European Journal of Endocrinology (2009) **161** 895–902 ISSN 0804-4643

CLINICAL STUDY

Effect of combination therapy with thyroxine (T_4) and 3,5,3′-triiodothyronine versus T_4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study

Birte Nygaard, Ebbe Winther Jensen, Jan Kvetny[1], Anne Jarløv[2] and Jens Faber

Department of Endocrinology, Herlev Hospital, University of Copenhagen, Herlev Ringvej, DK-2730 Herlev, Denmark, [1]Department of Endocrinology, Esbjerg Hospital, Esbjerg, Denmark and [2]Department of Endocrinology, Frederiksberg Hospital, Frederiksberg, Denmark

(Correspondence should be addressed to B Nygaard; Email: binyg@heh.regionh.dk)

Abstract

Background: Treatment of hypothyroidism with 3,5,3′-triiodothyronine (T_3) is controversial. A recent meta-analysis concludes that no evidence is present in favour of using T_3. However, the analysis included a mixture of different patient groups and dose-regimens.
Objective: To compare the effect of combination therapy with thyroxine (T_4) and T_3 versus T_4 monotherapy in patients with hypothyroidism on stable T_4 substitution.
Study design: Double-blind, randomised cross-over. Fifty micrograms of the usual T_4 dose was replaced with either 20 μg T_3 or 50 μg T_4 for 12 weeks, followed by cross-over for another 12 weeks. The T_4 dose was regulated if needed, intending unaltered serum TSH levels.
Evaluation: Tests for quality of life (QOL) and depression (SF-36, Beck Depression Inventory, and SCL-90-R) at baseline and after both treatment periods.
Inclusion criteria: Serum TSH between 0.1 and 5.0 mU/l on unaltered T_4 substitution for 6 months.
Results: A total of 59 patients (55 women); median age 46 years. When comparing scores of QOL and depression on T_4 monotherapy versus T_4/T_3 combination therapy, significant differences were seen in 7 out of 11 scores, indicating a positive effect related to the combination therapy. Forty-nine percent preferred the combination and 15% monotherapy ($P=0.002$). Serum TSH remained unaltered between the groups as intended.
Conclusion: In a study design, where morning TSH levels were unaltered between groups combination therapy, (treated with T_3 20 μg once daily) was superior to monotherapy by evaluating several QOL, depression and anxiety rating scales as well as patients own preference.

European Journal of Endocrinology **161** 895–902

Introduction

The thyroid gland produces ~100 μg thyroxine (T_4) and 20 μg 3,5,3′-triiodothyronine (T_3) per day per 70 kg bodyweight (1). T_3 is the active hormone and ~80% of the T_3 circulating in the blood is originated by peripheral 5′-deiodination of T_4 (2). When patients are given T_4 as substitution therapy, it is assumed that the peripheral conversion into T_3 provides sufficient T_3 for the peripheral tissues. However, the intracellular concentration of deiodinase and the cellular uptake of T_3 is not equal in all tissue (3, 4). In thyroidectomised rats, a combination of T_4 and T_3 rather than monotherapy with T_4 was needed to restore normal T_3 concentrations in all tissues (5). These results indicate that T_3 originating from the thyroid gland and not only from local deiodination of T_4 seems needed to keep optimal balance in the tissues.

In hypothyroid humans substituted with T_4, the ratio of T_4/T_3 in serum is ~25% higher than in normal subjects with similar serum TSH levels (6). In spite of apparently optimal T_4 substitution therapy (securing normal serum TSH levels), reduced quality of life (QOL) has been described in these patients as compared to the healthy subjects (7).

In 1999, Bunevicius described an increase in well-being in substituted hypothyroid subjects when comparing combination therapy with T_4 and T_3 to monotherapy with T_4 (8). Later, ten studies have been performed including a total of ~1000 patients, and based on these studies a recent meta-analysis concluded that there seems to be no evidence supporting superior effect of combination treatment (9). However, the studies included in the meta-analysis were a mixture of different patient groups, including patients with previous thyroid cancer, autoimmune hypothyroidism, and subclinical as well as overt hypothyroidism. One of

DOI: 10.1530/EJE-09-0542
Online version via www.eje-online.org

the largest studies was a randomised, double-blind crossover study including 101 patients (10). However, the authors were unable to keep serum TSH levels at a similar level in the two treatment groups, mean serum TSH being 3 in the combination group and 1.5 mU/l in the monotherapy group ($P<0.001$).

The purpose of the present study was to compare the effect of comparable dose regimens, either combination therapy with T_4 and T_3 or monotherapy with T_4 in patients with known overt autoimmune hypothyroidism at the time of diagnosis, and on stable T_4 substitution therapy for at least 6 months at the time of investigation. Therefore, during substitution therapy with T_4 plus T_3 or T_4 alone serum TSH was monitored as the sole parameter with the aim of keeping serum TSH constant throughout the study period by allowing changes in the open label T_4 dose only.

Patients

Inclusion criteria. Overt, spontaneous hypothyroid subjects with serum TSH levels >20 mU/l, serum T_4 <60 nmol/l, and positive thyroid peroxidase (TPO) antibodies (>60 U/ml) at the time of diagnosis, as well as serum TSH within the range of 0.1–5.0 mU/l at the time of screening where the patients had been on unaltered T_4 substitution for at least 6 months, as well as age within 18–76 years.

Exclusion criteria. Pregnant women or women planning to be pregnant; patients with any other chronic disease, previous T_3 treatment, active *post partum* subacute thyroiditis, hypothyroidism due to surgery or radioiodine treatment. The patients were recruited from an endocrine clinic population.

Design

Randomised, double-blind, cross-over design. One tablet containing 50 μg of the usual T_4 dose was replaced with one tablet (identical appearance) containing either 20 μg T_3 or 50 μg T_4 for 12 weeks, followed by cross-over for another period of 12 weeks. Block randomisation was used: for every ten test boxes, five boxes in random order contained T_3 in the first treatment period and five in the second treatment period. Serum TSH levels were measured after 4 weeks (data on serum T_4 and T_3 measurements were blinded, and not seen before the study was closed or in case of exclusion during the study). The open label T_4 dose was regulated if needed, intending unaltered serum TSH levels as compared to baseline levels. The following algorithm was used: if serum TSH was <0.1 or >5.0 mU/l, or if serum TSH differed more than 1.5 mU/l from the value measured at inclusion, the T_4 dose was regulated by 25 μg. If serum TSH was >8 or <0.1 mU/l the dose was adjusted and another control measurement was made after another period of 4 weeks.

Owing to the shorter half-life time of T_3 as compared to T_4 and compared with a relatively long treatment period of 3 months, no wash-out period was included between the two test periods. All patients were recruited from the outpatient clinics at the 3 centers participating.

Evaluation

Serum levels of TSH, T_4, T_3, the T_3 uptake, and anti-TPO were measured on morning blood samples, before the intake of medicine. Body weight, body mass index (BMI), waist-to-hip ratio, bioimpedance and tests for QOL and depression were measured at baseline, and after both treatment periods. At the end of the study and before identifying the different treatment arms, the patients were asked which treatment period they preferred.

Methods

Thyroid function parameters were measured by Immulite 2500, PDC: TSH, normal range 0.4–4.0 mU/l, inter- and intra-assay coefficient of variation (CV) 5%; T_3, normal range 1.0–2.6 nmol/l, inter- and intra-assay CV 5–10%; T_4, normal range 60–140 nmol/l, inter- and intra-assay CV 5%; T_3 uptake, normal range 0.80–1.25 arbitrary units, inter- and intra-assay CV 4%. Free T_4 and T_3 indices (FT_4I and FT_3I) were calculated by multiplying the total hormone concentration with the T_3 uptake test. Anti-TPO levels were measured by BRAMHS anti-TPOn-Dynotest, normal range <60 U/ml, inter- and intra-assay CV 4%.

Body weight was measured by a Tanita MTA 5987 weight, the waist-to-hip ratio and BMI (body weight (kg) divided by height^2 (m)) were calculated. Bioimpedance was measured by Omron BF 300. QOL and depression were evaluated by three questionnaires: i) SF-36, according to the Danish version (11) focusing on the following items: general health, vitality, social functioning and mental health; ii) Beck Depression Inventory (12); iii) SCL 90-R scale according to the Danish version (13) focusing on the following items: somatisation, interpersonal sensitivity, depression, anxiety, global severity index and positive symptoms total.

Statistical analyses

To make the power calculation we use the following parameters from SF 36: 80% power, α 0.05, minimal difference 10 point. To evaluate general health we needed 43 patients, social functioning 56, mental health 34 and vitality 45. The minimum number of patients was decided to be 56 patients (13). Data were compared by *t*-test (for continuous variables) and Wilcoxon rank-sums test (for ordinary variables). Treatment preference was analyzed by χ^2.

Calculations were made using R statistical software version 2.9.0 (R Foundation for Statistical Computing, Vienna, Austria, 2009). All *P* values are two-sided. All variables were tested for normality. Before treatment effects were analyzed each endpoint was tested for carry-over effect.

To test carry-over effect we conducted a *t*-test between the two randomisation groups using the mean value of each subject at time point *x* and *y*. If carry-over effects exist the mean value would be different. We calculated the differences between groups as the difference from baseline values. This reduces patient-to-patient variation and hence makes it easier to detect carry-over effect. Period effect was only possible to estimate between intervention period 1 and intervention period 2. It is not possible to separate time and treatment effects between baseline and first treatment. The period effect was analyzed by paired sample *t*-tests. Calculations of treatment effects were made by a two-way ANOVA method. Treatment and placebo effect was calculated as *post-hoc* tests and corrected for multiple comparisons with a Bonferoni–Holm method (14). Corrected *P* values are shown in Table 1.

As the study included several endpoints a false discovery rate (FDR) method was used to correct for multiple tests (15).

The analysis was made as 'on-treatment' analysis, and the drop-out/excluded patient during the study were excluded from the final analysis.

Ethics

The project was accepted by the Danish Medicines Agency (no. 2612-1939), the Danish National Committee on Biomedical Research Ethics (no. KA02022ms), the Danish Data Protection Agency (no. 2002-41-2236), and the study was retrospectively registered in ClinicalTrials.gov (2007-09-18, Study ID T_4–T_3 hypothyroidism).

Results

Patients

A total of 180 patients were considered for inclusion; 68 patients accepted to participate, out of which nine dropped out during the study (seven in the first and two in the second period; see Fig. 1). The seven patients who dropped out during the first period were four treated with T_4 monotherapy (two due to lack of time, one planning pregnancy, and one due to concomitant antidepressive treatment) and three treated with the T_4/T_3 combination therapy (one became pregnant, one had cancer, and one due to lack of time). Two patients were excluded during the second period, both needed antidepressive medicine, one was on T_4/T_3 combination therapy during the first period and felt much better than before inclusion, but the symptoms recurred during the second period. The other patient received the T_4/T_3 combination therapy in the second period of the study and felt better, but still needed antidepressive therapy. This left us with 59 patients for evaluation (55 women, baseline data: see Table 2). Changes in thyroid function, weight, bioimpedance, waist-to-hip ratio before and after T_4 monotherapy and T_4/T_3 combination therapy are presented in Table 3. No significant changes were seen except the expected changes in FT_4 and FT_3.

QOL and depression scores

Data for QOL and depression are listed in Tables 1 and 4.

Table 1 Changes in scores of quality of life (QOL) and psychological well-being prior to randomisation, on thyroxine (T_4) monotherapy compared to T_4/3,5,3′-triiodothyronine (T_3) combination therapy. ($n=59$).

***n*=59**	**Prior to randomisation**	**On T_4 mono-therapy**	**On T_4/T_3 combination therapy**	**T_4 treatment versus T_3/T_4 combination therapy** (*P* value)	**Baseline versus usual T_4 therapy placebo effect** (*P* value)
BDI	10.2+0.9	7.6+0.8	5.7+0.7	**0.01***	0.002*
General health	64+3.0	66+2.9	72+2.6	**0.02***	0.30
Social functioning	78+2.7	85+2.6	90+1.8	**0.07**	0.008*
Mental health	72+2.0	76+2.0	80+1.7	**0.04**	0.04*
Vitality	50+3.0	59+3.1	65+2.7	**0.02***	0.0004*
Somatisation	1.00+0.10	0.77+0.08	0.68+0.09	**0.12**	0.0002*
Interpersonal sensitivity	0.77+0.08	0.53+0.07	0.43+0.06	**0.12**	0.0002*
Depression	0.99+0.08	0.75+0.09	0.57+0.08	**0.01***	0.003*
Anxiety	0.60+0.07	0.49+0.06	0.35+0.06	**0.01***	0.04*
GSI	0.75+0.06	0.56+0.06	0.45+0.06	**0.01***	0.0001*
PST	1.65+0.06	1.42+0.05	1.29+0.07	**0.02***	0.0001*
Calculated significance level (FDR thresholds (14))*				**0.032**	0.045

P values describe the effect of T_4/T_3 treatment, and the placebo effect. Data are presented as mean±S.E.M. Note that for SF-36 higher scores indicate better QOL, whereas higher scores for BDI and SCL 90-R indicate worse psychological well-being. Treatment and placebo effect was calculated as *post-hoc* tests and corrected for multiple comparisons with a Bonferroni–Holm method (14). Corrected *P* values are shown. As the study included several endpoints a FDR method was used to correct for multiple tests (15). *Indicates significant *P* values below the calculated FDR thresholds.

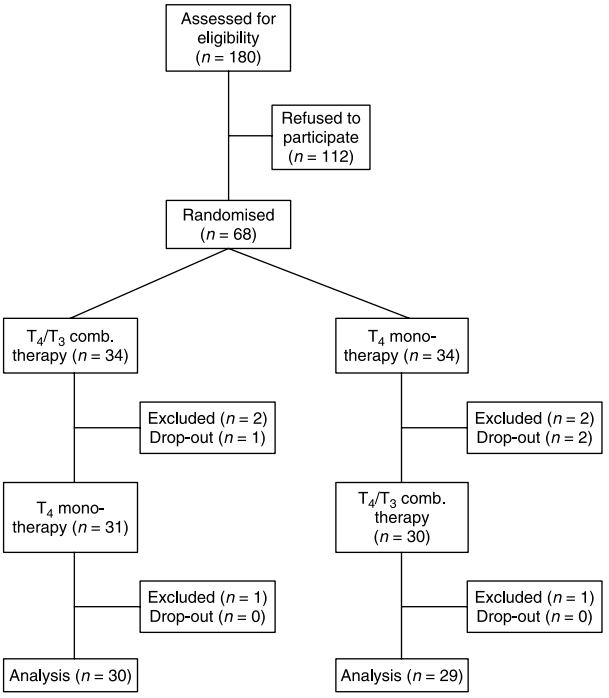

Figure 1 Consort diagram showing the flow of participants through each stage of the trial.

When comparing data in the T_4 monotherapy period versus data in the T_4/T_3 combination therapy period 7 out of 11 were significant, indicating an effect related to the combination T_4/T_3 therapy – our primary results. Evaluating data prior to randomisation versus data on T_4 monotherapy a significant effect on the QOL was seen in 10 out of 11 parameters indicating a placebo effect – a secondary result. No carry-over effect or period/time effect was seen. No significant correlations between changes in weight and QOL scores were seen. Baseline QOL data from the dropouts/excluded patients ($n=9$) compared to the patients fully fitting the study ($n=59$) are shown in Table 5.

Preferred treatment

When asking the patients which treatment period they preferred, 35% had no preference, 49% preferred the combination and 15% preferred monotherapy (therapeutic gain 34% (95% confidence interval (CI) 13.4–54) $P=0.002$). Patients preferring the combination therapy were characterised by having higher depression scores at baseline than patients without preference (SCL 90-R score depression median 1.23 (0.62–1.69 (25–75% percentile)) compared to 0.77 (0.31–1.38; $P=0.049$), as well as in the social functioning SF36 score, 88 compared to 75 ($P=0.037$).

Thyroid function

No correlation between serum TSH, FT_3I or FT_4I as compared to QOL at baseline could be demonstrated. No differences were seen in thyroid function parameters at the time of randomisation in patients preferring the combination therapy compared to patients without preference (serum TSH 1.48 mU/l compared to 0.969 mU/l ($P=0.489$), FT_3I 1.55 compared to 1.67 ($P=0.198$)).

Changes in T_4 dose

The open label T_4 dose was reduced due to decreasing serum TSH in ten patients, in seven during the T_4/T_3 combination period therapy and in three during T_4 monotherapy. The T_4 dose was increased in three patients, all of them in the T_4 monotherapy period. These changes in the T_4 dose resulted in stable serum TSH levels with no difference between the two treatment groups as intended (Table 3).

Table 2 Patient data prior to randomisation.

	Group 1 ($n=30$; combination T_4/T_3 therapy during the first period)	**Group 2** ($n=29$; combination T_4/T_3 therapy during the second period)
TSH at diagnosis (mU/l)	Median (25–75% percentile) 43.5 (31–95)	Median (25–75% percentile) 82.5 (47–120) (NS, $P=0.10$)
Age (years)	46.5±13.1	47.6±12.3
Time since euthyroidism was obtained due to T_4 substitution (months)	Median (25–75% percentile) 12.0 (8.0–34.5)	Median (25–75% percentile) 14.0 (11.5–36.0)
Height (cm)	170.5±8.3	169.1±6.6
Body weight (kg)	76.3+11.8	72.8+9.4
BMI	26.0+4.1	25.2+3.3
Bioimpedance (units)	31.6+6.6	31.1+5.9
Waist-to-hip ratio	1.24+0.11	1.24+0.9
Anti-TPO pos >60 U/ml per neg	24/29	26/30
Male/female	2/27	2/28

Data are listed as mean±S.D. and compared by *t*-test (for continuous variables) and median and 25–75% percentiles and Wilcoxon rank-sums test (for ordinary variables).

Table 3 Changes in thyroid function, weight, bioimpedance, waist-to-hip ratio before and after thyroxine (T_4) plus 3,5,3′-triiodothyronine (T_3) combination therapy and T_4 monotherapy ($n=59$).

	Prior to randomisation	T_4 monotherapy	T_4/T_3 combination therapy
TSH (mU/l)	1.104 (0.550–2.173)	0.990 (0.594–1.897)	0.756 (0.232–1.785) $P=0.07$
Free T_4I (units)	124±29	123±30	77±32 $P<0.001$
Free T_3I (units)	1.61±0.37	1.7±0.61	2.4±1.0 $P<0.001$
Anti-TPO (U/ml)	1271 (287–3000) (50 pt had positive TPO-Ab at the time of inclusion)	607 (221–2030)	481 (209–2057) $P=0.97$
T_4 dose (μg/day)	129±29	81±29.7 (+50 T_4)	77+29 (+20 T_3) NS
Body weight (kg)	74.4±10.7	74.6±11.8	72.9±14.7 NS
Bioimpedance (units)	31.4±6.2	31.4±6.4	30.1±7.8 NS
Waist-to-hip ratio	1.24±0.1	1.21±0.1	1.23±0.12 NS

Data are listed as mean±S.D. or median and 25–75% percentile. Statistical analysis: monotherapy versus combination therapy.

Side effects

No differences with regard to side effects were seen. During T_4/T_3 combination therapy five subjects experienced side effects: palpitations ($n=3$), excessive sweating ($n=1$), and psychological instability ($n=1$)); during T_4 monotherapy: nine subjects reported side effects: palpitations ($n=5$), excessive sweating (1), and psychological instability (3).

Discussion

A recent meta-analysis (9) has evaluated a total of 11 studies including ∼1000 patients and concluded that there seemed to be no evidence of better well-being related to combination therapy with T_4 and T_3 as compared to T_4 monotherapy alone in hypothyroid patients on stable substitution therapy. However, the differences in the included patient groups, the doses of T_4 and T_3, and the time of treatment varied markedly, which make the included studies difficult to compare. Three large studies have been published. Appelhoff *et al.* (16) included 141 patients in a non-cross-over, double-blind study with three treatment arms. All patients in this study had chronic autoimmune thyroiditis and were recruited from general practice regardless of their satisfaction (81% of the invited patients participated). T_4 monotherapy was compared to a combination therapy with either a T_4:T_3 ratio 10:1 or a T_4:T_3 ratio 5:1. The authors were unable to demonstrate any differences in mood, fatigue, or psychological symptoms.

The second study by Walsh *et al.* (10), included 101 patients treated in a cross-over, double-blind design exchanging 50 μg of T_4 with 10 μg of T_3 (ratio 5:1). No differences of cognitive function, QOL scores or thyroid disease-related symptoms were found.

The largest study by Saravanan *et al.* (17) including 573 patients using the same T_4/T_3 exchange as Walsh (ratio 5:1) used a non-cross-over, double-blind study and found a significant greater reduction in psychiatric cases (definition: when a total score of symptoms represents psychiatric illness) in the combination therapy group as compared to monotherapy with T_4 (19.2 vs 26.6% odds ratio (OR) 0.61, 95% CI 0.42–0.90; $P=0.01$), as well as an improvement in an anxiety score (hospital anxiety and depression scale, HADS) at 3 months (OR 0.61; 95% CI 0.32–0.95; $P=0.033$). However, no differences were seen at 12 months. They concluded that in general there was no long lasting beneficial effect of combination therapy, but it seemed possible that a subgroup of patients did benefit.

However, none of these three studies managed to keep serum TSH levels stable and similar between the treatment groups, which seems essential if the effect is to be compared. In the study by Appelhof *et al.* (16), serum TSH at the time of evaluation was mean 0.64 mU/l in the T_4-treated group, but 0.35 mU/l in the T_4:T_3 ratio of 10:1 group, and 0.07 mU/l in the 5:1 group, the differences being statistically significant ($P<0.01$). In the study by Walsh *et al.* (10), mean serum TSH at the time of evaluation was 1.5 mU/l in the T_4-treated group, but 3.1 mU/l ($P<0.001$) during the combination therapy period (10). Finally, in the study from Saravanan *et al.* (17) median serum TSH was 0.78 mU/l during T_4 monotherapy compared to 1.21 mU/l during combination therapy ($P<0.001$).

The present study was initiated before the meta-analysis in 2006. Based on the negative results we considered stopping the study. However, we thought that the design of our study was stronger than in most of the studies included in the meta-analysis. Therefore,

Table 4 Changes in scores of quality of life and psychological well-being at baseline, on thyroxine (T_4) monotherapy and on T_4/3,5,3′-triiodothyronine (T_3) combination therapy comparing group 1 ($n=30$, treated with combination T_4/T_4 therapy during the first period followed by monotherapy with T_4 during the second period) with group 2 ($n=29$, treated with monotherapy with T_4 during the first period followed by combination T_4/T_4 therapy during the second period).

	Period to T_4/T_3 combination therapy	Prior to randomisation	On T_4 mono-therapy	On T_4/T_3 combination therapy	Carry over effect	Period effect
BDI (scores 0–63, 0 best)	1	11.3±1.1	9.7±1.1	6.0±1.1	0.89	0.05
	2	9.1±1.1	5.7±1.1	5.3±1.1		
SF 36 (scores 0–100, 100 best)						
General health	1	64±4	66±4	72±4	0.92	0.88
	2	64±4	66±4	71±4		
Social functioning	1	73±3	84±3	90±3	0.08	0.61
	2	82±3	86±3	89±3		
Mental health	1	67±2.6	73±2.6	79±2.6	0.16	0.58
	2	75±2.6	78±2.6	81±2.6		
Vitality	1	50±4.2	59±4.2	62±4.2	0.55	0.28
	2	50±4.1	58±4.1	67±4.1		
SCL-90-R (scores 0–4, 0 best)						
Somatisation	1	0.99±0.13	0.81±0.13	0.68±0.13	0.92	0.58
	2	1.02±0.12	0.74±0.12	0.68±0.12		
Interpersonal sensitivity	1	0.81±0.10	0.36±0.10	0.50±0.10	0.43	0.54
	2	0.73±0.10	0.43±0.10	0.36±0.10		
Depression	1	1.06±0.12	0.87±0.12	0.64±0.12	0.65	0.46
	2	0.92±0.12	0.63±0.12	0.51±0.12		
Anxiety	1	0.67±0.09	0.57±0.09	0.37±0.09	0.58	0.35
	2	0.53±0.09	0.42±0.09	0.33±0.09		
Global severity index (GSI)	1	0.81±0.08	0.65±0.08	0.48±0.08	0.95	0.34
	2	0.67±0.08	0.48±0.08	0.41±0.08		
Positive symptoms total (PST)	1	1.68±0.09	1.47±0.09	1.32±0.09	0.74	0.81
	2	1.63±0.08	1.35±0.08	1.26±0.08		

Data are presented as mean±S.E.M.

we decided to continue the study. In the present study, we wanted to evaluate a patient group with the same phenotype (overt hypothyroidism due to autoimmune thyroiditis, on a stable and sufficient T_4 substitution dose for a prolonged period (>6 months), in order to avoid the heterogeneity seen in most of the previous studies. Pursuing this approach we were able to demonstrate a significant effect on QOL and depression scores of T_4/T_3 combination therapy compared to usual T_4 monotherapy.

Table 5 Quality of life and psychological well-being prior to randomisation in all included patients $n=68$.

	Prior to randomisation ($n=59$)	Prior to randomisation ($n=9$ drop out/eks pt)	*P*
BDI	10.2+0.9	9.9+2.7	0.71
General health	64+3.0	45+7.2	0.02
Social functioning	78+2.7	53+5.9	0.003
Mental health	72+2.0	68+6.1	0.54
Vitality	50+3.0	47+5.2	0.70
Somatisation	1.00+0.10	1.45+0.25	0.10
Interpersonal sensitivity	0.77+0.08	0.64+0.16	0.66
Depression	0.99+0.08	0.97+0.25	0.91
Anxiety	0.60+0.07	1.67+0.71	0.27
GSI	0.75+0.06	0.85+0.19	0.57
PST	1.65+0.06	1.67+0.15	0.88

eks pt, excluded patients.

The strengths in our study include a large sample size and cross-over design making it possible for the patients to compare the two treatment modalities.

A weakness of our study was the T_3 formulation. The T_3 dose was given at a standard dose 20 μg once daily and not as the optimal replacement, which would be to divide the dose or give a slow release preparation and give the dose at a ratio of the given T_4 dose. In our combination therapy arm we used a ratio of T_4:T_3 of 2.5:1 since we replaced 50 μg T_4 with 20 μg of T_3, and the ratio of given T_4/T_3 in the present study is a mean of 4:1 with a range from 2.5:1 to 8:1. Thus, we used a higher dose of T_3 than was used in most of the previous studies (7.5–12.5 μg). This resulted in serum T_4/serum T_3 of mean 77/2.4 (see Table 3), which is lower than seen in healthy controls. We did not study of diurnal variation in secretion of TSH, and it is possible that the given treatment resulted in high levels of serum-T_3 and suppressed serum-TSH during daytime. However, we managed to keep serum TSH stable (measured before morning medication) during the study period and similar between therapy groups. This raises the possibility that the widely quoted T_3-to-T_4 potency ratio of 5:1 (on microgram to microgram basis) (1) is incorrect. This accepted statement is based on older studies using bioassays that predate modern more sensitive TSH assays.

This is in accordance with other claims that the potency ratio is about 3:1 of 4:1 (18).

Another weakness of our study is the blinding of the study. The investigator and the patients were aware of changes in the T_4 treatment during the study period. However, a large placebo effect was seen indicating a high level of blinding.

At the end of the study, when treatment modalities were still blinded, a significantly higher proportion of patients preferred the combination therapy. In four previous studies patients' preference was also assessed (10, 16, 17, 19). In one study using high doses of T_3 (40–60 μg), the monotherapy regimen with T_4 was preferred (19). One study (10) did not find any preference, whereas in two studies (16, 17) combination therapy was preferred: in the study by Appelhof *et al.* (16), combination therapy was preferred by 41% in the T_4:T_3 ratio 10:1 group and by 52% in the T_4:T_3 ratio 5:1 group, as compared to 29% of the T_4 monotherapy group ($P=0.024$, both combination groups). In this study, a significant decrease in body weight was found and the decrease in weight correlated with increased satisfaction with study medication. In the study by Escobar-Morreale *et al.* (20), 69% of the patients preferred combination therapy compared to 8% preferring T_4 alone and 23% had no preference ($P=0.015$). In the present study, there was a non-significant decrease in body weight during the period on T_4/T_3 combination treatment as compared to T_4 monotherapy. In the study by Appelhof *et al.* (16), a correlation between satisfactions with the study medicine was found. In our study, we could not demonstrate a correlation between changes in QOL and reduction in body weight.

In our study, we found a large placebo effect, in accordance with a previous study (17), demonstrating a 39% relative improvement in psychiatric cases in the placebo group.

In several older, nevertheless well designed studies in patients with severe depression, T_3 has been studied as an additional treatment to the depression treatment, testing the hypothesis that T_3 treatment could shorten the period of depression. Several of these studies found a beneficial effect (for review – see (21)). However, many of the patients in these studies were treated with doses of T_3 causing iatrogenic borderline or overt hyperthyroidism. These studies have formed the basis for the hypothesis that the addition of T_3-to-T_4 therapy in hypothyroid patients with depression could relieve symptoms of depression (21). This has primarily been investigated in small studies, but recently Sawka *et al.* (22) performed a well-designed randomised, double-blind, controlled non-cross-over study including 40 patients on combination therapy with T_4 and T_3 versus the usual T_4 monotherapy. However, they found no significant difference in SCL-90 scores between the two groups.

A large number of patients were considered for inclusion in the present study, and ∼2/3 refused to participate. Although the design of the study was simple and not time-consuming, these patients did not want to participate, simply because they felt well. This might indicate that not feeling well on T_4 monotherapy is a minor problem. On the contrary, almost 50% of those who did volunteer to participate described some degree of reduced QOL, indicating that the subjects under study might have represented a selected group feeling 'more miserable' than the general population. We do not think that this invalidates the study, but it emphasises that any effect might be greater in more symptomatic individuals.

Our study thus suggests that a subgroup of patients may benefit from combined T_4/T_3 therapy. In this context it is interesting that a recently identified polymorphism in the gene coding for the type two deiodinase, the enzyme responsible for the regulation of T_3 availability to the tissues, has been proposed in order to help identifying subgroups more likely to benefit from T_4/T_3 combination therapy (23). Another polymorphism, located in OATP1C1, a thyroid hormone transporter expressed at the blood–brain barrier, has been associated with fatigue and depression (24). Both polymorphisms have been evaluated in the study population by Appelhof *et al.* (16), but did not correlate to appreciation of T_4/T_3 combination therapy (25).

Conclusion

In a study design where TSH levels did not change from baseline values and were unaltered between treatment groups, T_4/T_3 combination therapy T_3 (20 μg) given once daily seemed superior to T_4 monotherapy in a group with a high baseline psychological morbidity and autoimmune hypothyroidism. The findings are consistent with Appelhoff *et al.* (22) but further studies carefully designed to focus on this area are required.

Declaration of interest

None of the authors have any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The study was supported economically by The Agnes and Knut Mørk's Foundation, Denmark.

References

1 Leonard JL & Koehrle J. Intracellular pathways of iodothyronine metabolism. In *Werner and Ingbar's the Thyroid. A Fundamental and Clinical Text*, edn 7, pp 125–161. Eds LE Bravermann & RD Utiger. Philadelphia: Lippencott-Raven, 1996.

2 Pilo A, Iervasi G, Vitek F, Ferdeghini M, Cazzoula F & Bianchi R. Thyroidal and peripheral production of 3,5,3′-triiodithyronine in humans by multicompartmental analysis. *American Journal of Physiology* 1990 **258** E715–E726.

3 Kaplan MM & Yaskoski KA. Phenolic and thyrosyl ring deiodination of iodothyronines in rat brain homogenates. *Journal of Clinical Investigation* 1980 **66** 551–562.
4 van Doorn J, Roelfsema F & van der Heide D. Concentration of thyroxine and 3,5,3′ triiodothyronine at 34 different sites in euthyroid rats as determined by an isometric equilibrium technique. *Endocrinology* 1985 **117** 1201–1208.
5 Escobar-Morreale HF, Escobar del Rey F, Obregon MJ & Morealle de Escobar G. Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues in the thyroidectomized rat. *Endocrinology* 1996 **137** 2490–2502.
6 Woeber KA. Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. *Journal of Endocrinological Investigation* 2002 **25** 106–109.
7 Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R & Dayan CM. Psychological well-being in patients on adequate doses of L-thyroxine: result of a large controlled community-based questionnaire study. *Clinical Endocrinology* 2002 **57** 577–585.
8 Bunevicius R, Kazanavicius G, Zalinkevicius R & Prange AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *New England Journal of Medicine* 1999 **340** 424–470.
9 Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A & Leibovici L. Thyroxine–triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism. Metaanalysis of randomized controlled trials. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2562–2599.
10 Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC & Cussons AJ. 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. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 4543–4550.
11 Bjørner JB, Damsgaaard MT, Watt T, Bech P, Rasmusen NK, Kristensen TS, Modvig J & Thunedborg K. *Danish Manual to SF-36*. A questionaire to health status. Copenhagen, LIF, 1997.
12 Beck AT & Steer RA. Beck depression inventory. In *Handbook of Psychiatric Measures*, pp 519–523. Eds AJ Rush, HA Pincus & MB Fist, Washington DC: American Psychiatric Association Press, 2000.
13 Derogatis LR. *SCL-90R, Symptom Checklist-90-R. Vejledning til Administration og Scoring*. Copenhagen, Dansk Psykologisk Forlag. 2007.
14 Holm S. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* 1979 **6** 65–70.
15 Benjamini Y, Drai D, Elmer G, Kafkafi N & Golani I. Controlling the false discovery rate in behavior genetics research. *Behavioural Brain Research* 2001 **125** 279–284.
16 Appelhof BC, Fliers E, Wekking EM, Schene AH, Heyser J, Tijssen JGP, Endert E, van Weert HCMP & Wiersinga WM. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind randomized controlled clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 2666–2674.
17 Saravanan P, Simmons DJ, Greenwood R, Peters TJ & Colin CM. Partial substitution of thyroxine (T_4) with triiodothyronine in patients on T_4 replacement therapy: results of a large community-based randomized controlled study. *Journal of Clinical Endocrinology* 2005 **90** 805–812.
18 Larsen PR. Thyroid–pituitary interaction: feedback regulation of thyrotrophine secretion by thyroid hormone. *New England Journal of Medicine* 1982 **306** 23–32.
19 Smith RN, Taylor SA & Massey JC. Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. *BMJ* 1970 **4** 145–148.
20 Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V & Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. *Annals of Internal Medicine* 2005 **142** 412–424.
21 Kirkegaard C & Faber J. The role of thyroid hormones in depression. *European Journal of Endocrinology* 1998 **138** 1–9.
22 Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM & Joffe RT. Does a combination regime of thyroxine (T_4) and 3,5,3′-triiodothyronine improve depression symptoms better than T_4 alone in patients with hypothyroidism? Results of a double-blind, randomized controlled trial *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 4551–4555.
23 Peeters RP, van Toor H, Klootwijk W, de Rijke YB, Kuioer GG, Uitterlinden AG & Visser TJ. Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 2880–2888.
24 Appelhof BC, Peeters RP, Wiersinga WM, Visser TJ, Wekking EM, Huyser J, Schene AH, Tijssen JG, Hoogendijk WJ & Fliers E. Polymorphisms in type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3′-triiodothyronine therapy. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 6296–6299.
25 Van der Deure WM, Appelhof BC, Peters RP, Wiersinga WM, Wekking EM, Heyser J, Schene AH, Tijssen JG, Hoogendijk WJ, Visser TJ & Fliers E. Polymorphism in the brain thyroid hormone transporter OATP1C1 are associated with fatigue and depression in hypothyroid patients. *Clinical Endocrinology* 2008 **69** 804–811.

Received 3 July 2009
Accepted 6 August 2009