Levothyroxine Therapy in Patients with Thyroid Disease

Susan J. Mandel, MD; Gregory A. Brent, MD; and P. Reed Larsen, MD

■ *Purpose:* To review the indications for and the proper monitoring of levothyroxine therapy in patients with thyroid disease.

■ *Data Sources:* Relevant English language articles published from 1966 to 1992 were identified through a MEDLINE search and manual searches of both identified articles and selected endocrinology texts.

■ *Study Selection:* Studies, case reports, and review articles that contained data on the pathophysiologic aspects of relevant thyroid disorders and on the pharmacologic aspects of, indications for, and administration of levothyroxine therapy.

■ *Data Extraction:* Data on the epidemiology, clinical manifestations, complications, and treatment of thyroid disorders were analyzed with respect to patient selection, methods, diagnostic criteria, and conclusions. These data were used to develop a rational approach to the management of such patients.

■ *Results of Data Synthesis:* Levothyroxine is a reliable and commonly prescribed drug to treat thyroid disease, but excessive dosage may have adverse effects. In patients with hypothyroidism, levothyroxine is used as replacement therapy. For most patients, therapy can be initiated with a full replacement dosage (1.6 μg/kg body weight), which is usually 75 to 100 μg/day for women and 100 to 150 μg/d for men. The goal is to normalize the serum thyroid-stimulating hormone concentration. Levothyroxine is also used to suppress the serum thyroid-stimulating hormone concentration. A trial of thyroid-stimulating hormone suppressive therapy is indicated for most patients with benign solitary nonfunctioning thyroid nodules and for those with a history of thyroid cancer. Levothyroxine in non–thyroid-stimulating hormone-suppressive doses may also be indicated for patients with nontoxic multinodular goiter and for certain patients after lobectomy for benign thyroid nodules.

■ *Conclusions:* With proper patient monitoring, levothyroxine replacement therapy should be effective, inexpensive, and free of complications. Recommendations for thyroid-stimulating hormone suppression with levothyroxine are based on risk–benefit considerations of the biologic characteristics of the thyroid disorder and the individual patient.

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From Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. For current author addresses, see end of text.

Levothyroxine is one of the 13 most commonly prescribed medications in the United States, with more than 15 million prescriptions filled annually (1). It is given as either physiologic replacement therapy in patients with hypothyroidism or as interventional therapy to suppress thyroid-stimulating hormone (TSH) secretion in patients with nodular thyroid disease or thyroid cancer. Overt hypothyroidism occurs in 1.5% to 2% of women and in 0.2% of men (2), and its incidence increases with age; among persons older than 60 years, 6% of women and 2.5% of men have serum TSH levels greater than twice the upper limit of normal (3). Thyroid nodules are present in 0.8% of men but occur in 5% of women and increase in incidence after 45 years of age (2). Thyroid cancer is the most common endocrine cancer, with an annual incidence of 10 000 new cases in the United States (4).

Measurement of serum TSH permits precise levothyroxine dosage, both in replacement therapy, where serum concentrations are maintained in the normal range, and in TSH suppressive therapy, where supraphysiologic doses of levothyroxine are given to maintain the serum TSH concentration below normal. In addition to suppressing serum TSH, excess levothyroxine administration is associated with other signs of thyrotoxicosis at the tissue level. Decreased bone mineral density (5–8) and an accelerated rate of bone loss (9) have been reported in both pre- and postmenopausal women receiving sufficient levothyroxine to yield subnormal serum TSH levels. Consequently, excess levothyroxine therapy, either intentional or inadvertent, is not as innocuous as was once supposed, at least for women. Unintentional over-replacement is still a common problem. In several recent studies, as many as 50% of patients receiving levothyroxine replacement therapy who were clinically euthyroid were actually overtreated, as judged by their suppressed serum TSH concentrations (10, 11). Furthermore, TSH assays sufficiently sensitive to permit accurate quantitation of subnormal values are, unfortunately, still not routine in certain areas of the United States (12).

We review the physiologic, pharmacologic, and therapeutic aspects of therapy with levothyroxine. Because the benefit–risk considerations are distinctly different for replacement and interventional therapy, these are discussed separately. For some patients with nodular thyroid disease, conflicting or insufficient data may not allow an unequivocal consensus recommendation. In such circumstances, we review the existing evidence and provide a rational strategy for treatment.

Background

Thyroid Hormone Physiology and Thyroid-Pituitary Regulation

Thyroxine (T_4) and 3,5,3′ triiodothyronine (T_3), so named because of the number of iodide atoms bound to

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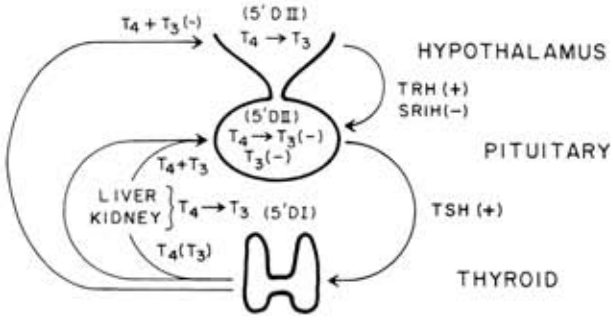

Figure 1. Role of thyroxine (T_4) and 3,5,3′ triiodothyronine (T_3) in the feedback regulation of thyrotropin-releasing hormone (*TRH*) and thyroid-stimulating hormone (*TSH*) secretion. Thyroxine is secreted by the thyroid but must be deiodinated to T_3 to produce its effects. This conversion may occur in the liver or kidney, catalyzed by the type I 5′ deiodinase (5′ DI), or intracellularly in the pituitary and central nervous system, catalyzed by the type II 5′ deiodinase (5′ DII). Somatostatin (*SRIH*) also inhibits TSH secretion. Reprinted with permission (Larsen PR, Ingbar SH. The thyroid. In: Wilson JE, Foster DW; eds. Williams Textbook of Endocrinology. 8th ed. Philadelphia: WB Saunders; 1991:357-487).

a thyronine backbone, are the main circulating thyroid hormones. Thyroxine is produced only by the thyroid. However, in euthyroid humans, only 20% of circulating T_3 is secreted by the thyroid and 80% is produced in extra-thyroidal tissue by monodeiodination of T_4. About 40% of the T_4 is deiodinated to T_3 in the liver and kidney (13) by the recently cloned type I deiodinase, a selenoprotein (14, 15). The presence of selenocysteine renders this T_4 to T_3 conversion process sensitive to levels of dietary selenium as well as to inhibition by propylthiouracil (16). Illness, caloric deprivation, and various drugs and radiographic contrast agents also inhibit deiodination of T_4 to T_3 (13). In addition, T_4 is metabolized by other pathways not resulting in T_3 generation, such as sulfation and inner-ring deiodination or glucuronidation leading to biliary excretion.

It is T_3 that enters the cell nucleus, binds to its nuclear receptor, and regulates transcription of thyroid hormone-responsive genes, resulting in the physiologic changes associated with thyroid hormone (17). To understand the effects of T_4 and its therapeutic use, it is important to appreciate the differences in the quantity and sources of T_3 in the nuclei of different tissues. Nearly all of nuclear T_3 present in the liver, kidney, skeletal muscle, and heart of euthyroid rats originates from serum T_3. However, the pituitary and central nervous system differ in that local conversion of T_4 to T_3 by the type II deiodinase within these tissues contributes equally (pituitary) or as much as 80% (cerebral cortex) to the nuclear-bound T_3 (these studies are reviewed in reference 13). Thus, although most peripheral tissues depend primarily on circulating T_3, the pituitary and central nervous system are sensitive to both circulating T_4 and T_3 (18–21). These concepts are summarized in Figure 1.

Thyroid-stimulating Hormone Assay

Because of the precise feedback relation between circulating thyroid hormones and pituitary TSH secretion, measurements of serum TSH concentrations are essential in the management of patients receiving levothyroxine therapy. The limit of detection of the new immunometric assays currently in use is at least 10 times lower than that of the original radioimmunoassays, and the new assays can reliably distinguish between normal and suppressed serum TSH concentrations (22–25). Furthermore, the basal serum TSH concentration is proportional to the TSH response to thyrotropin-releasing hormone (TRH), making TRH stimulation tests obsolete (22, 26). The only caveat to this generalization concerns patients with central hypothyroidism. Because the current strategy for monitoring levothyroxine therapy depends so heavily on TSH measurement, it is also important to recognize those factors, independent of thyroid hormones, that influence TSH secretion (Table 1). For the purposes of this review, the commonly accepted normal range of 0.5 to 5.0 mU/L is used for serum TSH.

Pharmacologic Aspects of Levothyroxine Preparations

Levothyroxine is synthetically produced but identical to T_4 secreted by the thyroid. According to the United States Pharmacopeia, the T_4 content of tablets must be between 90% and 110% of the stated amount, as measured by high pressure liquid chromatography (27). The gastrointestinal absorption of levothyroxine is approximately 80% (28) and does not differ in the hypothyroid or euthyroid state (29). Absorption occurs along the entire human small intestine, but the rapidity decreases distally (30, 31). After ingestion of levothyroxine, serum T_4 levels peak at 2 to 4 hours (average increase, 10% to 15% over basal concentrations) and remain above this basal level for up to 6 hours (32, 33). The increase in serum T_3 levels after levothyroxine administration is slow because of the time required for T_4 to T_3 conversion. Serum T_3 concentrations are generally stable during maintenance levothyroxine therapy, unlike after administration of triiodothyronine itself (34). Several proprietary and multiple generic levothyroxine preparations are available. Many formulations are marketed in several convenient strengths (25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and

Table 1. Situations Associated with Thyroid-stimulating Hormone Suppression

Physiologic states
Autonomous thyroid function (nodular thyroid disease, subclinical Graves disease)
Nonthyroidal illness
Chorionic gonadotropin excess (first trimester of pregnancy, hyperemesis gravidarum, molar pregnancy, choriocarcinoma)
Recovery after therapy for hyperthyroidism or after painless or postpartum thyroiditis
Central hypothyroidism
Pharmacologic situations
Supraphysiologic levothyroxine therapy
Glucocorticoid therapy
Acute administration of dopamine or dopaminergic agents (bromocriptine)
Acute administration of somatostatin and somatostatin analogs (octreotide)

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Table 2. Circumstances in Which Levothyroxine Requirements May Be Altered*

Increased levothyroxine requirements
Malabsorption (31)
Gastrointestinal disorders
Mucosal diseases of the small bowel (for example, sprue)
After jejunoileal bypass and small-bowel resection
Diabetic diarrhea
Cirrhosis
Pregnancy (35, 36)
Therapy with certain pharmacologic agents
Drugs that block absorption
Cholestyramine (37)
Sucralfate (38)
Aluminum hydroxide (39)
Ferrous sulfate (40)
Possibly lovastatin (41)
Drugs that increase nondeiodinative T_4 clearance
Rifampin (42)
Carbamazepine (43)
Possibly phenytoin (44)
Drugs that block T_4 to T_3 conversion
Amiodarone (45, 46)
Selenium deficiency
Decreased levothyroxine requirements
Aging (65 years and older) (47, 48)

* References are given in parentheses.

300 μg) that allow precise dosage with a single tablet, enhancing compliance.

Changes in Levothyroxine Requirements

Several conditions or drugs may alter levothyroxine requirements for both replacement and interventional therapy (Table 2). The serum TSH level should be monitored more often in these circumstances, and the levothyroxine dose should be adjusted to maintain the serum TSH level in the normal range for hypothyroid patients receiving replacement therapy or at its appropriate therapeutic level for those receiving suppressive therapy. During pregnancy, the average increase in levothyroxine requirements is 45%, and monitoring should be carried out every 2 months (35, 36). After delivery, the dose can be immediately reduced to the prepregnancy level and the serum TSH level should be measured again 6 weeks after delivery. Patients should be instructed to take levothyroxine at least 3 hours after the administration of medications that may interfere with its intestinal absorption (Table 2). In general, the increase in the levothyroxine requirement will be less than twofold (43, 46). Thyroid function tests should be checked 1 month after the initiation of therapy with such agents, and the levothyroxine dose should be adjusted accordingly. If the drug is then withdrawn, the levothyroxine dosage may have to be decreased. Rifampin (42), carbamazepine (43), and possibly phenytoin (44) accelerate T_4 clearance via pathways that do not lead to T_3 production, thereby increasing levothyroxine requirements. Amiodarone competitively inhibits T_4 to T_3 conversion (45).

Physiologic Effects of Excessive Levothyroxine Administration

There is growing evidence that excess levothyroxine administration, as defined by a suppressed serum TSH concentration, is associated with physiologic alterations in peripheral tissue. Cardiac changes include shortening of systolic time intervals (49, 50) and increases in nocturnal heart rate (51). Hepatic enzymes (alanine aminotransferase) and proteins (sex hormone–binding globulin, ferritin) may also be increased (52, 53), and red blood cell ouabain binding is decreased (54). Thyroid hormone accelerates bone turnover. Both serum osteocalcin, a marker of this turnover, and urinary pyridinium cross-link excretion, a more specific indicator of bone resorption, are increased in women receiving supraphysiologic levothyroxine doses (55, 56). Premenopausal women treated with excess levothyroxine show predominantly cortical bone loss, measured in the wrist and hip, as opposed to trabecular bone loss, measured in the spine (5–7). Similarly treated postmenopausal women show reductions in both trabecular and cortical bone mineral density (7–9). The development of osteopenia during TSH suppressive therapy is of special concern because 70% of patients with nodular thyroid disease and thyroid cancer are women and supraphysiologic treatment is often maintained for many decades.

Replacement Therapy with Levothyroxine

Primary Hypothyroidism

Most patients with primary hypothyroidism can be treated satisfactorily with levothyroxine at an average daily dose of about 1.6 μg/kg ideal body weight (28, 57). Requirements for infants (10 to 15 μg/kg body weight) and children (>2 μg/kg body weight and age dependent) are substantially higher (58). Levothyroxine requirements decrease with age because of diminished thyroid hormone metabolism (47, 48). The cause of the hypothyroidism may also influence dosage. The mean levothyroxine replacement dose for patients with spontaneous hypothyroidism is reportedly higher than that for those with hypothyroidism caused by ^{131}I treatment of hyperthyroidism caused by Graves disease (57, 59). This is probably due to the continued production of thyroid-stimulating antibodies, which induce thyroid hormone production in portions of the thyroid not completely destroyed. Where ^{131}I doses have resulted in complete thyroid ablation, the replacement dose may be the same as that for spontaneous hypothyroidism. The degree of serum TSH elevation at diagnosis is also positively correlated with the optimal replacement levothyroxine dose (60).

The sensitivity of the new TSH assays and the relatively narrow normal range for serum TSH make its normalization a reasonable goal in managing these patients (11, 61–64). With appropriate therapy, the serum TSH concentration should be between 0.5 and 3.0 mU/L. Our approach to levothyroxine therapy in healthy adult hypothyroid patients (younger than 65 years old) is to initiate a full replacement dose of about 1.6 μg/kg body weight (or ideal body weight in cases of significant obesity). The dose is between 75 and 100 μg/d in most women and between 100 and 150 μg/d in most men. Serum TSH levels decrease gradually and should first be rechecked after 2 months of therapy. The higher the initial serum TSH level is, the longer it takes

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to return to normal (65). If the serum TSH concentration is not normal by 4 months and the serum free T_4 index has increased, indicating compliance, the daily levothyroxine dose can be increased by 25 μg. Thyroid function tests are repeated 6 to 8 weeks later. The serum TSH concentration should be measured again 6 months after normalization to ensure that it has stabilized, because the metabolic clearance of T_4 may increase once hypothyroidism is corrected (66). In a levothyroxine-treated patient with primary hypothyroidism, a serum TSH concentration below normal usually indicates overtreatment (*see* Table 1 for exceptions). If this occurs, the dosage should be reduced slightly and the serum TSH concentration should be measured 3 months later. After an appropriate dosage is established, an annual TSH assay is sufficient to monitor therapy. Free thyroid hormone indices adjust for individual variations in circulating thyroid hormone–binding proteins and are used as an estimate of free thyroid hormone concentrations (67). Patients receiving adequate therapy with levothyroxine generally have a serum free T_4 index in the upper half of the normal range (28). However, a free T_4 index measurement is not usually required for periodic monitoring of patients receiving a stable levothyroxine dosage, unless the serum TSH concentration is elevated and questions of bioavailability or compliance arise.

Hypothyroid patients who have cardiac disease or are elderly (65 years and older) and could have unrecognized cardiac disease should be treated more cautiously because of the higher potential for adverse effects from levothyroxine therapy. Thyroid hormone augments both heart rate and contractility, thus increasing myocardial oxygen consumption. Because of the improved myocardial contractility, both end diastolic volume (preload) and systemic vascular resistance (afterload) are reduced, thus decreasing oxygen consumption (68). Theoretically, these opposing influences on oxygen consumption should cancel out. In a study of 1503 hypothyroid patients, 2% (average age, 71 years) developed new-onset angina during levothyroxine therapy. In patients with preexisting angina, symptoms disappeared or improved in 38%, did not change in 45%, and worsened in 16% (69). However, the overall 1-year cardiovascular mortality rate was only 3%, which is less than the overall reported mortality rate for all patients with coronary artery disease during that period (70). Therefore, levothyroxine therapy for hypothyroid patients with heart disease and for elderly persons without overt heart disease should be initiated at 25 μg/d, with increments of 25 μg at 8-week intervals, until the serum TSH level returns to normal. If a patient first develops angina after initiation of levothyroxine, therapy should be stopped, pending the evaluation of the cardiac disease. If existing anginal symptoms worsen, either the dose should be reduced or the drug should be withdrawn, and the cardiac disease should be re-evaluated. In untreated hypothyroid patients, cardiac and noncardiac surgery, as well as angioplasty, can be done without increased mortality (71–74). Severely hypothyroid patients may also be at higher risk for the development of postoperative myxedema coma. These recommendations are summarized in Table 3.

Table 3. Physiologic Replacement Therapy in Hypothyroid Patients*

Initiation of levothyroxine therapy
Healthy patients < 65 years old
Full daily replacement dose (1.6 μg/kg ideal body weight)
Women: 75 to 100 μg/d
Men: 100 to 150 μg/d
Patients ≥ 65 years old or with a history of cardiac disease
Begin with 25 μg/d
Increase dose by 25-μg increments at 8-week intervals until serum thyroid-stimulating hormone concentration falls to normal
If cardiac symptoms develop or worsen, evaluate cardiac disease and modify levothyroxine therapy (*see* text).

* For monitoring levothyroxine therapy in patients with primary hypothyroidism, measurement of serum thyroid-stimulating hormone is adequate, and concentrations should be maintained between 0.5 and 3.0 mU/L. For monitoring therapy in patients with central hypothyroidism, measurement of the serum free thyroxine index is appropriate, and it should be maintained in the upper half of the normal range.

Therapy for primary hypothyroidism is usually lifelong, although as many as 20% of patients with Hashimoto thyroiditis may have a spontaneous recovery (75). Even when the replacement dose is appropriately determined and monitored, it is still unclear whether women receiving levothyroxine replacement therapy are at increased risk for decreased bone mineral density. Two recent cross-sectional studies of this issue have yielded conflicting results (76, 77) that should be resolved by future longitudinal studies in which the rate of bone loss is examined. Once the correct levothyroxine dose is established, annual monitoring suffices for the compliant patient. Circumstances in which dosage requirements may change are listed in Table 2. Intermittent noncompliance with levothyroxine therapy can sometimes be recognized by a serum TSH concentration that is more than twice the upper limit of normal despite a normal serum free T_4 index (78). These results identify a patient who either may have stopped taking the medication or had taken it erratically and then resumed therapy shortly before testing. After ingestion of levothyroxine, the serum T_4 concentration increases more rapidly than the serum TSH concentration decreases. If the serum TSH concentration increases in a compliant patient who does not have any of the clinical problems listed in Table 2, the possibility of reduced bioavailability of the preparation used can be investigated by switching to a different brand.

Myxedema Coma

A rare medical emergency, myxedema coma has a mortality rate of approximately 80% in untreated persons (79). It represents the terminal stage of decompensated hypothyroidism and is often precipitated by coexisting medical conditions or drugs. The clinical hallmarks of myxedema coma include hypothermia, lethargy, respiratory acidosis, cardiovascular shock, and, ultimately, coma. Controversial aspects of its management include choice of thyroid hormone (T_4 or T_3), dosage, and route of administration. Because of the rarity of myxedema coma, no controlled clinical trials have been done to compare various thyroid hormone regimens.

Intravenous levothyroxine in bolus doses of 300 to

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500 μg was successfully administered in one study (79). Intravenous administration restores serum thyroid hormone concentrations more rapidly than does oral administration (80), and the dose is based on the calculated levothyroxine deficit (79). The average volume of levothyroxine distribution in a 70-kg man is 7 L, and, thus, 420 μg should increase the serum T_4 level by 77 nmol/L (6 μg/dL). Larger doses probably provide no increased benefit (81). Advocates of triiodothyronine therapy argue that the drug's more rapid onset of action more quickly reverses myxedema coma (82, 83). Furthermore, because T_3 is the biologically active hormone and T_4 to T_3 conversion is inhibited because of hypothyroidism and concomitant systemic illness, repletion of serum T_4 levels may be insufficient (84). Patients with myxedema coma have been successfully treated with triiodothyronine alone (83, 84) or with a combination of triiodothyronine and levothyroxine (85), as well as with levothyroxine alone. Despite the theoretic benefit of T_3 therapy, higher serum T_3 levels and older age have been associated with fatal outcome after therapy (85).

We and others (86) recommend immediate administration of an intravenous bolus dose of levothyroxine designed to raise the serum T_4 level to 77 to 90 nmol/L (6 to 7 μg/dL, usually about 500 μg). The following day, a daily levothyroxine dose of 75 to 100 μg should be given intravenously until the patient's vital signs become stable and gastrointestinal function returns to normal, permitting oral administration. Glucocorticoids should also be administered until coexistent adrenal insufficiency can be ruled out. In addition, cardiorespiratory, neurologic, and renal function must be appropriately monitored (86).

Secondary or Central Hypothyroidism

Central hypothyroidism results from pituitary or hypothalamic disease. Serum TSH concentrations range from low (87) to elevated. In patients with elevated values, TSH is immunoreactive but has reduced biologic potency (88, 89), explaining the paradoxical association of increased serum TSH concentrations with hypothyroidism. We recommend instituting therapy as outlined for patients with primary hypothyroidism (*see* Table 3). Before levothyroxine therapy is initiated, the possibility of secondary adrenal insufficiency should be considered. If present, glucocorticoid replacement should precede levothyroxine therapy. The adequacy of levothyroxine treatment is assessed by measuring the serum free T_4 index, which should be maintained in the upper half of the normal range, and by monitoring the patient clinically. Serum TSH concentrations may even decrease to subnormal levels with levothyroxine therapy (90).

Subclinical Hypothyroidism

An elevated serum TSH concentration in association with normal serum free T_3 and free T_4 concentrations constitutes subclinical hypothyroidism. Most patients are asymptomatic. Because of the log-linear relation between serum TSH concentrations and free T_4 levels, small reductions in the serum free T_4 concentrations are transformed into larger increases in TSH levels (25). Hence, subclinical hypothyroidism can be identified while the serum free T_4 levels are still in the normal range.

Whether patients with subclinical hypothyroidism require treatment can be determined by answering specific questions. Levothyroxine therapy must be justified by its ability to ameliorate biochemical or physiologic abnormalities. First, does an elevated serum TSH concentration presage the development of overt hypothyroidism? Neither a mildly elevated serum TSH concentration (6 to 10 mU/L) nor the presence of antithyroid antibodies (directed against thyroglobulin or peroxidase) alone increases the risk for overt hypothyroidism. However, women who have both elevated serum TSH levels and detectable thyroid autoantibodies have a 5% annual incidence of overt hypothyroidism (91). Furthermore, in elderly patients (age > 65 years), this combination is more ominous, with 80% of such patients developing overt hypothyroidism in a 4-year period (92). For patients who have only elevated serum TSH concentrations, the serum TSH concentrations tend to stabilize (92) or decrease (91), without development of thyroid failure. Patients with subclinical hypothyroidism after ^{131}I therapy for Graves disease may progress to overt hypothyroidism more often (93). Thus, patients with minimally elevated serum TSH values (<10 mU/L), who have negative tests for thyroid autoantibodies and who have never received ^{131}I treatment, are unlikely to develop clinical hypothyroidism in the next several years.

Second, is the action of thyroid hormone decreased in tissues other than the pituitary in patients with subclinical hypothyroidism? Studies evaluating the biologic efficacy of thyroid hormone therapy in subclinical hypothyroidism have focused on serum lipoprotein concentrations, indices of cardiac function, cognitive performance, and subjective symptoms. Although serum total cholesterol and triglyceride levels in patients with subclinical hypothyroidism are similar to those of normal persons (94–97), individual serum lipoprotein concentrations and lipid fractions may be improved with therapy. Serum low-density lipoprotein concentrations decrease (mean decrease, 22%) in association with a reduction in mean serum TSH concentrations (from 16.6 to 3.1 mU/L) in patients treated with levothyroxine (97). Increases in serum high-density lipoprotein levels after treatment of subclinical hypothyroidism have been reported (96). The total cholesterol/high-density lipoprotein and the low-density lipoprotein/high-density lipoprotein ratios, which are correlated with cardiovascular risk, decrease with therapy (95–97).

Cardiac function was studied in a randomized 1-year trial of levothyroxine therapy (mean dose, 71 μg/d) in patients with subclinical hypothyroidism. No difference was found in systolic time intervals between the treatment and placebo groups, although the values became normal in the five patients with the most abnormal baseline values (94). In other studies, cardiac contractility improved with therapy, as shown by a 10% mean increase in left ventricular ejection fraction with maxi-

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mal exercise (98, 99). Whether these changes alone are justification for therapy is unclear.

With respect to cognitive function, only 25% of patients scored better on psychometric testing during therapy. However, this subgroup could not be prospectively identified by pretreatment values (100). In another randomized study, hypothyroid symptoms improved in 51% of patients receiving levothyroxine and in 25% of the patients receiving placebo (94).

Based on these considerations, we recommend replacement therapy for all patients with serum TSH values higher than 10 mU/L and for those with concentrations higher than 5 mU/L when a goiter or thyroid autoantibodies are present. Patients with symptoms less clearly related to subclinical hypothyroidism, such as infertility, menstrual cycle irregularities, and depression, who also have mildly elevated serum TSH concentrations, pose a difficult management problem. In the absence of clinical contraindications, we recommend replacement therapy for at least 1 year after informing patients of risks and benefits. Therapy should be directed at reducing the serum TSH concentration to normal, which is usually accomplished with a subreplacement dose of 1.0 μg/kg per day (50 to 75 μg). For all other patients, treatment can be withheld and the serum TSH and thyroid autoantibody levels can be monitored at yearly intervals.

Patients Receiving Levothyroxine Therapy for Unclear Indications

Clinicians may be confronted with a patient taking thyroid hormone without a documented appropriate indication. For example, in the Framingham study, approximately 20% of patients were taking thyroid hormone for inappropriate reasons (101). To establish that such therapy is required, the serum TSH concentration and free T_4 index should be measured. If this initial serum TSH value is elevated, the levothyroxine dose should be increased incrementally until the serum TSH concentration becomes normal. If the initial serum TSH level is normal, the levothyroxine dose should be decreased by 50% and remeasured 4 weeks later. However, if the initial serum TSH value is suppressed, the serum TSH concentration should not be rechecked until pituitary TSH secretion has recovered, at least 2 months after reducing the levothyroxine dose. On reexamination, levothyroxine therapy should be either discontinued if the serum TSH and free T_4 index are normal or restarted at a full replacement dose if the serum TSH is elevated. All patients should be re-evaluated 2 months later.

Changing from Other Thyroid Hormone Preparations to Levothyroxine

The clinician may also be caring for patients who are taking other thyroid hormone preparations that contain mixtures of levothyroxine and triiodothyronine. These tablets contain either synthetic iodothyronines (liotrix) or are prepared from desiccated animal thyroid glands and are dispensed as grains or grain equivalents. To avoid the postabsorptive supraphysiologic serum T_3 concentrations that occur during therapy with these agents, we usually recommend switching patients to levothyroxine. One grain is equivalent to 0.075 to 0.1 mg of levothyroxine (102), and a substitution can be made on this basis with consideration of the patient's weight.

Thyroid-stimulating Hormone Suppressive Levothyroxine Therapy

The rationale for suppression therapy is that both the growth and function of abnormal thyroid tissue may decline when TSH secretion is reduced. This intentional overdosage with levothyroxine requires more rigorous consideration of risks and benefits. The dosage should be based on the biology of the thyroid disorder, the patient being treated, and the desired clinical response, rather than on achieving a uniform degree of TSH suppression in all conditions. No controlled studies have been done that compare the efficacy of various degrees of TSH reduction on the course of either benign or malignant thyroid nodular diseases. Although we discuss levothyroxine therapy for patients with nodular disease and thyroid cancer, the diagnostic evaluation of such patients is beyond the scope of this review.

Thyroid-stimulating Hormone Suppression in Patients with Nodular Thyroid Disease

The efficacy of TSH suppression in patients with nodular thyroid disease is controversial (103–109). Most studies have confounding variables, such as the inclusion of patients with thyroiditis, iodine deficiency, or nodules with cystic degeneration or functional autonomy, as well as lack of objective quantitation of nodule size and of randomized control groups.

Solitary Nodules in Patients without Previous Thyroid Irradiation

In 15% to 30% of patients with solitary, nonfunctioning nodules, the nodules decrease 50% or more in size without therapy (103–105). In three prospective, randomized studies of a total of 167 patients with mean treatment periods ranging from 6 months to 1.5 years, levothyroxine therapy was not more effective than placebo in reducing nodule size (103–105). Suppression of TSH was documented in two studies (104, 105), but not in the third (103). In one study (103), nodule volume was evaluated sequentially and decreased from baseline after 6 months in patients receiving levothyroxine but not in those receiving placebo ($P < 0.05$). In other studies, nodule size decreased more than 50% in 56% of levothyroxine-treated patients in whom TSH secretion was suppressed (106) and in 37% of those in whom it was not (107). Although both of these studies lacked placebo groups for comparison, the percentage of patients whose nodules decreased in size is higher than the 15% to 30% spontaneous regression rate. Pretreatment variables (patient age, nodule duration and pretreatment size, TRH–induced TSH response) cannot predict nodule responsiveness to levothyroxine therapy (104).

In patients with negative findings in fine-needle aspi-

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rates from a solitary, nonfunctioning nodule and a normal or increased serum TSH concentration, we recommend a trial of TSH suppressive therapy to determine nodule responsiveness. For premenopausal women and men who are 60 years or younger, a levothyroxine dose that will reduce the serum TSH concentration to 0.05 to 0.1 mU/L can be given; usually a dose of 100 to 150 μg/d suffices. Because of the more serious adverse effects of over-replacement in postmenopausal women, men older than 60 years, and patients with a history of cardiac disease, a lower levothyroxine dose sufficient to reduce serum TSH concentrations to 0.1 to 0.3 mU/L is used. Levothyroxine should be continued for 1 year, and nodule size should be monitored by clinical measurement or ultrasonography. If the nodule enlarges, levothyroxine therapy should be stopped. Further diagnostic evaluation, such as repeated aspiration or possibly surgery, may be warranted. If the nodule remains the same or decreases in size, therapy should be discontinued for 6 months and resumed only if the nodule enlarges.

Nontoxic Multinodular Goiter

Sporadic nontoxic multinodular goiters are pathologically diverse, with cystic, colloid, cellular, hemorrhagic, and fibrotic components. Furthermore, the natural history is characterized by unpredictable periods of stability in size and of enlargement. Areas of autonomous function also develop over time. These variables make it difficult to evaluate the efficacy of levothyroxine therapy in patients with multinodular goiters. Furthermore, 5% to 10% of these goiters may decrease in size spontaneously (108, 109). In a recent randomized study of 115 patients, a reduction in total thyroid volume of more than 13% (measured by ultrasonography) occurred in 58% of patients treated with TSH suppressive levothyroxine therapy for 9 months; after therapy was discontinued, the thyroid volume increased. However, changes in nodule size were not assessed specifically (108). A similar response to levothyroxine was reported in an earlier randomized study of 40 patients, but TSH suppression was not necessary to achieve this result (109).

If the baseline serum TSH concentration is more than 1.0 mU/L, it is logical to give levothyroxine therapy to lower the serum TSH level to the low-normal range (0.5 to 1.0 mU/L). If goiter size decreases or remains stable, therapy should be continued indefinitely, with periodic monitoring of serum TSH to assess the possible development of functional autonomy. This should be suspected if the serum TSH concentration decreases and indicates the need for further diagnostic assessment. If the goiter enlarges, further evaluation for malignancy is warranted. If the baseline serum TSH level is low-normal (0.5 to 1.0 mU/L), levothyroxine therapy should not be given because the thyroid gland may have already become autonomous. Such patients can be followed clinically and biochemically.

Postoperative Recurrence of Nodular Thyroid Disease

Postoperative levothyroxine therapy may be necessary to prevent clinical hypothyroidism, which occurs in most patients who have bilateral thyroid surgery but only in a few who have unilateral surgery (110). Levothyroxine therapy has also been advocated to prevent the development of nodules in the remnant after surgery. In the only randomized trial to compare levothyroxine therapy and "no therapy" for this purpose, no difference in thyroid size was found in the study groups after 1 year using ultrasonography (111). In several large retrospective series with a total of 659 patients and mean observation periods ranging from 5 to 8 years, postoperative levothyroxine administration did not decrease the frequency of recurrent goiter, which was 10% at 8 years (110, 112, 113). In one large retrospective study, prophylactic postoperative levothyroxine therapy prevented goiter recurrence, but the control group was small (114).

Until studies show more definitively that postoperative levothyroxine therapy prevents goiter recurrence, we do not recommend therapy after simple lobectomy if the serum TSH concentration is normal 1 year after surgery. Replacement dosages of levothyroxine should be given postoperatively if the likelihood of developing hypothyroidism is high, such as after bilateral thyroidectomy (110) or a lobectomy in a patient with circulating thyroid autoantibodies (115).

Diffuse Goiter

Diffuse nontoxic goiter can occur in either an endemic (iodine deficiency, environmental goitrogens) or sporadic (autoimmune) pattern. Thyroid enlargement results from excessive replication of thyroid epithelial cells, predominantly under the stimulus of TSH, as well as from cellular infiltration and fibrosis. The main cause of endemic goiter is iodine deficiency, which does not exist in North America. Iodine repletion is the appropriate therapy and is as effective as levothyroxine in decreasing goiter size (116). Patients with goitrous autoimmune thyroiditis usually have high titers of thyroid antimicrosomal antibodies and are often hypothyroid. Levothyroxine therapy is given to both euthyroid and hypothyroid patients with chronic goitrous thyroiditis. In one recent study, the return to normal of the serum TSH level resulted in a mean decrease of 32% in thyroid volume in such patients, with almost 50% attaining normal thyroid size after 2 years of therapy (117).

Patients with a History of Irradiation of the Thyroid

For patients who, as infants or children, received head and neck irradiation for benign conditions (tinea capitis, enlarged tonsils or thymus, acne), prophylactic levothyroxine therapy is effective in decreasing recurrence after surgical resection of benign nodules. The dose should be sufficient to lower the serum TSH concentration to 0.5 to 1.0 mU/L, because the one study showing therapeutic efficacy did not document TSH suppression in the treated group that received "at least [100 μg] of levothyroxine," and these patients probably did not have suppressed TSH values at this dose (118). However, therapy is not warranted for such irradiated patients who have no evident thyroid abnormalities (119). Patients who received neck irradiation in child-

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hood as therapy for Hodgkin disease, neuroblastoma, Wilms tumor, and leukemia have an increased incidence of hypothyroidism and thyroid nodules (120). Because TSH increases the risk for radiation-induced thyroid cancer (121), levothyroxine therapy should be started if the serum TSH concentration increases above 3 mU/L and the serum TSH concentration should be maintained in the lower part of the normal range (0.5 to 1.0 mU/L). Patients receiving neck irradiation as adults (lymphomas, breast cancer) are at risk for developing hypothyroidism (122). The serum TSH concentration should be monitored, and patients with elevated values should receive replacement levothyroxine.

Thyroid Cancer

Differentiated thyroid cancers (papillary and follicular) account for more than 90% of all thyroid cancers. We do not discuss medullary thyroid cancer because TSH suppression has no proven therapeutic benefit in patients with this condition. Initial treatment is surgery, which cures most patients. Most patients will also be rendered hypothyroid. However, because the natural history of differentiated thyroid cancer is characterized by slow growth, patients must be followed for several decades before they can be considered cured. During this period, the standard treatment is supraphysiologic doses of levothyroxine to suppress TSH secretion. The rationale for TSH suppression is the evidence that differentiated thyroid cancer cells increase their adenylate cyclase activity and grow in response to TSH because of the presence of TSH receptors (123). Thus, TSH may serve as a growth factor for any residual tumor cells.

No randomized trials evaluating the efficacy of TSH suppression in patients with thyroid cancer have been done. In one large retrospective study, patients who had surgery for papillary thyroid cancer treated with thyroid hormone had a cumulative recurrence rate of 17% at 10 years compared with a rate of 34% in patients who had not received thyroid hormone (124). However, another large study failed to show any improvement in survival with thyroid hormone therapy (125). These findings suggest that thyroid hormone is tumorstatic, not tumoricidal, but they do not address the specific issue of TSH suppression (124, 125). In addition to being retrospective, these studies did not document the degree of TSH suppression and patient compliance.

The consensus recommendation is that TSH suppression therapy should be given postoperatively to all patients with differentiated thyroid cancer (124, 126). What defines the appropriate degree of TSH suppression necessary to inhibit potential tumor growth is not known. No studies evaluating this issue have been done and very large numbers of patients would be needed to detect differences. It is also unclear whether greater degrees of TSH suppression result in further reductions of serum levels of thyroglobulin, a glycoprotein that is synthesized by both normal and differentiated malignant thyroid cells and is used as a tumor marker in patients who undergo thyroidectomy (22, 57). The issue of TSH suppression for patients with thyroid cancer is further compounded by the rapid development of successive generations of TSH assays with progressively greater sensitivities. Thus, a serum TSH concentration of less than 0.1 mU/L, suppressed according to a second-generation assay, may be readily detectable by a third-generation assay (limit, 0.01 to 0.05 mU/L) (25). It is pertinent to recognize that the normal range is the same for all of these assays. Thus, the term "undetectable" is a relative one, defined by the sensitivity of the TSH assay used.

The accepted practice is to suppress serum TSH concentrations to less than 0.1 mU/L. Levothyroxine is used for maintenance therapy, and the average daily dose required for TSH suppression in these athyreotic patients is usually 2.2 to 2.5 μg/kg, which is higher than a replacement dose (57, 124). This dose of levothyroxine is within the range that has been associated with tissue manifestations of hyperthyroidism, such as osteopenia. The morbidity of lifelong mild hyperthyroidism has not been quantified, but it has generally been felt to be outweighed by the risk for cancer recurrence. However, this issue has not been analyzed in a prospective study. There is a considerable heterogeneity of prognoses in patients with papillary thyroid cancer, which accounts for more than 85% of cases of differentiated (nonmedullary) thyroid cancer (127). More than three fourths of these patients can be considered to be low risk (women <50 years old, men <40 years old, primary tumor <4 cm in diameter, no extension through thyroid capsule) (124, 128–130). The incidence of local recurrence is greatest during the first 5 years after surgery (131). Therefore, during this initial postoperative period, the serum TSH concentration in such patients should be maintained between 0.05 to 0.1 mU/L, documented using a third-generation TSH assay. However, because such patients have a survival rate of more than 98% at 20 years (127, 129, 130), a strong argument can be made for reducing the levothyroxine dosage, allowing the serum TSH concentration to increase to 0.1 to 0.3 mU/L, assuming the disease has not recurred. For patients at high risk for papillary cancer, those with follicular or Hurthle cell cancer (more aggressive histologic types of differentiated thyroid cancer), and those with metastatic disease, the serum TSH concentration should be maintained at 0.01 to 0.1 mU/L as measured using a third-generation assay. Such patients should also be followed by a specialist in the management of thyroid cancer.

The availability of the more sensitive TSH assays makes it necessary to determine if greater degrees of TSH suppression significantly affect the natural history of thyroid disorders such as thyroid cancer and nodular thyroid disease. Furthermore, future prospective studies must evaluate the long-term physiologic effects of thyrotoxicosis induced by the therapeutic administration of supraphysiologic doses of levothyroxine to define the risk of this therapy.

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Requests for Reprints: P. Reed Larsen, MD, Thyroid Division, Brigham and Women's Hospital, 75 Francis Street, Boston MA 02115.

Current Author Addresses: Drs. Mandel, Brent, and Larsen: Thyroid Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

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