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Thyroxine vs Thyroxine Plus Triiodothyronine in Treatment of Hypothyroidism After Thyroidectomy for Graves' Disease

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It was recently demonstrated that treatment with levorotatory thyroxine (T_4) plus triiodothyronine (T_3) compared with treatment with T_4 alone improves psychologic functioning in hypothyroid patients with thyroid cancer or autoimmune thyroiditis. In the present double-blind crossover study, we again compared the effects of combined thyroid replacement vs monotherapy on psychologic function, endocrine function, cardiovascular function, and body composition. The patients were women who were hypothyroid after thyroidectomy for Graves' disease. The substitution of 10 μg of T_3 for 50 μg of T_4 caused a statistically significant decrease in free T_4 concentration but no significant change in T_3 or thyroid-stimulating hormone concentration. Symptoms of hypothyroidism and of hyperthyroidism tended to decrease on a standard symptom scale after combined treatment. With combined hormone replacement, mental state tended to improve on some mood scales but not on cognitive tests. We found alterations in left ventricular diastolic function but no change in body composition after the combined treatment regimen. These preliminary findings in a small group of patients with Graves' disease are consistent with earlier findings that thyroid replacement with T_4–T_3 combination improves mental functioning.

Key Words: Graves' disease; hypothyroidism; triidothyronine; levorotatory thyroxine.

Introduction

The thyroid gland secretes both levorotatory thyroxine (T_4) and triiodothyronine (T_3). It is the only source of T_4, secreting about 100 μg/d. The gland also secretes at least 6 μg of T_3/d, about 24 μg more coming from deiodination of T_4 by tissues *(1)*. It is conventional to provide thyroid replacement treatment with T_4 alone in the belief that each tissue will make T_3, the more potent hormone, sufficient to its needs. Nevertheless, it has long been noted that after treatment with T_4 alone not all patients are entirely well *(2)*. Not all tissues are equally able to perform deiodination of T_4 to T_3 *(3)*, and some of them may be differentially sensitive to the low T_3 concentration usually observed after replacement with T_4 alone. Brain, or some parts of it *(4)*; the cardiovascular system *(5)*; and body weight *(6)* are especially sensitive to minor changes in the thyroid economy.

In a previous report *(7)* our group described the results of treating 33 patients with hypothyroidism with T_4 alone or with a reduced amount of T_4 (50 μg) combined with a small amount of T_3 (12.5 μg). Improvements in mood state and cognitive functioning as well as in concentration of sex hormone–binding globulin (SHBG) occurred after combined treatment. Later, we reported that these effects were related to the cause of hypothyroidism *(8)*; that is, improvement in psychologic functioning was expressed more evidently in patients with thyroid cancer than in patients with autoimmune thyroiditis. Patients with treated Graves' disease were not included in that study.

In the present double-blind, crossover study we compared mental effects, cardiovascular effects, and changes in body composition after combined replacement with T_4 plus T_3 vs monotherapy with T_4 alone in thyroidectomized patients with Graves' disease.

Materials and Methods

Patients

Patients were invited to participate in the study if they attended the Institute of Endocrinology of the Kaunas Medical University in Kaunas, Lithuania; if they had had subtotal thyroidectomy for Graves' disease (diagnosis supported by histopathologic assessment of thyroid tissue); if they received at least 100 μg/d of T_4 to achieve euthyroidism; if they had no other significant illness; and if they gave written, informed consent. Thirteen female patients were recruited and 10 patients completed the study (mean age: 34 yr; range: 19–58 yr). Two patients were excluded from the study, one owing to pregnancy, and the other owing to high TSH concentration at baseline. One patient refused to

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Table 1
Thyroid Hormone Concentration, Thyroid Symptoms, Psychological Function, Echocardiographic Findings, and Body Composition in 10 Hypothyroid Patients with Graves' Disease at Baseline, After Treatment with T_4, and After Treatment with T_4 Plus T_3 (mean ± SD)

				Wilcoxon test[a]		
	Baseline (1)	T_4 treatment (2)	T_4 plus T_3 treatment (3)	1 vs 2	1 vs 3	2 vs 3
Hormone						
Free T_4 (pmol/L)	20.7 ± 6.2	21.1 ± 4.9	12.3 ± 4.1	NS	0.008	0.008
Total T_3 (nmol/L)	—	3.5 ± 1.0	3.8 ± 1.4	—	—	NS
Thyrotropin (mIU/L)	1.02 ± 1.53	0.45 ± 0.48	0.47 ± 0.46	NS	NS	NS
SHBG (nmol/L)	—	76 ± 31	78 ± 36	—	—	NS
Thyroid symptoms scale						
Hypothyroidism	14.1 ± 7.3	11.1 ± 4.8	8.1 ± 4.1	0.06	0.01	0.08
Hyperthyroidism	4.6 ± 2.2	4.4 ± 2.2	3.2 ± 1.8	NS	0.06	0.10
Mood						
BDI	8.2 ± 6.5	5.2 ± 5.1	3.3 ± 3.5	NS	0.10	NS
POMS: global score	16 ± 17	14 ± 21	10 ± 21	NS	NS	NS
VAS						
Tension	32 ± 20	30 ± 22	19 ± 15	NS	0.03	0.09
Sadness	26 ± 22	31 ± 24	17 ± 18	NS	NS	0.08
Confusion	28 ± 21	22 ± 22	13 ± 14	NS	0.07	0.09
Digit Symbol Test						
Pairs recalled	5.8 ± 3.0	7.9 ± 1.7	8.5 ± 1.1	0.03	0.04	NS
Raw score	56 ± 11	62 ± 6	62 ± 6	0.02	0.07	NS
Digit Span Test						
Forward	6.2 ± 1.3	6.9 ± 2.3	7.1 ± 2.2	NS	0.08	NS
Backward	5.3 ± 1.1	6.3 ± 0.9	5.9 ± 1.7	0.03	NS	NS
Echocardiography (n = 8)						
Heart rate (beats/min)	—	72 ± 10	66 ± 6	—	—	NS
Left ventricular ejection fraction (%)	—	63 ± 9	61 ± 6	—	—	NS
Early to late diastolic velocity ratio	—	1.76 ± 0.61	1.79 ± 0.34	—	—	NS
Early diastolic velocity of mitral annulus motion (cm/s)	—	17.6 ± 2.4	16.7 ± 2.9	—	—	0.05
Body composition						
Weight (kg)	—	67 ± 21	66 ± 22	—	—	NS
BMI (kg/m^2)	—	24 ± 9	24 ± 10	—	—	NS
Lean mass (kg)	—	43 ± 5	43 ± 5	—	—	NS
Fat mass (kg)	—	24 ± 18	23 ± 20	—	—	NS
Water mass (L)	—	31 ± 4	31 ± 4	—	—	NS

[a]NS, not significant.

continue the study without explanation, while on combined treatment. The pretreatment dose of T_4 used for thyroid replacement was 100 µg in seven patients and 150 µg in three patients. Baseline hormone concentration, results of psychologic tests, and clinical measurements are provided in Table 1.

Study Design

Each patient took her usual dose of T_4 up to and including the first day of the study. On this day she was assigned, according to a prearranged randomized schedule, to receive T_4 alone for 5 wk or to receive T_4 plus T_3 for 5 wk. After 5 wk the alternate treatment was given. Each patient's regimen was based on her usual dose of T_4 given in usual tablet form. However, during combined therapy 10 µg of T_3 was substituted for 50 µg of T_4. Tablets containing thyroid hormones were provided by Merck, Germany. We used 10 µg of T_3 instead of 12.5 µg, used in our earlier studies *(7,8)*, because the smaller dose may be more physiologic *(13)*. Tablets of T_4 and tablets of the T_4–T_3 combination were identical in shape and color. Patients took medications once daily, half an hour before breakfast.

At the end of the first 5-wk period, each patient was given a second batch of tablets. Patients and investigators

were not informed of treatment sequence. Patients, when asked at the end of each treatment period, said that they had taken their medications as instructed.

Evaluations

Patients were systematically studied at baseline and the last day of the two treatment periods. Having omitted breakfast but having taken their thyroid medication about 2 h earlier, they reported to the clinic at 9:00 AM. Blood was drawn for measurement of biochemical variables. Serum samples were frozen so that the samples from all the patients could be analyzed at the same time for a given variable. TSH was measured by immunoradiometric assay with kits obtained from Orion Diagnostica Spectria (Finland), with a sensitivity of 0.05 μU/mL. Serum-free T_4 (CIS Bio International, France) and total T_3 were measured by radioimmunoassay (Immunotech, Czech Republic). SHBG was assessed by immunoradiometric assay (Orion Diagnostica). Intraassay variation was between 3 and 6%.

For assessment of symptoms of thyroid dysfunction, we used a self-rating scale that included symptoms of hypothyroidism from the Billewicz index for hypothyroidism *(14)* and symptoms of hyperthyroidism from a symptom rating scale devised by Klein et al. *(15)*.

For assessments of mood state and cognitive function, each patient had the same examiner for whichever variable was being measured. Three mood scales were used: the BDI *(16)*, the Profile of Mood States (POMS) *(17)*, and VAS. The BDI is a self-rating scale consisting of 21 items. Scores of 10 or less indicate normal mood variation while scores of 11 or more reflect increasing degrees of depression. The POMS measures affective states. The subject responds to 65 items, each pertaining to an aspect of subjective state, on a scale from 0 to 4. Scores for combinations of items are added, yielding values for six aspects of mood and a global score. VAS provided detailed ratings of mood. Each scale consists of a pair of contrasting phrases, such as "sad as possible" and "happy as possible," at either end of a 100-mm line. The patient marks the point on each line best corresponding to her state at that time.

Cognitive functioning was measured by the use of two tests: the Digit Symbol Test, and the Digit Span Test of the Wechsler Adult Intelligence Scale *(18)*. In the Digit Symbol Test, a key is shown that pairs each of the numbers 1 through 9 with a nonsense symbol. Below are rows of pairs of squares; the upper square contains a number, and the lower square is blank. Using the key, the patient is allowed 90 s to complete each pair of squares, entering the appropriate symbol. The raw score consists of the number of correct entries completed in 90 s or until completion of the third row, whichever occurs first. The score indicates psychomotor performance. Without using the key, the subject then attempts to recall which symbol matched each number. The number of pairs correctly recalled indicates incidental learning. In the first part of the Digit Span Test, the subject is required to repeat spoken numbers with increasing numbers of digits, indicating immediate auditory attention. The second part of the test requires the subject to repeat the numbers in reverse order, indicating mental flexibility.

Echocardiography was performed for evaluation of left ventricular function by use of an HP Sonos 5500 echocardiograph. Ejection (EF) was measured for systolic function, and transmitral flow Doppler recording and tissue Doppler imaging of mitral annulus motion were performed for diastolic function analysis. Echocardiography was performed in 8 of 10 patients. In two patients precise measurement was impossible: in one case owing to atrial septal defect, in the other owing to bad quality of echocardiographic imaging.

Body composition was assessed by use of a body composition monitoring unit, Bodystat 1500. The device operates on the principle of analysis of bioelectrical impedance. Body composition consists of the determination of the body's lean and fat weight, which together make up the total body weight. Lean weight is defined as everything that is not a fat and includes skeleton, muscles, viscera, and total body water.

Statistical Analysis

Descriptive values are given as a mean ± SD. The differences between measurements were compared using Wilcoxon signed rank test. In all calculations we considered $p < 0.05$ as significant, but values between $p = 0.05$ and $p = 0.1$ are reported.

Results

Table 1 shows the values obtained at baseline and after two experimental treatment regimens in this preliminary study of a small group of women with Graves' disease who had been treated with subtotal thyroidectomy.

A striking finding was this: dependent variables after T_4 treatment in the experimental regimen were often quite different from values at baseline, when the same dose of T_4 presumably was in effect. All changes were in the direction of enhanced mental activity and decreased symptoms of hypothyroidism. Thus, T_4 treatment in the experimental regimen improved performance on the Digit Symbol Test and on backward recall on the Digit Span Test. The effect on thyroid-stimulating hormone (TSH) is noteworthy: it was numerically substantial but not statistically significant, probably owing to large variance. Indeed, the variance for the mean values for most parameters, under whichever condition, was large in this group of patients.

Combined hormone treatment produced a similar number of significant changes as did monotherapy in comparison to baseline levels. Thus, to a statistically significant degree, the substitution of 10 μg of T_3 for 50 μg of T_4 reduced the concentration of free T_4, as well as the symptoms of hypothyroidism and subjective tension, while improving pairs recalled on the Digit Symbol Test. In addition, it tended

to reduce the symptoms of hyperthyroidism, to improve mood on the Beck Depression Inventory (BDI) as well as feeling of confusion on the Visual Analog Scale (VAS), and to improve the raw score on the Digit Symbol Test and forward recall on the Digit Span Test. Only two differences between combined treatment and monotherapy on dependent variables were statistically significant: the effect on concentration of free T_4 and the effect on diastolic velocity of mitral annulus motion. Substantially the same after the two regimens were ejection fraction and early to late diastolic velocity ratio of transmitral flow and heart rate. In a similar way, there were no differential effects of the two treatments on body mass index (BMI), lean body mass, fat body mass, or water body mass. However, there was a strong tendency toward a decrease in symptoms of both hypothyroidism and hyperthyroidism on the standard symptoms scale as well as toward mood improvement on VAS scales after T_4–T_3 combination in comparison with the experimental T_4 treatment regimen.

At the end of the study, patients were asked about treatment preference. Six patients preferred combined treatment, reporting increased energy, better performance, and decreased "tension in the eyes." Two patients preferred monotherapy with T_4, reporting better mood and less fatigue, and two found no difference. Two patients reported "sensitiveness of the heart," and one reported hand tremor while taking T_4 alone.

Discussion

These preliminary findings on treatment of hypothyroidism with T_3 plus T_4 combination in comparison with monotherapy with T_4 in hypothyroid patients with treated Graves' disease are consistent with our previous data that improvement in mental functioning after combined thyroid hormone replacement is related to the cause of hypothyroidism *(8)*. The benefits of substituting some T_3 for some T_4 in patients with Graves' disease in the present study were not as evident as those that we found in patients with thyroid cancer in an earlier report and were close to findings in patients with autoimmune thyroiditis *(8)*. After total thyroidectomy, as for cancer, patients totally lack T_3 secretion and, absent T_3 administration, are completely dependent on deiodination by tissues for its supply. In Graves' disease, as in autoimmune thyroiditis *(8)*, residual thyroid tissue may continue to secrete T_3. The influence of T_3 production, by residual thyroid tissue, on the results of the present study is supported by the lack of significant change in T_3 concentration after the two treatment regimens.

Our data, though preliminary, raise an important question: Is a dose of 10 μg of T_3 sufficient to substitute for 50 μg of T_4? In our previous studies *(7,8)* we used 12.5 μg for this purpose and found a more robust separation of the effects of the two hormones. The previously cited factors could contribute to this observation, but some findings suggest that 10 μg of T_3 is indeed insufficient. After combined therapy there was no enhanced suppression of TSH. In a similar way there was no increase in concentration of total T_3, although there was indeed suppression of total T_4. Finally, there was a null effect of combined therapy on measures pertaining to body mass and body fat, while cardiovascular data gave direct evidence that the dose of T_3 may have been inadequate to maintain euthyroidism, at least as expressed in these parameters.

As in hypothyroidism owing to other causes *(7)*, only combined treatment produces a pattern of thyroid hormone in serum that almost reaches normal. Peripheral concentration of thyroid hormones is a major mechanism controlling thyroid economy and production of T_3 in the brain *(3)*. We also noted that combined therapy not only reduced the symptoms of hypothyroidism but tended to reduce the symptoms of hyperthyroidism as well, exerting what might be regarded as a stabilizing effect.

We have noted the large variance that occurred in many results. Poor baseline compliance with prescribed medication, and thus uncertain compliance during the study, is a possible contributing factor. Another possibility requires mention—in Graves' disease residual thyroid tissue may be autonomous; that is, it may not be regulated by TSH in the usual manner *(9)*, a factor that could only add to the variability of findings.

An overarching question remains unanswered: When thyroid hormone replacement is needed, is T_4 alone the best, or even a sufficient, treatment? In addition to our work, other observations address this question. Carr et al. *(10)* have suggested that for a patient to achieve a sense of full well-being he or she needs to take a dose of T_4 that is 50 μg in excess of the dose needed to restore normal concentrations of TSH. Tigas et al. *(11)* reported that a dose of T_4 that restores TSH to normal nevertheless allows unwanted weight gain. Escobar-Morreale et al. *(12)*, studying thyroidectomized rats, found that T_4 alone will not restore T_3 concentrations to normal in all tissues; T_3 administration is needed as well. Conclusive study with a larger hypothyroid population, especially of patients who do not feel entirely well while receiving T_4 monotherapy, is needed to answer this question.

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