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Combined Therapy with Levothyroxine and Liothyronine in Two Ratios, Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: a Double-Blind, Randomized, Controlled Clinical Trial

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Controversy remains about the value of combined treatment with levothyroxine (LT_4) and liothyronine (LT_3), compared with LT_4 alone in primary hypothyroidism. We compared combined treatment with LT_4 and LT_3 in a ratio of 5:1 or 10:1 with LT_4 monotherapy. We conducted a double-blind, randomized, controlled trial in 141 patients (18–70 yr old) with primary autoimmune hypothyroidism, recruited via general practitioners. Inclusion criteria included: LT_4 treatment for 6 months or more, a stable dose for 6 wk or more, and serum TSH levels between 0.11 and 4.0 μU/ml (mU/liter). Randomization groups were: 1) continuation of LT_4 (n = 48); 2) LT_4/LT_3, ratio 10:1 (n = 46); and 3) LT_4/LT_3, ratio 5:1 (n = 47). Subjective preference of study medication after 15 wk, compared with usual LT_4, was the primary outcome measure. Secondary outcomes included scores on questionnaires on mood, fatigue, psychological symptoms, and a substantial set of neurocognitive tests. Study medication was preferred to usual treatment by 29.2, 41.3, and 52.2% in the LT_4, 10:1 ratio, and 5:1 ratio groups, respectively (χ^2 test for trend, $P = 0.024$). This linear trend was not substantiated by results on any of the secondary outcome measures: scores on questionnaires and neurocognitive tests consistently ameliorated, but the amelioration was not different among the treatment groups. Median end point serum TSH was 0.64 μU/ml (mU/liter), 0.35 μU/ml (mU/liter), and 0.07 μU/ml (mU/liter), respectively [ANOVA on ln(TSH) for linear trend, $P < 0.01$]. Mean body weight change was +0.1, −0.5, and −1.7 kg, respectively (ANOVA for trend, $P = 0.01$). Decrease in weight, but not decrease in serum TSH was correlated with increased satisfaction with study medication. Of the patients who preferred combined LT_4/LT_3 therapy, 44% had serum TSH less than 0.11 μU/ml (mU/liter). Patients preferred combined LT_4/LT_3 therapy to usual LT_4 therapy, but changes in mood, fatigue, well-being, and neurocognitive functions could not satisfactorily explain why the primary outcome was in favor of LT_4/LT_3 combination therapy. Decrease in body weight was associated with satisfaction with study medication. (*J Clin Endocrinol Metab* 90: 2666–2674, 2005)

IT IS A well-known clinical notion that a fair proportion of patients with hypothyroidism remains with health complaints, despite substitution therapy with levothyroxine and normalization of serum TSH values. The prevalence of these complaints was the subject of a recent survey study (1), reporting that in a group of hypothyroid patients with a recent normal TSH, compared with controls, an excess of 13% was not satisfied with their health status, which may reflect dissatisfaction with their substitution therapy. Four complaints in particular appeared to be prominent in patients compared with controls: feeling tired and lethargic, putting on weight, aches and pains all over the body, and clumsiness.

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Abbreviations: CVLT, California Verbal Learning Test; fT_4, free T_4; LT_3, liothyronine; LT_4, levothyroxine; MCT, Memory Comparison Task; MFI-20, Multidimensional Fatigue Inventory consisting of 20 questions; POMS, Profile of Mood States; Rand-36, Rand 36-item health survey; RBMT, Rivermead Behavioral Memory Test; skeletal AP, bone fraction of alkaline phophatase; TPO-Ab, thyroid peroxidase antibody.

Studies in thyroidectomized rats have shown that replacement therapy with levothyroxine (LT_4) alone does not ensure euthyroidism in all tissues. Euthyroidism in all tissues could be achieved only by combined treatment with LT_4 and liothyronine (LT_3). These findings implicate that, in humans, standard LT_4 therapy might not be sufficient to restore euthyroidism in all tissues either. The cerebral cortex, however, is able to maintain T_3 homeostasis over a wide range of plasma T_4 and T_3 levels (2, 3).

In 1999 the results of a crossover trial investigating combined treatment of hypothyroidism with LT_4 and LT_3 were published. The authors concluded that substitution of 50 μg LT_4 by 12.5 μg LT_3 daily resulted in improved scores on mood scales and neurocognitive tests (4). These remarkable findings elicited quite a bit of discussion: is the current standard replacement therapy with LT_4 alone the optimal treatment for hypothyroidism? In 2003 the results of three more trials investigating the value of combined treatment with LT_4 and LT_3, compared with LT_3 alone, were published, but none of these replicated the finding of any advantageous effects of LT_4/LT_3 combined therapy on measures of well-being and

neurocognitive functioning (5–7). An extensive review of the qualities and pitfalls of these studies was published in this journal (8).

A consistent limitation of these trials was that a fixed amount of LT_4 was substituted with a fixed amount of LT_3, leading to very variable ratios of LT_4 and LT_3 that are unlikely to have comparable effects. A more recent and equally negative trial did supply a fixed LT_4 to LT_3 molar ratio of 14:1 to a small group of patients with mainly postsurgery and postradioiodine hypothyroidism (35). In the present larger trial (n = 141), we studied whether combined treatment with LT_4 and LT_3 in any of two different weight ratios (5:1 and 10:1) was preferred over LT_4 monotherapy in a homogeneous group of patients with primary autoimmune hypothyroidism.

Subjects and Methods

This study was carried out between October 2001 and December 2003 at the Academic Medical Center of the University of Amsterdam. The protocol was approved by the institutional ethics review committee, and all randomized patients provided written informed consent.

Subjects

Patients could participate if they were between 18 and 70 yr of age and had been on an adequate dose of LT_4 replacement therapy for primary autoimmune hypothyroidism for at least 6 months. An adequate dose of LT_4 was defined as resulting in a serum TSH between 0.11 and 4.0 μU/ml (mU/liter), as measured in the morning before LT_4 intake.

Participants were excluded if they: 1) had a history of congenital hypothyroidism, hyperthyroidism, thyroidectomy, ^{131}I-therapy, or thyroid cancer; 2) had angina pectoris (New York Heart Association functional class II or greater), paroxysmal supraventricular tachycardia, or any serious unstable medical condition; 3) were pregnant or within 6 months postpartum; and 4) had insufficient understanding of the Dutch language.

Patients were recruited from 13 general practices in the cities of Amsterdam and Almere. At these practices, prescribing records were checked to identify all patients receiving LT_4 treatment (n = 590). Subsequently clinical records were checked for obvious/apparent inclusion and exclusion criteria, after which 303 seemingly eligible patients were invited by a letter from the general practice to participate in this clinical trial. Of these, 246 patients (81%) responded to the letter, 237 of whom agreed to receive detailed information about the trial. Three patients could not be reached after the initial contact, and 56 would or could not participate for personal reasons (*e.g.* not able to combine trial visits with work, no means of transportation, no interest in trial any longer). The remaining 178 were invited for a screening visit. If not adequately supplied with LT_4, patients received a dose adjustment and were invited for a new screening visit 6 weeks or more later. Six patients failed to reach adequate LT_4 supplementation before closure of the inclusion period. Another 31 had to be excluded from participation for the following reasons: no primary autoimmune hypothyroidism (n = 9), no current LT_4 treatment (n = 5), LT_4 treatment less than 6 months (n = 3), pregnancy (n = 5), insufficient understanding of Dutch language (n = 6), age (n = 1), angina pectoris (n = 1), or paroxysmal supraventricular tachycardia (n = 1). One hundred forty-one participated in the trial, 46 (33%) of these after dose adjustment(s) resulting in a serum TSH level within inclusion criteria.

Study design

During a screening visit at the Academic Medical Centre inclusion and exclusion criteria were checked, an electrocardiogram was made, and the presence of current major depressive disorder was assessed by means of the Structured Clinical Interview for Axis I Diagnostic and statistical manual of mental disorders-IV Disorders (9). If eligible, patients were randomly assigned to one of three treatment arms by means of a computer-generated list such that for every six patients, two were assigned to each treatment arm. Randomization was stratified for patients with current major depressive disorder (n = 10). Patients in arm 1 were assigned to receive LT_4 only, patients in arm 2 received LT_4 and LT_3 in a ratio of 10:1, and patients in arm 3 received LT_4 and LT_3 in a ratio of 5:1. For patients in the combination treatment arms, the study medication dosage was calculated by subtracting 25 μg from their LT_4 dose at time of inclusion, then adding the amount of LT_3 conform treatment arm ratio, *e.g.* a patient adequately substituted with 100 μg LT_4 at inclusion, assigned to the 5:1 ratio treatment arm, would receive 75 μg LT_4 (100–25 μg) and 15 μg of LT_3 (75:15 μg, equivalent with 5:1 ratio), whereas one assigned to the 10:1 ratio treatment arm would receive 75 μg LT_4 (100–25 μg) and 7.5 μg LT_3 (75:7.5 μg, equivalent with 10:1 ratio).

On the first day of the trial (baseline visit), patients arrived in the morning in fasting state. After laboratory testing and physical measurements, patients took their usual dose of LT_4 and had breakfast at the Academic Medical Centre. About an hour later, they proceeded with the neurocognitive testing session, which lasted for approximately 1.5 h, and handed over the baseline set of questionnaires that they had filled out on the day before the baseline visit.

From the next day on, patients were instructed to take the first portion of study medication in the morning before breakfast and the second portion 12 h later. The daily dosage (LT_4 or both LT_4 and LT_3) was divided into two portions and filled out in weekly medication blister packs.

After 5 wk of study medication, serum TSH was measured again at our laboratory in the morning. If needed, the study medication dose was adjusted: the LT_4 dose was decreased with 12.5 μg if serum TSH was between 0.01 and 0.11 μU/ml (mU/liter) or with 25 μg if TSH was 0.01 μU/ml (mU/liter) or less. If serum TSH was more than 4.0 μU/ml (mU/liter), the LT_4 dose was increased with 25 μg LT_4. The LT_3 dose was subsequently adjusted according to the ratio to which the participant was randomized.

In the LT_4 group, a dose adjustment was needed in 15 of 45 participants (33%); in the 10:1 LT_4/LT_3 group, this was 20 of 44 (46%) and in the 5:1 LT_4/LT_3 group 27 of 46 (59%).

The adjusted study medication was given from wk 7 to 15. At both 5 and 10 wk after the baseline visit, patients filled out the set of questionnaires, and the main outcome, side complaints, and resting heart rate were assessed.

For the end point visit after 15 wk, the same time schedule was maintained as for the baseline visit, repeating all measurements in the same order and at the same time of day.

Neither the investigators nor the patients were aware of the treatment assignments throughout the trial.

Outcome measures

The main end point of the trial was the subjective appreciation of the study medication by the patient, which was rated on a 5-point scale as much better, somewhat better, the same, somewhat worse, or much worse, compared with their usual LT_4 medication from before the trial at every visit. For the main outcome analysis, a dichotomy was made between those who preferred study medication over their usual medication (*i.e.* somewhat or much better) and those who did not. Patients were encouraged to volunteer positive and negative effects of the study medication at each visit.

Questionnaires

Well-being of patients was measured by means of a set of self-report questionnaires at baseline and after 5, 10, and 15 wk of treatment, filled out the day before the study visit. The set included the 32-item Profile of Mood States Dutch shortened version (POMS), designed to monitor changes in mood states (10); the original Dutch version of the Multidimensional Fatigue Inventory (MFI-20), consisting of 20 questions and designed to measure (changes in) fatigue (11); the mental health and vitality subscales of the Rand 36-item health survey (Rand-36) (12); and the (Dutch version of) the Symptom Checklist (SCL-90), a 90-item self-report scale containing eight subscales measuring multidimensional psychopathology (13).

Neurocognitive tests

Neurocognitive functioning was measured at baseline and after 15 wk of study medication and included tests of attention and working memory [Digit Span subtest of the Wechsler Adult Intelligence Scale (14)], learning and memory [Dutch version of the Story Recall from the Rivermead Behavioral Memory Test (RBMT) (15, 16) and the Dutch adaptation of the California Verbal Learning Test (CVLT) (17, 18)], psychomotor speed (Dutch adaptation of the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-III) (14, 19), speed of memory processing [Memory Comparison Task (MCT), computer version (20) and paper-and-pencil version (21)], and attention [Dutch adaptation of the Paced Auditory Serial Attention Task (22, 23)]. All tests were administered by a trained psychometrician under supervision of a clinical neuropsychologist.

Biochemical measurements

All blood samples were collected in the morning before medication was ingested, approximately 24 h after the last usual medication dose (baseline measurements) and 12 h after the last study medication dose (at 5 and 15 wk).

Baseline and end point fasting laboratory tests included levels of serum TSH, free T_4 (fT_4), T_3, SHBG, and anti-thyroid peroxidase antibodies (TPO-Ab), cholesterol and triglycerides, osteocalcin, and bone fraction of alkaline phophatase (skeletal AP).

Serum TSH and fT_4 were measured by time-resolved fluoroimmunoassay (Wallac Oy, Turku, Finland), serum T_3 by in-house RIA methods (24), SHBG by immunoradiometric assay (Farmos Diagnostica, Turku, Finland), TPO-Ab by chemiluminescence immunoassay (Brahms, Berlin, Germany), osteocalcin by immunoradiometric assay (INCSTAR, Stillwater, MN), skeletal AP by enzyme immunoassay (Alkphase-B; Metra Biosystems Inc., Mountain View, CA), and cholesterol and triglycerides by enzymatic colorimetric methods (Modular p800; Roche Diagnostics, Indianapolis, IN).

Intra- and interassay coefficients of variation were, respectively, 1–2 and 3–4% (TSH), 4–6 and 5–8% (fT_4), 3–4 and 7–8% (T_3), 2–5 and 3–6% (SHBG), 3–7 and 8–12% (TPO-Ab), 4–6 and 4–9% (osteocalcin), 4–7 and 6–9% (skeletal AP), 1–3 and 1–2% (cholesterol), and 1–2 and 1% (triglycerides). Detection limits were 0.01 μU/ml (mU/liter) for TSH, 0.2 ng/dl (2 pmol/liter) for fT_4, 20 ng/dl (0.3 nmol/liter) for T_3, 5 nmol/liter for SHBG, 30 kU/liter for TPO-Ab, 0.5 μg/liter for osteocalcin, 0.7 U/liter for skeletal AP, 1.0 mmol/liter for cholesterol, 0.1 mmol/liter for triglycerides.

Statistical analysis

Analyses for the primary outcome were performed according to the intention-to-treat principle. For all other analyses, last observations were carried forward; if no follow-up measurement was available for a certain parameter (because of drop-out or not completing the test for other reasons), the patient was excluded from the analyses of that particular parameter. Within-group baseline and end point scores were analyzed by means of paired *t* tests.

Because the primary outcome showed a linear trend over the three treatment groups in accordance with an increasing proportion of LT_3, all statistical comparisons among the three treatment groups were analyzed by χ^2 for trend or ANOVA for linear trend. Serum TSH was log transformed to normalize the distribution before statistical analysis. Statistical significance was defined as a two-tailed $P < 0.05$. All statistical analyses were performed using SPSS (version 11.5; SPSS, Chicago, IL).

Results

Of 141 randomized patients, 130 (92%) completed 15 wk of study medication (Fig. 1). One participant (5:1 group) withdrew because of unexpected travel abroad for family matters and was excluded from all analyses. Seven patients withdrew because of side effects, four in the LT_4 group and three in the 10:1 group. Various side effects were mentioned (*e.g.* fatigue, dizziness, muscle aches, irritability), but no specific complaints could be identified for those on combination therapy. Patients who withdrew because of side effects were considered not to prefer study medication to their usual treatment and were all included in the primary outcome analysis (n = 140). Three patients did not show up for the end point visit, one because of illness unrelated to study medication (5:1 group) and two because of personal time constraints (both 10:1 group). When available, follow-up data were carried forward. Baseline characteristics of the three groups were similar (Table 1). Ten patients with current

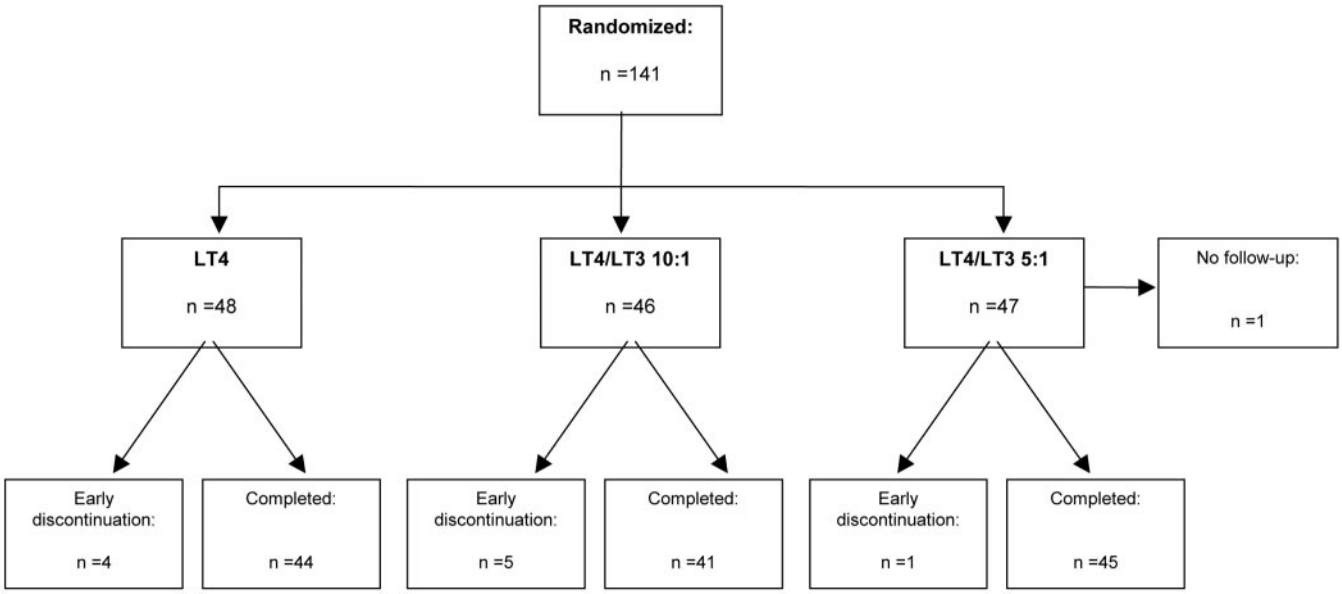

FIG. 1. Use of study medication.

TABLE 1. Baseline characteristics

	LT_4 (n = 48)	LT_4/LT_3 10:1 (n = 46)	LT_4/LT_3 5:1 (n = 47)
Female (n, %)	41 (85)	38 (83)	41 (89)
Age (yr)	48.5 ± 9.4	46.8 ± 9.8	49.8 ± 9.4
Duration of substitution therapy (yr)	6.5 ± 5.7	7.8 ± 5.7	8.3 ± 7.7
Serum TSH at inclusion (μU/ml; median, range)	1.0 (0.11–3.9)	1.1 (0.17–4.0)	1.0 (0.13–4.0)
Levothyroxine dose (μg/kg · d)	1.48 ± 0.51	1.61 ± 0.63	1.73 ± 0.80
Positive TPO-ab (n, %)[a]	38 (79)	37 (80)	36 (78)
Current major depressive disorder (n, %)	3 (6)	4 (9)	3 (7)

Data are presented as mean ± SD unless indicated otherwise. Conversion factor to SI units is ×1 for TSH (mU/liter).
[a] Cut-off value for positive TPO-ab was 60 kU/liter.

major depressive disorder were included (three, four, and three in the LT_4, 10:1, and 5:1 group, respectively).

Biochemistry results and clinical parameters

End point serum TSH and fT_4 were decreased in the combination therapy groups, compared with baseline, whereas serum T_3 increased. The changes showed a clear and significant relationship with LT_3 proportions in the study medication, with the most prominent changes in the 5:1 combination therapy group (Table 2). Regarding markers for peripheral thyrometabolic state, serum SHBG increased, cholesterol decreased, and triglycerides did not change in the combined treatment groups. Changes in osteocalcin and skeletal AP did not show a significant relationship with LT_3 proportion in the study medication. However, skeletal AP and osteocalcin significantly increased for patients in the 5:1 ratio group (paired *t* tests).

In both LT_4/LT_3 combination groups, there was a decrease in weight, most pronounced in the 5:1 group (mean decrease of 1.7 kg), and pulse rate increased in the 5:1 group (mean increase 3.9 beats/min) (Table 2). Blood pressure did not significantly change.

Treatment preference, questionnaires, and neurocognitive function tests

Primary outcome analysis (Fig. 2) shows that study medication was preferred to usual treatment by 14 of 48 patients (29.2%) in the LT_4 group, 19 of 46 patients (41.3%) in the 10:1 ratio group, and 24 of 46 patients (52.2%) in the 5:1 ratio group (χ^2 test for trend, $P = 0.024$). This suggests a linear increase in satisfaction with study medication with an increasing proportion of LT_3.

Table 3 shows the baseline and change scores on the questionnaires. Compared with baseline, all three treatment groups showed improvements in all subscale scores of all questionnaires at end point, with the only exceptions of the MFI-20 physical fatigue subscale score for the 10:1 group and the SCL-90 agoraphobia subscale score for the LT_4 group. Many within-group improvements were significant when baseline and end point scores were compared by means of paired *t* tests. There was no significant difference among the three groups in the mean improvement on any of the subscale scores.

Table 4 shows the raw baseline and change scores of the neurocognitive tests. One of the test results (CVLT immediate recall) showed a significant linear relation with treatment

TABLE 2. Biochemical and clinical parameters at baseline and 15 wk

	LT_4 (n = 45)[a]		LT_4/LT_3 10:1 (n = 44)[a]		LT_4/LT_3 5:1 (n = 46)[a]		P^b
	Baseline	15 wk	Baseline	15 wk	Baseline	15 wk	
TSH (mU/liter)[c]	1.0 (0.46–1.6)	0.64 (0.18–1.9)[d]	1.1 (0.51–2.2)	0.35 (0.09–1.3)[e]	1.0 (0.52–2.7)	0.07 (0.02–1.05)[e]	<0.01
fT_4 (ng/dl)	1.15 ± 0.18	1.18 ± 0.21	1.15 ± 0.26	1.02 ± 0.26[d]	1.18 ± 0.24	1.00 ± 0.34[e]	<0.01
T_3 (ng/dl)	111 ± 18	111 ± 19	109 ± 21	119 ± 26[d]	115 ± 25	143 ± 38[e]	<0.01
SHBG (nmol/liter)	52 ± 33	55 ± 32	55 ± 37	58 ± 37	53 ± 35	68 ± 40[e]	0.02
Cholesterol (mg/dl)	206 ± 33	200 ± 32	201 ± 39	189 ± 41[e]	215 ± 46	197 ± 45[e]	0.03
Triglycerides (mg/dl)	106 ± 66	108 ± 70	94 ± 50	100 ± 65	122 ± 59	120 ± 52	0.71
Osteocalcin (μg/liter)	1.1 ± 1.2	1.3 ± 1.2	1.0 ± 1.0	1.4 ± 1.2	1.3 ± 1.2	1.8 ± 1.6[d]	0.18
Skeletal AP (U/liter)	16.8 ± 4.3	17.9 ± 6.2	19.8 ± 6.6	20.5 ± 8.2	19.8 ± 10.1	22.4 ± 10.3[d]	0.17
Weight (kg)	80.3 ± 19.3	80.4 ± 19.0	80.5 ± 18.7	80.0 ± 18.3	82.4 ± 23.1	80.6 ± 23.2[d]	0.01
Pulse rate (bpm)	69 ± 10	69 ± 8	71 ± 9	71 ± 10	72 ± 11	76 ± 11[d]	0.03
Blood pressure							
Systolic (mm Hg)	125 ± 22	121 ± 20[d]	125 ± 16	125.0 ± 18.0	133 ± 20	133.0 ± 20.0	0.09
Diastolic (mm Hg)	73 ± 11	71 ± 9.0	73 ± 9	73.0 ± 9.0	75 ± 12	74.0 ± 12.0	0.76

Data are presented as mean ± SD unless otherwise specified. Conversion factors to SI units are ×1 for TSH (mU/liter); ×12.87 for fT_4 (pmol/liter); ×0.01563 for T_3 (nmol/liter); ×0.02586 for cholesterol (mmol/liter); ×0.01129 for triglycerides (mmol/liter). Patients for whom no follow-up measurement was available were excluded from the analysis.
[a] n for TSH and pulse rate; for other parameters n = 44 (LT_4), n = 41 (10:1), n = 45 (5:1).
[b] Anova test for linearity.
[c] Data are presented as median (25 and 75 percentiles) and with statistical analysis after log-transformation to normalize distribution.
[d] Mean change within group significant on a $P < 0.05$ level or [e]on a $P < 0.01$ level.

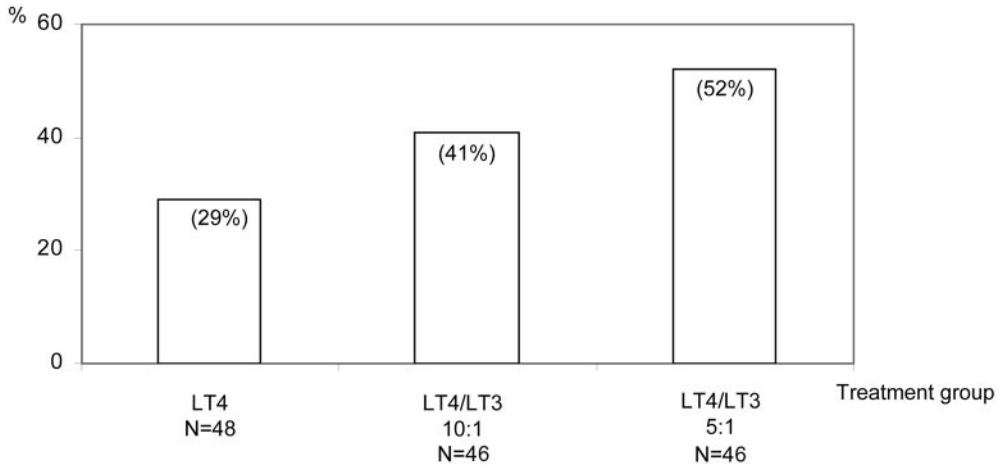

FIG. 2. Percentage of participants preferring study medication to usual treatment. χ^2 test for trend: $P = 0.024$.

but with the largest improvement in the LT_4 group and the least in the 5:1 LT_4/LT_3 group. Many of the within-group test results were improved at end point, compared with baseline, several of them significantly.

Subgroup analyses

Patients with current major depressive disorder (n = 10) had higher baseline scores on the questionnaires in comparison with those without depression (or lower in the case of vigor/vitality subscales), indicative of more complaints. The primary outcome was in favor of LT_4/LT_3 combination therapy: none of the three depressed patients having received LT_4 only preferred study medication over usual therapy, whereas all three depressed patients who received LT_4/LT_3 in a 5:1 ratio preferred study medication over usual LT_4 therapy. Of four patients in the 10:1 group, one preferred study medication, whereas three did not. Like in the total group, there were improvements on almost all questionnaire subscale scores but without clear differences among the treatment groups. As for the neurocognitive tests, most, but not all, baseline test results were worse for depressed patients, compared with nondepressed patients, and most scores were

TABLE 3. Questionnaires: baseline and change scores

	LT_4 (n = 45)[a]		LT_4/LT_3 10:1 (n = 45)[a]		LT_4/LT_3 5:1 (n = 45)[a]		P^b
	Baseline	Change	Baseline	Change	Baseline	Change	
POMS							
Depression	6.5 ± 7.9	−1.4 ± 6.5	4.9 ± 6.8	−2.0 ± 3.9[d]	4.9 ± 6.0	−1.0 ± 4.4	0.77
Anger	7.8 ± 6.6	−2.0 ± 4.9[d]	6.9 ± 5.8	−1.7 ± 5.3[c]	5.3 ± 5.1	−2.8 ± 5.3[c]	0.74
Fatigue	12.4 ± 6.6	−3.0 ± 6.2[d]	9.7 ± 7.0	−2.2 ± 6.9[c]	9.2 ± 6.6	−2.8 ± 5.3[d]	0.87
Vigor	8.1 ± 4.4	0.9 ± 3.8	8.8 ± 3.8	0.1 ± 5.3	8.8 ± 4.3	1.4 ± 4.0[c]	0.54
Tension	6.3 ± 6.0	−0.8 ± 3.9	5.9 ± 6.0	−2.3 ± 5.3[d]	6.6 ± 5.1	−1.9 ± 3.8[d]	0.22
MFI							
General fatigue	16.7 ± 3.3	−2.4 ± 3.5[d]	14.5 ± 4.3	−0.7 ± 4.4	14.0 ± 5.9	−2.5 ± 4.0[d]	0.86
Physical fatigue	14.7 ± 3.5	−1.6 ± 3.8[d]	12.4 ± 4.1	0.4 ± 4.4	11.7 ± 4.2	−1.1 ± 3.8	0.55
Reduced activity	12.6 ± 4.6	−1.7 ± 3.8[d]	11.2 ± 4.6	−0.3 ± 4.7	10.8 ± 4.6	−0.7 ± 3.6	0.27
Reduced motivation	12.0 ± 4.4	−1.2 ± 3.5[c]	10.7 ± 3.7	−0.5 ± 4.1	10.5 ± 4.6	−0.9 ± 4.0	0.74
Mental fatigue	13.2 ± 5.5	−1.8 ± 4.2[d]	12.4 ± 4.4	−0.8 ± 3.9	12.4 ± 4.6	−1.2 ± 4.0[c]	0.51
Rand							
Vitality	36.6 ± 19.1	8.3 ± 18.5[d]	44.6 ± 18.8	4.8 ± 22.2	48.1 ± 24.2	9.7 ± 16.2[d]	0.74
Mental health	63.9 ± 19.9	5.4 ± 16.1[c]	65.2 ± 18.5	5.4 ± 18.6	65.7 ± 19.9	6.0 ± 15.5[c]	0.86
SCL-90							
Agoraphobia	8.9 ± 4.4	0.1 ± 2.5	8.7 ± 2.7	−0.8 ± 2.1[c]	9.2 ± 4.6	−0.4 ± 2.5	0.31
Anxiety	15.6 ± 6.5	−1.0 ± 2.8[c]	15.9 ± 6.6	−1.9 ± 6.2	15.8 ± 6.3	−0.8 ± 3.8	0.86
Depression	31.5 ± 12.3	−6.2 ± 8.1[d]	27.9 ± 11.5	−4.0 ± 7.9[d]	28.1 ± 10.7	−3.2 ± 6.4[d]	0.06
Somatic complaints	24.6 ± 7.6	−2.6 ± 4.8[d]	24.6 ± 8.8	−3.0 ± 8.8[c]	23.0 ± 8.3	−2.4 ± 5.6[d]	0.94
Insufficient functioning	20.7 ± 7.5	−3.4 ± 5.1[d]	18.3 ± 6.6	−2.1 ± 5.8[c]	18.9 ± 6.6	−2.5 ± 5.3[d]	0.43
Paranoid ideation	29.8 ± 12.9	−3.8 ± 6.6[d]	28.1 ± 11.4	−3.9 ± 7.3[d]	27.8 ± 9.3	−3.5 ± 6.4[d]	0.81
Hostility	9.2 ± 3.1	−1.2 ± 2.6[d]	9.1 ± 3.4	−1.3 ± 2.9[d]	7.8 ± 3.3	−0.4 ± 2.1	0.15
Sleeping	7.4 ± 3.8	−1.3 ± 3.2[d]	6.8 ± 3.3	−0.7 ± 2.6	6.9 ± 3.6	−0.6 ± 2.1	0.21
Total score	161.6 ± 50.9	−20.7 ± 26.0[d]	152.0 ± 49.4	−19.0 ± 36.2[d]	150.5 ± 48.5	−14.5 ± 24.1[d]	0.32

Data are presented as mean ± SD unless otherwise specified. Higher scores indicate more complaints, except for the POMS vigor and both Rand subscales, where lower scores indicate more complaints.

[a] Patients for whom no follow up questionnaire was available were excluded from the analysis (n = 3 in LT_4, n = 1 in 10:1 and n = 2 in 5:1 groups).

[b] Test for linearity.

[c] Mean change within group significant on a $p < 0.05$ level or [d]on a $p < 0.01$ level (paired t test).

TABLE 4. Neurocognitive tests: baseline and change scores

	n	LT_4		LT_4/T_3 10:1		LT_4/T_3 5:1		P^a
		Baseline	Change	Baseline	Change	Baseline	Change	
Cognitive speed								
Digit Symbol								
Raw score (sec)	126	76 ± 20	4 ± 12[b]	70 ± 20	5 ± 12[b]	74 ± 19	5 ± 11[b]	0.91
MCT (paper & pencil version)								
1 letter (sec)	125	26 ± 5	−1.1 ± 4	27 ± 8	−1.3 ± 7	26 ± 7	−0.4 ± 5	0.52
2 letters (sec)	125	36 ± 6	0.0 ± 6	37 ± 11	−1.0 ± 8	37 ± 10	0.4 ± 8	0.79
3 letters (sec)	125	44 ± 10	−1.0 ± 8	46 ± 15	−1.7 ± 10	46 ± 12	−2.1 ± 8	0.57
4 letters (sec)	124	57 ± 14	−0.2 ± 10	58 ± 20	0.4 ± 18	57 ± 15	−0.9 ± 13	0.82
MCT (computer version)								
3 letters (sec)	122	608 ± 79	−1 ± 50	645 ± 104	−11 ± 67	613 ± 84	−23 ± 48[b]	0.08
4 letters (sec)	122	607 ± 66	−14 ± 52	640 ± 88	−28 ± 50[b]	609 ± 71	−20 ± 40	0.56
5 letters (sec)	122	662 ± 73	−18 ± 62	699 ± 87	−25 ± 45[b]	671 ± 70	−20 ± 50[b]	0.93
Intercept (sec)	122	545 ± 129	15 ± 110	579 ± 144	−1 ± 120	545 ± 126	−25 ± 91	0.09
Slope	122	27 ± 34	−9 ± 36	27 ± 31	−7 ± 33	29 ± 31	1 ± 29	0.15
Attention								
PASAT								
Total score (No)	114	231 ± 42	18 ± 20[c]	229 ± 49	23 ± 23[c]	221 ± 47	26 ± 21[c]	0.08
Memory								
Digit Symbol								
Pairs	126	12 ± 4	1.7 ± 3[b]	12 ± 5	0.6 ± 3	10 ± 5	1.5 ± 3[b]	0.89
Free reproduction	126	7 ± 1	0.6 ± 1[b]	7 ± 1	0.2 ± 1	7 ± 1	0.4 ± 1[b]	0.55
Digit Span								
Forward recall	125	9 ± 2	−0.1 ± 2	8 ± 2	0.2 ± 2	9 ± 2	0.1 ± 1	0.58
Backward recall	123	6 ± 2	0.7 ± 2[b]	6 ± 2	0.1 ± 2	6 ± 2	0.5 ± 2	0.52
CVLT								
Immediate recall (No)	127	52 ± 12	4.4 ± 11[b]	50 ± 11	3.3 ± 8[b]	51 ± 9	0.4 ± 7	0.03
Delayed recall (No)	127	13 ± 3	0.6 ± 2	12 ± 4	0.5 ± 3	12 ± 3	0.6 ± 3	0.93
Recognition (No)	127	1 ± 2	−0.4 ± 2	1 ± 2	0.5 ± 2[b]	1 ± 2	0.0 ± 1	0.23
Rivermead (stories)								
Immediate recall (No)	125	17 ± 6	1.6 ± 6	16 ± 6	0.7 ± 5	16 ± 6	0.6 ± 4	0.32
Delayed recall (No)	125	15 ± 7	0.4 ± 6	13 ± 6	0.5 ± 5	13 ± 6	0.5 ± 3	0.96
Proportion recalled (%)	125	84 ± 17	−4.6 ± 23	77 ± 20	0.1 ± 26	79 ± 17	1.6 ± 18	0.20

Data are presented as mean ± SD unless otherwise specified. Patients for whom no follow-up questionnaire was available were excluded from the analysis.

[a] Test for linearity.

[b] Mean change within group significant on a $P < 0.05$ level or [c]on a $P < 0.01$ level.

somewhat improved at end point. Again, there were no clear differences in change scores among the treatment groups.

To check whether the group with relatively many complaints would especially benefit from LT_4/LT_3 therapy, another subgroup analysis was performed on the tertile of patients with the highest SCL-90 total scores. However, results for this subgroup (n = 47: 18, 16, and 13 in the LT_4, 10:1, and 5:1 groups, respectively) remained similar with those of the whole group.

In several cases end point TSH was suppressed, less than 0.11 μU/ml (mU/liter). This occurred in seven of 45 (16%) patients in the LT_4 group, 13 of 44 (30%) in the 10:1 group, and 25 of 46 (54%) patients in the 5:1 ratio group, so there was a clear linear relation with treatment (χ^2 test for trend, $P <$ 0,01). Of the patients who preferred combined LT_4/LT_3 therapy, 44% had serum TSH less than 0.11 μU/ml (mU/liter). At 15 wk, serum TSH was above 4.0 μU/ml (mU/liter) in two (4%), three (7%), and three (7%) patients in the LT_4, 10:1, and 5:1 groups, respectively.

A *post hoc* subgroup analysis (n = 90) was carried out in subjects in whom end point serum TSH was not suppressed. For this subgroup the median TSH at 15 wk was 0.84 μU/ml (mU/liter) for those who had received LT_4 and 0.82 μU/ml (mU/liter) and 1.2 μU/ml (mU/liter) for the patients in the 10:1 and 5:1 LT_4/LT_3 combination groups, respectively (ANOVA for linear trend, $P = 0.61$). Mean fT_4 was 1.15 ng/dl (14.8 pmol/liter), 0.92 ng/dl (11.9 pmol/liter), and 0.78 ng/dl (10.1 pmol/liter) and mean T_3 levels 110 ng/dl (1.69 nmol/liter), 114 ng/dl (1.75 nmol/liter), and 127 ng/dl (1.95 nmol/liter) for patients in the LT_4, 10:1 LT_4/LT_3, and 5:1 LT_4/LT_3 groups, respectively (ANOVA for linear trend, $P <$ 0.01 and $P = 0.01$, respectively). SHBG did not differ among the groups. For the primary outcome, the results remained similar, with 29, 45, and 48% in the LT_4, 10:1, and 5:1 treatment groups, respectively, preferring study medication over their usual mediation, but this was not significant anymore (χ^2 test for trend, $P = 0.13$). Again, this linear trend was not found on any of the secondary outcome measures.

For the whole group, satisfaction with study medication was not correlated with either end point TSH or change in TSH. Increased preference for study medication as measured on the original five-point scale was correlated with weight loss (Pearson correlation between primary outcome and baseline-end point difference in weight: −0.188; $P = 0.03$).

Discussion

The results of this study, with 140 patients included in the primary outcome analysis, show a linear relation in the proportion of patients preferring study medication over usual

LT_4 treatment in relation to the treatment group, with proportions of 29.2, 41.3, and 52.2% in the LT_4, 10:1 ratio, and 5:1 ratio groups, respectively. However, this increase in satisfaction with an increasing proportion of LT_3 in the study medication was not reflected on any of the secondary outcome measures, which included questionnaires on mood, fatigue, quality of life, and general psychopathology as well as a substantial set of neurocognitive tests addressing attention and memory functions. Median end point serum TSH was 0.64, 0.35, and 0.07 μU/ml (mU/liter), respectively [ANOVA on ln(TSH) for linear trend $P < 0.01$]. Decrease in weight but not decrease in serum TSH was correlated with increased satisfaction with study medication.

This clinical trial investigating combined LT_4/LT_3 therapy is the largest thus far and the first to confirm a certain beneficial effect of combination therapy with both LT_4 and LT_3 since the publication by Bunevicius *et al.* (4) on this matter. Several of the methodological issues that have been raised in relation to that trial were avoided in the present trial. Bunevicius and Prange (25) included both patients with autoimmune hypothyroidism and those with thyroid carcinoma. In a later subgroup analysis, it appeared that only patients who had been treated for thyroid cancer benefited from LT_4/LT_3 therapy, whereas beneficial effects were absent in the group of patients with autoimmune hypothyroidism. In the present trial, we included a relatively large and homogeneous group of patients, all with autoimmune pathogenesis of hypothyroidism.

Because in the Dutch health care system, all inhabitants are enlisted with a family physician who will diagnose and treat most patients with hypothyroidism, we avoided selection bias by not recruiting from a second-line health care institution but from primary care. We invited all eligible patients to participate, regardless of their satisfaction with treatment.

Patients were treated for a period of 15 wk, which is long enough to reach a steady-state balance after an eventual dose adjustment (26). To attenuate the effect of the rapid absorption and short half-life of LT_3, all study medication was divided into two equal daily portions. It has been argued that in studies on the effects of LT_4 plus LT_3, only sustained-release LT_3 preparations should be used to avoid nonphysiological T_3 peaks. We agree that this would probably better mimic the continuous physiological thyroid gland secretion. However, the fact is that sustained-release preparations are not commercially available as yet. A first report on the endocrine results of treatment with an in-house slow-release LT_3 preparation has very recently been published, concluding that no T_3 serum peaks are present with this preparation (27). Nevertheless, no chemical characteristics of the preparation were given, and even with this preparation, LT_4/LT_3 ratios were not truly physiological (28). Furthermore, endocrine data were available on the first 9 h post ingestion only, leaving uncertainties about the slow-release properties over 24 h.

We considered it crucial to supply fixed proportions of LT_4 to LT_3 because is seems unlikely that the effect of combination therapy would be independent of the proportion of LT_3, which ranged from 3:1 to 15:1 in the trial by Bunevicius *et al.* (4). A molar ratio of 14:1 has been reported to approach the physiological production of the human thyroid gland (29), but we cannot be certain about the comparability of bioavailability of secreted *vs.* absorbed thyroid hormones due to the first-pass effect of the liver for one reason. Therefore, we chose to include two different ratios to further elucidate what proportion of LT_3 is most adequate.

A limitation of this study is that the combined therapy medication regimens led to overtreatment in many patients, *e.g.* the median end point TSH in the 5:1 group was 0.07, which implies that serum TSH was suppressed less than 0.07 μU/ml (mU/liter) in half of the patients in this group. The elevated heart rate in the 5:1 LT_4/LT_3 group and the weight loss in both combination groups are consistent with some degree of overreplacement. Apparently the problem of overtreatment was not sufficiently avoided by the dose adjustment after 5 wk according to the study protocol. It has been reported that some patients achieve the desired sense of well-being only when taking LT_4 in a dose of 50 μg in excess of that necessary to restore serum TSH to normal (30), so one might conclude that a certain degree of overtreatment results in satisfaction with study medication and might fully explain the primary outcome results. It is of interest that also in the study by Bunevicius *et al.* (4), a significant number of patients had suppressed TSH levels. However, in this study we found no correlation between change in serum TSH and the primary outcome.

The choice of outcome measures was complicated by the fact that, although the clinical notice that a substantial minority of hypothyroid patients remain with complaints is widespread, only sparse literature was available on the precise nature and prevalence of these complaints (31). By consequence, one could not be sure in what domains improvements were to be expected. We therefore chose to regard the subjective satisfaction with study medication as the primary outcome instead of one of the questionnaire or neurocognitive test outcomes because that choice would have been an arbitrary one. And in fact, it is the subjective dissatisfaction of biochemically adequately treated patients that forms the main incentive for this line of research. Only recently a community-based study confirmed impairment in psychological well-being of patients on adequate LT_4 replacement, compared with controls of similar age and sex (1). Putting on weight was one of the four complaints that were clearly more prevalent in hypothyroid patients than controls. It is therefore interesting that we found weight loss to be correlated with satisfaction with study medication.

Another notable finding is the fact that there was an improvement in scores on virtually all subscales of all outcome measures in all three groups. Because improvements were not consistently related to the treatment arm, this is likely to result from a practice effect or Hawthorne effect: benefit from improved routine care within a trial and from being investigated (32). It has been noted before that many hypothyroid patients find their physicians to be unsympathetic and dismissive of their symptoms (1), which may explain the extent of these aspecific trial effects in this study investigating the possibility to relief these uncomprehended complaints.

As for the safety of LT_4/LT_3 combination therapy, the majority of patients who dropped out because of side complaints appeared to belong to the LT_4 monotherapy group (four of seven), whereas no one in the 5:1 LT_4/LT_3 group

dropped out because of side complaints. However, in the 5:1 group, one patient known to have recurrent episodes of atrial premature beats absent at baseline was found to have atrial premature beats after the first 5 wk of study medication, which disappeared again after a dose adjustment at 5 wk. Although the apparent overtreatment with our LT_4/LT_3 medication schedules did not result in an excess of withdrawals in these groups, one should be aware that exogenous subclinical thyrotoxicosis is a risk factor for atrial fibrillation and may possibly lead to osteoporosis (33).

Although the primary outcome was in favor of LT_4/LT_3 combination therapy, we believe the results of this study do not currently support LT_4/LT_3 therapy as a standard treatment of patients with hypothyroidism, given the fact that the subjective preference for combination therapy was not embodied by more objective secondary outcomes, whereas loss of body weight, the plausible explanation for the subjective preference, may be due (at least partly) to overtreatment. Nevertheless, the outcome of this study does not preclude the possibility that a certain subgroup of patients may benefit from combined LT_4/LT_3 therapy. Recently identified polymorphisms, *i.e.* in type 2 deiodinase, important in the regulation of T_3 availability, may help to identify subgroups more likely to benefit from LT_4/LT_3 therapy (34).

In summary, we found that patients treated for autoimmune hypothyroidism preferred combination therapy with LT_4 and LT_3 over usual substitution therapy with LT_4 alone. This was not substantiated by larger improvements on questionnaires measuring mood, fatigue, and well-being or on neurocognitive tests concerning attention and memory functions. However, we did find decrease in weight to be associated with the proportion of LT_3 in substitution treatment as well as satisfaction with study medication, which might explain the satisfaction with LT_4/LT_3 combination therapy. A limitation of the study is that many patients in the combined therapy groups had end point TSH levels below the normally accepted range. We recommend that future studies assure that TSH levels are maintained within the reference range. These studies should take into account whether LT_4/LT_3 combination therapy improves control of body weight in patients with hypothyroidism. In addition, it may be that LT_4/LT_3 combination therapy proves beneficial for only a certain subgroup.

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