Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study

Thanh D. Hoang, Cara H. Olsen, Vinh Q. Mai, Patrick W. Clyde, and Mohamed K. M. Shakir

Department of Endocrinology (T.D.H., V.Q.M., P.W.C., M.K.M.S.), Walter Reed National Military Medical Center, Bethesda, Maryland 20889; and Department of Preventive Medicine and Biometrics (C.H.O.), Uniformed Services University of Health Sciences, Bethesda, Maryland 20814

Context: Patients previously treated with desiccated thyroid extract (DTE), when being switched to levothyroxine (L-T_4), occasionally did not feel as well despite adequate dosing based on serum TSH levels.

Objective: Our objective was to investigate the effectiveness of DTE compared with L-T_4 in hypothyroid patients.

Design and Setting: We conducted a randomized, double-blind, crossover study at a tertiary care center.

Patients: Patients (n = 70, age 18–65 years) diagnosed with primary hypothyroidism on a stable dose of L-T_4 for 6 months were included in the study.

Intervention: Patients were randomized to either DTE or L-T_4 for 16 weeks and then crossed over for the same duration.

Outcome Measures: Biochemical and neurocognitive tests at baseline and at the end of each treatment period were evaluated.

Results: There were no differences in symptoms and neurocognitive measurements between the 2 therapies. Patients lost 3 lb on DTE treatment (172.9 ± 36.4 lb vs 175.7 ± 37.7 lb, $P < .001$). At the end of the study, 34 patients (48.6%) preferred DTE, 13 (18.6%) preferred L-T_4, and 23 (32.9%) had no preference. In the subgroup analyses, those patients who preferred DTE lost 4 lb during the DTE treatment, and their subjective symptoms were significantly better while taking DTE as measured by the general health questionnaire-12 and thyroid symptom questionnaire ($P < .001$ for both). Five variables were predictors of preference for DTE.

Conclusion: DTE therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over L-T_4. DTE therapy may be relevant for some hypothyroid patients. **(*J Clin Endocrinol Metab* 98: 1982–1990, 2013)**

Although most endocrinologists recommend synthetic L-T_4 for the treatment of hypothyroidism, a common endocrine disorder (1–3), there is still uncertainty regarding combination synthetic levothyroxine/liothyronine (L-T_4/T_3) therapy and desiccated thyroid therapy (DTE). Many patients claim that they do not feel as well when being switched from DTE to L-T_4 therapy. There is an ongoing demand for pharmaceutical companies to con-

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Abbreviations: AMI, auditory memory index; BDI, Beck Depression Inventory; BP, blood pressure; CI, confidence interval; DMI, delayed memory index; DTE, desiccated thyroid therapy; GHQ, general health questionnaire; HDL, high-density lipoprotein; IMI, immediate memory index; OR, odds ratio; QOL, quality of life; TSQ, thyroid symptom questionnaire; USP, U.S. Pharmacopeia; VMI, visual memory index; VWMI, visual working memory index; WMS-IV, Wechsler memory scale, fourth edition.

tinue manufacturing DTE, which is now standardized by measuring T_4 and T_3 content (U.S. Pharmacopeia [USP] 35-NF 30) (4).

There have not been any randomized double-blind studies to compare the clinical effectiveness of synthetic L-T_4 with DTE. It is imperative to further investigate the efficacy of DTE in hypothyroid patients. We conducted a randomized, double-blind, crossover study to evaluate the efficacy of DTE vs L-T_4 in hypothyroid patients by assessing symptoms, cognitive function, and sense of general well-being.

Our hypothesis was that hypothyroid patients on DTE may have a decrease in symptoms, an improvement of cognitive function, and an increase in sense of well-being/quality of life (QOL) equivalently compared with L-T_4.

Patients and Methods

Study patients

Patients (age 18–65 years) enrolled in the military healthcare system who had been diagnosed with primary hypothyroidism and were on a stable dose of L-T_4 for at least 6 months were studied. There were only 2 patients taking DTE, Armour thyroid (75 and 105 mg/d, respectively), before the study, and the remaining patients were on L-T_4. Patients were excluded for the following: pregnancy, coronary artery disease, chronic obstructive lung disease, malabsorption disorder, gastrointestinal surgeries, significant renal or liver dysfunction, seizure disorders, any active cancer, uncontrolled psychosis, and psychotropic medications, corticosteroids, amiodarone, iron supplements, sucralfate, proton pump inhibitors, and cholestyramine. There were 21% of patients (n = 15) with hypertension; 23% (n = 16) with hyperlipidemia, and 9% (n = 6) with diabetes mellitus type 2. Two patients were on low-dose β-blocker therapy. No change of medications was made during the study.

Study design

The proposed study design was a prospective, randomized, double-blind, crossover study, conducted at the Walter Reed National Military Medical Center in Bethesda, Maryland. The Walter Reed National Military Medical Center Institutional Review Board approved the study, and written informed consent was obtained from all patients. Patients were randomized to receive either DTE or L-T_4 in identical appearing capsules (Capsuline Inc, Pompano Beach, Florida; Armour thyroid tablets, USP, from Forest Pharmaceuticals, St. Louis, Missouri; Synthroid, levothyroxine sodium tablets, USP, from Abbott Laboratories, North Chicago, Illinois). Each grain (65 mg) of Armour thyroid provides 38 μg L-T_4 and 9 μg liothyronine (T_3), analyzed by HPLC under the standard preparation in the USP 35-NF 30 guidelines. The initial DTE dose was chosen by using the conversion table from USP Drug information 2000 to convert L-T_4 to DTE: 1 mg DTE = 1.667 μg L-T_4 (see Table 6). Research pharmacists prepared thyroid capsules of various strengths of L-T_4 and DTE and ensured the expiration dates and proper dispensing of these capsules. Compliance to medication was confirmed by pill counting. A physician not involved in randomization maintained the concealed randomization list, which was stratified in blocks of 10 according to a computer-generated random number table. All study participants and investigators were blinded throughout the study.

We verified that patients had stable normal serum TSH levels before testing. Patients underwent memory testing using the Wechsler memory scale, fourth edition (WMS-IV) (Pearson, PsychCorp, San Antonio, Texas) (5, 6), Beck Depression Inventory (BDI) (Pearson, PsychCorp) (7), a thyroid symptom questionnaire (TSQ) (modified from Jaeschke et al [8] and Cooper et al [9]), and a QOL general health questionnaire (GHQ)-12 (10). We designed our own TSQ that was modeled after the hypothyroid-specific questionnaires developed by Jaeschke et al (8) and Cooper et al (9) and includes the symptoms frequently associated with hypothyroidism that improved with thyroid hormone therapy (Supplemental Appendix, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). We have used these TSQ questionnaires in a previously published paper by Clyde et al (11). We performed a complete physical examination and obtained an electrocardiogram, serum TSH, free T_4, total T_4, total T_3, T_3 resin uptake, rT_3, SHBG, and a lipid panel at baseline and on the last day of each 16-week treatment period. Patients were counseled regarding the importance of taking the thyroid preparations on an empty stomach with water only and to take other medications and breakfast at least 1 hour later. Any medications that have potential to interfere with T_4 absorption such as iron, calcium, Metamucil, certain soy-containing preparations, multivitamins, etc, were taken at least 4 hours later. Laboratory tests were obtained in the morning after an overnight fast of at least 10 hours, and on this day, patients were advised to take their thyroid capsules and wait for 1 hour before eating breakfast and/or taking other medications.

After 6 weeks on the study medication, TSH levels were checked and the medication adjusted to maintain a TSH level between 0.5 and 3.0 μIU/mL. Once the serum TSH level was in the desired range, patients continued the medication for an additional minimum period of 12 weeks. Patients were then crossed over to the other treatment arm for 16 weeks with TSH being checked at 6 weeks as during the first period (goal TSH 0.5–3.0 μIU/mL), and testing was repeated at the end of the treatment period.

Biochemical measurements

Serum TSH, free T_4, total T_3, and SHBG were measured by the electrochemiluminescence immunoassay (Cobas 8000; Roche Diagnostics, Indianapolis, Indianapolis); serum total T_4 and T_3 resin uptake by enzyme immunoassay (AU 5400; Beckman Coulter, Irving, Texas); serum free T_4 by direct dialysis and rT_3 by RIA (Calbiotech, Spring Valley, California; and Radim, Pomezia, Italy, respectively). The intra- and interassay variabilities of the assays were 2.3% and 5.1% for TSH, 4.4% and 7.8% for T_3, and 1.7% and 4.8% for free T_4.

Clinical measurements included body weight (in pounds), resting heart rate, and blood pressure (BP).

Outcome measures

Primary outcome measures, such as the TSQ, the GHQ-12, the WMS-IV, and the BDI were completed at baseline and at the end of each treatment period.

The WMS-IV included auditory memory index (AMI), visual memory index (VMI), visual working memory index (VWMI),

immediate memory index (IMI), and delayed memory index (DMI). The BDI is a self-rating scale of 21 items, in which scores of 10 or less indicate normal mood variation and scores of 11 or more reflect increasing levels of depression. Clinically important depression is associated with scores of 20 or more (7).

At the completion of the study, each patient was asked which treatment (the first or the second) he or she preferred.

Statistical analysis

Differences between drugs were evaluated using mixed linear models in SAS version 9 (SAS Institute Inc, Cary, North Carolina). The model included fixed effects for period, randomization group, and drug and subject nested within randomization group as a random effect. The baseline value of the dependent variable was included as a fixed covariate. Models of patient preference were similar, with the addition of patient preference and the interaction between drug and patient preference as fixed effects. Linear contrasts were used to estimate the difference between DTE and L-T_4 separately for patients who preferred each drug and to compare the DTE − L-T_4 differences between the 2 groups of patients. P values $< .05$ were considered statistically significant.

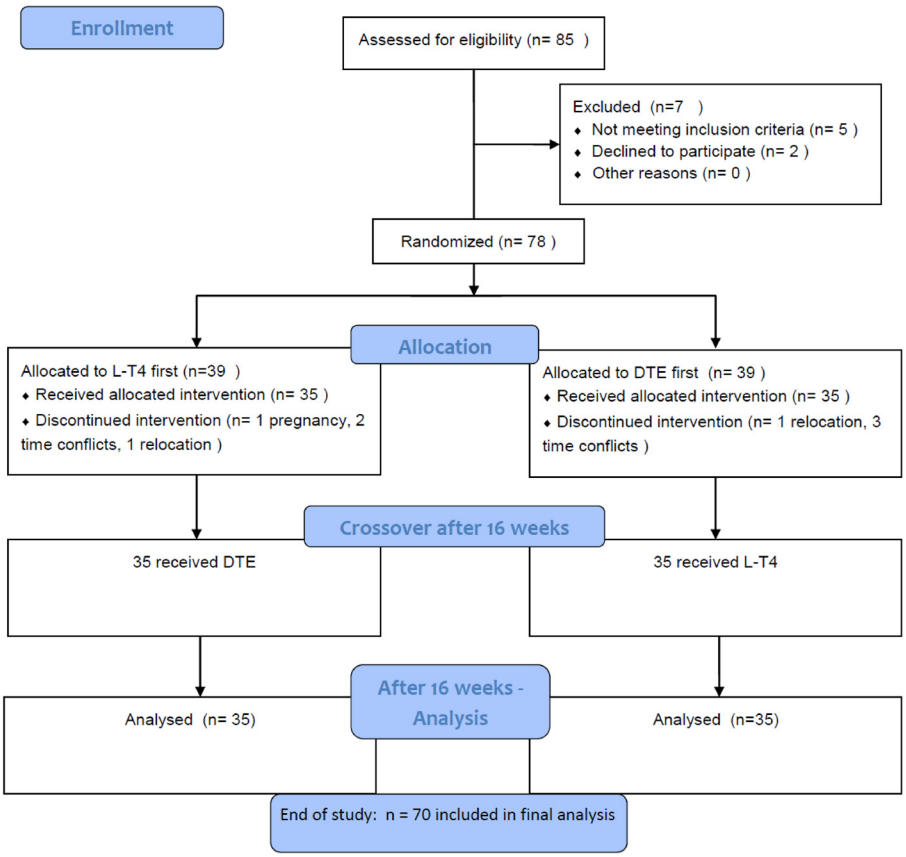
Subgroup analyses were performed for 3 groups (group 1, those who preferred DTE; group 2, those who preferred L-T_4; and group 3, those who had no preference). For these subgroup analyses, P values were adjusted for baseline.

Stepwise logistic regression was used to identify significant predictors of preference for DTE. The dependent variable in the model was preference for DTE vs L-T_4; patients with no preference were excluded from the analysis. Independent variables were constructed by subtracting each patient's value while on the L-T_4 arm from his or her value while on the DTE arm, so positive differences indicate that the patient had a higher value while on DTE. Differences were constructed for each of the measured variables and entered into the logistic regression model. Variables were entered into the model in order of statistical significance, with a cutoff of $P < .10$ for entry into the model. Variables were dropped from the model if their significance fell above .15. All variables were included in the stepwise selection except for rT_3. This variable was missing for several patients and was not associated with clinical preference in bivariate analyses so was excluded from the modeling process to retain the full sample.

On the basis of a previous study by Clyde et al (11), using the TSQ index as the outcome measure, the means of the 2 groups (L-T_4 and combination L-T_4 + T_3) were 58 and 50 with the respective SDs of 23 and 12. Sample size for this crossover study was based on a paired t test with a 5%, 2-sided significance level and assumed a SD of 23 and a within-subjects correlation of 0.5. A sample size of 67 is required for 80% power to detect a difference of 8 points on the TSQ. Accounting for a dropout rate of up to 25%, the necessary sample size is estimated to be 90 enrollees.

Results

Seventy-eight patients were enrolled, and 70 patients (53 female, 17 male) completed the study (Figure 1). Baseline



* Patients included male and female beneficiaries of the military health care system between the ages of 18 to 65 who had been diagnosed with primary hypothyroidism and were on a stable dose of L-T4 for at least 6 months. 78 patients were enrolled, 70 completed the study (10% drop-out rate).

* Patients were excluded for the following: pregnancy, coronary artery disease, chronic obstructive lung disease, malabsorption disorder, gastrointestinal surgeries, significant renal or liver dysfunction, seizure disorders, any active cancer, uncontrolled psychosis, and psychotropic medications, corticosteroids, amiodarone, iron supplements, sucralfate, proton pump inhibitors, and cholestyramine.

Figure 1. Flow diagram: enrollment, allocation, and completion of the study.

characteristics of the 70 patients are shown in Table 1. Average age of the patients was 50.7 years, and 50% of the patients had autoimmune hypothyroidism. The mean dose of L-T_4 at baseline was 112.4 (36.3) μg/d.

Table 1. Baseline Patient Characteristics

	Patient Characteristics (n = 70)
Age, y	50.66 (range 23–65)
Gender, n (%)	
Female	53 (75.71)
Male	17 (24.29)
Race, n (%)	
Caucasian	52 (74.29)
African-American	11 (15.71)
Asian	4 (5.71)
Hispanic	3 (4.29)
Cause of hypothyroidism, n (%)	
Autoimmune	35 (50.00)
Idiopathic	14 (20.00)
Post-RAI	10 (14.29)
Post-surgical	8 (11.43)
Post-radiation	3 (4.28)
Dose of L-T_4, mean ± SD μg/d	112.4 ± 36.30 (range 75–211)
Clinical measures	
Heart rate, beats/min	73.36 ± 11.31
Systolic BP, mm Hg	124.66 ± 13.54
Diastolic BP, mm Hg	77.60 ± 8.08
Weight, lb	174.31 ± 37.56
Neuropsychological measures	
GHQ-12	10.61 ± 3.60
TSQ- 36	13.91 ± 7.09
BDI score	5.23 ± 5.10
AMI score	112.78 ± 15.93
VMI score	107.08 ± 16.65
VWMI score	108.77 ± 12.69
IMI score	109.83 ± 15.37
DMI score	112.76 ± 17.61
Biochemical measures	
Total cholesterol (<200 mg/dL)	194.77 ± 33.50
LDL cholesterol (<130 mg/dL)	114.33 ± 29.53
HDL cholesterol (>40 mg/dL)	60.70 ± 15.92
Triglyceride (<150 mg/dL)	102.57 ± 59.88
Total T_3 (60–181 ng/dL)	94.62 ± 25.16
T_3 resin uptake (22%–35%)	31.81 ± 3.32
rT_3 (11–32 ng/dL)	32.26 ± 12.85
TSH (0.27–4.20 μIU/mL)	1.69 ± 0.78
Total T_4 (4.5–12 μg/dL)	9.10 ± 2.11
Free T_4 (0.89–1.76 ng/dL)	1.34 ± 0.27
Free T_4 direct (0.8–2.7 ng/dL)	1.89 ± 0.49
SHBG (17–124 nmol/L)	64.41 ± 45.98

Abbreviations: LDL, low-density lipoprotein; RAI, radioactive iodine therapy.

Primary outcome measures

Overall, the patients showed no difference in symptoms scores, general health questionnaires, or neuropsychological testing. However, there was a trend toward improvement in GHQ-12, TSQ, and auditory memory index during DTE period (P = .098, P = .121, and P = .081, respectively).

Clinical/biochemical measures

There was a decrease of 2.86 lb in the weight of patients during DTE therapy compared with L-T_4 therapy (P < .001) (Table 2). No significant changes occurred in heart rate or BP during the study.

There were no differences in the lipid profiles, except a slightly lower high-density lipoprotein (HDL) level (P = .028). During the DTE treatment, patients had higher levels of serum total T_3 and TSH but lower serum levels of T_3 resin uptake, total T_4, free T_4, and free T_4 by direct dialysis. The TSH range was 0.56 to 3.0 μIU/mL for the DTE period, 0.54 to 3.0 μIU/mL for baseline, and 0.51 to 3.0 μIU/mL for the L-T_4 period. None of the study patients had TSH outside of the reference range. SHBG level did not differ between the 2 treatments.

Clinical preference

At the end of the study, 34 patients (49%) preferred DTE, 13 (19%) preferred L-T_4, and 23 (33%) had no preference. Preference for DTE over L-T_4 was statistically significant (χ^2 [1] = 9.38; P = .002).

Subgroup analyses

Patients preferring DTE had an average of 4 lb weight loss during the DTE treatment compared with the L-T_4 treatment (P < .001), and their subjective symptoms, such as concentration, memory, sleep, decision-making capability, happiness, and energy level, were significantly better while taking DTE as indicated by lower GHQ-12 and TSQ scores (P < .001 for both comparisons) (Supplemental Table 1). The BDI was nearly (P = .057) improved. Auditory memory also improved in these patients during the DTE treatment period (P = .041). There was no difference in the visual memory index, visual working memory index, immediate memory index, or delayed memory index scores during each treatment period.

Supplemental Tables 2 and 3 show the results for the patients who preferred L-T_4 and those who had no preference, respectively. There was no significant difference in physical, symptomatic, or neuropsychological measurements.

In addition to comparing either DTE or L-T_4 treatment with the other treatment as above, Supplemental Table 4 shows that in the DTE-preference group (34 patients), pa-

Table 2. Physical Measurements, Neuropsychological Measurements, and Biochemical Laboratory Results at the End of the DTE Treatment Period vs the L-T_4 Treatment Period[a]

	DTE Treatment (n = 70)	L-T_4 Treatment (n = 70)	*P* Value
Clinical measures			
Heart Rate (bpm)	73.70 ± 11.78	74.38 ± 12.11	.587
Systolic BP, mm Hg	122.66 ± 13.98	124.09 ± 15.53	.342
Diastolic BP, mm Hg	77.66 ± 8.54	78.22 ± 8.83	.475
Weight, lb	172.87 ± 36.37	175.73 ± 37.68	<.0001
Neuropsychological measures			
GHQ-12	9.78 ± 4.33	10.97 ± 4.89	.098
TSQ-36	11.76 ± 6.70	13.16 ± 6.64	.121
BDI score	4.41 ± 4.71	4.81 ± 4.89	.474
AMI score	127.81 ± 13.06	125.65 ± 13.27	.081
VMI score	120.81 ± 15.68	120.03 ± 16.93	.575
VWMI score	116.68 ± 15.44	116.13 ± 15.87	.697
IMI score	124.04 ± 13.75	122.81 ± 14.57	.231
DMI score	129.61 ± 13.99	127.85 ± 15.70	.222
Biochemical measures			
Total cholesterol (<200 mg/dL)	190.87 ± 34.70	195.68 ± 35.19	.105
LDL cholesterol (<130 mg/dL)	110.83 ± 29.46	113.22 ± 30.17	.418
HDL cholesterol (>40 mg/dL)	60.97 ± 15.16	63.22 ± 15.25	.028
Triglyceride (<150 mg/dL)	103.33 ± 55.83	106.11 ± 56.93	.176
Total T_3 (60–181 ng/dL)	138.96 ± 47.26	89.13 ± 19.48	<.0001
T_3 resin uptake (22%–35%)	30.34 ± 3.28	31.81 ± 3.38	<.0001
rT_3 (11–32 ng/dL)	21.08 ± 10.88	31.37 ± 12.08	<.0001
TSH (0.27–4.20 uIU/mL)	1.67 ± 0.77	1.30 ± 0.63	.0032
Total T_4 (4.5–12 μg/dL)	5.88 ± 1.34	9.26 ± 2.05	<.0001
Free T_4 (0.89–1.76 ng/dL)	0.85 ± 0.16	1.36 ± 0.27	<.0001
Free T_4 direct (0.8–2.7 ng/dL)	1.21 ± 0.35	2.09 ± 0.63	<.0001
SHBG (17–124 nmol/L)	65.50 ± 48.17	66.14 ± 46.54	.951

Abbreviation: LDL, low-density lipoprotein.

[a] Results are shown as means ± SD.

tients did better on their neuropsychological measures compared with their baseline, as indicated by GHQ-12, TSQ, BDI, AMI, VMI, VWMI, IMI, and DMI scores. Supplemental Table 5 shows that in the L-T_4-preference group (13 patients), patients did better compared with their baseline only on the Wechsler test, measured by the AMI, VMI, VWMI, IMI, and DMI.

Table 3 shows the characteristics of the patients who preferred DTE versus L-T_4 and those who had no preference. Autoimmune hypothyroidism is the most common diagnosis in all 3 groups. Compared with those patients who preferred L-T_4 therapy, the patients who preferred DTE weighed more (not statistically significant) and had higher triglyceride level ($P = .029$); otherwise, there was no significant difference between the 3 groups.

Predictors of preference for DTE

The TSQ was the best predictor for clinical preference for DTE over L-T_4 (Table 4). The odds ratio (OR) for TSQ was 0.763 (95% confidence interval [CI], 0.621 to 0.937; $P = .010$), indicating that patients with higher TSQ values on DTE than on L-T_4 were less likely to prefer DTE. TSQ was the only significant predictor of preference in univariate models. Among 34 patients who preferred DTE, 25 (74%) had a TSQ score that was lower on DTE than on L-T_4, whereas among 13 patients who preferred L-T_4, only 3 (23%) had a TSQ score that was lower on DTE than on L-T_4 ($P = .002$).

The OR for VWMI was 0.840 (95% CI, 0.715–0.986; $P = .033$), indicating that patients with higher VWMI values on DTE than on L-T_4 were significantly less likely to prefer DTE. Other variables were serum T_3 resin uptake (OR = 6.84; 95% CI, 1.378–33.963; $P = .019$), free T_4 (OR < 0.001; 95% CI, <0.001 to 0.033; $P = .020$), SHBG (OR = 1.18; 95% CI, 1.009–1.387; $P = .039$).

Of note, although Supplemental Tables 1 and 2 suggest that the difference in weight between the DTE and L-T_4 treatments was greater in patients who preferred DTE, this association did not reach statistical significance. The unadjusted OR relating weight difference to preference for DTE was 0.982 (95% CI, 0.895–1.077; $P = .70$), indicating that patients with lower weight on DTE than on L-T_4 exhibited no significant preference for DTE.

Table 5 showed the mean doses of either L-T_4 or DTE at which level the patients remained euthyroid at the goal TSH of 0.5 to 3.0 μIU/mL. The dose of L-T_4 at baseline was 112.4 (36.30) μg/d (range 75–211 μg/d). The dose of cap-

Table 3. Baseline Characteristics of Those Who Preferred DTE vs Those Who Preferred L-T_4 vs Those Who Had No Preference[a]

	DTE Preference (n = 34)	L-T_4 Preference (n = 13)	No Preference (n = 23)	*P* Values
Age	50.97 ± 9.66	47.85 ± 11.39	51.78 ± 8.56	.488
Gender	26 F, 8 M	11 F, 2 M	16 F, 7 M	.664
Ethnicity	25 C, 6 AF, 2 H, 1A	10 C, 1 AF, 1A, 1 H	17 C, 4 AF, 2 A	.453
Diagnoses, n (%)				.433
Autoimmune thyroiditis	20 (58.8)	6 (46.2)	9 (39.1)	
Idiopathic	4 (11.8)	3 (23.1)	7 (30.4)	
Post-ablation	5 (14.7)	3 (23.1)	2 (8.7)	
Post-surgical	4 (11.8)	1 (7.7)	3 (13.1)	
Post-radiation	1 (2.9)	0 (0)	2 (8.7)	
Weight, lb	178.95 ± 38.38	162.80 ± 31.70	173.95 ± 39.44	.425
Neuropsychological measures				
GHQ-12	11.32 ± 4.07	9.69 ± 3.47	10.09 ± 2.78	.268
TSQ-36	15.26 ± 7.18	13.85 ± 6.16	11.96 ± 7.26	.227
Beck Depression Index score	6.62 ± 5.35	3.54 ± 3.12	4.13 ± 5.23	.080
AMI score	116.41 ± 15.71	105.46 ± 19.84	111.56 ± 12.54	.097
VMI score	108.70 ± 17.87	103.92 ± 17.47	106.48 ± 14.60	.669
VWMI score	110.53 ± 13.34	108.08 ± 11.16	106.56 ± 12.65	.507
IMI score	112.12 ± 16.48	105.31 ± 17.20	109.00 ± 12.30	.384
DMI score	116.03 ± 17.72	105.00 ± 20.22	112.30 ± 15.04	.157
Biochemical measures				
Total cholesterol (<200 mg/dL)	193.35 ± 35.09	197.77 ± 29.87	195.17 ± 34.33	.921
LDL cholesterol (<130 mg/dL)	114.15 ± 32.81	114.77 ± 23.26	114.35 ± 28.70	.998
HDL cholesterol (>40 mg/dL)	62.18 ± 14.28	66.69 ± 14.93	55.13 ± 17.63	.083
Triglyceride (<150 mg/dL)	93.32 ± 39.63	80.54 ± 33.45	128.69 ± 84.53	.029
Total T_3 (60–181 ng/dL)	96.95 ± 31.18	96.08 ± 20.93	90.34 ± 16.07	.613
T_3 resin uptake (22%–35%)	31.85 ± 3.35	31.31 ± 2.59	32.04 ± 3.73	.817
T_3 reverse (11–32 ng/dL)	34.07 ± 14.81	25.00 ± 2.45	30.81 ± 9.74	.366
TSH (0.27–4.20 uIU/mL)	1.73 ± 0.76	1.48 ± 0.90	1.77 ± 0.76	.553
Total T_4 (4.5–12 μg/dL)	9.44 ± 2.29	8.98 ± 1.99	8.66 ± 1.87	.387
Free T_4 (0.89–1.76 ng/dL)	1.36 ± 0.31	1.24 ± 0.19	1.36 ± 0.24	.307
FT_4 direct (0.8–2.7 ng/dL)	1.98 ± 0.51	1.85 ± 0.41	1.81 ± 0.51	.431
SHBG (17–124 nmol/L)	68.63 ± 54.77	67.90 ± 32.40	56.22 ± 38.14	.586

Abbreviations: A, Asian; AF, African-American; C, Caucasian; F, female; H, Hispanic; LDL (low density lipid); M, male.

[a] *P* values are based on Fisher's exact test (for proportions) or ANOVA (for means). Unless indicated otherwise, values are shown as means ± SD.

sulated L-T_4 during the study was 119.16 (38.94) μg/d (range 75–225 μg/d); and the dose of capsulated DTE during the study was 80.63 (29.97) mg/d (range 43–172 mg/d). Therefore, 1 mg DTE would be approximately equivalent to 1.47 μg L-T_4. Table 6 showed the traditional conversion chart for DTE and L-T_4 (60 mg DTE = 100 μg L-T_4) according to the U.S. Pharmacopoeia, Drug Information 2000, 20th edition (12). Table 7 suggests a new conversion chart for DTE and L-T_4 according to our results.

Table 4. OR Estimates of Various Predictors of Preference for DTE

Parameters	OR	95% CI	*P* Value
TSQ	0.763	0.621–0.937	.0098
VWMI	0.840	0.715–0.986	.0330
Serum T_3 resin uptake	6.841	1.378–33.963	.0187
Serum free T_4	<0.001	<0.001–0.033	.0199
Serum SHBG	1.183	1.009–1.387	.0388

Adverse effects

No adverse effects were reported with any of the treatments. All patients tolerated both treatments equally well.

Discussion

Earlier studies reported that DTE and L-T_4 effectively increased patients' metabolic rates (13–17). In 1978, a study by Jackson and Cobb (18) evaluated the changes in serum thyroid hormone concentrations when switching from

Table 5. Dosages of L-T_4 at Baseline and at the End of Each Treatment Period

	Dose
Baseline L-T_4, μg/d	112.4 ± 36.30 (75–211)
DTE capsule dose, mg/d	80.63 ± 29.97 (43–172)
L-T_4 capsule dose, μg/d	119.16 ± 38.94 (75–225)

Values are shown as means ± SD with ranges in parentheses.

Table 6. L-T_4 and Its Equivalent Dose of DTE[a]

	Dose								
L-T_4, μg	100	112	125	137	150	175	200	225	250
DTE, mg	60	67	75	82.2	90	105	120	135	150

[a] From USP Drug information 2000 (12): 1 mg DTE = 1.667 μg L-T_4.

DTE to L-T_4 in 40 patients. Six of 40 patients experienced hyperthyroid symptoms while on DTE, which disappeared completely in 3 and diminished in the other 3 patients after the change to L-T_4. However, no previous studies evaluated QOL and other parameters when comparing DTE and L-T_4. Other limitations with previous studies include improper hormone standardization of DTE, use of first-generation TSH assay, etc. The present method of manufacturing DTE has improved the standardization of these drugs. Furthermore, some believe that T_1 (monoiodothyronine) and T_2 (diiodothyronine) may have other beneficial effects (19).

Previously, many studies had compared L-T_4/T_3 therapy to L-T_4 monotherapy; (11, 20–31); however, only a few studies showed beneficial effects of combination L-T_4/T_3 therapy(21, 22, 25–27, 30, 31). Panicker et al (31) reported greater improvement with combination L-T_4/T_3 therapy in patients with CC genotype of the rs225014 polymorphism in the deiodinase 2 gene. Although we have not tested the genotypes in our patients, it may be interesting to investigate this further in patients who show a preference for DTE (31, 32).

It is unclear whether studies comparing L-T_4 alone with L-T_4/T_3 combination therapy can be extrapolated to DTE. Our study has shown DTE therapy caused modest weight loss, and nearly half (48.6%) of the study patients expressed preference for DTE over L-T_4. This is the first prospective, randomized, double-blind, crossover study of DTE and L-T_4 therapy in hypothyroid patients. We chose to randomize the patients in 2 groups and then cross over to better evaluate for any practice effect or placebo effect. Crossover studies also increase the statistical power of a study with a given number of patients. A minimal period of 16 weeks was chosen to stabilize the effects of the treatment. A test of carryover was conducted for each of the 24 outcome variables. Only 1 outcome variable (VWMI) had an unadjusted P value $< .05$ for carryover.

Table 7. Recommended Conversion Based on Results From This Study[a]

	Dose								
L-T_4, μg	88	100	112	125	137	150	175	200	250
DTE (mg)	60	68	76	85	93	102	119	136	170

[a] For conversion: 1 mg DTE = 1.47 μg L-T_4.

This is consistent with what would be expected by chance alone if there is no carryover effect in the study.

Overall, the patients lost approximately 3 lb during the DTE treatment compared with L-T_4 treatment ($P <$ .0001). Despite the increase in serum T_3 level, the DTE treatment did not cause any symptoms pertaining to the cardiovascular system or changes in heart rate and BP. This may be related to various deiodinase activities and various correlations between tissue concentration of T_3 and circulating T_3 levels (33–37). The clinical significance of the lower HDL level as seen in our study during the DTE treatment may need further evaluation for long-term effects, especially in patients with high risks for coronary artery disease.

It should be noted that previous studies on L-T_4 versus L-T_4 plus L-T_3 had problems with reduced TSH in the L-T_4 plus T_3 arm, suggesting slight overtreatment, which could affect the outcome. However, our study showed significantly higher TSH in the DTE-treated group, which suggests that the improvement observed in the DTE-treated group is not mediated through the changes in TSH levels. It should also be noted that there may not be a clinically significant difference between the levels of TSH of 1.67 and 1.30 μIU/mL as shown by Walsh et al (38). Boeving et al (39) demonstrated a higher relative increase in resting energy expenditure in the low-normal TSH group (0.4–2.0 mIU/L) than the high-normal TSH group (2.0–4.0 mIU/L) and no difference in other variables. The TSH range was 0.54 to 3.0 μIU/mL for baseline, 0.56 to 3.0 μIU/mL after the DTE period, and 0.51 to 3.0 μIU/mL after the L-T_4 period (Supplemental Figure 1).

In the subgroup analyses, those patients who preferred DTE lost approximately 4 lb during the DTE treatment compared with L-T_4 treatment. In addition, their general well-being and thyroid symptoms were significantly better (as evidenced by lower GHQ-12 and TSQ scores). The higher AMI also supports an improvement in cognitive function. These findings were absent in those who preferred L-T_4 or had no preference. It is possible that DTE treatment offers subtle improvements in well-being that may not be detected by the relatively insensitive methods used in the study.

A stepwise logistic regression was performed to identify significant predictors of preference for DTE: TSQ, VWMI, T_3 resin uptake, free T_4, and SHBG levels. It is not clear how these 5 predictors influence the preference for DTE. The other variables were not significantly associated with clinical preference; however, this does not mean that they were not associated at all with clinical preference. Many of the measured variables were significant in univariate analyses and highly correlated with each other, and the logistic

regression approach selected only the strongest of these associations. These findings need further explanations.

In this study, DTE and L-T_4 were administered in a once-per-day dosing. Sawin (40) in 1978 compared T_4 and desiccated thyroid in 15 patients with clinical primary hypothyroidism. These investigators found that the biological activity of T_4 in micrograms is equivalent to desiccated thyroid in milligrams. However, these studies did not use a third-generation TSH assay, free T_4 assay, or total T_3 levels and hence may lack accuracy. Our study shows that 60 mg DTE is approximately equivalent to 88 μg L-T_4 (conversion factor of 1.47) and that DTE can be effective when taken once daily. It is possible that the short half-life of liothyronine in DTE may not result in maximally beneficial effects of DTE (as compared with DTE twice daily). It is important to note that the rise seen in serum T_3 levels (Supplemental Table 6) with DTE may cause adverse effects in patients with underlying coronary heart disease, and this requires further evaluation.

The limitations of our study include small sample size, low sensitivity of some of the neurocognitive tests and biochemical measures, and no genetic testing for deiodinase polymorphisms. No formal adjustment was made for multiple comparisons, so some significant findings may be due to type I error. If the Bonferroni correction is applied to the analysis of 24 different outcome variables, P values $< .002$ would be considered statistically significant. Even though this correction is known to be conservative, most of our significant findings still fall below the .002 threshold. The strengths of our study are adequate duration of therapy to evaluate the potential effects, measures of both subjective symptoms/clinical preference and biochemical testing, and a homogeneous group of clinically hypothyroid patients without history of thyroid cancer.

Conclusions

The results of this short-term investigation with a relatively small number of subjects indicate that thyroid hormone therapy with once-daily DTE in place of L-T_4 causes modest weight loss and possible improvements in symptoms and mental health without appreciable adverse effects. Studies with a longer duration would clarify the efficacy and safety of DTE.

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Address all correspondence and requests for reprints to: Mohamed K.M. Shakir, MD, Department of Endocrinology, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, Maryland 20889-5600. E-mail: mohamed.k.shakir.civ@health.mil.

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