CLINICAL STUDY

Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study

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Abstract

Background: Treatment of hypothyroidism with 3,5,3'-triiodothyronine (T3) is controversial. A recent meta-analysis concludes that no evidence is present in favour of using T3. However, the analysis included a mixture of different patient groups and dose-regimens.

Objective: To compare the effect of combination therapy with thyroxine (T4) and T3 versus T4 monotherapy in patients with hypothyroidism on stable T4 substitution.

Study design: Double-blind, randomised cross-over. Fifty micrograms of the usual T4 dose was replaced with either 20 μg T3 or 50 μg T4 for 12 weeks, followed by cross-over for another 12 weeks. The T4 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 T4 substitution for 6 months.

Results: A total of 59 patients (55 women); median age 46 years. When comparing scores of QOL and depression on T4 monotherapy versus T4/T3 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 T3 20 μg once daily) was superior to monotherapy by evaluating several QOL, depression and anxiety rating scales as well as patients own preference.

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Introduction

The thyroid gland produces ∼100 μg thyroxine (T4) and 20 μg 3,5,3'-triiodothyronine (T3) per day per 70 kg bodyweight (1). T3 is the active hormone and ∼80% of the T3 circulating in the blood is originated by peripheral 5'-deiodination of T4 (2). When patients are given T4 as substitution therapy, it is assumed that the peripheral conversion into T3 provides sufficient T3 for the peripheral tissues. However, the intracellular concentration of deiodinase and the cellular uptake of T3 is not equal in all tissue (3, 4). In thyroidectomised rats, a combination of T4 and T3 rather than monotherapy with T4 was needed to restore normal T3 concentrations in all tissues (5). These results indicate that T3 originating from the thyroid gland and not only from local deiodination of T4 seems needed to keep optimal balance in the tissues.

In hypothyroid humans substituted with T4, the ratio of T3/T4 in serum is ∼25% higher than in normal subjects with similar serum TSH levels (6). In spite of apparently optimal T4 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 wellbeing in substituted hypothyroid subjects when comparing combination therapy with T4 and T3 to monotherapy with T4 (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
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 T₄ and T₃ or monotherapy with T₄ in
patients with known overt autoimmune hypothyroid-
ism at the time of diagnosis, and on stable T₄
substitution therapy for at least 6 months at the time
of investigation. Therefore, during substitution therapy
with T₄ plus T₃ or T₄ 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 T₄ dose only.

**Patients**

**Inclusion criteria**. Overt, spontaneous hypothyroid subjects
with serum TSH levels > 20 mU/l, serum T₄ < 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 T₄ 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 T₃ treatment, active post
partum subacute thyroiditis, hypothyroidism due to
surgery or radiiodine 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 T₄ dose was replaced with
one tablet (identical appearance) containing either
20 μg T₃ or 50 μg T₄ 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 T₃ in the first treatment period
and five in the second treatment period. Serum TSH
levels were measured after 4 weeks (data on serum T₃
and T₄ measurements were blinded, and not seen before
the study was closed or in case of exclusion during the
study). The open label T₄ 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 T₄ 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 T₃ as compared
to T₄ 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 T₃, T₄, T₃, the T₃ 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 Immu-
lite 2500, PDC: TSH, normal range 0.4–4.0 mU/l inter-
and intra-assay coefficient of variation (CV) 5%; T₃,
normal range 1.0–2.6 nmol/l, inter- and intra-assay CV
5–10%; T₄, normal range 60–140 nmol/l, inter- and
intra-assay CV 5%; T₃ uptake, normal range 0.80–1.25
arbitrary units, inter- and intra-assay CV 4%. Free T₄
and T₃ indices (FT₄I and FT₃I) were calculated by
multiplying the total hormone concentration with the
T₃ uptake test. Anti-TPO levels were measured by
BRAMHS anti-TPO-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 height² (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 function-
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 χ².
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 Bonferroni–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 T4–T3 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 T4 monotherapy (two due to lack of time, one planning pregnancy, and one due to concomitant antidepressive treatment) and three treated with the T4/T3 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 T4/T3 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 T4/T3 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 T4 monotherapy and T4/T3 combination therapy are presented in Table 3. No significant changes were seen except the expected changes in FT4 and FT3.

**QOL and depression scores**

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

### Table 1

<table>
<thead>
<tr>
<th>n = 59</th>
<th>Prior to randomisation</th>
<th>On T4 monotherapy</th>
<th>On T4/T3 combination therapy</th>
<th>T4 treatment versus usual T4 therapy (P value)</th>
<th>Baseline versus T4/T3 combination therapy (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>10.2 ± 0.9</td>
<td>7.6 ± 0.8</td>
<td>5.7 ± 0.7</td>
<td>0.01*</td>
<td>0.002*</td>
</tr>
<tr>
<td>General health</td>
<td>64 ± 3.0</td>
<td>66 ± 2.9</td>
<td>72 ± 2.6</td>
<td>0.02*</td>
<td>0.30</td>
</tr>
<tr>
<td>Social functioning</td>
<td>78 ± 2.7</td>
<td>85 ± 2.6</td>
<td>90 ± 1.8</td>
<td>0.07</td>
<td>0.008*</td>
</tr>
<tr>
<td>Mental health</td>
<td>72 ± 2.0</td>
<td>78 ± 2.0</td>
<td>80 ± 1.7</td>
<td>0.04</td>
<td>0.04*</td>
</tr>
<tr>
<td>Vitality</td>
<td>50 ± 3.0</td>
<td>59 ± 3.1</td>
<td>65 ± 2.7</td>
<td>0.02*</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Somatisation</td>
<td>1.00 ± 0.10</td>
<td>0.77 ± 0.08</td>
<td>0.68 ± 0.09</td>
<td>0.12</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>0.77 ± 0.08</td>
<td>0.53 ± 0.07</td>
<td>0.43 ± 0.06</td>
<td>0.12</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Depression</td>
<td>0.99 ± 0.08</td>
<td>0.75 ± 0.09</td>
<td>0.57 ± 0.08</td>
<td>0.01*</td>
<td>0.003*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.60 ± 0.07</td>
<td>0.49 ± 0.06</td>
<td>0.35 ± 0.06</td>
<td>0.01*</td>
<td>0.04*</td>
</tr>
<tr>
<td>GSI</td>
<td>0.75 ± 0.06</td>
<td>0.56 ± 0.06</td>
<td>0.45 ± 0.06</td>
<td>0.01*</td>
<td>0.0001*</td>
</tr>
<tr>
<td>PST</td>
<td>1.65 ± 0.06</td>
<td>1.42 ± 0.05</td>
<td>1.29 ± 0.07</td>
<td>0.02*</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Calculated significance level (FDR thresholds (14))*</td>
<td></td>
<td></td>
<td></td>
<td>0.032</td>
<td>0.045</td>
</tr>
</tbody>
</table>

P values describe the effect of T4/T3 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.
When comparing data in the T₄ monotherapy period versus data in the T₄/T₃ combination therapy period 7 out of 11 were significant, indicating an effect related to the combination T₄/T₃ therapy – our primary results. Evaluating data prior to randomisation versus data on T₄ 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, FT₃ or FT₄ 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), FT₃ 1.55 compared to 1.67 (P=0.198)).

**Changes in T₄ dose**

The open label T₄ dose was reduced due to decreasing serum TSH in ten patients, in seven during the T₄/T₃ combination period therapy and in three during T₄ monotherapy. The T₄ dose was increased in three patients, all of them in the T₄ monotherapy period. These changes in the T₄ 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.](www.eje-online.org)
Table 3 Changes in thyroid function, weight, bioimpedance, waist-to-hip ratio before and after thyroxine (T4) plus 3,5,3'-triiodothyronine (T₃) combination therapy and T₄ monotherapy (n=59).

<table>
<thead>
<tr>
<th></th>
<th>Prior to randomisation</th>
<th>T₄ monotherapy</th>
<th>T₄/T₃ combination therapy</th>
</tr>
</thead>
</table>
| TSH (mU/l)               | 1.104 (0.550–2.173)    | 0.990 (0.594–1.897) | 0.756 (0.232–1.785)  
|                          | P=0.07                 |                 | P<0.001                  |
| Free T₄ (units)          | 124 ± 29               | 123 ± 30        | 77 ± 32                  |
|                          |                        |                 | P<0.001                  |
| Free T₃ (units)          | 1.61 ± 0.37            | 1.7 ± 0.61      | 2.4 ± 1.0                |
|                          |                        |                 | P<0.001                  |
| Anti-TPO (U/ml)          | 1271 (287–3000)        | 607 (221–2030)  | 481 (209–2057)           |
|                          |                        |                 | P<0.001                  |
| T₄ dose (µg/day)         | 129 ± 29               | 81 ± 29.7 (+50 T₄) | 77 ± 29 (+20 T₃)   |
|                          |                        |                 | 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 T₄/T₃ combination therapy five subjects experienced side effects: palpitations (n=3), excessive sweating (n=1), and psychological instability (n=1); during T₄ 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 T₄ and T₃ as compared to T₄ monotherapy alone in hypothyroid patients on stable substitution therapy. However, the differences in the included patient groups, the doses of T₄ and T₃, 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). T₄ monotherapy was compared to a combination therapy with either a T₄:T₃ ratio 10:1 or a T₄:T₃ 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 T₄ with 10 µg of T₃ (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 T₄/T₃ 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 T₄ (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 T₄-treated group, but 0.35 mU/l in the T₄:T₃ 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 T₄-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 T₄ 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,
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 T₄ 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 T₄/T₃ combination therapy compared to usual T₄ monotherapy.

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 T₃ formulation. The T₃ 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 T₃ dose. In our combination therapy arm we used a ratio of T₄:T₃ of 2.5:1 since we replaced 50 μg T₃ with 20 μg of T₄, and the ratio of given T₄/T₃ 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 T₃ than was used in most of the previous studies (7.5–12.5 μg). This resulted in serum T₄/serum T₃ 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-T₃ 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 T₃-to-T₄ 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.

Table 4 Changes in scores of quality of life and psychological well-being at baseline, on thyroidine (T₄) monotherapy and on T₄/3,5,3’-triiodothyronine (T₃) combination therapy comparing group 1 (n = 30, treated with combination T₄/T₃ therapy during the first period followed by monotherapy with T₄ during the second period) with group 2 (n = 29, treated with monotherapy with T₄ during the first period followed by combination T₄/T₃ therapy during the second period).

<table>
<thead>
<tr>
<th></th>
<th>Period to T₄/T₃ combination therapy</th>
<th>Prior to randomisation</th>
<th>On T₄ monotherapy</th>
<th>On T₄/T₃ combination therapy</th>
<th>Carry over effect</th>
<th>Period effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI (scores 0–63, 0 best)</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>SF 36 (scores 0–100, 100 best)</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>General health</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Social functioning</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Mental health</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Vitality</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>SCL-90-R (scores 0–4, 0 best)</td>
<td></td>
<td>1.65 ± 0.4</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.25</td>
<td>0.08</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.E.M.
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 T₄ 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 T₃ (40–60 µg), the monotherapy regimen with T₄ 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 T₄:T₃ ratio 10:1 group and by 52% in the T₄:T₃ ratio 5:1 group, as compared to 29% of the T₄ 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 T₄ 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 T₄/T₃ combination treatment as compared to T₄ 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, T₃ has been studied as an additional treatment to the depression treatment, testing the hypothesis that T₃ 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 T₃ causing iatrogenic borderline or overt hyperthyroidism. These studies have formed the basis for the hypothesis that the addition of T₃-to-T₄ 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 T₄ and T₃ versus the usual T₄ 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 T₄ 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 T₄/T₃ 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 T₃ availability to the tissues, has been proposed in order to help identifying subgroups more likely to benefit from T₄/T₃ 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 T₄/T₃ combination therapy (25).

Conclusion

In a study design where TSH levels did not change from baseline values and were unaltered between treatment groups, T₄/T₃ combination therapy T₃ (20 µg) given once daily seemed superior to T₄ 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.

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References


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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.


22 Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM & Joffe RT. Does a combination regime of thyroxine (T4) and 3,5,3′-triiodothyronine improve depression symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized controlled trial *Journal of Clinical Endocrinology and Metabolism* 2003 88 4551–4555.


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