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Combined Thyroxine/Liothyronine Treatment Does Not Improve Well-Being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomized Controlled Trial in Patients with Primary Hypothyroidism

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T_4 is standard treatment for hypothyroidism. A recent study reported that combined T_4/liothyronine (T_3) treatment improved well-being and cognitive function compared with T_4 alone. We conducted a double-blind, randomized, controlled trial with a crossover design in 110 patients (101 completers) with primary hypothyroidism in which liothyronine 10 μg was substituted for 50 μg of the patients' usual T_4 dose. No significant ($P < 0.05$) difference between T_4 and combined T_4/T_3 treatment was demonstrated on cognitive function, quality of life scores, Thyroid Symptom Questionnaire scores, subjective satisfaction with treatment, or eight of 10 visual analog scales assessing symptoms. For the General Health Questionnaire-28 and visual analog scales assessing anxiety and nausea, scores were significantly ($P < 0.05$) worse for combined treatment than for T_4 alone. Serum TSH was lower during T_4 treatment than during combined T_4/T_3 treatment (mean ± SEM, 1.5 ± 0.2 *vs.* 3.1 ± 0.2 mU/liter; $P < 0.001$), a potentially confounding factor; however, subgroup analysis of subjects with comparable serum TSH concentrations during each treatment showed no benefit from combined treatment compared with T_4 alone. We conclude that in the doses used in this study, combined T_4/T_3 treatment does not improve well-being, cognitive function, or quality of life compared with T_4 alone. (*J Clin Endocrinol Metab* 88: 4543–4550, 2003)

THYROXINE (T_4) IS THE standard replacement therapy for hypothyroidism (1), but in some patients, symptoms of ill health persist despite T_4 treatment. It is not clear whether this is because of comorbidity or because standard T_4 replacement is in some way inadequate for some individuals (2–4).

T_4 has little intrinsic biological activity, and its metabolic effects are achieved by peripheral conversion to liothyronine (T_3). The thyroid also secretes T_3 directly, and in humans this accounts for about 20% of the body's total T_3 production (5). A truly physiological thyroid replacement regimen would therefore include both T_4 and T_3. Combined T_4/T_3 therapy was widely used in the past, in the form of desiccated thyroid, but with the availability of synthetically prepared T_4, the latter preparation became preferred on account of its long half-life, stable pharmacokinetics, and more precise standardization (6). A clinical trial published in 1970 compared combined T_4/T_3 treatment with T_4 alone and found that T_4 was better tolerated (7); however, the doses of both T_4 and T_3 that were used would now be regarded as excessive.

Recent studies revived interest in combined T_4/T_3 treatment for hypothyroidism. In rats rendered hypothyroid by thyroidectomy and radioiodine treatment, T_4 alone failed to normalize circulating and tissue concentrations of T_4 and T_3, but this was achieved with combined T_4/T_3 treatment (8, 9). Subsequently, a small clinical trial reported by Bunevicius *et al.* (10) found that partial substitution of liothyronine for T_4 resulted in improved mood, well-being, and measures of cognitive function compared with T_4 alone and was preferred by most of the patients. If these results are confirmed, combined T_4/T_3 treatment might become standard thyroid replacement therapy.

We conducted a double-blind, randomized, controlled trial comparing the effects of combined T_4/T_3 treatment and T_4 alone on symptoms of hypothyroidism, quality of life, cognitive function, and subjective satisfaction with T_4 therapy.

Patients and Methods

Patients and recruitment

Recruitment to the study commenced in April 2000, and the study was completed in November 2002. We aimed to enroll both subjects with persistent symptoms despite T_4 therapy and also subjects who felt well while taking T_4, but specific recruitment targets were not set for these subgroups. Inclusion criteria were primary hypothyroidism of at least 6-month duration, a stable dose of T_4 of 100 μg/d or more, no change in T_4 dosage in the previous 2 months, and serum TSH concentration between 0.1–4.0 mU/liter (reference range in our laboratory, 0.3–4.0 mU/liter) at a screening visit. The diagnosis of hypothyroidism was confirmed from medical or laboratory records or by contacting primary

Abbreviations: GHQ-28, General Health Questionnaire 28; SF-36, Short Form 36; TSQ, Thyroid Symptom Questionnaire.

care physicians; in a few patients with long-standing hypothyroidism, this was not possible.

The principal exclusion criteria were major comorbidity, current or recent T_3 treatment, history of thyroid cancer requiring suppression of TSH secretion, cardiac disease, and use of drugs that affect thyroid hormone secretion, metabolism, or bioavailability or measures of thyroid hormone action. Untreated major depression was an exclusion criterion, but patients receiving antidepressant treatment were eligible, provided treatment had been unchanged for the past 3 months and was likely to continue for the duration of the study.

Recruitment was from endocrinology outpatient clinics and private practices (n = 49), primary care physicians (n = 9), and local advertisement (n = 52). Thirty-one subjects who responded to advertisements were screened by telephone and were ineligible or declined to particpate; a further 20 subjects attended a screening visit, but were deemed ineligible or declined to participate.

At the screening visit, subjects were classified either as satisfied (adequate clinical response to T_4 with no persistent symptoms) or dissatisfied (persisting symptoms despite T_4 replacement) by a single clinician (J.P.W.) based on the clinical history. Typical complaints among dissatisfied patients were tiredness, impaired well-being, or weight gain. A clinical history and physical examination were performed, and routine blood tests (blood count, serum creatinine, and liver function tests in all patients; serum calcium and iron studies where indicated) were performed to exclude comorbidities that might account for symptoms of ill-health.

Study design, treatments, and evaluation

The study had a double-blind, crossover design, with the order of treatment randomized in permuted blocks of 10 using sealed envelopes. Fifty-six patients were randomized to T_4, followed by combined T_4/T_3 treatment, and 54 patients were randomized to combined treatment first. At study entry, patients reduced their daily T_4 dose by 50 μg and took the study medication (either 50 μg T_4 or 10 μg liothyronine (Tertroxin, Boots Healthcare Australia, North Ryde, New South Wales, Australia) in capsules of identical appearance) in addition to their reduced T_4 dose. Treatment periods lasted 10 wk, separated by a 4-wk period during which patients resumed their usual T_4 dosage. Liothyronine (10 μg/d) was used because this dose is thought to be bioequivalent to 50 μg T_4 (11) and is similar to the dose of 12.5 μg/d used by Bunevicius *et al.* (10). In Australia, liothyronine is available only as a 20-μg tablet, and it was therefore impractical to replicate exactly the dose used by Bunevicius *et al.*

At baseline and at the end of each treatment period, subjects attended after an overnight fast and before taking T_4 or study medication (*i.e.* 24 h after the previous dose). Venous blood and a random urine sample were collected for measurement of serum TSH, free T_4, and free T_3; serum SHBG and plasma cholesterol (markers of thyroid hormone action on liver); plasma alkaline phosphatase, serum osteocalcin, and urinary deoxypyridinoline/creatinine ratio (markers of thyroid hormone action on bone). Symptoms and signs of hypothyroidism were assessed using the Billewicz scale as modified by Zulewski *et al.* (12), which gives a tissue hypothyroidism score out of 13. Resting pulse rate and blood pressure were measured in the supine position as cardiovascular markers of thyroid hormone action, and ankle reflex relaxation time was assessed using a photomotogram (13). Treatment compliance was assessed by counting unused capsules.

At each visit, patients self-administered three questionnaires: the Short Form 36 (SF-36), the General Health Questionnaire 28 (GHQ-28), and the Thyroid Symptom Questionnaire (TSQ). The SF-36 (14) was selected as a generic quality of life instrument that has been validated in the Australian population (15). It consists of eight individual scales and two composite scales: the physical component summary and mental component summary scores. The GHQ-28 (16) was selected as a well-validated and widely used measure of psychological function or disturbance, which has previously been used to assess patients with thyroid disease (3, 17). It consists of a global score and four subscales: somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression. The TSQ (3) was selected as a disease-specific instrument and has been shown to be sensitive in detecting impaired well-being in T_4-treated subjects. The SF-36 was scored by standard methods (14). The GHQ-28 and TSQ were scored using a four-point Likert scale, with each response scored 0, 1, 2, or 3 (3, 16).

Subjects also completed 10 visual analog scales, each consisting of a pair of phrases, such as "as sad as possible" or "as happy as possible" at either end of a 100-mm line, giving a score in millimeters from the left-hand end. The scales assessed general well-being, happiness/sadness, confusion, anxiety, irritability, tiredness, feeling hot/cold, sickness/nausea, blurred vision, and aches and pains. Visual analog scales have been shown to be useful in assessing hypothyroid symptoms and responses to treatment (10, 18). Subjective satisfaction or dissatisfaction with each treatment was rated on a 4-point scale, ranging from "very satisfied: my thyroid treatment seems very effective" (scoring 0) to "very dissatisfied: my thyroid treatment doesn't seem to work at all" (scoring 3). At the final visit, patients were asked which treatment they preferred.

Cognitive function was assessed by a clinical psychologist using three standard, well validated tests: the Symbol Digit Modalities Test (19), which assesses cognitive efficiency and ability to undertake a novel task; the Trail Making Test Parts A and B (20), which assesses visual search, attention, mental flexibility, and motor function; and the Digit Span Sub-Test (both Forwards and Backwards) of the Wechsler Adult Intelligence Scale III (21), which assesses immediate auditory memory, attention, and concentration.

Biochemistry methods

TSH, free T_4, and free T_3 were measured by chemiluminescence immunoassay on the Abbott Diagnostics Architect (Abbott Diagnostics, North Ryde, Australia). SHBG was measured by enzyme immunoassay using chemiluminescence substrate on Immulite 2000 (Diagnostic Products, Los Angeles, CA). Deoxypyridinoline was measured by an in-house ion paired reverse phase HPLC with fluorescence detection (22). Osteocalcin was measured by in-house RIA (23). Cholesterol and alkaline phosphatase were analyzed by standard biochemical methods on a Hitachi 917 analyzer (Roche, Indianapolis, IN). Intra- and interassay coefficients of variation were as follows: TSH, 1.2 and 2.9%; free T_4, 3.8 and 3.6%; free T_3, 3.0 and 5.1%; SHBG, 4.1 and 6.0%; and osteocalcin, 12.3 and 14.5%, respectively; the interassay coefficient of variation for deoxypyridinoline was 8.0%.

Statistical analysis

Baseline characteristics for the satisfied and dissatisfied groups were compared by *t* test (for continuous variables), Wilcoxon rank-sums test (for ordinal variables), or Fisher's exact test; descriptive data are presented as the mean ± SD. Quality of life scores, cognitive function tests, and clinical and biochemical data were analyzed by repeated measures ANOVA using PROC GLM, a procedure within SAS*, to compare the effects of treatments after adjusting for subject and period effects; data are presented as the adjusted mean ± SEM. Treatment preference was analyzed by χ^2 test. The significance level was set at 0.05.

There were four prespecified subgroup analyses: 1) patients classified at baseline as satisfied or dissatisfied with T_4 treatment, as a differential symptomatic response to treatment was possible; 2) patients with serum T_3 less than 3 pmol/liter (the lower limit of the reference range) at baseline, as such patients might be in some way deficient in T_3, compared with those with a normal serum T_3 concentration; 3) patients with serum TSH below 2 mU/liter at baseline compared with those with TSH of 2 mU/liter or more, as some authorities recommend that serum TSH should be in the lower reference range in T_4-treated patients (24, 25); and 4) patients with autoimmune hypothyroidism compared with those with postsurgical and postradioiodine hypothyroidism.

Power calculations

Sample size calculations were based on published data (3, 15, 18, 26); in all cases, α was set at 0.05. For the SF-36, a sample size of 70 subjects gave 90% power to detect a 2-point difference between treatments in the physical or mental component summary scores; this is clinically meaningful, as the 1995 Australian National Health Survey found a 2.2-point difference in the physical component summary score and a 5.4-point difference in the mental component summary score between subjects with and without thyroid disease (Australian Bureau of Statistics, personal communication). No data were available for the GHQ-28 using

4-point Likert scoring on which to base calculations; however, for the abbreviated GHQ-12, a sample size of 100 subjects would give 80% power to detect a clinically meaningful 2-point difference between treatments. This suggested that a sample size of 100 was reasonable in the present study using the GHQ-28. For the TSQ, a sample size of 82 subjects gave 80% power to detect a 2-point difference between treatments. For the Symbol Digit Modality Test, a sample size of 82 subjects gave 90% power to detect a 5-point difference; for the Digit Span Test (Backwards), 38 patients were needed for 90% power to detect a one-digit difference; and for the Trail Making Test (Part B), 100 subjects were required to give 80% power to detect a 5-sec difference between treatments. The required sample size was, therefore, 100, and the recruitment target was set at 110 to allow for withdrawals.

Ethical approval

The study protocol was approved by the human research ethics committee of Sir Charles Gairdner Hospital. Informed consent was obtained from all participants.

Results

Baseline characteristics and retention

The baseline characteristics of the 110 study subjects, and the satisfied and dissatisfied subgroups are shown in Table 1. Ninety-four patients (85%) had autoimmune or idiopathic hypothyroidism; of 12 patients with postsurgical hypothyroidism, three had a history of Graves' disease, and one of Hashimoto's disease, whereas three of four patients with radioiodine-induced hypothyroidism had a history of Graves' disease. Dissatisfied subjects tended to be younger than satisfied subjects and had significantly worse quality of life (determined by SF-36) and more symptoms and signs of hypothyroidism (as determined by TSQ and Zulewski score). A history of depression was more common in the dissatisfied group, but not significantly so (33% *vs.* 18%; $P = 0.13$). More dissatisfied subjects were taking antidepressants at baseline (16% *vs.* 2%; $P = 0.02$), but this accounted for only a minority of patients. Psychological well-being was significantly worse in dissatisfied patients, as determined by the total GHQ-28 score, but only a few subjects in each subgroup had a GHQ score greater than 39 (4% of satisfied *vs.* 11% of dissatisfied subjects; $P = 0.29$), the accepted threshold score for the detection of psychiatric disorder (27). Dissatisfied subjects had worse scores for somatic symptoms, anxiety/insomnia, and social dysfunction, but there was no difference between subgroups in scores for severe depression. Comorbidities other than depression were not more prevalent among dissatisfied subjects. T_4 dosage and baseline serum TSH were not significantly different between subgroups; serum TSH was less than 2 mU/liter in 67% of satisfied subjects and in 74% of dissatisfied subjects.

Of 110 subjects recruited, 101 (92%) completed the study. Of the nine subjects who withdrew, seven were female. Rea-

TABLE 1. Baseline characteristics (mean ± SD) of the study population

	All Patients (n = 110)	Satisfied (n = 49)	Dissatisfied (n = 61)	*P* value
Female	101 (92%)	42 (86%)	59 (97%)	0.08
Age (yr)	47.7 ± 11.7	51.7 ± 11.6	44.4 ± 10.7	<0.001
Weight (kg)	78.8 ± 15.6	77.2 ± 14.7	80.0 ± 16.3	0.34
Body mass index (kg/m^2)	29.2 ± 5.5	28.5 ± 4.6	29.7 ± 6.1	0.29
Duration of hypothyroidism (yr)	8.0 ± 8.3	8.5 ± 8.7	7.6 ± 8.0	0.53
Cause of hypothyroidism				
Autoimmune	94 (85%)	44 (90%)	50 (82%)	0.29
Surgery	12 (11%)	3 (6%)	9 (15%)	0.22
Radioiodine	4 (4%)	2 (4%)	2 (3%)	1.00
Thyroxine dose (μg/d)	136 ± 36	136 ± 40	136 ± 33	0.91
Comorbidities and treatments				
History of depression	29 (26%)	9 (18%)	20 (33%)	0.13
Current antidepressant treatment	11 (10%)	1 (2%)	10 (16%)	0.021
Hypertension on treatment	9 (8%)	4 (5%)	5 (8%)	1.00
Hyperlipidemia on treatment	10 (9%)	6 (12%)	4 (7%)	0.33
Postmenopausal on HRT	22 (20%)	12 (24%)	10 (16%)	0.34
Other comorbidities	16 (14%)	7 (14%)	9 (15%)	1.00
Other prescribed drugs	14 (12%)	7 (14%)	7 (11%)	0.78
Serum TSH (mU/liter)	1.4 ± 1.2	1.5 ± 1.2	1.3 ± 1.1	0.45
Serum free T_4 (pmol/liter)	15.3 ± 2.3	15.3 ± 2.3	15.4 ± 2.2	0.74
Serum free T_3 (pmol/liter)	3.4 ± 0.9	3.3 ± 0.8	3.5 ± 0.9	0.53
Zulewski score	4.4 ± 1.9	3.9 ± 1.8	4.9 ± 1.8	0.005
SF-36				
Physical component summary	47.0 ± 9.7	50.7 ± 7.9	44.0 ± 10.0	<0.001
Mental component summary	43.8 ± 11.0	46.7 ± 10.5	41.5 ± 11.0	0.014
GHQ-28				
Total score	23.4 ± 11.9	19.4 ± 9.8	26.6 ± 12.5	0.001
Somatic symptoms	7.0 ± 4.3	5.0 ± 3.4	8.7 ± 4.2	<0.001
Anxiety/insomnia	6.5 ± 4.5	5.5 ± 3.8	7.2 ± 4.5	0.050
Social dysfunction	8.2 ± 3.0	7.3 ± 2.4	9.0 ± 3.3	0.003
Severe depression	1.7 ± 3.2	1.6 ± 2.7	1.7 ± 3.6	0.86
TSQ	14.7 ± 5.6	12.6 ± 4.8	16.3 ± 5.7	<0.001
Treatment satisfaction score	1.2 ± 0.5	0.7 ± 0.6	1.7 ± 0.7	<0.001

Patients were classified as "Satisfied" or "Dissatisfied" based on the clinical history at the baseline visit; *P* values are for comparison of these two subgroups. Note that for SF-36, higher scores indicate better quality of life, whereas higher scores on GHQ-28 and TSQ indicate worse psychological or physical well-being. Reference ranges: TSH 0.3–4.0 mU/liter; free T_4 10–19 pmol/liter; free T_3 3.0–5.5 pmol/liter.

sons given for withdrawal were pregnancy (n = 2), surgery for unrelated conditions (n = 2), worsening symptoms (n = 2), inability to attend study visits (n = 1), nasal congestion and palpitations (n = 1), and depression and insomnia (n = 1). Compliance with treatment was good, with a mean of 98% of study capsules taken. No significant adverse effects were reported during treatment.

Quality of life, cognitive function, and treatment preference

The results of the quality of life measures at the end of each treatment are shown in Table 2. For the SF-36, there was no significant difference between T_4 and combined T_4/T_3 treatments for the physical component summary score, the mental component summary score, or any of the eight individual scales of the SF-36. For the GHQ-28, the overall score was significantly higher (indicating worse psychological well-being) for combined treatment compared with T_4 alone (18.3 ± 1.0 for T_4 *vs.* 21.2 ± 1.0 for T_4/T_3; $P = 0.033$). In each of the four subscales of the GHQ-28, the mean score was higher (indicating worse symptoms) for combined treatment than for T_4 alone, but the difference was statistically significant only for social dysfunction (6.7 ± 0.3 for T_4 *vs.* 7.7 ± 0.3 for T_4/T_3; $P = 0.028$). For the TSQ, there was no significant difference between T_4 and combined T_4/T_3 treatment.

TABLE 2. Quality of life scores (mean ± SEM) for all subjects at the end of each treatment

Questionnaire	Thyroxine alone	Combined thyroxine/T_3	*P* value
SF-36			
Physical component summary	48.2 ± 0.6	47.5 ± 0.6	0.36
Mental component summary	47.5 ± 0.9	47.0 ± 0.9	0.69
Physical functioning	82.6 ± 1.1	81.0 ± 1.1	0.31
Role–physical	71.4 ± 3.4	67.8 ± 3.4	0.44
Bodily pain	72.7 ± 1.4	70.2 ± 1.4	0.20
General health	66.3 ± 1.2	66.7 ± 1.2	0.82
Vitality	52.6 ± 2.0	50.2 ± 2.0	0.39
Social functioning	79.3 ± 1.9	79.5 ± 1.9	0.95
Role–emotional	79.1 ± 3.3	77.0 ± 3.3	0.64
Mental health	75.1 ± 1.2	73.8 ± 1.2	0.42
GHQ-28			
Total	18.3 ± 1.0	21.2 ± 1.0	0.033
Somatic symptoms	5.9 ± 0.4	6.7 ± 0.4	0.12
Anxiety/insomnia	4.9 ± 0.3	5.6 ± 0.3	0.10
Social dysfunction	6.7 ± 0.3	7.7 ± 0.3	0.028
Severe depression	0.8 ± 0.2	1.2 ± 0.2	0.10
TSQ	11.7 ± 0.5	12.5 ± 0.5	0.21
Visual analog scales			
General well-being	41.2 ± 2.1	43.1 ± 2.1	0.50
Happiness/sadness	36.1 ± 1.7	37.6 ± 1.7	0.53
Confusion	24.2 ± 1.9	26.9 ± 1.9	0.33
Anxiety	24.9 ± 1.8	30.7 ± 1.8	0.026
Irritability	34.4 ± 2.0	34.5 ± 2.1	0.99
Tiredness	50.5 ± 2.6	53.6 ± 2.7	0.41
Feeling hot/cold	28.9 ± 2.2	28.9 ± 2.2	0.98
Sickness/nausea	12.8 ± 1.6	17.4 ± 1.6	0.049
Blurred vision	24.2 ± 2.4	28.9 ± 2.4	0.17
Aches and pains	33.3 ± 1.9	34.1 ± 2.0	0.78
Treatment satisfaction	1.0 ± 0.1	1.1 ± 0.1	0.39

For visual analog scales, a higher score indicates worse symptoms, except for hot/cold where a higher score indicates feeling more cold. Patients were classified as "Satisfied" or "Dissatisfied" based on the clinical history at the baseline visit; *P* values are for comparison of these two subgroups. Note that for SF-36, higher scores indicate better quality of life, whereas higher scores on GHQ-28 and TSQ indicate worse psychological or physical well-being. Reference ranges: TSH 0.3–4.0 mU/liter; free T_4 10–19 pmol/liter; free T_3 3.0–5.5 pmol/liter.

There were no significant differences between treatments for eight of 10 visual analog scales. Anxiety scores were significantly worse for combined T_4/T_3 treatment than for T_4 (24.9 ± 1.8 for T_4 *vs.* 30.7 ± 1.8 for T_4/T_3; $P = 0.026$), as were scores for sickness/nausea (12.8 ± 1.6 for T_4 *vs.* 17.4 ± 1.6 for T_4/T_3; $P = 0.049$). The treatment satisfaction score did not differ significantly between treatments.

The results of the cognitive function tests are shown in Table 3. There was no significant difference between treatments in any of the tests.

Of 101 patients completing the study, 46 preferred T_4 treatment, 36 preferred combined T_4/T_3 treatment, and 18 had no preference. This is not different from results expected by chance ($P = 0.32$).

On analysis of the prespecified subgroups based on baseline variables [satisfied (n = 46) or dissatisfied (n = 55); TSH, <2 (n = 74) or ≥2 mU/liter (n = 27); free T_3, <3 (n = 34) or ≥3 pmol/liter (n = 67); autoimmune (n = 85), surgical (n = 12), or radioiodine-induced hypothyroidism (n = 4)], no subgroup could be identified in which combined T_4/T_3 treatment improved quality of life or cognitive function compared with T_4 alone. For the SF-36, there was no treatment difference in the physical or mental component summary scores. For individual SF-36 domains, subjects with baseline TSH below 2 mU/liter had better scores during T_4 treatment than combined T_4/T_3 treatment in physical functioning (T_4, 83.6 ± 1.3; T_4/T_3, 80.0 ± 1.3; $P = 0.045$) and bodily pain (74.0 ± 1.5 *vs.* 68.2 ± 1.5; $P < 0.01$), whereas subjects with baseline TSH of 2 mU/liter or more had apparent improvement in social functioning during combined T_4/T_3 treatment (T_4, 70.7 ± 3.8; T_4/T_3, 84.7 ± 3.8; $P = 0.016$). For the GHQ-28 total score, there were significant treatment differences between T_4 and T_4/T_3 treatment for satisfied patients (T_4, 17.3 ± 1.1; T_4/T_3, 21.0 ± 1.1; $P = 0.026$), and for subjects with baseline TSH less than 2 mU/liter (18.0 ± 1.1 *vs.* 21.7 ± 1.1; $P = 0.0252$); in each case the results favored T_4 therapy. There were no significant differences in GHQ subscales for any subgroup. For the TSQ score, there was a significant treatment difference for patients with baseline TSH below 2 mU/liter (T_4, 11.5 ± 0.6; T_4/T_3, 13.1 ± 0.6; $P = 0.042$), indicating fewer hypothyroid symptoms during T_4 therapy. For visual analog scales, scores for anxiety (T_4, 22.7 ± 2.6; T_4/T_3, 30.6 ± 2.6; $P = 0.026$) and blurred vision (T_4, 22.3 ± 3.4; T_4/T_3, 32.9 ± 3.5; $P = 0.034$) were significantly worse during combined treatment in patients who were satisfied at baseline, whereas nausea was significantly worse during combined treatment

TABLE 3. Cognitive function test scores (mean ± SEM) for all subjects at the end of each treatment

	Thyroxine alone	Combined thyroxine/T_3	*P* value
Symbol digit modalities test	56.2 ± 0.3	56.4 ± 0.4	0.72
Trail making test			
Part A (s)	24.7 ± 0.4	25.5 ± 0.4	0.18
Part B (s)	61.4 ± 1.5	61.9 ± 1.5	0.80
Digit span test			
Forward	8.5 ± 0.1	8.5 ± 0.1	0.99
Backward	7.0 ± 0.1	6.9 ± 0.1	0.74

in patients with serum free T_3 of 3 pmol/liter or more at baseline (T_4, 10.9 ± 2.1; T_4/T_3, 18.6 ± 2.1; $P = 0.011$).

Clinical parameters

There was no difference between treatments in weight, blood pressure, or ankle jerk relaxation time (Table 4). The resting pulse rate was significantly lower during combined treatment than with T_4 alone, but the magnitude of the difference was small (68.8 ± 0.5 for T_4 *vs.* 67.3 ± 0.5 for T_4/T_3; $P = 0.048$). The tissue hypothyroidism score measured by the methods of Zulewski *et al.* (12) was significantly higher (indicating a greater number of symptoms and signs of hypothyroidism) for combined treatment (3.5 ± 0.1 for T_4 *vs.* 3.9 ± 0.1 for T_4/T_3; $P = 0.041$).

Biochemistry results

During combined T_4/T_3 treatment, serum free T_4 was significantly ($P < 0.001$) lower than during T_4 treatment (Table 5), whereas there was no significant difference in serum free T_3 concentrations. Serum TSH was significantly higher during combined therapy compared with T_4 alone (1.5 ± 0.2 mU/liter for T_4 *vs.* 3.1 ± 0.2 for combined T_4/T_3; $P < 0.001$). Serum SHBG was significantly ($P < 0.01$) lower, and plasma cholesterol higher ($P = 0.015$) during combined treatment compared with T_4 alone.

Subgroup analysis taking into account differences in TSH between treatments

The increase in mean serum TSH concentration during combined T_4/T_3 treatment compared with T_4 alone raised the possibility that beneficial effects of combination therapy were being masked by mild tissue hypothyroidism during this treatment. To explore this possibility, a *post hoc* subgroup analysis was carried out in subjects (n = 39) whose serum TSH concentrations at the end of the two treatments differed by 0.99 mU/liter or less. The rationale for this was that serum TSH concentrations in individuals fluctuate over time, and if serum TSH differs by 0.99 mU/liter or more in the same (euthyroid) individual on two occasions, the difference is statistically significant at the 1% level (28). The results of this analysis are shown in Table 6. As expected, serum TSH no longer differed significantly between treatments, whereas the difference in serum free T_4 was similar to that in the group as a whole. Serum SHBG remained significantly lower during combined treatment compared with T_4, whereas differences in cholesterol, pulse rate, and Zulewski score were no longer significant. There were no significant treatment differences in SF-36 physical and mental component summary scores, individual scales of the SF-36 (data not shown), TSQ score, GHQ total score and subscales, treatment satisfaction score, or nine of 10 visual analog scales, nor was there any trend toward improved scores during combined treatment compared with T_4. For the visual analog scale assessing anxiety, scores remained significantly ($P = 0.035$) worse for combined T_4/T_3 treatment compared with T_4. In this subgroup, 16 subjects preferred T_4 treatment, 19 preferred combination therapy, and four had no preference, which was not significantly different from results expected by chance ($P = 0.61$).

Confounding factors

Potential confounding factors were identified in nine subjects who completed the study: compliance less than 90% (n = 3), intercurrent illness (n = 2), commencement or change in dose of antidepressant (n = 2), undiagnosed pregnancy (n = 1), and stopped sex hormone replacement (n = 1). Excluding these subjects from the analysis did not alter significance of the results, except for pulse rate, which was no longer significantly different between treatments (T_4, 68.5 ± 0.6; T_4/T_3, 67.2 ± 0.6; $P = 0.11$).

TABLE 4. Clinical parameters (means ± SEM) for all subjects at the end of each treatment

	Thyroxine alone	Combined thyroxine/T_3	*P* value
Weight (kg)	78.7 ± 0.1	78.6 ± 0.1	0.82
Pulse rate (beats/min)	68.8 ± 0.5	67.3 ± 0.5	0.048
Systolic BP (mm Hg)	123 ± 1	124 ± 1	0.51
Diastolic BP (mm Hg)	74 ± 1	75 ± 1	0.44
Ankle jerk relaxation time (msec)	347 ± 3	350 ± 3	0.48
Zulewski score	3.5 ± 0.1	3.9 ± 0.1	0.041

Discussion

In this study, no benefit of combined T_4/T_3 treatment over standard T_4 therapy could be demonstrated on quality of life, hypothyroid symptoms, cognitive function, subjective satisfaction with thyroid replacement therapy, or treatment preference. No subgroup of patients could be identified who benefited symptomatically from combined T_4/T_3 treatment; in particular, there was no evidence of benefit in the clinically important subgroup of patients complaining of persistent symptoms of hypothyroidism despite T_4 replacement.

TABLE 5. Biochemistry results (mean ± SEM) for all subjects at the end of each treatment

	Thyroxine alone	Combined thyroxine/T_3	*P* value
Serum TSH (mU/liter)	1.5 ± 0.2	3.1 ± 0.2	<0.001
Serum free T_4 (pmol/liter)	15.6 ± 0.2	11.4 ± 0.2	<0.001
Serum free T_3 (mU/liter)	3.7 ± 0.1	3.5 ± 0.1	0.16
Serum SHBG (nmol/liter)	49.4 ± 1.0	45.5 ± 1.0	<0.01
Plasma cholesterol (mmol/liter)	5.1 ± 0.04	5.2 ± 0.04	0.015
Plasma alkaline phosphatase (U/liter)	75.7 ± 0.7	76.8 ± 0.7	0.25
Urine DPD/creatinine ratio (μmol/mol)	16.7 ± 0.4	17.0 ± 0.4	0.56
Osteocalcin (μg/liter)	11.3 ± 0.8	12.4 ± 0.8	0.31

DPD, Deoxypyridinoline. Reference ranges: cholesterol <5.5 mmol/liter; alkaline phosphatase 35–135 U/liter; DPD/creatinine ratio <27 μmol/mol (premenopausal females); osteocalcin <10.5 μg/liter; TSH 0.3–4.0 mU/liter; free T_4 10–19 pmol/liter; free T_3 3.0–5.5 pmol/liter.

TABLE 6. Selected biochemical, clinical, and quality of life results (means ± SEM) in a subgroup of subjects (n = 39) whose serum TSH concentrations at the end of thyroxine and combined thyroxine/T_3 treatment differed by 0.99 mU/liter or less

	Thyroxine alone	Combined thyroxine/T_3	*P* value
Serum TSH (mU/liter)	1.1 ± 0.3	1.3 ± 0.3	0.48
Serum free T_4 (pmol/liter)	16.2 ± 0.3	12.2 ± 0.3	<0.001
Serum free T_3 (pmol/liter)	3.9 ± 0.1	3.8 ± 0.1	0.36
Serum SHBG (nmol/liter)	50.9 ± 4.8	44.6 ± 4.8	<0.01
Plasma cholesterol (mmol/liter)	5.0 ± 0.1	5.1 ± 0.1	0.44
Pulse rate	67.2 ± 1.4	66.1 ± 1.4	0.38
Zulewski score	3.6 ± 0.3	4.0 ± 0.3	0.14
SF-36			
Physical component summary	47.5 ± 1.4	48.0 ± 1.4	0.72
Mental component summary	49.0 ± 1.6	47.5 ± 1.6	0.45
GHQ-28			
Total	18.3 ± 1.7	20.8 ± 1.7	0.24
Somatic symptoms	5.9 ± 0.7	7.2 ± 0.7	0.11
Anxiety/insomnia	4.8 ± 0.6	5.3 ± 0.6	0.44
Social dysfunction	6.6 ± 0.5	7.2 ± 0.5	0.39
Severe depression	1.0 ± 0.3	1.1 ± 0.3	0.70
TSQ	11.7 ± 0.8	12.8 ± 0.8	0.32
Visual analog scales			
General wellbeing	38.0 ± 3.4	41.8 ± 3.4	0.99
Happiness/sadness	35.5 ± 2.9	37.6 ± 2.9	0.58
Confusion	23.4 ± 3.7	29.1 ± 3.7	0.19
Anxiety	22.3 ± 3.8	31.1 ± 3.8	0.035
Irritability	36.2 ± 4.0	33.6 ± 4.0	0.57
Tiredness	48.7 ± 4.3	52.1 ± 4.3	0.57
Feeling hot/cold	30.8 ± 4.2	25.9 ± 4.2	0.34
Sickness/nausea	13.4 ± 3.3	17.7 ± 3.3	0.25
Blurred vision	22.1 ± 4.6	25.0 ± 4.6	0.58
Aches and pains	31.1 ± 4.3	29.4 ± 4.3	0.71
Treatment satisfaction	1.0 ± 0.1	1.1 ± 0.1	0.88

Our results differ from those of Bunevicius *et al.* (10), who reported improved well-being and cognitive function with combined T_4/T_3 treatment. There are several possible explanations for this discrepancy. Firstly, the previous study was smaller (33 patients), and sample size calculations were not reported in the paper. Secondly, the majority of patients in the previous study had a history of thyroid cancer and were presumably receiving T_4 suppressive therapy (which sometimes causes adverse effects) rather than standard replacement therapy. They were therefore not representative of hypothyroid subjects in general. Thirdly, treatment periods in the previous study were only 5 wk, with no intervening washout period, which is barely long enough for steady state to be reached after changes in T_4 dosage. This may well have confounded the results. The treatments used in the two studies differed slightly, in that we substituted 10 μg liothyronine for 50 μg of the patients' usual T_4 dose, whereas Bunevicius *et al.* used 12.5 μg liothyronine, but it is unlikely that this accounts for the markedly different results of the studies. Our results are, however, consistent with those of another study (reported in abstract form) of 48 subjects with a parallel design, in which combined T_4/T_3 treatment did not improve symptoms compared with T_4 alone (29).

During combined T_4/T_3 treatment, the mean serum free T_4 concentration decreased, free T_3 was unchanged, and serum TSH increased compared with values during treatment with T_4 alone. The lack of difference in free T_3 concentrations was expected, because blood samples were taken 24 h after the previous dose of T_4 and T_3, and the plasma half-life of T_3 is less than 1 d (30). The increase in serum TSH concentrations was somewhat unexpected, as 10 μg liothyronine and 50 μg T_4 are thought to have similar biological potencies (11, 31, 32), and in the study by Bunevicius *et al.* (10), serum TSH concentrations did not differ significantly during T_4 and combined T_4/T_3 treatments. A key difference is that Bunevicius *et al.* took blood samples 2 h after ingestion of T_4 and liothyronine, when serum T_3 concentrations are likely to be at their peak (30), whereas we took samples 24 h after the previous dose. If circulating T_3 concentrations regulate TSH secretion (33), then because of the short half-life of T_3, it is possible that during combined T_4/T_3 treatment serum TSH concentrations increase slightly as serum T_3 concentrations decline and would be highest 24 h after the previous dose of thyroid hormone. This would explain the discrepancy between the two studies, but is speculative, as there have been no studies examining diurnal variation in TSH secretion during combined T_4/T_3 treatment. On the other hand, there is evidence that TSH secretion is effectively regulated by circulating T_4, rather than T_3 (34). The basis for this is the observation (in rats) that brain and pituitary derive a larger proportion of intracellular T_3 from local deiodination of circulating T_4 than do other tissues, in which intracellular T_3 is mainly derived from circulating T_3 (35). If this is true of humans, then it is possible that partial substitution of liothyronine for T_4 maintains euthyroidism in peripheral tissues despite increased TSH secretion. Finally, it is possible that the widely quoted liothyronine to T_4 potency ratio of 5:1 (on a microgram to microgram basis) is simply incorrect, because it is based on early studies using bioassays (30, 31) that predate sensitive TSH assays. Some authorities suggest that the potency ratio is lower, about 3:1 or 4:1 (34). The small, but statistically significant, changes in Zulewski score, pulse

rate, cholesterol, and SHBG during combination treatment compared with T_4 alone support this possibility.

Whatever the correct explanation, the increased serum TSH concentrations during combined T_4/T_3 treatment raised the possibility that subjects were relatively underreplaced during this arm of the study, thus masking the beneficial effects of combined treatment on well-being and symptoms of hypothyroidism. The results of the *post hoc* subgroup analysis make this unlikely, as no benefit of combined T_4/T_3 treatment over T_4 alone was observed in subjects whose serum TSH concentrations were similar during each treatment. Although such an analysis results in a loss of statistical power, one would expect to see a trend toward improved quality of life or cognitive function scores if combined treatment really were preferable to T_4. No such trend was evident. Furthermore, the number of subjects in this subgroup analysis (n = 39) is still larger than that in the study by Bunevicius *et al.* (10), which reported beneficial effects of combined treatment.

In the present study serum SHBG was lower, and plasma cholesterol higher during combined T_4/T_3 treatment compared with T_4 alone, suggesting a lesser effect of thyroid hormone on the liver. The difference in SHBG remained significant in the subgroup analysis correcting for differences in serum TSH. In contrast, Bunevicius *et al.* (10) found that SHBG increased during combined T_4/T_3 treatment compared with T_4, whereas cholesterol was unchanged. These discrepancies between the studies are unexplained.

Our results appear inconsistent with studies in rats, in which combined T_4/T_3 treatment was required to achieve tissue euthyroidism. This is readily explained by interspecies differences in thyroid hormone secretion and metabolism. In rats, direct thyroidal secretion accounts for a far higher proportion of total T_3 production than in humans (40% *vs.* 20%) (35). Accordingly, it may well be necessary to give both T_4 and T_3 to achieve physiological thyroid replacement in rats, but this appears to be unnecessary in humans.

The strengths of our study include its large sample size and crossover design, giving a high degree of statistical power, and the inclusion and categorization of subjects who were satisfied and those who were dissatisfied with T_4 treatment. It could be argued that the inclusion of dissatisfied subjects made the study group less representative of hypothyroid subjects in general, because it is thought that most hypothyroid subjects have a satisfactory symptomatic response to T_4 treatment. It is, however, the suboptimal response to T_4 in some patients that makes combined T_4/T_3 treatment a subject of interest, and so it would have been unreasonable to exclude dissatisfied subjects from the study. The drop-out rate in the study was not excessive, and compliance with treatment was high. A weakness of our study was the use of a fixed quantity of liothyronine as partial substitution for T_4 regardless of baseline T_4 dosage. This meant that during combination treatment, the ratio of T_4/T_3 administered differed between subjects, and differed from the theoretically optimal ratio of approximately 10:1 (36). In addition, liothyronine was administered once daily, whereas for optimal replacement, divided doses or a slow-release preparation would be preferable. However, these limitations also apply to the study by Bunevicius *et al.* (10), and as our primary intention was to confirm or refute that study, they do not detract from our conclusions. It remains possible that different dosing regimens or routes of administration (such as transdermal preparations) of thyroid hormones would achieve more physiological thyroid replacement and conceivably improve well-being in patients, but this remains to be demonstrated.

The reason why some patients with hypothyroidism experience persistent symptoms of ill health despite apparently adequate T_4 replacement is not known. Possible explanations include incorrect diagnosis, comorbidities, and suboptimal prescription or monitoring of T_4 therapy (2, 4). These are unlikely to account for symptoms in the dissatisfied subjects in our study, because the diagnosis was verified in most cases, patients with major comorbidities (other than treated depression) were excluded, and most patients had serum TSH concentrations in the lower reference range. Undiagnosed depression in dissatisfied patients is a possible explanation; although depression scores on the GHQ-28 subscale for depression were not different between dissatisfied and satisfied subjects, this subscale is designed to detect severe, rather than mild or moderate, depression (16, 27). More detailed clinical studies of unselected patients with hypothyroidism are required to explore this possibility further.

In conclusion, we found no evidence that combined T_4/T_3 replacement (in the dosage regimen used in this study) resulted in improved well-being, cognitive function, quality of life, or increased thyroid hormone action on peripheral tissues compared with T_4 alone. We were unable to confirm the results reported by Bunevicius *et al.* (10). Unless beneficial effects of combined T_4/T_3 treatment over T_4 alone can be convincingly demonstrated by others, T_4 should remain the standard treatment for hypothyroidism.

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