Triiodothyronine Levels in Athyreotic Individuals During Levothyroxine Therapy

Jacqueline Jonklaas, MD, PhD
Bruce Davidson, MD
Supna Bhagat, MD
Steven J. Soldin, PhD

Context Thyroidal production of triiodothyronine (T_3) is absent in athyreotic patients, leading to the suggestion that T_3 deficiency may be unavoidable during levothyroxine (LT_4) therapy. However, trials evaluating therapy with combined LT_4 and T_3 have failed to demonstrate any consistent advantage of combination therapy.

Objective To determine whether T_3 levels in patients treated with LT_4 therapy were truly lower than in the same patients with native thyroid function.

Design, Setting, and Patients A prospective study conducted in the General Clinical Research Center, Georgetown University Medical Center, Washington, DC, between January 30, 2004, and June 20, 2007, of 50 euthyroid study participants aged 18 to 65 years who were scheduled for total thyroidectomy for goiter, benign nodular disease, suspected thyroid cancer, or known thyroid cancer. Following thyroidectomy, patients were prescribed LT_4. Patients with benign thyroid disease and thyroid cancer were treated to achieve a normal and suppressed serum thyroid-stimulating hormone (TSH) level, respectively. The LT_4 dose was adjusted as necessary postoperatively to achieve the desired TSH goal.

Main Outcome Measure Thyroxine (tetraiodothyronine [T_4]), T_3, and TSH levels were measured twice preoperatively and twice postoperatively.

Results By the end of the study, there were no significant decreases in T_3 concentrations in patients receiving LT_4 therapy compared with their prethyroidectomy T_3 levels (mean, 127.2 ng/dL; 95% confidence interval [CI], 119.5-134.9 ng/dL vs 129.3 ng/dL; 95% CI, 121.9-136.7 ng/dL; $P=.64$). However, free T_4 concentrations were significantly higher in patients treated with LT_4 therapy (mean, 1.41 ng/dL; 95% CI, 1.33-1.49 ng/dL) compared with their native free T_4 levels (1.05 ng/dL; 95% CI, 1.00-1.10 ng/dL; $P<.001$). Serum TSH values of 4.5 mIU/L or less were achieved in 94% of patients by the end of the study. The T_3 concentrations were lower in the subgroup of patients whose therapy had not resulted in a TSH level of 4.5 mIU/L or less ($P<.001$).

Conclusion In our study, normal T_3 levels were achieved with traditional LT_4 therapy alone in patients who had undergone near-total or total thyroidectomy, which suggests that T_3 administration is not necessary to maintain serum T_3 values at their endogenous prethyroidectomy levels.

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THE OUTPUT OF THE HUMAN THYroid gland provides 15% to 20% of circulating triiodothyronine (T_3). Nevertheless, thyroxine (T_4) therapy, using synthetic levothyroxine (LT_4), is the standard of care for thyroid hormone therapy in patients with hypothyroidism. The regulated peripheral conversion of LT_4 to T_3 in humans has previously been demonstrated.[1-4] Such conversion thus makes it possible to achieve normal T_3 levels in humans treated with LT_4,[5] albeit with the necessity for maintaining T_4 levels at the higher end of the normal range.[6-13] However, prior studies have not compared T_3 levels on LT_4 with levels previously observed in euthyroid patients serving as their own control, therefore not addressing the question of whether individuals have deficient T_3 concentrations based on their own particular thyroid axis set point.

Despite documentation of LT_4 to T_3 conversion, there has long been interest in combining T_3 therapy with LT_4, based on the premise that T_3 levels may be lower or inappropriately balanced in patients treated with LT_4. It has been suggested that this putative T_3 deficiency may be associated with failure to fully reverse the symptoms of hypothyroidism.[14,15] Residual symptoms associated with LT_4 monotherapy have been hypothesized to include cognitive impairment, depression, and decreased psychomotor performance.[14,16-18] A recent study did document decrements in psychological function, working memory, and motor learning in euthyroid patients treated with LT_4.[12] However, these patients also had higher thyroid-stimulating hormone (TSH) values than the euthyroid control patients.

Many diverse human studies have been unable to demonstrate a consistent, objective benefit of T_3 combination therapy, despite initial studies suggesting improved mood and short-term

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Author Affiliations: Division of Endocrinology (Dr Jonklaas) and Departments of Medicine (Drs Jonklaas and Bhagat) and Otolaryngology-Head and Neck Surgery (Dr Davidson), and Bioanalytic Core Laboratory, General Clinical Research Center (Dr Soldin), Georgetown University Medical Center, Washington, DC; and Department of Laboratory Medicine, Children's National Medical Center, Washington, DC (Dr Soldin). Dr Bhagat is now with the Division of Endocrinology, Eastern Virginia Medical School, Hampton Roads, Virginia.
Corresponding Author: Jacqueline Jonklaas, MD, PhD, Division of Endocrinology, Georgetown University Hospital, Ste 232, Bldg D, 4000 Reservoir Rd NW, Washington, DC 20007 (jj@bc.georgetown.edu).

memory with T_3 supplementation.[19,20] These studies have included randomized placebo-controlled studies,[21-24] randomized parallel-design studies,[25,26] crossover studies,[19,20,27-32] studies focusing on patients with both hypothyroidism and depressive symptoms,[22,23] a study of patients with thyroid cancer,[32] and recent meta-analyses.[15,33] Some of these studies have flaws, such as production of iatrogenic hyperthyroidism with therapy,[19,25,27,28] small sample size,[20,27,28,30] different TSH levels in treatment groups,[29,30] failure to use athyreotic patients,[22,25,27] and failure to replicate the normal molar ratio of T_4:T_3.[19,21-23,25,29] Additional problems have included lack of placebo control[20,25,27] and improvement in symptoms in the placebo group.[21,24,28]

The inability to confirm that combined LT_4 and T_3 therapy is beneficial could potentially be interpreted in many different ways. It is possible that the T_3 doses used have been too high and too infrequently administered, or that sustained-release T_3 is necessary to simulate normal physiology. It is also possible that assessment tools lack the necessary sensitivity to detect subtle improvements in mood, cognitive functioning, and performance. Of interest, in 4 of these studies,[20,25,27,30] the combination therapy was preferred by patients, despite the lack of a demonstrable benefit. In 3 other studies, there was either no preference[29,32] or LT_4 was the preferred therapy.[31]

METHODS

Study Hypothesis

This study was designed to compare the circulating levels of T_4 and T_3 produced by the normally functioning thyroid gland with those levels resulting from standard thyroid hormone therapy in the same patient. Thyroid hormone levels were measured before thyroidectomy when individuals were not receiving thyroid hormone, and again after surgery when they were stabilized while receiving LT_4 therapy. We sought to document whether LT_4 therapy resulted in lower serum T_3 concentrations within individual patients. The null hypothesis was that T_3 levels in patients rendered euthyroid with LT_4 replacement would not be deficient. The study contained 2 subgroups of participants. Some patients were administered replacement LT_4 therapy, with their doses adjusted to keep their serum TSH level in the normal range; and others were administered suppression therapy because of a diagnosis of thyroid cancer, with their LT_4 doses adjusted to achieve a TSH level below the normal range.

Study Overview

The study was approved by the Georgetown University Institutional Review Board and performed in the General Clinical Research Center (GCRC) of Georgetown University Medical Center, Washington, DC. At the first study visit, written informed consent was obtained and participants' medications were then reviewed. Patient age, sex, and self-reported race and ethnicity were recorded according to GCRC protocol. A medical history was obtained and a physical examination was performed. Recorded parameters included weight, blood pressure, heart rate, thyroid examination, and neurological examination. Participants had 2 separate thyroid profiles drawn before their thyroidectomy. Two further thyroid profiles were obtained after thyroidectomy and stabilization while receiving LT_4 replacement therapy or suppression therapy. The medication history and physical examination were repeated at the end of the study. The sequence of events for the study is depicted in FIGURE 1. Patients with thyroid cancer had a delayed progression through the study if they required radioactive iodine treatment. Patients participated in the study for approximately 13 to 25 weeks, depending on their diagnosis following thyroidectomy. The study was conducted over a 42-month period. Enrollment was continuous during this period, with each study participant proceeding independently through the study.

Study Patients

Participants of both sexes aged 18 to 65 years were recruited from patients referred to the Department of Otolaryngology-Head and Neck Surgery, Georgetown University Medical Center, Washington, DC, for total or near-total thyroidectomy for goiter, nodular thyroid disease, suspected thyroid cancer, or known thyroid cancer. Patients who had a current or previous diagnosis of hyperthyroidism or hypothyroidism were excluded from the study. Patients who were expected to undergo thyroid lobectomy alone were not included in the study. Any patients who were expected to undergo total or near-total thyroidectomy but whose final surgery consisted of lobectomy were withdrawn from the study. Patients who had changes in their estrogen/progesterone therapy, oral contraceptives, or other medications known to affect thyroid hormone protein binding in the 6 weeks before the study were also excluded. Pregnant or lactating patients were not eligible. Patients with chronic, serious diseases such as cardiac, pulmonary, and renal disease or who were currently taking corticosteroid therapy were not eligible for study participation. Patients whose preoperative (first or second) thyroid profiles were abnormal were excluded from the study.

Thyroid Profiles and Physical Measurements

Each thyroid profile consisted of a serum TSH level, free thyroxine (FT_4), and total T_3. Most presurgical profiles were obtained 1 week and 1 day before thyroidectomy. Postsurgical thyroid profiles were usually drawn 8 and 16 weeks after thyroidectomy. These blood tests were drawn between 8:00 AM and 10:30 AM in a fasting state. The LT_4 administration was delayed until after phlebotomy for the postthyroidectomy sampling to obtain trough levels of thyroid hormones. Two separate presurgical profiles were included for each patient to minimize the effect of day-to-day fluctuations in thyroid hormone concentrations, TSH levels, and laboratory assays. Two postsurgical profiles were performed for the same reason, and also because of the likelihood that the initially selected dose of LT_4 would not achieve the desired TSH level. All thy-

roid profiles were drawn in the GCRC and analyzed by Quest Diagnostics (Madison, New Jersey), LabCorp (Burlington, North Carolina), or Georgetown University Laboratories (Washington, DC). All 4 thyroid profiles for each patient were analyzed by the same laboratory to minimize interassay variation. Samples were not analyzed in batches because of the long duration of the study, the need to adjust thyroid hormone dosages based on thyroid blood test results, and the fact that each study participant was proceeding independently through the study. In addition, an aliquot of each blood sample was analyzed for T_3 measured by liquid chromatography tandem mass spectrometry.

Thyroid-stimulating hormone levels were measured using a third-generation ultrasensitive immunochemiluminometric assay, with a sensitivity of 0.01 mIU/L (laboratory reference ranges, approximately 0.4-4.5 mIU/L). The FT_4 and T_3 levels were measured by chemiluminescent immunoassays. During the study period, reference ranges were approximately 0.80 to 1.80 ng/dL for FT_4 (to convert to pmol/L, multiply by 12.871) and 100 to 220 ng/dL for T_3 (to convert to nmol/L, multiply by 0.0154). Details of the liquid chromatography tandem mass spectrometry assay were previously described.[34] Anthropometric measures included weight and height. Weight was measured using a DS 504 Ohaus scale (Ohaus Corporation, Pine Brook, New Jersey); height measurements used an Accustat Stadiometer (Genentech, San Francisco, California). Physiological measurements were performed by standard procedures. Blood pressure and pulse rate were recorded after the patient had been in a seated position for at least 5 minutes. Medication history, dietary history, and medical history were obtained and recorded by using standardized case report forms.

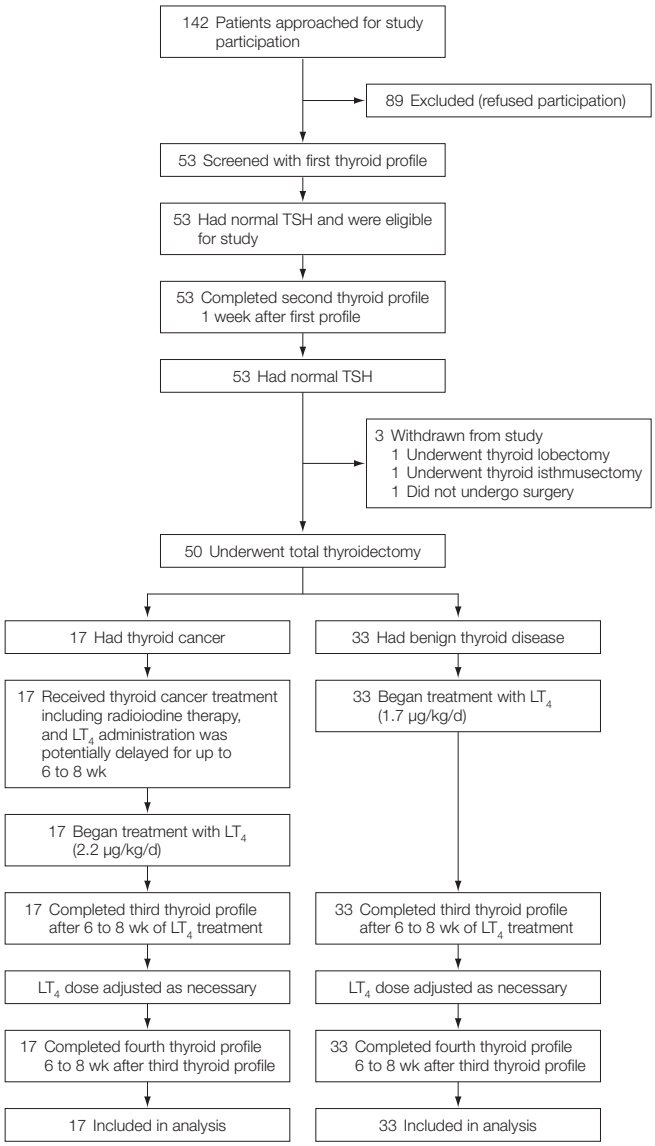
Thyroid Surgery

Thyroidectomy was performed at Georgetown University Hospital, Washington, DC, by a head and neck surgeon experienced in performing thyroid surgery. Any perioperative decisions regarding the extent of thyroid surgery were made by the patient's referring physician and surgeon, without regard for study involvement. Postoperative surgical care, treatment of hypocalcemia, and management of any other postoperative complications were uninfluenced by study participation.

LT_4 Administration

Study participants were all prescribed a name brand of LT_4. The particular brand was noted and adherence to the branded product was verified throughout the study. However, not all patients were taking the same brand name. Patients were asked to separate the time of ingestion of multivitamins or calcium supplements from the time of ingestion of their LT_4 by at least 2 hours and to take their LT_4 at least 60 minutes before breakfast. Participants were not permitted to take any T_3-containing products. Use of Armour

Figure 1. Sequence of Events for Patients Enrolled in the Study According to Pathological Diagnosis



TSH indicates thyroid-stimulating hormone; LT_4, levothyroxine.

Thyroid (a naturally derived thyroid replacement containing both T_4 and T_3), liotrix tablets (Thyrolar), or any other T_3-containing thyroid hormone preparation was grounds for discontinuation from the study. The only exception was the group of patients with thyroid cancer who were temporarily taking T_3 (liothyronine sodium [Cytomel]) as part of their preparation for radioiodine scanning and treatment. Patients with thyroid cancer who received liothyronine sodium therapy had not been taking liothyronine sodium for at least 6 weeks before their first postoperative thyroid profile. Postoperative LT_4 dosage was determined by the patient's pathological diagnosis. Patients with benign disease were initially administered 1.7 µg/kg of LT_4 daily with the goal of achieving a TSH level in the lower two-thirds of the normal range. Patients with thyroid cancer were administered 2.2 µg/kg of LT_4 daily with the goal of achieving a subnormal or suppressed TSH level. Absolute body weight, not ideal body weight, was used to calculate dosage. The LT_4 dosage adjustments were made between the 2 postoperative (third and fourth) thyroid profiles to achieve these goals.

Statistical Analysis

Our prospective study involved 2 cohorts of patients undergoing thyroidectomy. The 2 cohorts were patients with benign and malignant thyroid disease and therefore taking replacement or suppressive doses of LT_4, respectively. Interventions were performed between time points 2 and 3 (thyroidectomy and LT_4 initiation) and between time points 3 and 4 (LT_4 adjustment). Each patient served as his or her own control, thereby reducing the influence of intersubject variability in T_3 and FT_4 levels. Statistical services were provided by the GCRC biostatistics core using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). $P<.05$ was considered statistically significant. Statistical analysis showed that a sample size of 40 patients would be sufficient to detect a difference of 6 ng/dL between preoperative and postoperative T_3 levels for individual patients with 90% power and $\alpha = .05$. Data for this calculation were generated from cross-sectional chart review examining the variation between T_3 levels in individual patients. Ultimately, a sample size of 50 patients was used.

Statistical comparison was performed to determine differences in FT_4 and T_3 levels within individuals before and during thyroid hormone therapy. The null hypothesis was that LT_4 therapy did not result in any alteration of T_3 levels. The FT_4 and T_3 levels before and after thyroid hormone therapy were compared using the Wilcoxon signed rank test to determine whether patients had different thyroid hormone levels before and after their thyroidectomy. This nonparametric test was used for analysis because the data were not normally distributed. A Bonferroni correction for multiple comparisons was used. Data were also analyzed using repeated measures analysis of variance, including a random effect of the individual in the repeated measures model. The post hoc covariates considered were sex (male, female), gonadal status (premenopausal, menopausal), age, race/ethnicity (black, white, Asian, Hispanic), laboratory performing the immunoassay (LabCorp, Quest Diagnostics, Georgetown University Laboratories), surgeon (B.D. or other surgeon), initial LT_4 dose, brand of LT_4 (brand name 1 or brand name 2), and year of entry into the study (2004, 2005, 2006, 2007). Candidate covariate testing was performed by using analysis of variance to detect any signal of covariance, although numbers were inadequate for many of these covariates.

RESULTS

Our study was conducted between January 30, 2004, and June 20, 2007. A total of 142 euthyroid patients were approached to recruit the 50 patients who completed the study. Reasons for declining study participation were time demands of the study, inconvenience of study visits, and lack of interest in research studies. Three patients were withdrawn from the study after initiation. One patient was scheduled for a total thyroidectomy for a substernal goiter, but the final surgery was a lobectomy due to concern about recurrent laryngeal nerve injury. An additional patient scheduled for thyroidectomy for a large isthmus nodule instead underwent an isthmusectomy. A final patient with a multinodular goiter decided against pursuing thyroidectomy the day before surgery. Fifty patients completed the study and provided each of the 4 required blood samples. No patients were lost to follow-up. Patients in the study were operated on by 1 of 5 surgeons. However, 78% of the thyroidectomies were performed by 1 surgeon (B.D.). There were no cases of permanent postoperative hypoparathyroidism. However, 1 patient had a unilateral recurrent laryngeal nerve injury requiring speech therapy. There were no adverse events such as phlebotomy-related injuries, apparent allergies to LT_4 excipients, or clinical signs of overt hypothyroidism or hyperthyroidism associated with study participation.

The characteristics of the study patients are shown in TABLE 1. Thirty-seven patients (74%) were female and the mean age of study participants was 49 years. A total of 34 participants (68%) were white. Seventeen patients (34%) had a diagnosis of thyroid cancer. Thirty-four patients (68%) required an alteration in their LT_4 dose based on the results of their first postoperative thyroid profile.

There were no differences in blood pressure, pulse rate, deep tendon reflex relaxation, or any other physical examination findings, other than the absence of palpable thyroid tissue, in postoperative patients compared with their preoperative state. TABLE 2 shows the mean TSH, FT_4, and T_3 concentrations during the study. Time points 1 and 2 were prethyroidectomy (the mean of these 2 time points is displayed) and time points 3 and 4 were 2 successive postthyroidectomy assessments. All 4 time points are also displayed individually using box and whisker plots in FIGURE 2. Data are sepa-

rated according to whether the patients had a diagnosis of benign thyroid disease or thyroid cancer.

Serum TSH levels were significantly higher than prethyroidectomy values at time point 3, but not at time point 4 (Table 2 and Figure 2). Serum FT_4 levels increased significantly at postthyroidectomy time points 3 and 4 compared with the prethyroidectomy time points 1 and 2 (Table 2 and Figure 2). However, serum FT_4 levels did not differ between time points 3 and 4. Serum T_3 levels were lower at time point 3 but were fully recovered by time point 4 (Table 2 and Figure 2). Hence, the adjustment of LT_4 dosage performed after the third set of thyroid function tests to achieve goal serum TSH levels was associated with normalization of T_3 levels. The increase in FT_4 concentration associated with LT_4 therapy was well illustrated by the significantly increased ratio of FT_4 to T_3 that was observed in patients after they had been transitioned to LT_4 therapy (Table 2).

Serum T_3 levels for each individual patient during the study period are shown in FIGURE 3 for patients with benign thyroid disease and thyroid cancer, respectively. This plot displays the mean preoperative T_3 value and the postoperative T_3 value at time point 4 as a separate line for each patient. Time point 3 is not displayed in this plot, because this was primarily an adjustment or transition point. These plots also illustrate the intrasubject and intersubject variability in T_3 levels. Preoperative T_3 values within individuals can be observed to be both higher and lower than their postoperative T_3 values.

After thyroid surgery, patients had different TSH levels, both because of the impact of the calculated LT_4 dose on that particular patient and also because of the use of TSH suppression as a management tool for patients with thyroid cancer. A diagnosis of thyroid cancer was associated with lower TSH levels at time points 3 and 4 ($P = .003$ and $P = .002$, respectively), higher FT_4 values at time points 3 and 4 ($P = .006$ and $P = .01$, respectively), and a higher T_3 concentration measured by liquid chromatography tandem mass spectrometry at time point 4 ($P = .04$) than a diagnosis of hypothyroidism. Our conclusions did not appear to be altered by any of the remaining covariates used in the analyses. However, these categories were developed post hoc and, in many cases, there were insufficient patients to examine the effect of the covariate separately. However, study conclusions were affected by the serum TSH level achieved with LT_4 therapy.

Despite the use of a weight-based calculation to determine initial LT_4 dose, widely differing serum TSH values were achieved postoperatively (Figure 2 and FIGURE 4). Postthyroidectomy time points were divided into 3 groupings: those with TSH values more than 4.5 mIU/L, those with serum TSH values between 0.35 and 4.5 mIU/L, and those with TSH values less than 0.35 mIU/L (Figure 4). The mean T_3 concentration associated with each of these groups is shown for immunoassay and liquid chromatography tandem mass spectrometry measurements, respectively. A significantly lower mean T_3 was observed to be associated with the subset of postoperative TSH values more than 4.5 mIU/L, regardless of whether T_3 was measured by immunoassay or liquid chromatography tandem mass spectrometry. If postoperative TSH values were 0.35 to 4.5 mIU/L, the associated T_3 levels were not lower than the entire group. The TSH values less than 0.35 mIU/L were not associated with higher postoperative T_3 values.

Table 1. Characteristics of Study Participants (N = 50)

Characteristics	No. (%) of Patients
Diagnosis	
Benign thyroid disease	33 (66)
Thyroid cancer	17 (34)
Age, y	
<45	19 (38)
≥45	31 (62)
Sex	
Male	13 (26)
Female	37 (74)
Race/ethnicity	
White	34 (68)
Black	9 (18)
Hispanic	2 (4)
Asian	5 (10)
Gonadal status	
Female	
Premenopausal	19 (51)
Menopausal	18 (49)
Menopausal and taking hormone therapy	0
Male	
No exogenous testosterone	13 (100)
Exogenous teststerone	0
Surgeon	
B.D. (second author)	39 (78)
Other surgeons	11 (22)
Surgical complication	
Recurrent laryngeal nerve palsy	1 (2)
Hypoparathyroidism	0
Levothyroxine brand	
1	47 (94)
2	3 (6)
Laboratory performing immunoassay	
LabCorp	23 (46)
Quest Diagnostics	12 (24)
Georgetown University Laboratories	15 (30)
Entry into study, y	
2004	12 (24)
2005	10 (20)
2006	21 (42)
2007	7 (14)

COMMENT

Our study was unable to document any deficiency of T_3 in athyreotic patients treated with LT_4 replacement therapy. After adequate adjustment of their LT_4 doses, these patients had serum T_3 levels after thyroidectomy that were not significantly different from their T_3 levels before thyroidectomy. Serum T_3 concentrations were lower in patients who were taking inadequate LT_4 doses. This phenomenon was observed most clearly at the postthyroidectomy time point 3 (Figure 2 and Figure 4). Serum TSH concentrations of 4.5 mIU/L or more were associated with lower T_3 levels than TSH concentrations of 0.35 to 4.5 mIU/L. There was a lower mean T_3 value associated with TSH values of more than 4.5 mIU/L using liquid chromatography tandem mass spectrometry measurements compared with immunoassay measurements. Liquid chromatography tandem mass spectrometry is generally known to be a more specific assay[34] and, at least in the case of FT_4 measurement, agrees bet-

ter with equilibrium dialysis than immunoassay.[35] This is the first study to document T_3 sufficiency using patients treated with LT_4 as their own controls rather than using a nonidentical euthyroid control group. Although this information does not directly address the issue of whether patients might feel better taking combination therapy, it does suggest that such therapy is not necessary to replicate normal serum T_3 levels.

Clearly, our study simply documents circulating levels of thyroid hormones and does not measure thyroid gland hormone production or actual tissue levels. With respect to thyroid hormone tissue concentrations, a 1996 study[36] showed that tissue T_3 levels were lower in rats treated with LT_4 than in rats treated with combination therapy. We cannot exclude the possibility that cerebral T_3 levels were lower in our participants during their LT_4 therapy. However, there is no a priori reason to suspect this, given that serum T_3 levels remained the same. It could, admittedly, be hypothesized that cerebral production of T_3 by deiodinases could be down-regulated by the high-circulating FT_4 levels associated with the LT_4-treated state. In this prior animal study, a dose of LT_4 that normalized serum TSH was not studied. However, an earlier study[37] did demonstrate in rats that a higher dose of LT_4 that produced both normal serum TSH and normal serum T_3 concentrations could be used. If a higher dose of LT_4 had been unable to normalize serum TSH and serum T_3 in rats, this would be in contrast with the results from our study. The possibility remains that interspecies differences, such as the greater magnitude of thyroidal T_3 production in rats, would allow LT_4 therapy to produce tissue euthyroidism in humans but not rodents.

The FT_4 or T_4 levels have been demonstrated to be higher in euthyroid patients treated with LT_4 than in euthyroid controls in previous studies in humans.[6-13] In our study, we found that within the same patient, FT_4 levels were higher after thyroidectomy than before thyroidectomy. Our data confirm that higher FT_4 levels are a characteristic of LT_4 monotherapy. Furthermore, we postulate based on our data that this is necessary to normalize TSH and serum T_3 levels and thereby achieve euthyroidism. Whether there are adverse consequences of increased FT_4 levels, even when they are not accompanied by decreased serum TSH concentrations, remains to be investigated in future studies.

A potential limitation of our study is that the patients with benign thyroid disease had varying amounts of remnant thyroid tissue. However, it would seem unlikely that such thyroid remnants would function sufficiently to mask the ability to detect a decrement in T_3 concentrations with LT_4 replacement. Analysis included diagnosis as a covariate and patients with thyroid cancer, all of whom underwent remnant ablation with radioactive iodine, did not have lower postoperative T_3 levels compared with patients with hypothyroidism. This suggests that residual thyroid tissue was not contributing significantly to maintenance of circulating T_3 levels in patients with benign disease. This is in contrast with the findings from a previous study[20] in which some benefits of T_3 combination therapy were noted in the subgroup of patients with a diagnosis of thyroid cancer. However, patients with thyroid cancer were compared with those

Table 2. Concentrations of TSH, FT_4, and T_3 at Time Points 1 and 2, 3, and 4 by Diagnoses of Benign Thyroid Disease and Thyroid Cancer[a]

	Prethyroidectomy Time Points			Postthyroidectomy Time Points					
	Mean of 1 and 2			3			4		
Analytes	Total (N = 50)	Benign Thyroid Disease (n = 33)	Thyroid Cancer (n = 17)	Total (N = 50)	Benign Thyroid Disease (n = 33)	Thyroid Cancer (n = 17)	Total (N = 50)	Benign Thyroid Disease (n = 33)	Thyroid Cancer (n = 17)
TSH, mIU/L									
Mean (SD)	1.18 (0.58)	1.01 (0.51)	1.50 (0.59)	2.95 (4.24)	3.09 (3.85)	2.67 (5.03)	1.30 (1.89)	1.48 (1.65)	0.95 (2.31)
[95% CI]	[1.02-1.34]	[0.84-1.18]	[1.22-1.78]	[1.79-4.11][b]	[1.78-4.40][c]	[0.28-5.06]	[0.78-1.82]	[0.92-2.04]	[0-2.05]
FT_4, ng/dL									
Mean (SD)	1.05 (0.19)	1.06 (0.19)	1.04 (0.17)	1.39 (0.33)	1.30 (0.32)	1.55 (0.30)	1.41 (0.29)	1.34 (0.28)	1.54 (0.29)
[95% CI]	[1.00-1.10]	[0.95-1.17]	[0.96-1.12]	[1.30-1.48][d]	[1.19-1.41][d]	[1.41-1.69][d]	[1.33-1.49][d]	[1.24-1.44][d]	[1.40-1.68][d]
T_3 by immunoassay, ng/dL									
Mean (SD)	129.3 (26.7)	133.9 (25.3)	120.5 (27.8)	118.1 (32.0)	120.6 (29.5)	113.3 (26.8)	127.2 (27.9)	128.9 (29.1)	123.9 (24.3)
[95% CI]	[121.9-136.7]	[125.4-142.4]	[107.3-133.7]	[109.2-127.0][e]	[110.5-130.7][f]	[100.6-126.0]	[119.5-134.9]	[119.0-138.8]	[112.3-135.5]
T_3 by LC-MS-MS, ng/dL									
Mean (SD)	124.0 (24.3)	129.9 (24.9)	112.6 (18.6)	112.3 (37.8)	111.7 (39.1)	113.5 (36.4)	123.6 (29.3)	120.8 (28.9)	129.2 (29.9)
[95% CI]	[117.3-130.7]	[121.4-138.4]	[103.8-121.4]	[101.8-122.8][f]	[98.4-125.0][g]	[96.2-130.8]	[115.5-131.7]	[110.9-130.7]	[115.0-143.4][h]
Ratio ($FT_4 \times 100/T_3$)									
Mean (SD)	0.85 (0.22)	0.82 (0.21)	0.91 (0.25)	1.23 (0.37)	1.13 (0.28)	1.43 (0.43)	1.15 (0.29)	1.09 (0.28)	1.27 (0.27)
[95% CI]	[0.79-0.91]	[0.75-0.89]	[0.79-1.03]	[1.13-1.33][d]	[1.03-1.23][d]	[1.23-1.63][d]	[1.07-1.23][d]	[0.99-1.19][d]	[1.14-1.40][d]

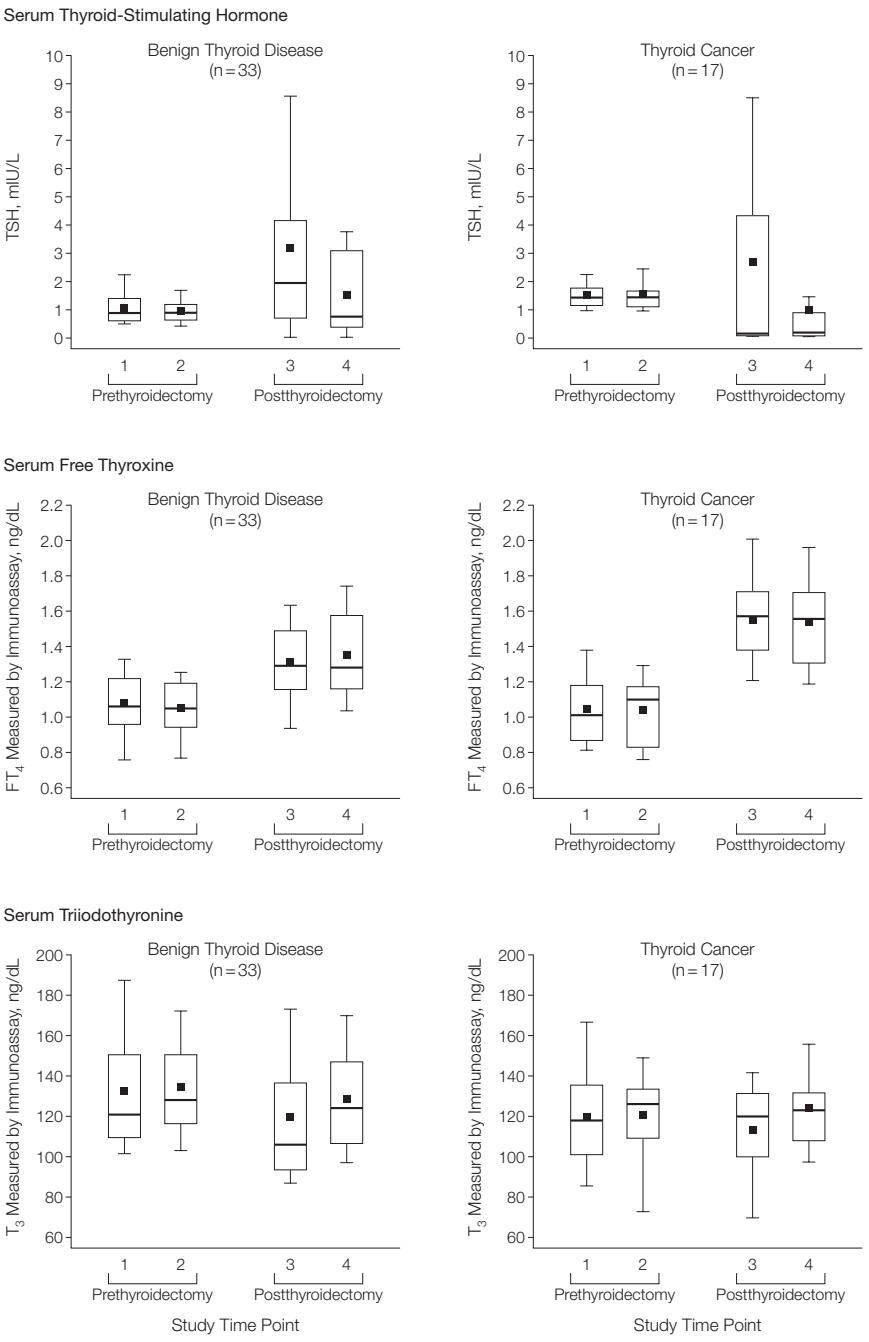
Abbreviations: CI, confidence interval; FT_4, free thyroxine; LC-MS-MS, liquid chromatography tandem mass spectrometry; T_3, total triiodothyronine; TSH, thyroid-stimulating hormone.
SI conversions: To convert FT_4 to pmol/L, multiply by 12.871; and T_3 to nmol/L, multiply by 0.0154.
[a]Time points 3 and 4 each were compared with the mean of time points 1 and 2. Significance was tested by using Wilcoxon signed rank test.
[b]$P = .03$. [c]$P = .002$. [d]$P < .001$. [e]$P = .046$. [f]$P = .04$. [g]$P = .02$. [h]$P = .01$.

with Hashimoto's hypothyroidism, whereas all our study participants had surgically induced hypothyroidism. Admittedly, another variable of a lower serum TSH level was also present in our patients with thyroid cancer. Subgroup analysis, however, showed that having a TSH level suppressed to less than 0.35 mIU/L did not raise postoperative T_3 levels beyond those observed in the group with TSH levels of 0.35 to 4.5 mIU/L (Figure 4).

Another potential limitation of our study is that it had a long duration. It is possible that temporal changes in variables such as laboratory assays, surgeon procedures, LT_4 formulation, and other factors could increase the variation in the measured hormones and thereby decrease the ability to detect changes in T_3 levels. However, including the year of entry into the study as a covariate did not alter study conclusions.

Our study did not examine satisfaction with LT_4 therapy. It was thought to be impossible to discern whether symptoms developing since LT_4 initiation were due to recent major surgery, thyroid cancer treatment, or the LT_4 therapy itself. However, we were unable to demonstrate different serum T_3 levels in patients treated with LT_4 therapy, when their therapy had been adjusted to achieve their target TSH levels, or when their TSH levels were less than 4.5 mIU/L. Based on this fact, there is no reason to hypothesize that patient dissatisfaction with LT_4 treatment is due to inability to achieve the same serum T_3 concentrations that are present in individuals with normal endogenous thyroid function. Certainly, declines in psychological and cognitive performance have been documented in euthyroid patients treated with LT_4, even though as a group these patients had a mean TSH level of 2.6 mIU/L.[12] Possibly, there is some characteristic of LT_4 therapy that does not fully replicate an important but as yet unidentified aspect of normal thyroid physiology. For example, it is possible that there is some differential regulation of and thereby different fluctuation in T_3 levels in endogenous function that is not replicated with LT_4 replacement. There might, therefore, be some use in evaluating patient satisfaction, psychological functioning, and motor performance during therapy with a sustained-release T_3 preparation, which might more closely replicate normal physiology. Pa-

Figure 2. Serum TSH, FT_4, and T_3 Concentrations at Study Time Points 1 to 4 for Patients With Benign Thyroid Disease or Thyroid Cancer



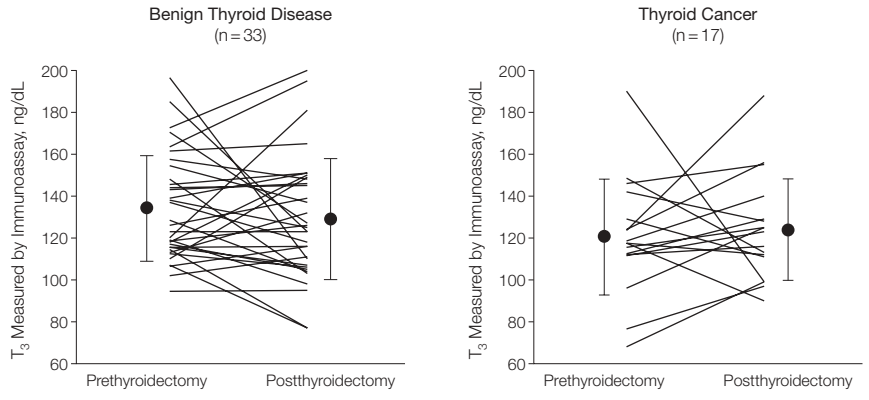
TSH indicates thyroid-stimulating hormone; FT_4, free thyroxine; T_3, triiodothyronine. To convert FT_4 to pmol/L, multiply by 12.871; and T_3 to nmol/L, multiply by 0.0154. Thyroidectomy and levothyroxine (LT_4) initiation occurred between time points 2 and 3. LT_4 adjustment was made between time points 3 and 4. The top, bottom, and middle lines of the boxes correspond to the 75th percentile, 25th percentile, and 50th percentile (median), respectively. The whiskers extend from the 10th percentile to the 90th percentile. The filled squares indicate the arithmetic mean.

tients receiving LT_4 therapy also clearly have higher FT_4/T_3 ratios than the ratios that were characteristic of their period of endogenous thyroid function. It is also possible that the high concentration of FT_4 that is necessary for normalization of T_3 levels during LT_4 therapy is associated by some unappreciated mechanism with an adverse impact on patients.

Circulating T_3 levels have been shown to be lower in individuals carrying certain deiodinase polymorphisms in some studies.[38,39] A subgroup of patients who remain dissatisfied with their LT_4 therapy may be individuals who carry a specific deiodinase polymorphism. It is possible that combination LT_4-T_3 therapy may be beneficial in these rare cases. We postulate that these deiodinase polymorphisms were probably not present in our small 50-patient sample, although some outlier T_3 values were observed (Figure 3). Only the group of patients with TSH levels higher than 4.5 mIU/L had T_3 levels lower than other groups of patients treated with LT_4. It would be more logical to assume that the T_3 deficiency in this group was caused by suboptimum LT_4 therapy rather than the presence of a deiodinase polymorphism.

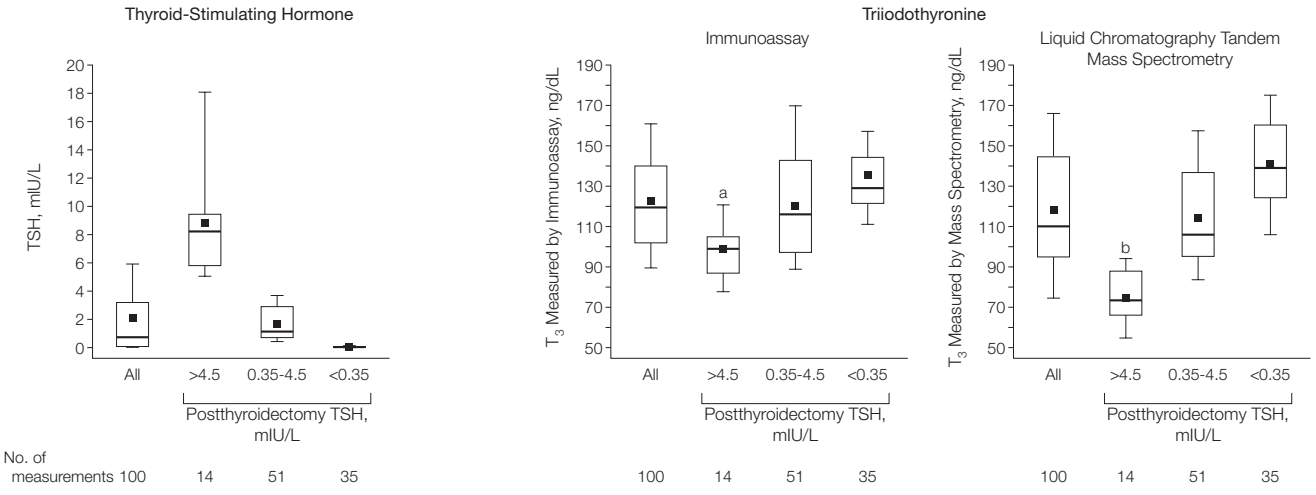
Based on our study results, it would appear reasonable to advise individual patients that physiological T_3 levels can indeed be replicated with LT_4 therapy. If it is assumed that maintenance of normal T_3 concentrations correlates with satisfactory replacement therapy, our results could provide one possible explanation for the failure of multiple studies to demonstrate a benefit of T_3 combination therapy. Our study, however, is limited by the fact that we did not document patients' symptoms. If adequate serum T_3 levels were also correlated with patient satisfaction or well-being, this would support the commonly held belief that LT_4 should remain the standard therapy for hypothyroidism and thyroid cancer.

Figure 3. Mean Prethyroidectomy T_3 and T_3 at Time Point 4 for Patients With Benign Thyroid Disease or Thyroid Cancer



T_3 indicates triiodothyronine. Mean prethyroidectomy T_3 (mean of time points 1 and 2) and T_3 at time point 4 (postthyroidectomy) measured by immunoassay are plotted on a single line. Each line is an individual patient. Filled circles and vertical lines indicate mean (SD), respectively. To convert T_3 to nmol/L, multiply by 0.0154.

Figure 4. Postthyroidectomy Serum TSH, Postthyroidectomy T_3 Measured by Immunoassay, and Postthyroidectomy T_3 Measured by Liquid Chromatography Tandem Mass Spectrometry by TSH Grouping



TSH indicates thyroid-stimulating hormone; T_3, triiodothyronine. To convert T_3 to nmol/L, multiply by 0.0154. The top, bottom, and middle lines of the boxes correspond to the 75th percentile, 25th percentile, and 50th percentile (median), respectively. The whiskers extend from the 10th percentile to the 90th percentile. The filled squares indicate the arithmetic mean. All individual postthyroidectomy values are displayed.

[a] $P = .01$ vs other postthyroidectomy TSH groupings.

[b] $P < .001$ vs other postthyroidectomy TSH groupings.

Author Contributions: Dr Jonklaas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jonklaas.
Acquisition of data: Jonklaas, Davidson, Bhagat, Soldin.
Analysis and interpretation of data: Jonklaas, Soldin.
Drafting of the manuscript: Jonklaas, Soldin.
Critical revision of the manuscript for important intellectual content: Jonklaas, Davidson, Bhagat, Soldin.
Statistical analysis: Jonklaas.
Obtained funding: Jonklaas, Soldin.
Administrative, technical, or material support: Jonklaas, Soldin.
Study supervision: Jonklaas, Davidson, Soldin.
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