 patients on L- T_4 replacement therapy suggested that there is a small number of patients with the Thr92AlaD2 polymorphism with impaired psychological well-being and a worse baseline General Health Questionnaire score during L- T_4 replacement therapy (31). This genotype was present in 16% of their study population (31) and was associated with greater clinical improvement on L- $T_4/L-T_3$ therapy compared with L- T_4 monotherapy (2.3 General Health Questionnaire points at 3 months and 1.4 points at 12 months). Interestingly, this polymorphism had no impact on circulating thyroid hormone levels (31).

Additional studies will be necessary to confirm the positive neuropsychiatric response to combined L- $T_4/L-T_3$ treatment vs monotherapy with L- T_4 in patients with the Thr92Ala polymorphism.

E. Effects of combination treatment with T_3 and T_4

T_3 has a half-life of only 1 day in contrast to the long 6- to 7-day half-life of T_4 . Wide fluctuations in serum T_3 levels can be observed after its administration (26). Given its short half-life, 3 daily doses of T_3 are usually required to obtain physiological and stable circulating T_3 levels (27). A modest 16% rise in FT $_4$ with no change in FT $_3$ levels can be observed in the first 4 hours after L- T_4 administration (379). In contrast, a marked rise of 42% in FT $_3$ levels can be detected within the first 4 hours ($T_3/T_4:T_4 = 6.24:4.63$ mU/L, $P < .001$) after L- T_3 administration. Moreover, mean exposure to FT $_3$, calculated as AUC is higher (L- $T_3/L-T_4:L-T_4 = 1148:1062$, $P < .0001$) during L- T_3 treatment (379). In addition, high FT $_3$ levels can persist during chronic L- T_3 treatment with potentially dangerous consequences on the heart and the onset of thyrotoxic symptoms (379).

Several randomized controlled studies have evaluated the effects of combination therapy with L- T_3 and L- T_4 . Several of these studies have had a parallel design, and others were double- or triple-blinded controlled studies with an appropriate crossover design (26). Three meta-analyses have evaluated the effects of combination treatment with L- T_3 and L- T_4 vs L- T_4 alone (380–382). The L- $T_4/L-T_3$ combination therapy had no advantage when compared with standard L- T_4 monotherapy in the meta-analysis performed by Grozinsky-Glasberg (380) on 11 RCTs, including a total of 1216 hypothyroid adult patients. In this examination, bodily pain, depression, anxiety, fatigue, QOL, body weight, total serum cholesterol and triglycerides, serum LDLs, and high-density lipoproteins were not different during treatment with L- T_4 alone and during combination therapy with L- T_4 and L- T_3 (380).

Similar results were reported in the meta-analysis by Ma et al (381) published in 2009, which included studies on a total of 1243 patients. L- $T_4/L-T_3$ combination therapy was not superior to L- T_4 monotherapy in terms of psychological and physical well-being with no statistically significant differences in the other variables. The third of the meta-analyses, by Joffe et al (382), on 9 controlled studies found no considerable differences of combination L- T_4 plus L- T_3 therapy vs L- T_4 alone on psychiatric symptoms.

Several meta-analyses have described beneficial therapeutic effects of L- T_3 given in combination with tricyclic antidepressants compared with placebo in euthyroid patients with resistant depression (383, 384). However, although some studies have investigated the effects of combined L- T_4 and L- T_3 treatment in depressed hypothyroid patients (385, 386), only one has reported a beneficial effect of this treatment in improving depression, mood, and cognition (385). Despite the lack of beneficial effects

of combination therapy vs monotherapy with L-T₄ described by the meta-analyses, 3 studies documented that L-T₄ plus L-T₃ therapy was preferred by the patients compared with L-T₄ monotherapy. Preference rates above 50% for combined therapy were observed in 66% of subjects in the study by Bunevicius et al (385), in 69% of patients studied by Escobar-Morreale et al (387), and in 52% of those in the study by Appelhof et al (388). Interestingly, this preference for combined therapy was observed in 2 studies in which serum TSH was suppressed (385, 388). In 2 double-blind randomized studies, the mean body weight decreased by 1.7 kg with combination treatment compared with monotherapy with L-T₄ (388, 389). In these 2 studies, the patient preference for combination therapy was associated with a significant reduction in body weight and improvement in BMI (388, 389). It should be underscored that some patients may feel better just because they are participating in a trial (the Hawthorne effect).

Few reports have evaluated peripheral parameters of thyroid hormone action (cardiovascular parameters, lipid profile, bone metabolism and structure, energy expenditure, or SHBG) during combined therapy; however, the conflicting findings and the relevant methodological limitations of these studies do not permit definitive conclusions on the effects of combination therapy and its potential beneficial effect (26). Euthyroidism was not reached in most of the available studies that used a fixed L-T₃ dose (ranging from 7.5–20 µg) (128, 386, 390–395) or a wide L-T₄ to L-T₃ ratio (from 3:1 to 15:1) (387–389, 396, 397). The physiological L-T₄ to L-T₃ ratio in humans is about 13:1 to 15:1, and therefore overtreatment or undertreatment (suppressed or elevated TSH or high or low FT₃ levels) was frequently associated with combined treatment in these studies (26). The presence of atrial arrhythmias has been reported in overtreated patients during combination treatment (128, 396). Once-daily T₃ dosage was used in most of the studies, and only a few studies divided the T₃ dosage into 2 daily doses (26).

The duration of combination therapy in all of these studies was restricted to only a few weeks, which may be an insufficient period to evaluate the peripheral effects of combined treatment. Moreover, a potential carryover effect might have been induced in these studies related to the long half-life of T₄ which could persist for a long time in some tissues such as the brain. Finally, other important limitations in establishing the effects of combined replacement therapy include the heterogeneity of the hypothyroid patients enrolled in the available studies (eg, athyreotic patients, patients with autoimmune Hashimoto's thyroiditis, and patients with hypothyroidism induced by radio-

iodine for previous hyperthyroidism), their wide age range, and the small sample size in several studies (26).

Prospective controlled trials will be necessary to evaluate the potential beneficial effects of combined T₃/T₄ treatment vs monotherapy with L-T₄ in patients with hypothyroidism. These trials should enroll homogeneous groups of patients to ascertain which patients could benefit from this treatment as well as employ the correct T₄ to T₃ ratio and monitor the appropriate peripheral parameters. Pharmacogenomic studies would help identify those patients that might benefit from combined treatment. Treatment with currently available formulations of T₃ do not result in a physiological or normal serum T₃ profile. A long-acting slow-release form of T₃ would be required to mimic normal physiological endogenous T₃ production in hypothyroid patients.

In the meantime, expert opinion and AACE, ATA, and ETA guidelines suggest avoiding treatment with T₃ in pregnant women and in patients with a history of arrhythmias or chronic ischemic heart disease (3, 26, 32). The addition of T₃ to T₄ monotherapy should be restricted to persistently symptomatic hypothyroid patients despite their biochemical euthyroidism during L-T₄ replacement therapy with the goal of achieving improved QOL. Because of the risks inherent in T₃ treatment, combined therapy should be managed only by skilled specialists and should require careful follow-up to detect and/or avoid possible adverse effects. Blood samples for evaluation of T₃ levels should be obtained before the morning dose. A liquid preparation that allows titration of dosage in drops is currently available in Europe and may prove useful for personalization of L-T₄/L-T₃ combined treatment.

F. Combination treatment with T₃ and T₄ in children with CoH

In children with CoH, a high serum TSH (10–20 mU/L) may persist in about 10% of patients treated with L-T₄ despite normal serum T₄. This has been explained as due to either undertreatment or an abnormal maturation of T₄ feedback control of TSH secretion. One study reported a prevalence of pituitary thyroid hormone resistance in about 43% of infants during the first year of life with an improvement toward 10% of cases during adolescence, suggesting that thyroid hormone resistance may improve with age (398). Overtreatment with high L-T₄ doses to normalize serum TSH may be contraindicated in this condition because of risk of induction of deleterious effects on growth and school performance. Combined treatment with L-T₃ and L-T₄ in a ratio of 4:1 was performed in 10 children aged over 5 years in an attempt to normalize T₃ levels in the central nervous system and improve serum TSH. Normalization of serum TSH levels was achieved in

about 7 months in children who were switched to combination treatment, although they had higher serum T_3 levels and lower serum T_4 levels than patients on treatment with $L-T_4$ alone (398).

IX. Replacement Therapy in Central Hypothyroidism

A. Treatment of CH in adults

$L-T_4$ therapy is the treatment of choice in patients with CH. Several studies have underscored the difficulty in achieving optimal substitutive $L-T_4$ therapy in patients with CH (399–401). The obvious difference with the management of primary hypothyroidism is that serum TSH levels cannot guide replacement therapy in CH.

There is no single optimum $L-T_4$ dose for CH, and dosage titration is rendered more difficult by the lack of serum TSH as a guide to therapy. The aim of replacement treatment of CH is to render the patient euthyroid by obtaining appropriate serum concentrations of thyroid hormones, and the serum FT_4 concentration generally represents the most useful marker for this purpose.

Koulouri et al (402) compared FT_4 values of patients with secondary hypothyroidism with those of patients with primary hypothyroidism who were adequately treated with $L-T_4$. The authors suggested that CH patients tend to be undertreated and that a goal FT_4 level of 16 pmol/L (ie, in the midnormal laboratory reference range of 9–25 pmol/L) would be adequate for treatment in most patients. Other authors have suggested that maintenance of FT_4 in the upper half of the normal range would be appropriate in CH (212, 403). Rather than these somewhat arbitrary FT_4 target levels, treatment of CH should be tailored. For example, as in older patients with primary hypothyroidism, it is important to consider lower doses of $L-T_4$ that result in FT_4 levels in the lower end of the reference range.

B. Limitations in peripheral markers of thyroid hormone action

The evaluation of peripheral parameters of thyroid hormone action (eg, cholesterol, creatinine phosphokinase, soluble IL-2 receptor, SHBG, angiotensin-converting enzyme, osteocalcin, cross-linked carboxyl-terminal telopeptide of type I collagen) could be useful in monitoring $L-T_4$ treatment in CH (212, 404). A recent study employed Doppler echocardiography to diagnose subclinical CH in patients with hypothalamic-pituitary disease (404). Unfortunately, evaluation of tissue parameters of thyroid hormone action can be frequently ineffective in CH due to confounding effects of concomitant pituitary deficiencies

in somatotrope, gonadal, or adrenal function or the coexistence of cardiac disease.

C. Interactions with other pituitary hormone deficiencies and hormone replacement

Alexopoulou et al (405) underscored the importance of concomitant replacement with other pituitary hormones. Contemporary use of other replacement hormones in CH may require adjustments of T_4 treatment dosage. Women under estrogen treatment and patients under GH treatment often will need a higher T_4 dose for serum FT_4 levels to remain in the euthyroid range (406). With initiation of thyroid hormone treatment in the presence of concomitant ACTH deficiency, there is risk of adrenal crisis due to adrenal insufficiency, and evaluation of the adrenal axis is indicated before starting $L-T_4$ (407). With documentation of adrenal insufficiency, steroid replacement should accompany $L-T_4$ replacement with establishment of a eu-adrenal state before achieving euthyroidism (407).

Initiation of estrogen therapy may increase $L-T_4$ requirements in hypothyroid patients due to augmented capacity of T_4 -binding plasma proteins (407), and dosage adjustment will serve to saturate binding sites and restore equilibrium between bound and free thyroid hormone.

Recombinant human GH (rhGH) treatment may interfere with the activity of the hypothalamus-pituitary-thyroid axis and $L-T_4$ substitutive therapy. In euthyroid individuals, the administration of rhGH induces a slight reduction of serum T_4 concentrations, an increase in serum T_3 concentrations, and a decrease in serum TSH levels without changes in rT_3 (406, 407). Moreover, rhGH treatment augments peripheral deiodination of T_4 to T_3 and the secretion of somatostatin, which in turn reduces pituitary TSH secretion (408). A significant reduction in serum T_4 levels without a substantial increase in serum TSH has been reported in about 36% of euthyroid adults with GH deficiency, with a consequent requirement for $L-T_4$ replacement therapy (409). In one study, 16% of patients with GH deficiency who were receiving $L-T_4$ replacement therapy required an increase in $L-T_4$ dose (409). GH deficiency may mask subclinical forms of CH, and patients on rhGH replacement therapy often require higher replacement doses of $L-T_4$ (406, 410).

D. Long-term cardiovascular risk in CH

A recent retrospective study showed that insufficient replacement therapy with thyroid hormone in central hypopituitary patients was associated with adverse cardiovascular risk factors independently of other pituitary replacement therapy. A decrease in FT_4 values during 4 years were associated with an improvement in BMI, diastolic BP, total cholesterol, and LDL-cholesterol after adjust-

Table 16. Management and Follow-Up of CH

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|---|
| Treatment should be started after the exclusion of adrenal insufficiency |
| The starting dose should be based on age and co-morbidity |
| FT ₄ should be maintained in the middle-normal (in the elderly) or in the upper part of the normal range (in young people) with a normal serum TSH |
| FT ₄ and TSH levels should be reassessed after replacement therapy with other pituitary hormones |
| Annual assessment (MRI or CT) of hypothalamic pituitary region |
| Doppler echocardiography may be useful during the follow-up in patients without comorbidities |

ment for changes in GH and hydrocortisone doses. These results support the importance of optimizing replacement therapy with thyroid hormone to reduce the cardiovascular risk in hypopituitary patients (411).

A summary of aspects of the management and follow-up of CH is shown in Table 16.

E. Treatment of CH in pediatric patients

Relatively higher L-T₄ doses are recommended in hypothyroid pediatric patients with CH than in adult patients. As is typically the practice in primary hypothyroidism, the treatment should be started with full-replacement L-T₄ doses to more rapidly achieve adequate circulating FT₄ levels and potentially improve neurological development (21, 413). L-T₄ doses should be adjusted every 2 to 4 weeks on the basis of results of measurement of FT₄ levels (21, 413).

F. Combination treatment with T₃ and T₄ in CH

A double-blind crossover study on 29 patients with CH compared 3 regimens of replacement therapy with thyroid hormone: 1) empirical L-T₄ dosage in patients with normal FT₄ values ($1 \pm 0.05 \mu\text{g}/\text{kg}$ body weight), 2) body weight-adapted L-T₄ dosage ($1.6 \mu\text{g}/\text{kg}$ body weight), and 3) body weight-adapted combination of L-T₄ and L-T₃ therapy (T₃ to T₄ ratio of 1:10) (414). Patients taking the L-T₄ therapy adapted to body weight were able to achieve a lower BMI and lower total cholesterol and LDL-cholesterol. Moreover, patients on the body weight-adapted arm of combined T₃/T₄ treatment obtained further beneficial effects as indicated by ankle reflex time and working memory, but at a cost of having suprathreshold serum FT₃ levels. These observations suggested that a dose of L-T₄ of $1.6 \mu\text{g}/\text{kg}$ body weight was associated with an improved prognosis in patients with CH. Because the 10:1 T₄ to T₃ ratio differs from the normal ratio of 14:1, additional studies on combination T₃ and T₄ treatment with a correct ratio might better clarify the potential role of combined treatment in patients with CH.

X. Replacement Therapy for Hypothyroidism in Specific Conditions

A. Pregnancy

1. Adverse effects of overt and SHypo, thyroid autoimmunity, and hypothyroxinemia in pregnancy

Hypothyroidism and autoimmune thyroid disease are common among women in reproductive age.

Pregnant women with overt hypothyroidism have decreased fertility and an increased risk of spontaneous abortion (17–19). A positive linear relationship between pregnancy loss and increased TSH values was reported by Benhadi et al (415) with the incidence of fetal demise increased by 60% for every doubling in serum TSH concentration. Women with reduced thyroid reserve may develop overt hypothyroidism during pregnancy (416, 417). The risk of progression to hypothyroidism is increased in pregnant women with positive thyroid autoantibodies during the first trimester and in women with iodine deficiency (416, 417). Early and late obstetric complications are increased in women with untreated overt hypothyroidism with a high risk of miscarriage, anemia, gestational hypertension, placental abruption, postpartum hemorrhages, and breech presentation (94, 418).

Additional adverse effects of hypothyroidism in pregnancy include the risk of adverse neonatal outcomes such as premature birth, low birth weight, and neonatal respiratory distress (9, 10).

Even SHypo or the presence of autoimmune thyroid disease may have adverse effects on the outcome in pregnant women. A recent meta-analysis selected 38 appropriate studies to evaluate the clinical significance of thyroid dysfunction and thyroid autoimmunity during pregnancy (419). This examination revealed that SHypo in early pregnancy may be responsible for an increased risk of preeclampsia (OR, 1.7; 95% CI, 1.1–2.6) and perinatal mortality (OR, 2.7; 95% CI, 1.6–4.7) compared with that in patients with normal thyroid function (419). Thyroid autoimmunity was associated with an increased risk of unexplained subfertility (OR, 1.5; 95% CI, 1.1–2.0), miscarriage (OR, 3.73; 95% CI, 1.8–7.6), recurrent miscarriage (OR, 2.3; 95% CI, 1.5–3.5), preterm birth (OR, 1.9; 95% CI, 1.1–3.5), and maternal postpartum thyroiditis (OR, 11.5; 95% CI, 5.6–24) when compared with the absence of thyroid antibodies (419). Another meta-analysis on 31 studies (19 cohort and 12 case-control) involving 12 126 women indicated that the odds of miscarriage were tripled (OR, 3.90; 95% CI, 2.48–6.12; $P < .001$) and the odds of preterm birth doubled in mothers with positive thyroid autoantibodies (OR, 2.07; 95% CI, 1.17–3.68; $P = .01$) (420). A meta-analysis of 4 prospective studies on 1098 subfertile women undergoing in vitro fer-

tilization reported a higher risk for miscarriage in subfertile women with autoimmune thyroid disease than controls (relative risk [RR], 1.99; 95% CI, 1.42–2.79; $P < .001$) (421).

Severe neurodevelopmental delay is associated with hypothyroidism (422, 423). Maternal thyroid deficiency may have detrimental effects on fetal brain development because of the essential role played by maternal thyroid hormones in early pregnancy because the fetal thyroid gland is not fully functional until approximately the 29th week. In one early study by Man et al (422), children born from mothers with inadequately treated hypothyroidism had significantly reduced intelligence quotients (IQs). The observations in the inadequately treated mothers in the latter study may relate to those of Haddow et al (178) of women with untreated SHypo during pregnancy whose offspring at 7–9 years of age had an average IQ score that was 7 points below the mean IQ of matched children born from mothers whose serum TSH levels were within the reference range ($P < .005$); 19% of these children had IQ scores less than 85 compared with 5% of the control group ($P < .07$).

The incidence of isolated hypothyroxinemia in pregnancy ranges from 2% to 25% with an increased risk in areas of moderate iodine deficiency. Conflicting results have been reported on the effects of isolated hypothyroxinemia and SHypo on fetal neurodevelopment because heterogeneous criteria have been used to define normal levels of maternal FT₄ and TSH during early pregnancy (424–427). In a Chinese population, maternal SHypo, hypothyroxinemia (at 16–20 weeks of gestation), or euthyroidism with elevated TPOAb titers were significant predictors of lower motor and intellectual development in the offspring evaluated at 25 to 30 months of age (426). Isolated hypothyroxinemia during the second trimester was not associated with significantly lower cognitive, language, and motor scores at age 2 years compared with scores for offspring of matched euthyroxinemic women in another study (427). The results of a recent review have suggested that the effects of maternal hypothyroxinemia on the offspring's neurocognitive development depends on the timing of this condition during pregnancy (424). A lower neurocognitive function has been observed in infancy and early childhood in the studies where maternal hypothyroxinemia have been investigated during early pregnancy; on the contrary, conflicting results have been observed when this condition has been assessed in mid-pregnancy. No association has been found during late pregnancy (424).

The Antenatal Thyroid Screening and Childhood Cognitive Function study (CATS) was a prospective, randomized, multicenter trial that involved almost 22 000 women

who were screened for thyroid disease within the first 16 weeks of gestation by means of TSH and FT₄ measurements (428). Patients were divided into 2 groups. In the screening group, thyroid function was evaluated at the time of recruitment, and women with a TSH >97.5th percentile and/or FT₄ <2.5th percentile were treated with L-T₄ at an initial dosage of 150 $\mu\text{g}/\text{d}$, starting at 13 weeks gestation. In the control group, patients had their blood tests at the time of recruitment, but their thyroid function test results were not known until after delivery. Thyroid dysfunction was found in 4.6% of patients in the screening group and in 5% in the control group. There were no differences in the patients' characteristics between the 2 groups (age, smoking, weight, education, or preterm birth). The standardized IQ of children in the control group was 100 points (404 children, 73.3% of the children of the women who tested positive), whereas the IQ of children in the screening group (390 children, 78.2% of the children of the women who tested positive) was 99.2 points ($P = .40$) (428). The proportion of patients with an IQ <85 points was 12.1% in the screening group vs 14.1% in the control group ($P = .39$). Therefore, no differences were found when controls were compared with different subgroups of patients, namely, women with elevated TSH only or low FT₄ only or women who started treatment either before or after 14 weeks gestation (428).

In contrast to the study of Haddow et al (178), the results of this study indicated that antenatal screening with treatment of the women discovered to have SHypo did not result in improved cognitive function in their children at 3 years of age. A possible explanation for the negative findings of this RCT might be that L-T₄ treatment started too late in pregnancy to exert a beneficial impact on brain development.

A recent study reported a consistent association between severe maternal hypothyroxinemia in early gestation (gestational weeks 6–18) and autistic symptoms in offspring. A 4-fold increase in the odds of having a probable autistic child (adjusted OR, 3.89; 95% CI, 1.83–8.20; $P < .001$) was associated in this study with hypothyroxinemia (429).

Iodine deficiency is the most common cause of maternal hypothyroxinemia. Some studies have evaluated the potential adverse effects of hypothyroxinemia during pregnancy in iodine-deficient areas. Irreversible fetal brain damage has been reported in the presence of severe iodine deficiency (65). A meta-analysis of 37 studies performed in China comparing IQs in children from iodine-sufficient and -deficient areas reported that the IQ of children exposed to severe iodine deficiency was reduced by 12.45 points and was recovered by 8.7 IQ points with iodine supplementation (430).

Children born from mothers with prolonged hypothyroxinemia living in iodine-deficient areas may have a deficit of motor and mental development and an increased incidence of attention deficit disorder, hyperactivity disorder, and reduced IQ with a higher risk of expressive language delay and nonverbal cognitive delay compared with controls (431–436). The World Health Organization recommends that iodine intake during pregnancy should be between 200 and 250 $\mu\text{g}/\text{d}$ and suggests that a median urinary iodine concentration of 150 to 249 $\mu\text{g}/\text{L}$ indicates adequate iodine intake in pregnant women (437). Data from the NHANES study reported that the median values for urinary iodine excretion of childbearing women were below the median values established by these World Health Organization recommendations (438). Therefore, a deficiency in iodine intake during pregnancy was found in the United States, and similar data have been reported in Europe (439). The 2012 Endocrine Society guidelines recommend that vitamins containing 150 to 200 μg iodine (potassium iodide or iodate) should be administered before conception to ensure that all pregnant women are protected from iodine deficiency during pregnancy (19). Breastfeeding women should maintain a daily intake of 250 μg of iodine to ensure a supply of 100 μg iodine per day to the infants.

2. Beneficial effects of replacement L-T_4 therapy in hypothyroid pregnant women

Adequate treatment with replacement doses of L-T_4 in early pregnancy improved the outcome of pregnancy in hypothyroid women in terms of maternal and neonatal morbidity (440, 441).

A significant 52% RR reduction in miscarriages (RR, 0.48; 95% CI, 0.25–0.92; $P = .03$) was reported after initiation of adequate L-T_4 therapy (440). Early fetal loss and preterm delivery were shown to be significantly reduced in adequately treated hypothyroid women compared with inadequately treated (4% vs 31% and 1.6% vs 12.5% respectively) (441). In a large prospective study, women with SHypo treated with L-T_4 had a significantly lower rate of obstetrical and neonatal complications compared with untreated women (442).

3. Treatment of hypothyroidism in pregnancy (differences among guidelines)

Guidelines have been published with recommendations for optimal treatment of thyroid hormone deficiency during pregnancy. The AACE and ATA guidelines on the diagnosis and treatment of thyroid disease during pregnancy and postpartum were published in 2011 (18). The first ES guidelines were first published in 2007 (17) and were revised by the inclusion of 27 new articles in 2012 (19). The ES task force

included members of the Asia and Oceania Thyroid Association and the Latin American Thyroid Society. The American College of Obstetrics and Gynecology published guidelines for diagnosis and treatment of hypothyroidism in 2007 that were reaffirmed in 2010 (443).

a. Treatment of overt hypothyroidism. The most recent ES guidelines recommend treatment of overt hypothyroidism in pregnant women (recommendation level A) because there is evidence that overt maternal hypothyroidism may lead to serious adverse effects on the fetus and mother (19). Therefore, L-T_4 treatment clearly should be considered in all pregnant women with a TSH concentration above the trimester-specific reference interval with a decreased FT_4 and in all women with a TSH concentration above 10.0 mU/L irrespective of the level of FT_4 (18, 19).

b. Treatment of SHypo and TPO⁺ women. The 2011 AACE-ATA guidelines recommended the treatment of SHypo in all women positive for TPOAb (18). On the contrary, the 2012 ES guidelines recommended L-T_4 replacement in women with SHypo who are TPOAb⁺ or TPOAb⁻ (19). A prospective trial demonstrated a 69% increase in the rate of spontaneous miscarriage in TPOAb⁻ women with TSH between 2.5 and 5 mU/L during the first trimester of pregnancy compared with women with TSH below 2.5 mU/L (444). However, there is no evidence of an improvement of neurological development in the offspring, and no prospective studies have demonstrated a benefit of treating TPOAb⁻ women. Consequently, the ES guidelines recommendations for treatment of SHypo in TPOAb⁻ patients are only based on expert opinion that the benefits of treatment outweigh the potential risk of not treating (recommendation level C; evidence fair for obstetrical outcome) (19). In contrast, the American College of Obstetrics and Gynecology recommends against treatment of SHypo (445).

The 2012 ES guidelines do not recommend treatment with L-T_4 in euthyroid women with positive thyroid antibodies because only 1 randomized trial has demonstrated a decrease in the miscarriage rate in euthyroid antibody-positive women during the first trimester (446). In this prospective, randomized trial, 984 unselected women were screened for TPOAb positivity and thyroid function tests during their first obstetrical appointment and were divided into 3 groups. Group A included TPOAb⁺ women treated with L-T_4 ; group B included TPOAb⁺ women who did not receive L-T_4 and Group C consisted of all TPOAb⁻ untreated women. The results demonstrated that the first-trimester miscarriage rate was significantly lower in groups A (3.5%) and C (2.4%) than in group B (13.8%) ($P < .05$) (446). Given the increased risk of progression to

hypothyroidism, the 2012 ES guidelines recommended that women with TPOAb⁺ antibodies should be monitored only every 4 to 6 weeks for the potential risk of serum TSH rising above the normal range during pregnancy as an indication of progression into hypothyroidism (19). An ongoing study from the United Kingdom, the TABLET (Thyroid Antibodies and L-Thyroxine) study, a multicenter placebo double-blind controlled trial, hopes to clarify the impact of L-T₄ therapy in euthyroid women with positive thyroid autoantibodies planning pregnancy.

There has been increased interest in the role of selenium deficiency in thyroid disease. Treatment with selenomethionine decreased TPOAb levels in euthyroid women with recurrent pregnancy loss and reduced the risk of postpartum thyroiditis (447, 448). However, large randomized studies are necessary to evaluate the potential benefits of selenium supplementation in pregnancy. At present, given the potential risk of developing diabetes, the guidelines suggest that selenium supplementation should not be recommended for TPOAb⁺ women during pregnancy.

c. Treatment of isolated hypothyroxinemia. The AACE-ATA guidelines do not recommend the treatment of isolated hypothyroxinemia (18).

Although there is no formal recommendation in the 2012 ES guidelines, the task force suggests that in patients with isolated hypothyroxinemia, “a partial replacement therapy may be initiated at the discretion of the caregiver, with continued monitoring” (19). Therefore, one may infer from the ES guidelines that initiation of treatment of this condition falls under the judgment of the clinician until new data might clarify the consequences of isolated hypothyroxinemia (19).

d. Recommendations on L-T₄ treatment and follow-up in pregnancy. The ES, AACE, ATA, and ETA guidelines recommend that oral L-T₄ should be used for treatment of maternal hypothyroidism (17–19). All guidelines recommend against the use of other thyroid preparations such as T₃ or desiccated thyroid (3, 17–19, 32). Rapid correction of hypothyroidism is advised as soon as diagnosed in pregnancy. The goal of L-T₄ treatment is to normalize maternal serum TSH values to within the trimester-specific pregnancy reference range (serum TSH <2.5 mU/L during the first trimester and <3.0 mU/L during the second and third trimester). Women who are already being treated with L-T₄ should increase their dosage to 30% to 50% above the preconception dosage by 4 to 6 weeks of gestation (17–19). The etiology of maternal hypothyroidism and the degree of elevation of the preconception level of TSH may guide clinicians on the magnitude of the increase in L-T₄ dosage. The increment should be greater in women with-

out residual functional thyroid tissue (eg, after radioiodine ablation or total thyroidectomy) than in those with residual thyroid tissue (eg, Hashimoto’s thyroiditis) (214).

About 30% to 50% of hypothyroid women being treated during pregnancy have a TSH concentration outside of the desired reference range (449). In a prospective study on 119 consecutive pregnancies, about 49% of women on L-T₄ replacement therapy had serum TSH outside the reference range (30% had elevated TSH concentrations, and 20% had low TSH concentrations) during the first trimester of pregnancy (449). The risk of fetal loss was significantly increased in these women compared with that in euthyroid pregnant women (449). Ideally, women with hypothyroidism should have their thyroid function evaluated before pregnancy to avoid the risks that are associated with maternal subclinical and overt hypothyroidism during pregnancy. Lower preconception TSH values (within the nonpregnant reference range) reduce the risk of TSH elevation during the first trimester. In the study by Rotondi et al (450), preconception TSH levels in the lower quartile of the reference range during L-T₄ therapy were associated with an adequate TSH level at the first evaluation during pregnancy. Similar findings were reported by Abalovich et al (451) and indicated that only 17.2% of women with preconception TSH below 1.2 mU/L needed an increment in L-T₄ dosage during pregnancy, whereas women with preconception TSH levels between 1.2 and 2.4 mU/L required a 50% increase in L-T₄ dosage.

There is evidence that high serum FT₄ levels during L-T₄ therapy should be avoided. In one study, high-normal FT₄ concentrations in early pregnancy (between 17.01 and 22.00 pmol/L) were associated with reduced fetal growth, resulting in 116 g lower birth weight as well as with an increased risk of small-for-gestational-age newborns (452). Similar results were reported by Shields et al (453) who found a significant positive associations between FT₄ in the cord blood at birth and birth weight.

Thyroid function tests should be repeated approximately 40 days after the first adjustment of L-T₄ dosage. Thereafter, maternal serum TSH should be monitored every 4 to 6 weeks because further L-T₄ dose adjustments are often required (17–19). In the postpartum period, L-T₄ should be reduced to the patient’s preconception dose (17–19), with TSH testing performed at approximately 6 weeks postpartum. According to the 2012 ES guidelines, women at high risk for postpartum thyroiditis (eg, women with TPO⁺, type 1 diabetes and/or a history of postpartum thyroiditis) should be screened with serum TSH at 6 to 12 weeks postpartum (19).

4. Screening for thyroid dysfunction in pregnancy

Different guidelines from the various professional societies for clinical endocrinologists, thyroidologists, and gynecologists have assessed the necessity for universal screening of healthy women for thyroid dysfunction. The American College of Obstetrics and Gynecologists does not recommend routine screening of thyroid function in pregnancy (443). The 2007 ES guidelines recommended case finding targeted to specific groups of patients who are at an increased risk of developing hypothyroidism such as women with 1) a personal or family history of thyroid disease, 2) goiter, 3) positive thyroid antibodies, 4) symptoms or clinical signs suggesting thyroid dysfunction, 5) history of autoimmune disease or type 1 diabetes mellitus, 6) infertility, 7) history of miscarriage or preterm delivery, and 8) a history of head and neck irradiation (17). Similar recommendations appear in the AACE-ATA guidelines, which also included an age of 30 years or greater as an additional criterion (18).

However, one report (454) indicated that screening only high-risk women will miss about one-third of patients who remain undiagnosed with overt hypothyroidism or SHypo. Another study supported this contention as screening of women at low risk identified sufficient cases of hypothyroidism to subsequently improve rates of obstetrical and fetal complications (442).

Screening pregnant women in the first trimester of pregnancy proved cost-effective for detecting and treating overt hypothyroidism in the study by Dosiou et al (455) by employing testing for either TSH or antiperoxidase antibody at the initial evaluation. The 2012 ES guidelines described conflicting opinions on the screening of hypothyroidism in women among the panel members. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit (19). Others recommended neither for nor against universal screening of all pregnant women at the time of their first visit or supported aggressive case findings to identify and test high-risk women by the ninth week or at the time of their first visit before and during pregnancy (19). Clarification of the more optimal approach to screening of pregnant women may have to await the results of some currently ongoing and future trials. One such trial is underway by the National Institutes of Health Maternal Fetal Medicine TSH study on 120 000 pregnant women and is assessing the outcomes of randomizing treatment or nontreatment of women with SHypo and isolated hypothyroxinemia. Another trial in China, the Subclinical Hypothyroid and Iodine Deficiency in Early Pregnancy and Women Planning for Pregnancy (SHEP) trial, will screen 21 500 and treat 4800 women to

evaluate the impact of prepregnant treatment of thyroid dysfunction on fetal brain development.

B. SHypo in the elderly

The diagnosis of SHypo in the elderly often may be more difficult than in younger patients. An increased serum TSH value in older individuals may frequently reflect the response to recovery from systemic illness or the previous use of drugs that had interfered with thyroid function. Moreover, in healthy individuals, serum TSH concentrations are higher in the elderly than in younger people because of a shift in the TSH distribution with age. Reanalysis of NHANES III data indicates that the 97.5th percentile of the TSH upper limit is approximately 5.9 mU/L in subjects aged 70 to 79 years and 7.5 mU/L in those 80 years and older (49).

Elderly people with SHypo seem to be less symptomatic than younger patients. In a large cross-sectional community-based study carried out in primary care practices in England, SHypo (defined as a TSH >5.5 mU/L) was not associated with cognitive dysfunction, anxiety, or depression in subjects ≥ 65 years of age, supporting the concept that a mild TSH increase need not be treated in the elderly in an attempt to improve the QOL (321). Four randomized placebo-controlled studies have reported marginal differences in cognitive function in elderly patients treated with L-T₄ compared with controls (456–459).

The largest RCT of L-T₄ replacement in an elderly cohort was performed by Parle (460) on 94 patients (mean age 73.8 years) with SHypo who were treated with L-T₄ for 53 weeks. No significant improvement in cognitive function tests was noted in the L-T₄-treated subjects compared with patients receiving placebo. In another community-based study of people aged 70 to 79 years, SHypo was associated with increased walking speed and retention of physical function across a 2-year follow up period compared with subjects with normal thyroid function (461). In this study, a TSH level of 7 mU/L was the cutoff point separating adults >70 years into 2 groups: those with mild SHypo (TSH level, 4.5–7.0 mU/L) and those with moderate SHypo (TSH level, 7–20 mU/L). No negative influence of SHypo was found after using functional mobility as a marker of health status in this elderly population (461).

A diagnosis of SHypo is of some concern because of the risk of progression to overt hypothyroidism, and this concern pertains in the elderly as well as in younger populations and has been examined in a limited number of studies. In the United States Cardiovascular Health Study on 3996 individuals aged at least 65 years, a serum TSH of 10 mU/L or higher and TPOAb positivity were independently associated with a significant risk of progression to overt

hypothyroidism (462). Persistence of SHypo without progression was observed in 56% of cases, whereas reversion to euthyroidism was significantly more common in patients with a TSH of 4.5 to 6.9 mU/L and with TPOAb negativity (462).

Of note in this regard are the results of 2 recent longitudinal studies that assessed the changes in TSH and thyroid hormone levels with aging and concluded that a mild progressive increase in TSH may be a marker of progression toward thyroid hormone deficiency only in younger patients (463, 464). In fact, a progressive increase in FT₄ levels and a decrease in FT₃ levels were associated with increases in serum TSH levels during the years of follow-up in elderly subjects. These data have been interpreted to suggest that higher FT₄ levels might be necessary in the elderly to achieve comparable TSH values as in younger subjects. The mild progressive TSH increase in elderly subjects might simply reflect the natural history of thyroid function in advanced age, which may relate to a decline in 5'-deiodinase activity with aging (59). These data have been cited to support recommendations for an increase in the upper limit of the reference range in the elderly and the exercise of caution in diagnosing SHypo in elderly subjects.

In regard to the risks of not treating SHypo in the elderly, 2 meta-analyses reported that an association between SHypo and CHD existed only in patients younger than 60 years (182, 183), and subgroup analysis in a third recent meta-analysis (184) revealed no evidence of greater risks of CHD events, CHD mortality, and total mortality among pooled participants over 80 years of age. HF may develop in healthy elderly subjects with SHypo and a TSH level above 10 mU/L (188). On the other hand, modestly increased serum TSH levels have been associated with longevity in several cross-sectional studies in elderly patients vs younger controls and in nonagenarians with reported familial longevity (49). A pattern of decreased mortality in SHypo was observed in the Leiden 85-Plus Study of 558 individuals aged 85 years who had been monitored for 4 years (101). There was no link between persistent SHypo and cardiovascular mortality (HR, 1.07; 95% CI, 0.87–1.31) in 679 patients with SHypo of at least 65 years of age, enrolled in the recent Cardiovascular Health Study and not taking thyroid preparations (465). Moreover, no association was found between SHypo, TSH level, or persistent TPOAbs and death in elderly subjects in the latter study (465). Conversely, FT₄ levels were positively associated with death (HR per ng/dL, 2.57; 95% CI, 1.32–5.02) (465).

The data of this important large epidemiological study, which measured TSH during the follow-up and included only subjects with persistent TSH elevations, suggest that

although TSH may increase over time in older individuals, these changes are not correlated with increased or decreased mortality. On the contrary, higher FT₄ levels are associated with AF and higher death rates in the elderly (341, 463).

Treatment of elderly subjects with mild thyroid hormone deficiency was not associated with benefit in the study by Razvi et al (193). Incident ischemic heart disease events, all-cause mortality, cause-specific mortality, and incident cerebrovascular events were comparable in older untreated and L-T₄-treated groups (193).

These findings raise concern in regard to possible overtreatment of mild TSH elevations in subjects of advanced age. Replacement therapy should be individualized in elderly and very elderly patients with serum TSH concentrations of more than 10 mU/L (9, 10). Only low doses of L-T₄ (25–50 µg/d) are often required to normalize serum TSH concentrations in elderly patients because of their decreased T₄ metabolism. The target or goal TSH serum concentration should be higher in individuals older than 70 years than in younger patients to mimic physiological values (eg, 4–7 mU/L). Although large randomized trials still are needed, existing evidence suggests that treatment of mild SHypo should probably be avoided in patients older than 60 years of age because there is no definitive evidence that these patients are symptomatic or that L-T₄ treatment will improve their QOL and/or reduce their cardiovascular mortality. As in younger patients, overtreatment with L-T₄ should be avoided because of the adverse cardiovascular and skeletal consequences of iatrogenic hyperthyroidism in elderly people.

C. Congenital hypothyroidism

Treatment with replacement doses of L-T₄ should be promptly started when the diagnosis of CoH is confirmed by means of an initial T₄ level <10th percentile and a TSH level >9 mU/L.

1. Time of TSH normalization

The goal of treatment in patients with CoH is to obtain prompt control of thyroid function after having made an early diagnosis. L-T₄ is the treatment of choice. The timing of L- therapy is important because an inverse relationship has been reported between IQ and the age at diagnosis of CoH (466). Infants with CoH treated in the first few weeks of life usually have a normal or slightly reduced IQ, whereas mean IQ was reduced to 89 when the diagnosis of CoH was delayed to 3 months of age, and it further declined to 71 with diagnosis between 3 and 6 months and to 34 after 6 months of age (467). A serum FT₄ level >129 nmol/L (below 10 µg/dL) should be reached as rapidly as possible, usually within 1 or 2 weeks after starting L-T₄

therapy to obtain a normal TSH after 1 month of treatment. Selva et al (468) reported that IQ was 10 points lower in children in whom the serum TSH and FT₄ levels were normalized over 2 weeks after starting L-T₄ treatment.

2. L-T₄ formulations for CoH

L-T₄ tablets are approved for treatment of CoH in the United States; administration is facilitated by crushing the tablets, mixing with water, and giving with a spoon. In Europe, a liquid L-T₄ formulation is available with administration of the desired dosage by a dropper. In one study, a liquid formulation of L-T₄ was administered to 28 consecutive newborns with primary CoH (469) in a median starting dose of 12.3 μg L-T₄/kg/d that was reduced to about 5 μg L-T₄/kg/d after 9 months. The median time of normalization of TSH to ≤6 mU/L was 2 weeks. TSH levels normalized within a median of 1 week in 21 patients who received a median starting dosage of 12.7 μg L-T₄/kg (range 9.8–17.1 μg/kg), and after a median of 2 months in 7 patients receiving only 10.1 μg/kg (469). These results demonstrated comparable efficacy of the liquid formulation to that of L-T₄ tablets but in a formulation that is easier to administer.

However, a recent study by Cassio et al (470) of 42 consecutive infants with CH demonstrated that drops and tablets are not bioequivalent, especially in infants with severe hypothyroidism.

3. L-T₄ dosage in CoH

The American Academy of Pediatrics (AAP) (21) and the European Society for Pediatric Endocrinology (20) recommend an L-T₄ starting dose of 10–15 μg/kg by mouth once daily (about 37.5–50 μg/d).

Higher performance scores for behavior, reading, spelling, and math were reported in newborns who received 50 μg/d L-T₄ (12–17 μg/kg/d) vs 37.5 μg (10–15 μg/kg/d) (471). In one study, 83 infants were assigned to receive 3 different starting doses of thyroid hormone at birth (6.0–8.0 vs 8.1–10.0 and 10.1–15.0 μg/kg/d) (472). Evaluation at 4 years of age indicated that infants with severe CoH who had started L-T₄ treatment at the highest dose had the highest intellectual assessment scores (472). Some studies tailored the starting L-T₄ dose according to the severity of hypothyroidism. An L-T₄ dose of 15 μg/kg/d was started in infants with athyreosis, whereas 12 μg/kg/d was administered to infants with an ectopic gland and 10 μg/kg/d in infants with dyshormonogenesis. The outcome of this study indicated that FT₄ was normalized within 7 days in 78% of the infants and in 100% after 14 days of treatment (473).

The serum FT₄ or total T₄ should be maintained in the upper limit of the normal range during the first year of life

with target values of 130 to 206 nmol/L (10–16 μg/dL) for serum total T₄ and 18 to 30 pmol/L (1.4–2.3 ng/dL) for serum FT₄. Serum TSH should be kept below 5 mU/L (20, 21). The New England Collaborative Study reported that children with persistent serum T₄ below 10 μg/dL in the first year of life had an IQ that was 18 points lower compared with patients with T₄ above 10 μg/dL (474). Some studies have reported an increased risk of craniosynostosis, hyperactivity, delinquency, aggressiveness, and poor attention in children with CoH who were overtreated with L-T₄ (475).

4. Follow-up in patients with CoH

The AAP suggests that the measurement of serum T₄ or FT₄ and TSH should be performed 2 or 4 weeks after initial treatment with L-T₄ and then every 1 to 2 months during the first 6 months of life, every 3 to 4 months between 6 months and 3 years of age and subsequently every 6 to 12 months until growth is completed (21). Routine thyroid function tests should be repeated 4 weeks after a change in L-T₄ dosage (21). The European Society of Pediatric Endocrinology recommends monitoring T₄ or FT₄ every 1 or 2 weeks after the starting dose of L-T₄ until TSH and FT₄ are completely normalized (20). The AAP recommends performing a 30-day withdrawal of L-T₄ treatment to assess whether the diagnosis of CoH will be permanent at the age of 2 or 3 years in children whose initial thyroid scan did not show an ectopic or absent thyroid gland, with a serum TSH <50 mU/L at screening and who had no increase in TSH after the newborn period (21). Treatment with L-T₄ should be restarted if an elevated TSH develops after L-T₄ withdrawal.

Conversely, if the TSH remains normal after L-T₄ withdrawal, the diagnosis of CoH can be considered to have been only transient. One study suggested the use of rhTSH to perform thyroid scintigraphy to confirm the diagnosis of CoH so as to avoid the adverse effects of L-T₄ withdrawal (476). Another means of assessing whether the hypothyroidism will be permanent is to reduce the L-T₄ dosage by 50% for 30 days; if the serum TSH remains normal after this reduction, L-T₄ should be discontinued and thyroid function tests should be reevaluated subsequently to confirm maintenance of euthyroidism. Rabbiosi et al (477) reported that major risk factors for permanent CH were prematurity, first-degree familial history of goiter/nodules, thyroid hypoplasia at diagnosis, and high L-T₄ requirements at follow-up.

The management and follow-up of CoH are summarized in Table 17. No specific guidelines have been developed for monitoring genetic conditions associated with hypothyroidism.

Table 17. Management and Follow-Up of CoH

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|--|
| Treatment should be started at L-T ₄ dose of 10–15 $\mu\text{g}/\text{kg}/\text{d}$ |
| Target ranges for TT ₄ , FT ₄ , and TSH values during the first year |
| TT ₄ 130–206 nmol/L (10–16 $\mu\text{g}/\text{dL}$) |
| FT ₄ 18–30 pmol/L (1.4–2.3 ng/dL) |
| Serum TSH should be kept under 5 mU/L |
| Follow-up should be performed by TSH, TT ₄ , or FT ₄ evaluation |
| At 2 and 4 wk after starting L-T ₄ treatment |
| Every 1–2 mo during the first 6 mo of life |
| Every 3–4 mo between 6 mo and three y of age |
| Every 6–12 mo thereafter until growth is complete |
| 4 wk after any change in L-T ₄ dose |

Abbreviation: TT₄, total T₄.

D. Treatment of SHypo in children and adolescents

L-T₄ is the treatment of choice in children and adolescents. The L-T₄ dosage requirement in CoH progressively declines from 10 to 15 $\mu\text{g}/\text{kg}/\text{d}$ in infants to 4 to 5 $\mu\text{g}/\text{kg}/\text{d}$ by the age of 5 years due to a progressive decrease in the rate of T₄ turnover (20, 21).

The most common cause of acquired SHypo in children is autoimmune Hashimoto's thyroiditis. The risk of SHypo is particularly common in children with Down's syndrome and Turner syndrome (478, 479). Persistent SHypo may develop in children who are classified as false-positive at neonatal screening for the presence of short-term neonatal hyperthyrotropinemia. It has been suggested that the mild persistent TSH increase in these children may reflect congenital anatomic abnormalities such as hypoplasia and hemiagenesis and thyroid function alterations (480).

Some SHypo patients without features of autoimmune thyroiditis may have increased TSH due to thyroid resistance to the effect of TSH. Defined mutations in the TSH receptor gene have been reported in studies evaluating the etiology of SHypo in pediatric populations (481, 482).

Full replacement doses of L-T₄ should be administered when the diagnosis of hypothyroidism is formulated in children and adolescents. Transient psychosis and intracranial hypertension have been reported during the early phase of L-T₄ therapy as well as in subjects undergoing progressive increase of L-T₄ doses (483). In prepubertal children, bone maturation and pubertal development should be monitored. Currently, no recommendations or guidelines have been formulated on the management of SHypo in the pediatric population.

Few studies have assessed the risk of progression and the potential adverse effects of untreated SHypo in children and adolescents. Only 27 relevant articles (with overall data from a total of 4018 children) were identified in a recent review article that assessed the natural history of SHypo and the potential effects of replacement therapy with L-T₄ in children and adolescents (484). Among these selected studies, only 6 were longitudinal trials and only 4

were multicenter studies. In this analysis, children with SHypo had a lower risk of progression toward overt disease compared with the adult population, with the rate of progression ranging between 0% and 28.8% (484). However, children with initial TSH levels greater than 7.5 mU/L, particularly girls, were at a greater risk of persistent hypothyroidism (484).

Moreover, a progressive increase in TPOAbs and plasma TSH values were predictive factors for the development of persistent hypothyroidism (484). The presence of autoimmune thyroiditis, celiac disease, elevated TSH, and TPOAbs increased the risk of developing hypothyroidism by 4-, 3.4-, and 3.5-fold, respectively, in a retrospective study of 87 children with autoimmune thyroiditis who were compared with 59 children with isolated hyperthyrotropinemia (485). On the contrary, no predictive factors for progression were identified in patients with isolated hyperthyrotropinemia after a 3-year follow-up (486).

Few studies assessed the effects of replacement therapy in children with SHypo. Two longitudinal studies evaluated the effects of replacement doses of L-T₄ on growth velocity (487, 488). Cetinkaya et al (487) studied 24 prepubertal and 15 pubertal Turkish children with short stature and SHypo. They observed a significant improvement in growth velocity after 6 months and 1 year of treatment with L-T₄; this improvement was more significant in the pubertal group (487). On the contrary, no effects of replacement therapy with L-T₄ were reported on height and BMI in a longitudinal study of 69 patients with a mild increase in TSH (5–10 mU/L) treated for 2 years; however, growth velocity was not reported in this study (488). Similar results were noted in a retrospective study in which no significant difference in growth velocity was reported between treated and untreated SHypo children compared with a control group of short children with normal TSH (489). A significant improvement in growth velocity after L-T₄ treatment was reported in prepubertal hypothyroid children with diabetes (TSH >50 mU/L) compared with less severe hypothyroid patients (TSH level 10.1–50 mU/L) and to matched diabetic controls, with a more significant effect in children with higher TSH levels (490).

The NHANES III from the United States analyzed the cognitive function in 1327 adolescents aged between 13 and 16 years, of whom 1.7% had SHypo (491). The results of this study indicated no differences in neuropsychological test scores; SHypo was associated with better performance in some areas of cognitive function largely related to higher mean reading and block design scores in the SHypo children compared with the scores of 1275 euthyroid subjects (491). Similarly, no effects of L-T₄ on neuropsychological functions were reported in children with

SHypo in the study by Aijaz et al (492). Conflicting results have been reported in 2 studies that assessed the effect on L-T₄ on thyroid volume in children (493, 494). A significant reduction in thyroid volume was found with autoimmune SHypo in the study by Svensson et al (493); this was the only study that assessed thyroid volume by ultrasonography.

No large prospective trials have evaluated cardiovascular risk of SHypo in a pediatric population. Elevated TSH values in obese adolescents with nonalcoholic fatty liver disease were positively correlated with important metabolic and cardiovascular risk parameters such as total cholesterol, triglycerides, LDL-cholesterol, insulin, carotid intima-media thickness, and left ventricular mass (495). These findings could suggest that obese adolescents with nonalcoholic fatty liver disease and increased serum TSH may have an increased cardiovascular risk (495). However, caution should be exercised in making a diagnosis of SHypo in children with high TSH levels. This is because the overweight state and obesity are not infrequently associated with increased serum TSH in children; however, TSH normalization generally occurs after weight loss. Although treatment of adults with SHypo often has been discouraged on the basis of risk of overtreatment, oversuppression of TSH has been noted only infrequently in a pediatric population (484).

In summary, the literature suggests that treatment of SHypo may be useful in children with TSH > 10 mU/L and clinical signs or symptoms of thyroid hormone deficiency and when SHypo is associated with short stature and impaired growth velocity or increased thyroid volume. On the other hand, replacement therapy with L-T₄ is more difficult to justify when serum TSH is < 10 mU/L and in the absence of goiter and/or positive antithyroid antibodies, because of the low risk to progression to overt hypothyroidism in these children. Randomized controlled prospective studies will be necessary to clarify the necessity of treating milder degrees of SHypo in the pediatric age group.

E. Replacement therapy with L-T₄ in hypothyroid patients with comorbidities

1. Acute and chronic kidney disease

Thyroid hormones affect renal development and physiology, with significant changes in renal function, electrolytes, and water homeostasis noted in patients with thyroid dysfunction (496–498).

Hypothyroidism induces a decrease in glomerular filtration, hyponatremia, and reduced facilitation of water excretion (496). Renal disease, in turn, leads to significant changes in thyroid function. Chronic kidney disease

(CKD) is characterized by a low-T₃ syndrome that has been correlated with higher levels of markers of inflammation (highly sensitive C-reactive protein, IL-6, etc.), malnutrition (lower prealbumin and IGF-1), endothelial dysfunction, impaired cardiac function, and poor survival (497, 498). CKD patients also have an increased incidence of both primary overt hypothyroidism and SHypo.

In NHANES III, the prevalence of hypothyroidism was reported to be between 10.9% and 23.1% in patients with stage 2 to 5 CKD (499). Moreover, the prevalence of primary hypothyroidism increased with progressively lower levels of kidney function; more than 20% of those with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m² had clinical or primary SHypo after controlling for age, gender, and race/ethnicity (499). The prevalence of SHypo was reported to be about 18% in patients with CKD not requiring chronic dialysis and was independently associated with progressively lower eGFR (500). Patients with eGFR of < 60 mL/min/1.73 m² had an increased OR of primary SHypo after adjusting for age, gender, fasting plasma glucose, total cholesterol, and triglyceride concentrations (500).

Furthermore, a TSH level within the normal range was negatively associated with eGFR (501). In a cross-sectional, population-based study of 29 480 adults without previously known thyroid disease, the prevalence of CKD was higher in people with TSH in the middle and highest thirds of the reference range and CKD was more common in those with SHypo (501). Making a diagnosis of hypothyroidism may be difficult in patients with CKD because several of the signs and symptoms of thyroid hormone deficiency may be attributed to uremia. On the other hand, overt hypothyroidism may worsen renal hemodynamics by decreasing cardiac output, leading to a progressive decline in GFR. Therefore, the normalization of thyroid function with L-T₄ replacement therapy in hypothyroid patients may improve kidney function (502–507).

In a recent study that evaluated the effects of L-T₄ therapy on renal function in 309 patients with SHypo and stage 2 to 4 CKD (507), the overall rate of decline in eGFR was significantly greater in SHypo patients who did not receive L-T₄ treatment compared with the L-T₄ treatment group (507). Kaplan-Meier analysis indicated that renal event-free survival was significantly lower in the nontreatment group ($P \leq .01$). In a multivariate Cox regression analysis, thyroid hormone replacement therapy was found to be an independent predictor of renal outcome (HR, 0.28; 95% CI, 0.12–0.68; $P \leq .01$) (507).

SHypo has been identified as a strong predictor of all-cause mortality in chronic dialysis patients. In the study by Rhee et al (508), patients who were euthyroid during exogenous thyroid replacement were not at higher mortality

risk than spontaneous euthyroid controls, suggesting that L-T₄ replacement therapy could improve the prognosis of CKD patients on chronic dialysis. However, an issue of safety was raised by one study that evaluated the effects of L-T₄ in patients with acute renal failure and the euthyroid sick syndrome. In this prospective, randomized, placebo-controlled, double-blind trial, mortality was increased 3.3-fold with 300 µg/70 kg/d of iv L-T₄ for 2 days in patients with acute renal failure (509). The increased mortality was correlated with suppression of TSH, suggesting that euthyroid sick patients should not be replaced with thyroid hormone (509).

Hypothyroidism has also been described as a consequence, rather than the cause, of renal dysfunction. T₄ circulates in the bloodstream largely protein bound to the 3 major T₄ binding proteins, and the T₄-protein complex can be lost in the urine in the nephrotic syndrome. Thus, an undiagnosed nephrotic syndrome should be considered in some instances of persistent hypothyroidism. Similarly, in patients with known nephritic syndrome, it is essential to periodically monitor thyroid function and make any indicated adjustments in L-T₄ dosage as may be warranted by serum TSH levels.

In conclusion, the clinical experience reported in the literature suggests that thyroid hormone deficiency should be treated in patients with CKD and may also improve the kidney function. Because it may be more difficult to make a clinical diagnosis of hypothyroidism in patients with CKD, it may be worthwhile to consider screening for thyroid dysfunction in these patients.

2. Diabetes

Thyroid hormone has important effects on glucose homeostasis; it influences insulin levels and counterregulatory hormones, intestinal glucose absorption, hepatic glucose production, and fat and muscle uptake of glucose (510, 511). Insulin resistance has been reported in patients with overt hypothyroidism and SHypo and when present may further increase cardiovascular risk in patients with thyroid hormone deficiency, especially when associated with hyperlipidemia and hypertension (510–512). On the other hand, the prevalence of overt hypothyroidism and SHypo is increased in type 1 diabetes mellitus (T1DM), in T2DM patients with autoantibodies against glutamic acid decarboxylase 65, and in patients with metabolic syndrome (513–517).

A meta-analysis of 10 920 patients with diabetes indicated a prevalence of thyroid disease of 11% with an increased prevalence in women and no significant difference in frequency between T1DM and T2DM (518). A study of pediatric patients with T1DM found a rising prevalence of thyroid antibodies with age, from 3.5% in patients less than 5 years old up to 25% between 15 and 20 years of age

(519). Given this high frequency, screening for thyroid dysfunction is recommended in children and adolescents with T1DM (520). Consistent with this recommendation are current guidelines that suggest that baseline thyroid function tests should be measured in newly diagnosed patients with T1DM (518). The British Thyroid Association suggests TPOAb testing at baseline and TSH monitoring at yearly intervals in patients with T1DM (518). On the contrary, thyroid function tests are recommended in T2DM only when there is a suspicion of an autoimmune thyroid disease (518).

The coexistence of thyroid hormone deficiency may worsen the long-term morbidity in diabetic patients (521–523). SHypo may increase the risk of retinopathy and nephropathy in patients with diabetes (521–523). In a cross-sectional analysis on 588 patients with T2DM, SHypo was associated with a greater prevalence of diabetic nephropathy (OR, 3.15; 95% CI, 1.48–6.69) compared with euthyroid persons with diabetes (521). Moreover, the risk of cardiovascular events was significantly increased in T2DM persons with SHypo after adjustment for age, sex, cardiovascular risk factors, and medication (521). There are conflicting results on cardiovascular mortality in patients with diabetes and thyroid hormone deficiency (181, 524, 525).

A significant improvement of insulin sensitivity has been reported after replacement therapy with L-T₄ (526). On the basis of the latter studies, there may be a potential benefit in treating thyroid hormone deficiency in insulin-resistant diabetic patients, but prospective studies will be required to support this assumption.

3. Heart disease

Hypothyroidism is a cause of reversible HF (185–188). Moreover, hypothyroidism may frequently coexist in patients with chronic HF, with a prevalence of about 18% in all patients with HF and a higher prevalence (23%) among men and Hispanic subjects (527). The onset of hypothyroidism may exacerbate progression of HF in cardiac patients. A recent study assessed the prognostic role of thyroid function deficiency in 338 consecutive outpatients with chronic HF (528). The results of this study indicated that TSH, considered as a continuous variable, was significantly associated with HF events in multivariate analysis. Even mild or SHypo was independently associated with a greater likelihood of HF progression in patients with chronic HF (528).

These results may explain why the American College of Cardiology guidelines for HF published in 2010 recommended screening with serum TSH of all newly diagnosed cases of HF (529).

Hypothyroidism is associated with an increased risk of mortality in patients with acute and chronic cardiac dis-

ease. Iervasi et al (530) assessed the cardiac outcome in 3121 patients with chronic cardiac disease and subclinical thyroid dysfunction during a mean follow-up of 32 months. After adjustment for several risk factors, the HRs for cardiac and overall deaths were higher in patients with SHypo and low serum T_3 than in euthyroid patients (530).

The same authors evaluated the long-term prognostic role of subclinical thyroid disease in 1026 patients with acute cardiac disease. Similar to the results of the previous study, the HR for cardiac death was higher in patients with SHypo and the low- T_3 syndrome, after adjustment for several risk factors (531). Recently, the Sudden Cardiac Death in Heart Failure trial showed that patients with moderately symptomatic HF and abnormal thyroid function, either at baseline or during the 5-year follow-up, have had a 60% increase in the RR of death compared with those with normal thyroid function (532).

In summary, the cited results suggest that the onset of thyroid hormone deficiency may worsen the prognosis of cardiac disease and that replacement therapy with $L-T_4$ could be justified. However, adverse effects may accompany the long-term use of thyroid hormone, and prospective studies will be necessary to clarify the most appropriate therapeutic approach to improve the cardiovascular mortality in patients with thyroid hormone deficiency.

4. Treatment of MC

MC is a rare and under-recognized condition that usually occurs in elderly patients with longstanding hypothyroidism (40, 533, 534). About 300 cases of MC have been reported in the literature (535). Common precipitating factors of MC are hypothermia, infections (particularly influenza, pneumonia, and urosepsis), trauma, and certain medications (amiodarone, β -blocking drugs, narcotics, lithium, barbiturates, and sedatives). Anesthesia, discontinuation of $L-T_4$ replacement therapy, cerebrovascular events, congestive HF (CHF), or GI bleeding may play an important role in the onset of MC (536). Sinus bradycardia, low-voltage complexes on an electrocardiogram (ECG), complete heart block, nonspecific ST-T changes, prolongation of the QT interval, and increased QT dispersion, represent frequent findings at the ECG evaluation in patients with severe hypothyroidism. Polymorphic ventricular tachycardia (torsades de pointes), pericardial effusion, and MI are alarming complications of MC. An elevated creatine phosphokinase levels in association with nonspecific ECG findings may generate an incorrect diagnosis of MI.

Depression of cerebral function, hyponatremia, hypoglycemia, respiratory acidosis, hypoxia, hypercapnia, and reduced cerebral blood flow are frequent in the clinical presentation and may lead to respiratory failure and coma.

Cardiac function is depressed with low cardiac output, reduced inotropism and chronotropism, increased SVR, vasoconstriction, increased diastolic BP, reduced blood volume, and reduced glomerular filtration with water retention and nonpitting edema. Hyponatremia is often present as a result of decreased free water clearance and is usually associated with a low serum osmolality and high levels of creatinine and antidiuretic hormone.

The mortality rate of MC has been reported to be between 30% and 60%. Factors associated with a poor prognosis include advanced age, hypotension, and bradycardia at presentation, persistent hypothermia not responsive to treatment, sepsis, and intake of sedatives (537).

Sequential Organ Failure Assessment (SOFA) scores >6 and a high Acute Physiology and Chronic Health Evaluation (APACHE) II score may help clinicians identify patients at risk of mortality at an earlier stage (536, 537), and such patients should be hospitalized in an intensive care unit. Hypothermia, hypovolemia, and electrolyte abnormalities should be corrected. Mechanical ventilation may be necessary (538), and cardiovascular function should be monitored, especially after iv administration of thyroid hormone replacement therapy. The possibility of underlying infectious diseases should be investigated by means of blood and urine cultures and chest radiograph. Empiric treatment with broad-spectrum iv antibiotics can be considered. Most importantly, steroid supplementation and thyroid hormone replacement therapy should be promptly started. Hydrocortisone should be administered iv at a dosage of 50 to 100 mg every 6 to 8 hours to avoid the possible precipitation of an adrenal crisis in patients with central or autoimmune hypothyroidism who may have coincident marginal adrenal function due to underlying Addison's disease. Severe hyponatremia (<120 mEq/L) should be corrected with the administration of hypertonic saline solution (50–100 mL of 3% sodium chloride) followed by an iv bolus of 40 to 120 mg furosemide. Conivaptan and tolvaptan, nonpeptide inhibitors of antidiuretic hormone, could be useful in treating hyponatremia in MC where elevated vasopressin levels are present. Conivaptan has been successfully used to treat euvolemic hyponatremia in a starting dose of 20 mg by iv infusion followed by continued infusion at a rate of 20 mg/d for 2 to 4 days (539). Unfortunately, the rare routine availability of the vasopressin assay may limit the use of this helpful drug in MC.

Severe hypotension should be treated with the cautious administration of iv fluids (5% to 10% glucose in isotonic sodium chloride solution resuscitation plus hydrocortisone). Caution also should be exercised when using vasopressor drugs because these drugs might exacerbate cardiac arrhythmias with the iv administration of thyroid

hormone. About 200 μg of T_4 iv followed by 100 μg T_4 iv per day can be administered to restore vital functions in patients with severe coma. Alternatively, a 500- μg dose of oral L-T_4 should be promptly started and followed by 125 to 150 μg L-T_4 as a daily maintenance dose orally in patients who are able to take oral medication. Patients who received oral L-T_4 had no difference in the outcome from those receiving iv T_4 (537).

Because the onset of T_4 action may be delayed due to a reduced rate of activating conversion of T_4 to T_3 , iv L-T_3 administration may be more effective than T_4 . T_3 would be administered in a starting doses of 10 to 20 μg , followed by 10 μg every 4 hours for the first 24 hours and then 10 μg every 6 hours for 1 or 2 days until the patient sufficiently improves their cerebral function to take oral medication (540). Adverse cardiac events may develop during the early treatment of MC (arrhythmias or MI), especially with doses above 500 $\mu\text{g}/\text{d}$ of L-T_4 and 75 $\mu\text{g}/\text{d}$ of L-T_3 , leading to increased mortality (541). As a consequence, elderly patients and patients with comorbidities are more safely treated with lower doses of L-T_4 , usually in the range of 100 to 150 μg oral L-T_4 daily. In one report, 200 μg T_4

iv followed by 100 μg T_4 iv was both effective and safe when compared with higher doses of L-T_4 (537).

Combined therapy with T_4 and T_3 may also be useful. T_4 may be started with an initial dose of 4 $\mu\text{g}/\text{kg}$ lean body weight and may be followed by 100 μg 24 hours later with a further progressive reduction to 50 μg daily iv or orally. T_3 may also be started simultaneously with T_4 at a dose of 10 μg iv, and the same dose is given every 8 to 12 hours until the patient can take maintenance oral doses of T_4 . The treatment of MC is summarized in Table 18.

XI. L-T_4 Therapy in Benign and Malignant Thyroid Nodular Disease

A. L-T_4 therapy in benign hypofunctioning thyroid nodules

The incidental detection of unsuspected thyroid nodules or incidentalomas has dramatically increased in the last several years due in large part to the frequent use of ultrasound for the evaluation of the thyroid gland and lesions of the neck (10). Discovery of a thyroid nodule and presentation to an endocrinologist is relatively common.

Table 18. Treatment and Prognosis of MC

| |
|--|
| Monitoring in ICU setting |
| Treat precipitating factors |
| Hypoventilation: O_2 and mechanical ventilation |
| Hypotension: administration of iv fluids (5%–10% glucose in isotonic NaCl solution resuscitation plus hydrocortisone; caution with vasopressor drugs because they may exacerbate cardiac arrhythmias with iv thyroid replacement therapy) |
| Hypothermia treated with warm room temperature/blankets; avoid rapid rewarming because of peripheral vascular dilatation, which may precipitate hypotension and shock |
| Hypoglycemia: managed with dextrose infusion |
| Hyponatremia may be treated with saline solution and loop diuretics |
| Treat and then exclude coexisting adrenal insufficiency: hydrocortisone 50–100 iv every 6–8 h |
| Thyroid replacement therapy |
| Controversial: L-T_4 alone, L-T_3 alone, $\text{L-T}_4/\text{L-T}_3$ combination |
| L-T_4 administration |
| Parenteral replacement can be preferred initially due to bowel wall edema and gastric atony with unpredictable gastrointestinal absorption |
| L-T_4 : 200–500 μg iv followed by 50–100 μg iv per day in severe coma |
| Advantages: iv formulation, smaller risk of cardiac complications |
| Disadvantages: L-T_4 less metabolically active than L-T_3 |
| L-T_4 500 μg of oral dose followed by 150 μg of L-T_4 as maintenance dose in patients who are able to take oral medication |
| Liothyronine |
| L-T_3 starting doses of 10–20 μg , followed by 10 μg every 4 h for the first 24 h and then 10 μg every 6 h for 1 or 2 d |
| Advantages: biologically active, faster therapeutic |
| Disadvantages: higher risk of cardiac complications (ischemia, lethal arrhythmias) |
| Combined therapy with T_4 and T_3 |
| T_4 stated at a dose of 4 $\mu\text{g}/\text{kg}$ of lean body weight followed by 100 μg 24 h later with a further progressive reduction to 50 μg daily iv or orally; T_3 started simultaneously with T_4 at a dose of 10 μg iv, and the same dose is given every 8–12 h until the patient can take maintenance oral doses of T_4 |
| Prognosis |
| Mortality rate 30%–60% |
| Poor prognosis associated with |
| Initial temperature $<93^\circ\text{F}$ or no response to therapy within 3 d |
| Advanced age |
| Bradycardia |
| Hypotension |
| Cardiac complications (including MI, CHF) |
| Sequential Organ Failure Assessment (SOFA) scores more than 6 |
| High APACHE II score |

The prevalence of thyroid nodules is higher in women in areas of iodine deficiency and increases with advanced age, being up to 50% in individuals over the age of 50 years as may be found on ultrasound evaluation. Iodine deficiency is the most frequent contributing factor to the development of multinodular goiter. The pathogenesis begins with iodine deficiency leading to reduced thyroid hormone production, which in turn results in increased serum TSH, and TSH serves as a growth factor for thyroid epithelial cells.

A diffuse goiter is frequently observed in young subjects living in iodine-deficient areas whereas MNG is commonly observed in the elderly (65). The natural history of untreated isolated nodules and MNG is characterized by a progressive worsening; thyroid nodule volume increases over time, and the size of the surrounding thyroid tissue enlarges presumably due to TSH stimulation, increasing the risk of the onset of new nodules. Two retrospective studies from Japan and England have examined the natural history of untreated hypofunctioning thyroid nodules followed for an average of 15 and 5 years, respectively (542, 543). These studies have demonstrated that untreated solid thyroid nodules increased in size in about 13% to 15% of cases, whereas nodules with greater cystic content were less likely to grow (542, 543).

Thyroid autonomy may develop in one or more of the nodules in euthyroid elderly patients with MNG, leading to development of endogenous subclinical hyperthyroidism. This condition may then exist for several years, preceding the onset of overt disease and may be responsible for severe cardiovascular complications (544). Obstructive symptoms with airway compression, dysphagia, and paralysis of a recurrent laryngeal nerve may occur in the presence of a large MNG.

Approximately 5% to 10% of thyroid nodules may be malignant, and the risk of thyroid cancer may increase in people who were exposed to ionizing radiation in infancy and childhood.

Surgical treatment is recommended in the presence of large goiter with compressive symptoms, progressive growth of thyroid nodules, and documented or suspected thyroid malignancy (23–25, 545, 546).

Murray in 1891 (125) reported that the sc injection of sheep thyroid extract for the treatment of myxedema reduced the size of goiter. In 1953, Greer and Astwood (547) described goiter regression in two-thirds of patients treated with thyroid extract in an uncontrolled trial. Treatment with L-T₄ in doses sufficient to suppress TSH has long been used with the aim of preventing or reducing the growth of thyroid nodules or the formation of new nodules. However, the effectiveness of TSH suppression of thyroid nodules with L-T₄ has been controversial for decades.

Some meta-analyses have failed to show a clear benefit of TSH suppression in the management of nontoxic thyroid nodules, and this treatment is debated in terms of efficacy, the optimal level of TSH suppression, the optimal duration of treatment, and potential side effects. A critical examination of trials on TSH-suppressive therapy was performed in an early cumulative meta-analysis that evaluated the capacity of L-T₄-suppressive therapy to decrease the volume of a nontoxic solid thyroid nodule to <50% of its baseline value (548). The analysis indicated that L-T₄ treatment was associated with decreased nodule volume in 17% of patients and was able to inhibit growth in another 10% (548). In the meta-analysis by Castro et al (549) that included 6 randomized trials for a total of 346 patients, only 22% of patients treated with TSH-suppressive doses of L-T₄, compared with 10% in the control group, had a decrease in nodule volume by more than 50%. However, this degree of improvement during thyroid hormone therapy for longer than 6 months did not achieve statistical significance (549).

Nine studies were included in the meta-analysis of Richter et al (550), which indicated that T₄-suppressive therapy led to a nonsignificant improvement in the rate of response to therapy (defined as ≥50% nodule volume reduction by ultrasound) (pooled RR, 1.83; 95% CI, 0.9–3.73). The mean nodule volume or diameter reduction was not statistically significant between the L-T₄ treatment group and the control group (550). In the meta-analysis of Sdano et al (551), a thyroid hormone TSH suppression therapy (THST) appeared more likely than placebo or no treatment to significantly reduce benign thyroid nodule volume. Finally, a meta-analysis by Yousef et al (552) assessed the effects of THST on the basis of ultrasonography of the nodules rather than physical examination. A total of 417 patients were treated with L-T₄, and 326 patients received placebo. Of the 11 included studies, 8 were RCTs (6 single-center studies and 2 multicenter trials) and 3 were cohort studies. The analysis indicated that L-T₄-treated patients were up to twice as likely to have nodule reduction at the end of follow-up (minimum follow-up of 6 months) (552).

Given the results of these various studies and meta-analyses, it is understandable why the issue of THST for nodules remained controversial. It is relevant to consider some of the limits or confounding factors inherent in the studies or these meta-analyses including: 1) the heterogeneity of the patients evaluated, 2) the variability in L-T₄ treatment in terms of doses and duration of therapy, 3) the different definitions of response to treatment, 4) the different levels of TSH suppression obtained, 5) the various methods used to assess nodule volume, and 6) the inclusion of nodules with different characteristics (solid, mixed,

or cystic nodules). Moreover, the follow-up of some studies was relatively short, and the side effects were poorly documented.

A critical analysis of these results suggests that the reduction of nodule volume was more effective in those nodules of certain characteristics such as: 1) small nodules (<2.4 mL in volume or <1.7 cm in diameter); 2) recently diagnosed thyroid nodules, ie, nodules likely of shorter duration; 3) lesions with colloid features on cytological examination; 4) patients from geographic regions with borderline or frank iodine deficiency; and 5) nodules with cytological diagnosis of Hashimoto's thyroiditis. On the contrary, a reduction in size or volume was rarely observed in fibrotic, hyperplastic nodules.

Some degree of regrowth of nodules sometimes occurs after the cessation of L-T₄ therapy. Moreover, THST in doses that reduced TSH levels to <0.1 mU/L were more effective than those doses associated with TSH levels >0.1 mU/L (553). A few studies assessed the ability of L-T₄ to reduce or even prevent the development of additional nodules (554, 555). One 5-year follow-up study indicated that L-T₄ treatment was ineffective in achieving nodule shrinkage (TSH <0.1 mU/L) but was effective in significantly reducing the frequency of new nodules (554). Although still unsettled due to the heterogeneous results of these studies, it remains conceivable that L-T₄ therapy might be more efficient than placebo in preventing the development of additional nodules and the increase in the thyroid volume under certain specific clinical circumstances. This possibility is supported by a prospective multicenter, randomized, double-blind placebo-controlled French trial, in which THST was effective in reducing the growth of solitary thyroid nodules and in preventing the development of new nodules (555). Pharmacological doses of iodine have been used in some studies for the treatment of patients with MNG in areas of iodine deficiency (556). The rationale for iodine treatment is based on the known relationship of goiter development to iodine deficiency, and the possibility that part of the effect of L-T₄ therapy lies in the adjunctive provision of the iodine content of the L-T₄. Indeed, La Rosa et al (556) reported that patients receiving potassium iodide (1.5 mg every 2 weeks) had a decrease of their basal nodule volume by 23%.

Recently, a multicenter, double-blind, randomized, placebo-controlled trial (LISA trial) was performed in Germany to assess the effects of iodine and L-T₄ treatment in patients with nodular goiters, during a 12-month treatment period (557). A total of 1020 euthyroid patients aged 18 to 65 years with 1 or more thyroid nodules (minimal diameter 10 mm) participated in the study. They were recruited from 60 German centers and were randomized to evaluate whether the effect of combined T₄ plus iodine

therapy was superior to T₄, iodine, or placebo. L-T₄ therapy was administered in doses able to obtain a TSH target range of 0.2 to 0.8 mU/L. This study revealed that the volume of benign nodules greater than 1 cm in diameter was significantly reduced by TSH-suppressive L-T₄ doses in combination with iodine compared with T₄ alone, iodine alone, or placebo in an iodine-deficient German population (557). The nodule volume reduction was, respectively, -17.3% in the T₄ plus iodine group, -7.3% in the T₄ group, and -4.0% in the iodine group as compared with placebo. Thyroid volume reduction (-7.9%) was superior during combined L-T₄-iodine therapy compared with iodine (-5.2%); however, this reduction was comparable to L-T₄ alone (557).

Thus, in a region with an insufficient iodine supply, treatment with a combination of iodine and T₄ of patients with normal to modestly elevated TSH levels could serve to reduce thyroid nodule volume. However, we should caution that high doses of iodine may induce development of hyperthyroidism especially in elderly subjects. It should be noted that ATA management guidelines state that there is no benefit of THST of thyroid nodules proven benign by cytological examination (23, 24).

Another interesting aspect of the relationship between serum TSH and thyroid neoplasia is the growing body of literature indicating that a high serum TSH level may be an independent predictor for the development of thyroid cancer in patients with thyroid nodules (558, 559). Thus, several studies report a direct relationship between higher TSH levels and the risk of papillary thyroid cancer (PTC) in patients with nodular thyroid disease (558, 559). This may constitute another rationale for L-T₄ treatment of patients with nodules in hope of reducing the potential development of thyroid cancer by reducing serum TSH levels (560).

This approach is supported by the results of a recent study that investigated the effect of L-T₄ treatment on the frequency of PTC diagnosed by cytology in a large series of patients with nodular goiter. In this study, L-T₄-treated patients had a significantly lower serum TSH and enjoyed a lower prevalence of PTC (3.2% vs 5.1%; $P < .0001$) compared with untreated patients (560). The frequency of PTC was closely related to the serum TSH level, being lowest in patients with TSH below the reference range and highest in patients with TSH above the reference range and showing a progressive increase from the lower to the upper quartile of the TSH reference range (560).

Although the latter studies indicating a relationship between TSH and thyroid neoplasia have been very recent, the data should not have been surprising given the known mitogenic potential of TSH. Thus, TSH is known to stimulate thyroid cell proliferation and the growth of experi-

mental tumors with its removal shown to provoke accelerated tumor growth. Clinically, TSH levels can play a role in the progression of preexisting PTC (561–563). Furthermore, high TSH values have been associated with a more advanced stage of thyroid cancer (564–566). Conceivably, the link between Hashimoto's thyroiditis and a higher risk of PTC might be mediated as well by the likelihood of higher TSH levels in these patients.

All of these results clearly indicate that TSH suppression could affect the natural history of thyroid nodules.

A recent meta-analysis assessed the association between serum TSH and thyroid cancer by the evaluation of 28 studies, including a total of 42 032 subjects and 5786 thyroid cancer cases (567). This analysis confirmed that a higher serum TSH concentration is associated with a higher risk of thyroid cancer. The dose-response model OR was 1.72 (95% CI, 1.42–2.07) per mU/L TSH below 1 mU/L and changed to an OR of 1.16 (95% CI, 1.12–1.21) per mU/L TSH at levels of 1 mU/L and greater. In a prospective model, the odds of thyroid cancer were 3 times greater in patients with a serum TSH level of 4 mU/L compared with those with a serum TSH of 0 mU/L and doubled between a serum TSH level of 2.2 and 7 mU/L.

Future longitudinal studies are necessary to further assess this important issue before including serum TSH in a diagnostic nomogram for thyroid cancer prevention (567). Currently, L-T₄ treatment of thyroid nodules to prevent thyroid cancer is not recommended.

Of course, there are risks attendant to THST that pertain to their use for benign nodular disease and that have added to the debate and principally relate to the cardiac and skeletal side effects of this therapy (9). Specifically, THST can lead to an unintentional exogenous subclinical hyperthyroidism that may increase the risk of AF and may reduce BMD, especially in the elderly and postmenopausal women with even more harmful effects in patients with comorbidities (9). Although recent ATA guidelines do not recommend routine suppressive therapy with L-T₄ of benign thyroid nodule (23, 24), this treatment is still used among members of the ETA, especially in areas of borderline-low iodine intake (25).

According to AACE/AME/ETA guidelines, TSH suppression should be particularly avoided in postmenopausal women with evidence of low bone mass, in the elderly, and in those with cardiac disease; in those nodules with suspicious cytological lesions; and in general, in patients in whom the risk of this therapy outweighs its uncertain benefits (25). A THST can be considered in patients living in iodine-deficient areas, in young patients with small thyroid nodules, and in patients with nodular goiters with no evidence of functional autonomy. Raised FT₃ and FT₄ levels should be avoided during THST.

Open questions remain on THST which should be clarified in the future. In particular, it is unknown whether subnormal TSH may induce the same beneficial and adverse effects associated with an undetectable serum TSH. Therefore, it remains to be established what level of TSH suppression could be effective in improving thyroid nodule growth and malignancy without increasing the risk of adverse effects. Moreover, it will be necessary to understand how long patients should be treated with L-T₄ to improve the nodular disease and the risk of PTC, considering that the beneficial effect of this treatment might be lost when therapy is discontinued.

RCTs with a long period of follow-up will be required to evaluate the risk to benefit ratio of treatment with L-T₄ with the aim of reducing the risk of nodule or MNG growth, the risk of thyroid cancer, and the risk of adverse effects. The ability of L-T₄ treatment to prevent the development of functional autonomy in patients with nontoxic MNG has not been demonstrated. This important issue should be another objective of future controlled prospective clinical trials. It may be possible to identify a subgroup of patients with nodular disease in whom THST could be shown to be clearly beneficial.

B. L-T₄ therapy in DTC

Prolonged thyroid hormone-suppressive therapy has long been used to prevent the recurrence or progression of well-differentiated thyroid cancer. As alluded to above, experimental studies have shown that TSH stimulates thyroid cell proliferation, radioiodine uptake, and Tg production (568, 569). Moreover, clinical data have demonstrated that TSH suppression with L-T₄ reduces the likelihood of progression and/or recurrence of thyroid cancer (570–572). Several older studies have shown fewer cancer recurrences and cancer-related deaths in patients who have received TSH-suppressive L-T₄ doses than in those who have not received TSH-suppressive therapy (573, 574). These studies have supported the survival benefit of a high level of TSH suppression (ranging from 0.05–0.1 mU/L) especially in patients at high risk of recurrence after total thyroidectomy and thyroid remnant ablation, suggesting that a constant TSH suppression (≤ 0.1 mU/L) could improve relapse-free survival. Pujol et al reported that persistent TSH suppression < 0.05 mU/mL was associated with longer relapse-free survival compared with serum TSH levels of 1 mU/mL or higher (575). In this study, the degree of TSH suppression was an independent predictor of recurrence in the multivariate analysis (575).

These findings were confirmed by a meta-analysis including 10 studies that indicated the benefit of TSH suppression (576). However, these studies did not differentiate between the beneficial effects of TSH suppression

according to the aggressiveness of DTC. Moreover, all of the studies were limited by the lack of randomization and appropriate controls (576).

Recommendations for the degree of TSH-suppression therapy required have been modified in recent years because of appreciation of the risk of adverse effects of exogenous TSH suppression and the evidence that suppression may be necessary only in high-risk patients, whereas those patients who appear to be disease-free will enjoy excellent survival without suppression. Such recommendations have evolved related to studies such as that reported by Cooper et al (577) who performed a multicenter, prospective study using the database of the National Thyroid Cancer Cooperative Registry. This study assessed the results of 617 patients with PTC followed for a median of 4.5 years and showed that TSH suppression was an independent predictor of disease progression in high-risk patients. However, a greater degree of TSH suppression was not useful to prevent disease progression in patients at low risk for recurrence (577).

A second study from the National Thyroid Cancer Cooperative Registry included 2936 patients with DTC (578). This study confirmed that subnormal to undetectable serum TSH levels were necessary to improve overall survival and disease-specific survival in stage III and IV patients. On the contrary, this study proved that subnormal serum TSH levels were sufficient to improve the overall survival in stage II patients compared with normal or elevated serum TSH levels (578). A retrospective study assessed recurrence risk in 366 patients with DTC treated with total thyroidectomy and radioiodine ablation (579). In this study, serum TSH values >4.5 mU/L were an independent predictor of death. Furthermore, serum TSH levels >2 mU/L were associated with an increased risk of thyroid cancer-specific death and recurrences. However, no differences in deaths or recurrences were observed in patients who had their serum TSH levels maintained between 0.1 and 0.4 mU/L (580).

A recent RCT assessed the efficacy of TSH-suppression therapy on thyroid cancer recurrences (580). Low- and high-risk patients with PTC were stratified according to the AMES (age, metastasis, extension, and size) risk-group classification. Disease-free survival patients were randomly assigned to receive postoperative TSH-suppression therapy (group A) or not (group B). The 218 patients included in group A received doses of $L-T_4$ to keep serum TSH levels below 0.01 mU/L, and the 215 enrolled in group B were treated with $L-T_4$ doses to obtain a serum TSH level within the reference range (0.4–5.0 mU/L). Neck ultrasonography and chest computed tomography were used to detect recurrences. The results of this study indicated that disease-free survival was not different be-

tween those patients who were receiving TSH-suppressive doses and those in whom TSH remained within the reference range (580).

A recent retrospective study examined the survival of 157 DTC patients with distant metastases (581). The results indicated that DTC-specific survival was significantly improved in patients with a median TSH level ≤ 0.1 mU/L (median survival 15.8 years) than in those with a nonsuppressed TSH level (median survival 7.1 years; $P < .001$). However, no further improvement in survival was found when TSH suppression was lower than 0.1 mU/L (581). These results suggest that TSH-suppression therapy decreases the rate of recurrences and mortality only in patients with high-risk DTC. As a result of these studies, clinicians target aggressive TSH suppression with $L-T_4$ in patients with metastatic DTC, whereas less aggressive TSH suppression is deemed appropriate in disease-free patients.

Recent management guidelines allowed clinicians to stratify the degree of TSH suppression according to the degree of aggressiveness of thyroid cancer (24, 582–585). The ATA guidelines have defined risk of recurrence as either low, intermediate, or high based upon the patient's status after the initial therapy (thyroidectomy with or without radioiodine ablation) and recommends a risk-adapted titration of TSH suppression. The guidelines of both the ATA and ETA recommend maintaining undetectable serum TSH levels in high-risk patients beginning at the time of their initial management (24, 582). On the contrary, in low-risk patients who represent about 80% of all thyroid cancer patients, the ATA and ETA guidelines do not support any benefit from TSH suppression. Furthermore, ATA and ETA guidelines recommend that high-risk patients with evidence of persistent disease should have their serum TSH level maintained at <0.1 mU/L. And in those high-risk patients who have achieved a disease-free status after treatment, the ATA guidelines recommend maintaining the TSH level between 0.1 and 0.5 mU/L for 5 to 10 years of follow-up, whereas the ETA guidelines recommend a TSH level of <0.1 mU/L for 3 to 5 years. For low-risk patients, the ATA guidelines suggest that initial serum TSH levels may be between 0.1 and 0.5 mU/L, whereas the ETA guidelines suggest a suppressed TSH of <0.1 mU/L. In low-risk patients who are shown to be disease-free on follow-up testing, both guidelines recommend that serum TSH should be kept at the low end of the reference range (24, 582).

In addition to the potential for adverse effects on heart and bone, TSH-suppressive therapy is not without possible other risks in patients with DTC (586, 587). For example, a recent review noted an increased incidence of kidney, pancreas, ovarian, and breast cancers (586). A

Table 19. ATA Risk Assessment for DTC at the Time of Initial Surgery

| Low Risk | Intermediate Risk | High Risk |
|--|--|---|
| No local or distant metastases | Microscopic invasion into the perithyroidal soft tissues | Increased age (>45–50 y) |
| Complete surgery | Aggressive histology | Increased size (>4 cm) |
| No locoregional or vascular invasion | Vascular invasion | Macroscopic tumor invasion |
| No aggressive histology (eg, tall cell, insular, columnar cell carcinoma) | | Incomplete tumor resection |
| No uptake outside the thyroid bed on initial posttreatment scan (if performed) | | Distant metastases |
| | | Radioiodine uptake outside the thyroid bed after a posttreatment radioiodine scan performed after ablation of remnant thyroid |

large epidemiological study in Norway including 29 000 patients with suppressed TSH levels to less than 0.5 mU/L who had been monitored for 9 years confirmed an increased cancer incidence (HR, 1.34) (587). It has been postulated that integrin activation by TSH could be responsible for promoting angiogenesis through the activation of MAPK (or MAPK pathway) (588). Finally, an increased thyrotoxic periodic paralysis with profound hypokalemia and muscle paralysis due to overtreatment with L-T₄ was reported in Caucasians (589).

Therefore, the beneficial role or necessity for TSH-suppressive therapy in all patients with DTC is questioned today, given the above-mentioned recent randomized study that failed to show any benefit for TSH-suppressive therapy in patients at low risk levels and the overall increased risk of adverse cardiac and bone effects and the less likely but possible development of other cancers.

Stratification into a risk-adapted management scheme for L-T₄ therapy in patients with DTC was summarized in a recent review that considered the aggressiveness of the DTC as well as the potential adverse effects induced by iatrogenic subclinical hyperthyroidism (569). To this end, patient age and the presence of preexisting cardiovascular and skeletal risk factors were considered. Tables 19 and 20 stratify different potential patient categories according to the aggressiveness of DTC and the risk of adverse effects

of ExoSHyper. Stratification is based upon those data indicating that more aggressive TSH suppression is warranted in patients with high risk disease or recurrent tumor, whereas less aggressive TSH suppression is targeted for low-risk patients. The underlying concept holds that long-term treatment with L-T₄ should be individualized and balanced against the potential risk for adverse effects during the follow-up in patients who are both at high risk of recurrence and at high risk of adverse effects. Elderly patients with DTC, especially those with comorbidities, are usually at higher risk for both cancer progression and adverse effects from L-T₄ therapy. Therefore, these patients should undergo periodic cardiological evaluation and bone density assessment, whereas the degree of TSH suppression is individualized and adapted to the clinical situation, which may change with time. In high-risk patients who are clinically and biochemically free of disease during 5 to 10 years of follow-up, the degree of TSH-suppressive dosage can be lightened to achieve measurable serum TSH levels between 0.1 and 0.5 mU/L, whereas serum FT₄ should be maintained within its reference range.

Until the presence of residual disease can be ruled out, an undetectable TSH value (<0.1 mU/L) should be maintained in the first 1 to 3 years after initial diagnosis and treatment of patients at intermediate risk of thyroid can-

Table 20. Assessment of Risk of Adverse Effects From TSH-Suppressive Doses of L-T₄ in DTC Patients

| Mild Risk | Moderate Risk | Higher Risk |
|--|--|--|
| Young and middle-aged patients | Elderly subjects | Arrhythmias |
| Asymptomatic patients | Hypertension | Atrial fibrillation |
| No cardiovascular disease | Symptoms and signs of adrenergic overactivity | Comorbidities (eg, heart disease, diabetes, renal failure) |
| No alterations of cardiac rhythm | Cigarette smoking | Previous stroke or TIA |
| No symptoms of adrenergic overactivity | Cardiovascular risk factors | Left atrial dilatation |
| No cardiovascular risk factors | Postmenopausal women | Increased risk factors for stroke |
| No comorbidities Premenopausal women | Osteopenia | HF |
| Normal BMD | Men and women with risk factors for osteoporosis | CHD |
| No risk factors for osteoporosis | | Valvular heart disease |
| | | Vascular disease (coronary or peripheral arterial disease) |
| | | Osteoporosis |

Modified from Ref. 569.

cer. However, in those at high risk of adverse effects of therapy, the degree of TSH suppression should be reevaluated during the follow-up to obtain a normalization of serum TSH in disease-free patients, especially in the presence of significant comorbidities.

A TSH value between 0.1 and 0.5 mU/L is suggested for initial therapy in patients at low risk of cancer progression and a low risk of adverse effects. However, once cure or complete remission from cancer has been established, allowing serum TSH levels to drift up into the normal reference range is desirable, with a TSH target within the low-normal reference range (0.3–2 mU/L).

In patients at low risk of cancer progression and a high and intermediate risk of adverse effects, a TSH value between 0.5 and 1 mU/L would be reasonable for initial therapy, and a TSH value of 1 to 2 mU/L would be appropriate during the follow-up in disease-free patients.

In the future, drugs that specifically decrease pituitary TSH secretion without adverse effects on the cardiovascular system and the skeleton could be useful in high-risk DTC patients. This would be feasible by an integrated molecular and genetic approach to identify patients with DTC at high risk of recurrences who would benefit from TSH suppression.

XII. Appropriate and Inappropriate Use of L-T₄ Replacement Therapy in Other Conditions

A. Fatigue (Wilson's syndrome)

Wilson's syndrome refers to a cluster of debilitating symptoms in euthyroid patients. Dr E. Dennis Wilson, MD, of Florida suggests that this condition represents functional hypothyroidism, or a form of presumed thyroid hormone deficiency in euthyroid patients. Dr Wilson and/or his proteges consider that patients with this syndrome could be responsive to treatment with a special preparation of L-T₃. He maintains that patients with this syndrome may have abnormally low body temperatures (90% with temperatures 97.8°F or lower) together with symptoms indicative of hypothyroidism such as fatigue, fluid retention, inappropriate weight gain, unhealthy nails and skin, irritability, depression, memory loss, poor motivation, anxiety, panic attacks, joint aches, muscle aches, hypoglycemia, constipation, irritable bowel syndrome, and chronic fatigue. The evidence for beneficial effects of the T₃ preparation recommended for Wilson's syndrome is available on Dr Wilson's website on which are listed about 37 symptoms that are considered part of this condition (590). On the same website, the evidence justifying T₃ treatment is described (590). The evidence appears based on anecdotal reports and testimonials from people

who claim to feel better after taking T₃. The frequency of complaints attributed to Wilson's syndrome were reviewed some years ago in an interesting study published in the *Annals of Internal Medicine* called "Functional somatic syndromes" (591).

In 2005, the ATA published a position statement on Wilson's syndrome after reviewing the material presented on the Wilson's syndrome website (592). This statement concluded that the evidence supporting existence of this syndrome is inconclusive and without scientific merit. Moreover, the diagnostic criteria for Wilson's syndrome were considered vague or imprecise with potential risk of leading patients to mistaken or delayed diagnoses of other conditions. Finally, the prescribed dosage for T₃ for Wilson's syndrome was found to be inconsistent with normal physiology with clear potential for harmful effects on the heart and skeleton.

B. Replacement therapy with thyroid hormone in obese patients

Thyroid hormones are inappropriately and frequently used in a misguided attempt to induce weight loss in obese euthyroid subjects. However, reduced caloric intake with weight loss may induce a significant reduction in the serum FT₃ level with an increased rT₃ due to reduced 5'-deiodination. Thereafter, continuing caloric deprivation further reduces energy expenditure and the decreased T₃ levels may be responsible for the difficulties in maintaining or in achieving further weight loss (52).

Consequently, some workers have offered this alteration during caloric deprivation as a potential rationale for the use of thyroid hormone in obese subjects to improve their weight loss (52). Ideally, the best treatment of obesity should increase fat loss without decreasing skeletal muscle mass and without inducing cardiac arrhythmias. A recent meta-analysis assessed the results of T₃ therapy in 14 studies in obese subjects during caloric deprivation (6 randomized controlled studies and 8 prospective observational studies). Weight loss was significantly increased in only 5 studies with T₃ doses ranging from 38 to 117 μg/70 kg/d (593). T₃ therapy decreased serum TSH and T₄ concentrations. It is difficult to ascertain the effects of T₃ on resting metabolic rate, protein breakdown, fat loss, and heart rate due to the small number of obese subjects enrolled in each study and the poor quality of most of these studies. Therefore, the authors concluded that data available in the literature are inconclusive to evaluate the effectiveness of thyroid hormone therapy as a treatment for obesity (593). Prospective large controlled studies will be necessary to assess the potential beneficial effect of treatment of obese patients with thyroid hormones or their analogs.

C. Effects of replacement therapy with thyroid hormone in severe cardiac diseases and dyslipidemia

The physiological action of thyroid hormone is mediated by its genomic nuclear effects. These effects result from the binding of T_3 to specific nuclear TRs.

In the human heart, 2 TR genes are expressed and each gene generates 2 isoforms of receptors (TR α 1, TR α 2, TR β 1, and TR β 2) (129). TR α transcripts are abundant in the heart, whereas TR α 2 acts as a negative regulator because it functions by suppressing TR α 1 transcription (129). TR α 1 is widely expressed and has a high expression in cardiac and skeletal muscles. TR β 1 is predominantly expressed in the brain, liver, and kidney. TR β 2 expression is limited to the hypothalamus and pituitary (129).

1. Analogs of thyroid hormone for treatment of obesity and dyslipidemia

The selective activation of different TR-mediated pathways is a promising strategy for treating lipid disorders and obesity (594–598). Preclinical studies have suggested that thyromimetics might be useful for the treatment of obesity and dyslipidemia. Selective thyromimetics are synthetic analogs of thyroid hormones that can selectively stimulate TR β , avoiding harmful effects on the heart and bone. Animal data have suggested that thyromimetics might be useful in the treatment of obesity, hepatic steatosis, and atherosclerosis (599, 600). In the past, the Coronary Drug Project (1966–1975) performed a clinical experiment using dextro- T_4 for hyperlipidemia (601). However, overall mortality increased with dextro- T_4 despite reductions in serum cholesterol, possibly due to the high rates of contamination of dextro- T_4 preparations with the L-enantiomer (601).

a. 3,5,3'-Triiodothyroacetic acid. The decarboxylation and deamination of thyroid hormone leads to 3,5,3'-triiodothyroacetic acid (TRIAC; tiratricol), a naturally occurring metabolite of T_4 with thyromimetic activity. TRIAC has affinity for TR some 10 to 20 times that of T_3 . The first reports in rats postulated that TRIAC could serve as a favorable alternative agent for TSH suppression without adverse effects on the heart (602). It has been administered to patients with isolated pituitary resistance to thyroid hormone and was thought to have TSH-suppressive effects greater than T_4 . In a trial to assess the specific thyromimetic effects of tiratricol, 24 athyretic patients were randomized to blinded treatment with either TRIAC (24 μ g/kg twice daily) or L- T_4 (1.9 μ g/kg daily) to obtain a TSH level less than 0.1 mU/L (603). No significant differences were found between the 2 groups in terms of weight, resting metabolic rate, urea excretion, symptoms, and cardiovascular function. Plasma total and LDL-cholesterol

levels were significantly reduced, and SHBG was significantly increased in the tiratricol group compared with the L- T_4 group. However, adverse effects of TRIAC were seen in regard to increased bone resorption and turnover with marked elevation of osteocalcin, pyridinium cross-links, and urinary calcium. The study investigators concluded that TRIAC had increased hepatic and skeletal actions but did not have pituitary-specific selectivity (603). However, because TRIAC selectively increases the function of TR β 1 without affecting TR α 1, some utility became apparent for the treatment of symptomatic patients with selective pituitary resistance to thyroid hormone (604) and TSH-dependent hyperthyroidism (605). In euthyroid patients, TRIAC may significantly increase metabolic activity with induction of symptoms of hyperthyroidism, and it has been used inappropriately as a dietary supplement for weight loss. In the United States, the FDA has not approved use of tiratricol as a dietary supplement due to the potential risk of serious health consequences. It could have a role in the therapy of hypothyroid patients with accompanying hypercholesterolemia, but the negative effects on bone are a drawback.

b. Sobetirome. Development of sobetirome, or GC-1 (3,5-dimethyl-4-(4-hydroxy-3-isopropylbenzyl) phenoxy acetic acid), was derived from the first-generation TR β -selective agonists as a selective thyromimetic with 10-fold preferential action on TR β 1. It binds TR β with an affinity similar to T_3 but binds TR α with a 10-fold lower affinity (606). Sobetirome preferentially accumulates in the liver, reduces LDL-cholesterol, and initially was thought to have a promising role as an antiobesity agent because it is able to induce a 20% decrease in fat mass and improve lipid profile without reduction in food intake and without affecting the heart or BMD (607). Treatment of rats with 3 μ g T_3 /100 g body weight and equimolar amounts of GC-1 (3 μ g GC-1/100 g body weight) both resulted in a loss of fat mass. However, T_3 caused widespread loss of muscle mass, whereas GC-1 had no effect (608). There was optimism that a second generation of highly selective TR β agonists or compounds would have additional tissue-specific effects (ie, at the level of adipose tissue) and demonstrate promise for the treatment of obesity and type 2 diabetes.

c. KB141. KB141 is another TR β agonist that is approximately 15 times more selective for TR β than for TR α in vitro and is able to induce weight loss and reduce cholesterol and lipoprotein (a) with no effect on heart rate (609).

d. Eprotirome (KB2115). KB2115 (eprotirome; 3-(3,5-dibromo-4-(4-hydroxy-3-(1-methylethyl)- phenoxy)-phe-

nyl)-amino-3-oxopropanoic acid) is a TR β -selective ligand that is preferentially taken up by the liver.

A randomized, placebo-controlled, double-blind, multicenter trial was performed to assess the safety and efficacy of KB2115 in lowering the level of serum LDL-cholesterol in patients with hypercholesterolemia who were already receiving simvastatin or atorvastatin but had persistent LDL levels above 116 mg/dL. Eprotirome induced a 23% to 29% decrease in LDL-cholesterol and a 22% to 38% lowering in triglycerides with a 37% to 45% decrease in apolipoprotein A1 and apolipoprotein B (610). Serum T₄ was decreased but remained within the reference range without significant changes in serum TSH or T₃. There were no observed changes in body weight in patients receiving eprotirome (610). No potentially deleterious cardiac or bone effects were found using this drug, and only a minor transient increase in liver enzymes was observed, but unfortunately, cartilage damage in long-term dog models led to the withdrawal of eprotirome from clinical trials (611). Sternal cartilage maturation was impaired with chondrocyte loss and structural changes noted in multiple areas. The mechanism may relate to overactivity of normal T₃ effects on regulation of chondrocyte proliferation.

2. Thyroid hormone and thyroid hormone analogs for treatment of HF

Recent interest in the potential role of thyroid hormones in heart disease is due to the following considerations: 1) evidence of positive effects of thyroid hormone on the heart and vascular function (172), 2) proof that even mild thyroid hormone deficiency is associated with a worse prognosis in cardiac patients (528, 529), and 3) the fact that important changes in thyroid hormone metabolism have been reported in patients with severe cardiac disease, including HF, MI, and patients with ischemic heart disease undergoing coronary artery bypass (612, 613).

A low-T₃ syndrome occurs in approximately 20% to 30% of patients with HF with a significantly higher incidence in patients with New York Heart Association class III-IV than in those with New York Heart Association class I-II. The basic pathophysiological mechanisms underlying the low-T₃ syndrome are related to the reduced activity of 5'-monodeiodinase, resulting in a significant fall in circulating T₃ levels with a consequent increase in rT₃ (612, 613).

This condition has long been interpreted as reflecting a beneficial state in patients with HF because it was considered an adaptive process to reduce energy expenditure, negative nitrogen balance, and metabolic demand. However, some experimental and clinical evidence has begun to

modify this interpretation (612, 613). Studies performed in patients after acute MI or cardiopulmonary bypass and in those with chronic HF have demonstrated the negative prognostic impact of low-T₃ syndrome and the potential improvement of cardiac dysfunction after thyroid hormone administration (614–621).

Experimental and clinical studies in HF have confirmed that a low-T₃ state is associated with a return to a fetal gene program with the development of a hypothyroid-like cardiac condition (a shift from α -myosin heavy chain to β -myosin heavy chain and a decreased sarcoplasmic reticulum calcium ATPase), leading to a subsequent worsening in cardiac remodeling and a progressive decline in cardiac function (619–625). These observations have led to studies examining the administration of L-T₄, L-T₃, or thyroid hormone analogs to patients with HF to potentially improve their prognosis (35, 622–635). The first study was performed by Hamilton et al (626) and was a small nonrandomized trial with administration of an iv bolus of L-T₃ followed by L-T₃ infusion in patients with advanced HF and low-T₃ syndrome. Cardiac output improved significantly 2 hours after T₃ administration with a significant decrease in SVR. Interestingly, heart rate did not change and there were no side effects attributable to the intervention (626).

a. Treatment with thyroid hormone. In 2 randomized placebo-controlled studies, Moruzzi et al (627, 628) assessed the cardiovascular short-term and long-term effects of L-T₄ administered orally at a dose of 0.1 mg/d in patients with dilated cardiomyopathy. In both of these studies, L-T₄ significantly improved cardiac function and enhanced resting left ventricular ejection fraction, cardiac output, and exercise capacity (627, 628).

Malik et al (629) administered iv L-T₄ (20 μ g/h) in 10 consecutive patients with severe systolic HF that had progressed to cardiogenic shock. The authors observed a significant improvement in cardiac index, pulmonary capillary wedge pressure, and mean arterial pressure 24 and 36 hours after L-T₄ administration.

Iervasi et al (630) administered physiological doses of L-T₃ (20 μ g/d/m² body surface) for a period of 96 hours in 6 patients with advanced HF and low-T₃ syndrome. These authors observed a progressive reduction in SVR, an increase in LV ejection fraction, and an improvement of cardiac output after T₃ administration (630).

In a more recent placebo-controlled study, the same authors administered a 3-day L-T₃ infusion in patients with chronic and stable dilated cardiomyopathy and low-T₃ syndrome (631). They reported an improved cardiac performance that was not associated with an increase in myocardial O₂ consumption and an increase in total

cardiac work. Moreover, a concomitant improvement of the neuroendocrine pattern with decreased noradrenaline plasma levels and N-terminal prohormone of brain natriuretic peptide was seen (631). No randomized trials have compared the effects of L-T₄ vs L-T₃ in similar clinical settings.

b. 3,5-Diiodothyropropionic acid. 3,5-Diiodothyropropionic acid (DITPA), a thyroid hormone analog, has cardiac inotropic selectivity compared with thyroid hormone with minimal effects on heart rate and metabolic activity (632). This thyromimetic drug has been used to treat CHF with promising preliminary results (35, 633, 634).

Long-term administration of DITPA also stimulates coronary arteriolar growth without inducing cardiac hypertrophy by upregulating key angiogenic growth factors (635). In a recent RCT in patients with stable CHF, DITPA had no effect on CHF symptoms and was generally poorly tolerated (35); however, DITPA was able to improve cardiac index and diastolic function and to decrease SVR. Total and LDL-cholesterol values and triglycerides improved and weight loss of an average of 11 pounds was noted (35). The weight loss may have been related to GI side effects that were common in the patients treated with DITPA (35). DITPA induced suppression of the hypothalamic-pituitary-thyroid axis and had a negative effect on bone due to increased bone turnover (35). Unfortunately, several adverse events led to its withdrawal from clinical trials.

Although all of these studies have documented the potential beneficial effects of thyroid hormone and its analogs, large prospective studies are needed to assess the potential therapeutic use of thyroid hormones in treating and/or preventing HF. The risks of such therapy should be underscored because high doses of thyroid hormone, especially during infusion or over a prolonged period, may have detrimental effects on the heart after an initial improvement in cardiac performance. Future research will be important to establish which drug (T₃, T₄, or analogs) could be useful in treating cardiac patients, including the best schedule (dosage of thyroid hormone and route of administration) for therapy. A total of 1500 patients would be needed to detect enhanced survival by 20% with 95% confidence, with mortality due to nonthyroidal illness of 20%.

D. Replacement therapy with thyroid hormone for postoperative nonthyroidal illnesses

The low-T₃ syndrome is also often associated with major surgical procedures (612, 613, 621).

The profile of thyroid hormone measurements show a progressive decline in T₄ and T₃ after coronary artery by-

pass surgery (621). Low T₃ levels usually develop after surgery due to the effects on T₄ conversion to T₃ of cytokines and the administration of corticosteroids. T₃ levels spontaneously improve 6 to 7 days after surgery. Patients with lower T₃ values in the postoperative period have an increased risk of death and complications (621).

A recent meta-analysis assessed the results of 13 RCTs of euthyroid adult patients that evaluated the effect of thyroid hormone after cardiac surgery in patients with nonthyroidal illnesses (636). T₃ therapy was administered iv in 10 studies and orally in 3 studies. High T₃ iv doses (0.175–0.333 μg/kg/h for 6–9 hours) were employed in 7 studies, whereas low doses (0.0275–0.0333 μg/kg/hr for 14 to 24 hours), were used in three studies. Both high- and low-doses of both iv and oral T₃ therapy significantly increased cardiac index at 4 to 6 hours in pooled analysis in patients after coronary artery bypass grafting surgery (636). The effects on SVR, heart rate, pulmonary capillary wedge pressure, new-onset AF, inotropic function, and serum TSH and T₄ were considered inconclusive (636). The data were considered insufficient to evaluate the duration of either the stay in the intensive care unit or in the hospital (636). Mortality was not significantly altered by high-dose iv T₃ therapy and was not able to be assessed for low-dose iv or oral T₃ (636).

The quality of all of the studies included in this meta-analysis was considered high because all of the trials were double-blinded and placebo-controlled. However, the small number of studies and the small number of enrolled subjects was responsible for the inconclusive findings of this otherwise accurate meta-analysis.

Replacement therapy with thyroid hormone is not recommended in postoperative cardiac patients because clinical benefits and potential adverse effects are not adequately addressed. Further prospective studies are required to assess potential beneficial effects of thyroid hormone on cardiac work, myocardial oxygen consumption, ischemia, infarction, and arrhythmias.

E. Thyroid hormone therapy for the surgical or perioperative patient

Surgical patients demonstrate the spectrum of altered thyroid function tests associated with the euthyroid sick syndrome or nonthyroidal systemic illness.

Notwithstanding the very low serum T₃ levels that may be seen in sick patients, we do not believe that there is a role for T₃ treatment for the overwhelming majority of these patients. An exception to this practice may be the patient with head injury and prolonged coma in whom pituitary dysfunction may lead to secondary hypothyroidism. Even only relative starvation or nutritional deficiency for a few days will elicit the euthyroid sick (or low-T₃) syndrome.

Indeed, a fall in free and total serum T_3 with a rise in rT_3 may be seen after only an overnight fast in preparation for surgery.

It is likely that both a patient's sense of well-being and the general process of wound healing and postoperative recovery may be negatively impacted by thyroid hormone deficiency. Given that thyroid hormone action affects virtually all body systems, it is important in the perioperative patient to restore therapy, either iv or as soon as oral dosage may be given, to avoid cardiovascular, GI, or renal dysfunction (637). The older patient with hypothyroidism and underlying cardiovascular disease may be particularly at risk, because a worsened hypothyroid state can cause impaired cardiac contractility with reduced cardiac output, increased angina, reduced blood volume, and increased peripheral vascular resistance. The surgical patient most at risk is one with preexisting coronary artery disease or CHF. In general, it is best to undergo general anesthesia and surgery while euthyroid (637). Hence, thyroid hormone deficiency should be corrected before elective surgical procedures. However, in the case of emergent procedures including cardiac bypass surgery for impending MI, it has been proposed that hypothyroid patients can safely undergo the surgery and have postoperative restoration of euthyroidism. In the latter patient population, rigorous attention to intraoperative anesthesia and postoperative ventilation and recovery will be essential for an optimal outcome. Pulmonary function may be impaired by hypothyroidism in such patients due to reduced lung volumes or reduced ventilatory excursions from muscle weakness, reduced exercise capacity, or obesity when present (637). The slowed metabolism of drugs often administered in the perioperative period can also play a role, including analgesics, narcotics, and hypnotics. Impaired renal function in hypothyroidism may be a factor for those drugs largely eliminated via the kidneys. Moreover, the physician should be alert to the possibility of a coagulopathy complicating surgery in the hypothyroid patient (637). Bleeding thought secondary to relative factor VIII deficiency with prolonged partial thromboplastin time has been described as well as enhanced coagulation due to a prolonged half-life of factors II, VII, and X. In the postoperative setting, the latter patients may be at increased risk for deep venous thrombosis and pulmonary embolism. Finally, unexplained hypotension in the perioperative patient with a history of hypothyroidism may be a clue to the presence of partial or subclinical adrenal insufficiency which should be considered, ruled out, and/or treated if confirmed or strongly suspected.

F. Treatment of MCT8 deficiency

Deficiency of MCT8 causes Allan-Herndon-Dudley syndrome of childhood psychomotor retardation marked by high serum T_3 , low T_4 , and normal or high TSH due to impaired access of T_4 to the brain. Access of DITPA to the brain is independent of MCT8, and in a multicenter trial on 4 children affected by MCT8 deficiency, the administration of DITPA (1–2 mg/kg/d) for 26 to 40 months completely normalized thyroid function tests; reduced SHBG, heart rate, and ferritin; increased cholesterol levels; and reduced the hypermetabolism and the tendency for weight loss (412).

XIV. The Future of Replacement Therapy With Thyroid Hormone

TSH level is not an optimal marker of adequate thyroid hormone replacement therapy in all hypothyroid patients. In the future, the use of other more sensitive peripheral markers of thyroid hormone action at tissue levels might help clinicians to personalize the treatment of thyroid hormone deficiency.

Large prospective studies are necessary to clarify the potential adverse effects of mild subclinical hypothyroidism to improve the treatment of this mild form of thyroid hormone deficiency, especially in children and elderly patients.

Prospective randomized controlled studies are necessary to evaluate whether replacement therapy with $L-T_4$ may improve or completely counteract the adverse effects of even mild hypothyroidism and its attendant risks.

In the future, appropriate RCTs will clarify the potential beneficial effects of combination treatment with T_3 and T_4 vs $L-T_4$ monotherapy especially in thyroidectomized patients and in patients with certain polymorphisms in deiodinase activity.

A long-acting slow-release form of T_3 will be required to obtain physiological and stable TSH levels with a circadian T_3 rhythm over 24 hours.

Randomized controlled studies are necessary to evaluate the potential therapeutic use of thyroid hormones and their analogs in treating low- T_3 syndrome in patients with HF and nonthyroidal illnesses.

Future studies will clarify whether TSH-suppressive therapy of thyroid nodules may prevent the development of thyroid cancer. The discovery of thyroid hormone analogs that suppress pituitary TSH secretion with less effect on the cardiovascular system and the skeleton might improve the treatment of patients with aggressive DTC.

Acknowledgments

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Disclosure Summary: B.B. has been a speaker at symposia organized by Merck Serono and IBSA, is part of the Editorial Board of the European Journal of Endocrinology, Thyroid, European Thyroid Journal, and Frontiers in Thyroid Endocrinology. L.W. serves as a consultant for Asurogen, Inc; Genzyme, Inc; and IBSA, Inc, and as Editor-in-Chief of the *Journal of Clinical Endocrinology and Metabolism*.

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