EFFECTS OF THYROXINE AS COMPARED WITH THYROXINE PLUS TRIIODOTHYRONINE IN PATIENTS WITH HYPOTHYROIDISM

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ABSTRACT

Background   Patients with hypothyroidism are usually treated with thyroxine (levothyroxine) only, although both thyroxine and triiodothyronine are secreted by the normal thyroid gland. Whether thyroid secretion of triiodothyronine is physiologically important is unknown.

Methods   We compared the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) in 33 patients with hypothyroidism. Each patient was studied for two five-week periods. During one period, the patient received his or her usual dose of thyroxine. During the other, the patient received a regimen in which 50 μg of the usual dose of thyroxine was replaced by 12.5 μg of triiodothyronine. The order in which each patient received the two treatments was randomized. Biochemical, physiologic, and psychological tests were performed at the end of each treatment period.

Results   The patients had lower serum free and total thyroxine concentrations and higher serum total triiodothyronine concentrations after treatment with thyroxine plus triiodothyronine than after thyroxine alone, whereas the serum thyrotropin concentrations were similar after both treatments. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine. The pulse rate and serum sex hormone–binding globulin concentrations were slightly higher after treatment with thyroxine plus triiodothyronine, but blood pressure, serum lipid concentrations, and the results of neurophysiologic tests were similar after the two treatments.

Conclusions   In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland. (N Engl J Med 1999;340:424-9.)
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T HERE are two thyroid hormones, thyroxine and triiodothyronine. The daily production of thyroxine is about 100 μg, all produced by the thyroid gland. The daily production of triiodothyronine is about 30 μg, of which about 20 percent is produced by the thyroid gland and 80 percent by deiodination of thyroxine in extrathyroidal tissues.[1] Not all tissues that need thyroid hormone are equally able to convert thyroxine to triiodothyronine, the active form of the hormone.[2] Nevertheless, most patients with hypothyroidism are treated only with thyroxine (levothyroxine). Although this treatment is effective, some patients with hypothyroidism treated with thyroxine are not entirely well.[3] This observation, plus the existence of differences in the rate of conversion of thyroxine to triiodothyronine in different tissues,[2] prompted us to compare the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) on thyroid hormone actions in the brain, pituitary gland, and other organs in patients with hypothyroidism.

METHODS

Patients

We invited patients with chronic autoimmune thyroiditis or thyroid cancer treated by near-total thyroidectomy who received care at the Institute of Endocrinology of Kaunas Medical University in Kaunas, Lithuania, to participate in the study if they were totally, or nearly totally, dependent on exogenous thyroxine. The patients with chronic autoimmune thyroiditis were receiving replacement therapy with thyroxine, and the patients with cancer were receiving thyroxine as suppressive therapy. Patients with other serious medical illnesses were excluded.

Thirty-five patients were enrolled, and 33 completed the study: 31 women and 2 men, with a mean ($\pm$SD) age of 46$\pm$13 years (Table 1). Sixteen patients had chronic autoimmune thyroiditis, and 17 had thyroid cancer. The mean dose of thyroxine at base line was 175$\pm$53 μg per day; the range was from 100 μg per day (five patients) to 300 μg per day (two patients). The mean duration of treatment was 73$\pm$72 months. In all patients the dosage had been stable for at least three months. The mean score on the Hamilton Rating Scale for Depression (the 21-item "long" version) was 9.8$\pm$5.4, on a scale from 0 (indicating no depression) to 69 (the maximal theoretical score).[4] Four women had major depression, as defined and diagnosed by standard instruments.[5,6] One patient withdrew from the study because she became pregnant, and another because of anxiety. The study was approved by the institutional review board of Kaunas Medical University, and all patients gave written informed consent.

Study Protocol

Patients took their usual dose of thyroxine through the first day of the study. On this day each patient was assigned, according to a prearranged randomization schedule, either to receive thyroxine alone for five weeks, then thyroxine plus triiodothyronine for five weeks, or to receive thyroxine plus triiodothyronine for five weeks, then thyroxine alone for five weeks. The thyroxine (Berlin-Chemie, Berlin, Germany) was given as 50-μg tablets at each pa-

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	THYROXINE FIRST (N=17)	THYROXINE PLUS TRIIODOTHYRONINE FIRST (N=16)	ALL PATIENTS (N=33)
Sex (no. of patients)			
Female	15	16	31
Male	2	0	2
Age (yr)	45±10	48±15	46±13
Cause of hypothyroidism (no. of patients)			
Chronic autoimmune thyroiditis	4	12	16
Thyroid cancer	13	4	17
Prestudy dose of thyroxine (μg/day)	181±56	169±51	175±53
Duration of therapy (mo)	54±41	92±96	73±72
Serum thyrotropin (μU/ml)	0.3±0.8	1.5±1.8	0.7±1.4
No. of patients with undetectable serum thyrotropin (<0.05 μU/ml)	1	2	3
Serum free thyroxine (ng/dl)†	2.0±0.7	1.9±0.5	2.0±0.6
Hamilton depression score‡	10.0±5.5	9.5±5.3	9.8±5.4
Current depression (no. of patients)§	2	2	4

*Plus–minus values are means ±SD.

†To convert values for serum free thyroxine to picomoles per liter, multiply by 12.87.

‡The 21-item version of the Hamilton Rating Scale for Depression was used.[4]

§Current depression was determined with use of the Structured Clinical Interview in the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised.[5,6]

tient's usual total dose, but 50 μg of the dose of thyroxine was replaced by a capsule. These capsules contained either 50 μg of thyroxine or 12.5 μg of triiodothyronine (Berlin-Chemie), depending on the assigned treatment. They were prepared by a pharmacist and were identical in appearance. If, for example, a patient had been treated with 200 μg of thyroxine per day, he or she was instructed to take 150 μg of the usual thyroxine tablets plus one capsule each morning. If the patient had been assigned to receive thyroxine alone, the capsule contained 50 μg of thyroxine; if the patient had been assigned to receive thyroxine plus triiodothyronine, the capsule contained 12.5 μg of triiodothyronine. Patients took the medications once daily, half an hour before breakfast.

At the end of each five-week period, the patients were given another batch of tablets and capsules. Only the pharmacist knew which capsules had been dispensed. At the end of each treatment phase, all patients, when asked, said that they had taken their medications as instructed, but remaining pills were not counted.

Evaluations

The patients were systematically studied on the last day of each five-week treatment period. They reported to the clinic at about 9 a.m., having omitted breakfast but having taken their thyroid hormone about two hours earlier. Venous blood was taken for measurements of serum thyrotropin, thyroid hormones, cholesterol, triglycerides, and sex hormone–binding globulin.[7] Physiologic tests were performed. Assessments were made of cognitive function and psychological state. Each patient had the same examiner for whatever variable was being measured at each session, and the examiners were unaware of the patients' treatment assignments.

Biochemical Measurements

Serum samples were frozen, allowing the samples from all the patients to be analyzed at the same time for each variable. Serum thyrotropin was measured by immunoradiometric assay with kits obtained from Orion Diagnostica (Espoo, Finland), with a sensitivity of 0.05 μU per milliliter. Serum free and total thyroxine and triiodothyronine were measured with radioimmunoassay kits (Orion Diagnostica). Serum total cholesterol and triglycerides were measured by enzymatic colorimetric methods (Sera-Pak Cholesterol Fast Color kit and Sera-Pak Triglycerides Fast Color kit, Bayer, Tarrytown, N.Y.). Serum sex hormone–binding globulin was measured with immunoenzymometric assay kits (Medix Biochemica, Kauniainen, Finland). The intraassay variation ranged from 3 to 6 percent.

Physiologic Measurements

Cardiovascular System

The pulse rate was recorded after the patient had been supine for five minutes. Blood pressure was measured in the sitting position. Electrocardiography was performed at both sessions, and all the results were normal.

Peripheral Nervous System

The sensory threshold (minimal detectable intensity of vibration) was measured with a biothesiometer (Model PVD, Biomedical, Newbury, Ohio) applied to the tip of the fourth finger and the tip of the fourth toe.[8] The Achilles tendon reflex was measured with an electroneuromyograph (Type LT1, Medicor, Budapest, Hungary).[9]

Psychological Assessment

Psychological assessment was performed according to the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised (DSM-III-R).[5] Symptoms were recorded according to the Structured Clinical Interview of the DSM-III-R for assessment of nonpsychotic disorders (Lithuanian edition).[6]

Cognitive functioning was assessed by three standard tests: the Digit Symbol Test,[10] the Digit Span Test of the Wechsler Adult Intelligence Scale,[10] and the Visual Scanning Test.[11] In the Digit Symbol Test, a key is provided that pairs each of the numbers 1 through 9 with a nonsense symbol. Below are rows of pairs of squares, the upper of which contains a number, the lower of which is blank. With the key available, the subject is allowed 90 seconds to complete each pair of squares by entering the appropriate symbol. The raw score is the number of correct entries completed in 90 seconds or until completion of the third row, whichever occurs first. This score measures psychomotor performance. With the key unavailable, the subject is then asked to recall which symbol matched each number. The number of pairs correctly recalled is a measure of incidental learning. Then the subject copies 70 symbols. The less time is required for completion, the greater the subject's psychomotor speed.

The first part of the Digit Span Test requires the subject to repeat spoken numbers with increasing numbers of digits; it measures immediate auditory attention. The second part, which requires the subject to repeat the numbers in reverse order, measures mental flexibility.

The Visual Scanning Test assesses distractibility and visual inattentiveness. The subject is shown a "target" symbol and then presented with a paper with a matrix of symbols containing 60 targets. The patient circles all the target symbols that he or she can find. The time needed to complete the test, omissions, and errors are scored.

The Hamilton Rating Scale for Depression (21-item "long" version)[4] was used to assess the severity of depressive symptoms. Clinically important depression is associated with scores of 20 or more.

Three scales were completed by the patients: the Beck Depression Inventory,[12] the Spielberger State–Trait Anxiety Inventory,[13]

TABLE 2. BIOCHEMICAL AND PHYSIOLOGIC VALUES AT THE END
OF EACH TREATMENT PERIOD.*

VALUE†	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE‡	NORMAL RANGE
Serum thyrotropin (μU/ml)	0.8±2.5	0.5±1.1	0.56	0.3–5.0
No. of patients with undetectable serum thyrotropin (<0.05 μU/ml)	7	5	—	—
Serum free thyroxine (ng/dl)	2.3±0.7	1.8±0.6	<0.001	0.7–2.1
Serum total thyroxine (μg/dl)	15.2±3.8	11.3±3.3	<0.001	4–11
Serum total triiodothyronine (ng/dl)	87±38	117±42	<0.001	75–175
Serum triglycerides (mg/dl)	129±54	132±55	0.76	47–228
Serum cholesterol (mg/dl)	219±46	217±43	0.66	152–268
Serum sex hormone–binding globulin (μg/dl)	2.6±1.3	3.1±1.5	0.007	0.4–3.5
Pulse rate at rest (beats/min)	69±11	72±12	0.04	—
Blood pressure while seated (mm Hg)				
Systolic	130±21	124±18	0.18	—
Diastolic	79±12	77±14	0.52	—
Sensory threshold (V)				
4th Finger	7.5±2.6	7.4±2.4	0.87	6–10
4th Toe	9.4±3.0	9.3±2.9	0.89	8–12
Achilles reflex relaxation half-time (msec)	282±22	286±28	0.28	240–320

*Plus–minus values are means ±SD.

†To convert values for serum free and total thyroxine to picomoles per liter and nanomoles per liter, respectively, multiply by 12.87. To convert values for serum triiodothyronine to nanomoles per liter, multiply by 0.015. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

‡P values were calculated by paired t-tests.

and the Profile of Mood States.[14] The Beck Depression Inventory is a self-rating scale of 21 items, in which scores of 10 or less indicate normal mood variation and scores of 11 or more reflect increasing degrees of depression. The Spielberger State–Trait Anxiety Inventory is a self-rating scale consisting of 20 items; scores below 50 are normal. The Profile of Mood States assesses affective states. The subject rates 65 items, each pertaining to an aspect of subjective state, on a scale from 0 to 4. When the scores for combinations of items are added, values for six aspects of mood and a global score are obtained.

Fifteen visual-analogue scales provided more detailed ratings of mood and physical symptoms by the patients. Each scale consisted of a pair of phrases, such as "as sad as possible" and "as happy as possible," at either end of a 100-mm line. The patient placed a mark at the point best corresponding to his or her state at that time. Measurement of the marks from the beginning of the line generated a score.

At the completion of the study, each patient was asked which treatment (the first or the second) he or she preferred.

Statistical Analysis

Paired t-tests were used to compare paired data from the two treatment periods. Nonpaired t-tests were used to compare values in subgroups of patients — for example, depressed and nondepressed patients. Results pertaining to the patients' treatment preferences were evaluated with use of McNemar's test. Probability values were based on two-sided analyses of test results.

RESULTS

The patients' biochemical and physiologic values after each treatment period are shown in Table 2. As expected, the mean serum free and total thyroxine concentrations were lower and the mean serum total triiodothyronine concentration was higher after treatment with thyroxine plus triiodothyronine than after treatment with thyroxine alone. The mean serum thyrotropin concentrations were similar after the two treatments. The mean serum cholesterol and triglyceride concentrations also were similar after the two treatments, whereas the mean serum sex hormone–binding globulin concentration was significantly higher after treatment with thyroxine plus triiodothyronine, suggesting that thyroid hormone action was greater after treatment with thyroxine plus triiodothyronine. The mean pulse rate at rest was slightly higher after treatment with thyroxine plus triiodothyronine, but mean blood-pressure values and neurophysiologic findings were similar after the two treatments.

Scores pertaining to cognitive functioning and mood were within normal limits, except that patients were marginally less able to recall digit–symbol pairs correctly on the Digit Symbol Test after treatment with thyroxine alone (Table 3). Among the 17 comparisons, 6 pairs showed an advantage (P<0.05) for treatment with thyroxine plus triiodothyronine and none for treatment with thyroxine alone.

TABLE 3. PSYCHOMETRIC FINDINGS AT THE END OF EACH TREATMENT PERIOD.*

TEST OR SCALE	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE†	NORMAL VALUE
Cognitive performance				
Digit Symbol Test				
Pairs recalled correctly	5.5±2.3	6.3±2.1	0.04	>6
Time (sec)	58±15	56±16	0.07	—
Raw score	48±12	47±12	0.76	>43
Digit Span Test				
Backward recall of digits	5.5±1.6	6.0±1.3	0.05	>5
Forward recall of digits	6.9±1.9	6.9±1.8	0.99	>5
Visual Scanning Test				
Time (sec)	75±23	71±25	0.15	<120
Total correct	58±2	59±2	0.53	>56
Errors	1.7±1.8	1.5±2.1	0.58	<3
Mood scores				
Beck Depression Inventory	9.8±7.7	7.9±5.3	0.10	<11
Spielberger State–Trait Anxiety Inventory	44±11	45±8	0.38	<50
Profile of Mood States				
Global score	33±28	24±24	0.01	—
Fatigue–inertia	9.3±4.3	7.2±3.9	0.001	<18
Depression–dejection	13.4±9.5	10.5±8.9	0.01	<26
Anger–hostility	9.1±7.3	7.3±5.2	0.04	<17
Confusion–bewilderment	5.3±4.5	4.3±3.5	0.13	<17
Tension–anxiety	8.5±5.3	7.7±5.4	0.23	<21
Vigor–activity	12.4±4.6	13.0±3.7	0.39	>9

*Among the 17 tests, patients had better results after treatment with thyroxine plus triiodothyronine on 14; 6 of these differences were significant ($P<0.05$). On two tests performance was better after thyroxine treatment; neither difference was significant. Forward recall of digits was essentially the same after both treatments. Plus–minus values are means ±SD.

†P values were calculated by paired t-tests.

Performance after thyroxine-plus-triiodothyronine treatment was significantly better ($P<0.05$) on parts of two of the three tests of cognitive performance (Table 3). The higher scores for recall of pairs on the Digit Symbol Test indicated better incidental learning, and the higher scores for recalling digits in reverse order on the Digit Span Test indicated improved mental flexibility and attention.

The three self-rating mood scales pertained to depression, anxiety, or both. After thyroxine-plus-triiodothyronine treatment, the patients tended to be less depressed (shown by lower scores on the Beck Depression Inventory), and their global scores and scores on the three subscales (fatigue–inertia, depression–dejection, and anger–hostility) of the Profile of Mood States were significantly lower ($P<0.05$), indicating improvement, than scores after treatment with thyroxine alone (Table 3).

Eight visual-analogue scales pertained to mood and seven to physical symptoms (Table 4). Patients scored their mood as significantly better after thyroxine-plus-triiodothyronine treatment on seven of the eight mood scales ($P<0.04$) and scored their physical symptoms as significantly improved on three of seven scales ($P<0.02$). Patients reported only slight physical problems at both evaluations. Their mean visual-analogue scores were closer to "no symptoms" than to "severe symptoms" — that is, less than 50, the middle of each test line.

When asked at the end of the study whether they preferred the first or second treatment, 20 patients preferred thyroxine plus triiodothyronine, 11 had no preference, and 2 preferred thyroxine alone ($P=0.001$). The order of treatment was unrelated to preference. The two patients who preferred thyroxine had noticed that they felt slightly "nervous" during combined treatment. The 20 patients who preferred thyroxine plus triiodothyronine had noticed that they were more energetic, had better concentration, and simply felt better. One woman became anxious during treatment with thyroxine plus triiodothyronine and was withdrawn from the study.

The order of treatment did not affect the results. To determine whether triiodothyronine was more beneficial in patients receiving either high ratios of triiodothyronine to thyroxine (i.e., those who received lower doses of thyroxine at base line) or low ratios, we compared the results from the 20 patients who were taking 100 to 150 μg of thyroxine at base line with those from the 13 patients who were taking 200 to 300 μg. The results were similar in the two groups. There was also no difference between

SCALE	AFTER THYROXINE (N=33)	AFTER THYROXINE PLUS TRIIODOTHYRONINE (N=33)	P VALUE†
Mood			
Sad	40±24	26±19	<0.001
Confused	34±24	23±20	<0.001
Fearful	30±29	20±22	0.001
Irritable	39±28	27±22	0.002
Tense	42±29	28±23	0.007
Angry	32±28	25±20	0.02
Tired	49±26	39±28	0.04
Agitated	39±30	34±26	0.18
Physical symptoms			
Feel cold	37±27	23±24	0.004
Blurred vision	30±29	22±27	0.01
Nauseated	22±23	13±17	0.02
Sleepy	39±29	29±27	0.09
Light-headed	35±26	31±28	0.22
Drowsy	36±27	31±25	0.29
Feel hot	24±21	25±27	0.80

*On every scale, a lower score represents a more favorable state. Scores of 0 or 100 are theoretically possible but are rarely encountered. Plus–minus values are means ±SD.

†P values were calculated by paired t-tests.

the responses of the 4 patients with depression and those of the 29 patients without depression. Finally, the advantage of thyroxine plus triiodothyronine was not limited to only a few patients. Analysis of the psychological variables for which combined therapy was most beneficial (Tables 3 and 4) showed that most patients derived at least some benefit from the addition of triiodothyronine (data not shown).

DISCUSSION

Patients with hypothyroidism benefited when 12.5 μg of triiodothyronine was substituted for 50 μg of thyroxine in their treatment regimens. They performed better on standard neuropsychological tasks, and their psychological state improved. The differences in most physiologic variables were slight, but in any case, these are insensitive indicators of thyroid hormone actions. Pulse rates and serum sex hormone–binding globulin concentrations were higher after treatment with thyroxine plus triiodothyronine, indicating a slightly greater effect on the heart and liver.[7] Serum thyroxine concentrations were lower and triiodothyronine concentrations were higher after treatment with thyroxine plus triiodothyronine, but serum thyrotropin concentrations, a sensitive measure of thyroid hormone action, were similar after the two treatments. The apparent difference in physiologic responses could reflect differences in tissue uptake of the hormones, in the conversion of thyroxine to triiodothyronine, or in thyroid hormone receptors.[15,16]

The variables related to mental function for which the substitution of triiodothyronine resulted in benefit require fuller description. On tests of cognitive performance and self-rating scales for mood, patients scored in the normal range on 16 of 17 measures after both treatments (Table 3), but on 6 of the tests or scales they performed or felt significantly better after receiving thyroxine plus triiodothyronine. These results were reinforced by results on the visual-analogue scales. No test result was better after treatment with thyroxine alone. It seems clear that treatment with thyroxine plus triiodothyronine improved the quality of life for most patients. We think that five weeks was probably long enough for the maximal effect of the treatments to be detected, but we cannot be sure.

Despite these results, it is clear that the substitution of triiodothyronine for a portion of regular thyroxine therapy is not sufficient treatment for depression, because the 4 depressed patients benefited from triiodothyronine substitution no more than the other 29 patients. Nevertheless, in depressed patients who have normal thyroid hormone concentrations, the addition of triiodothyronine to standard antidepressant-drug treatment can be beneficial.[17]

This study extends two others in which different regimens of thyroxine and triiodothyronine were compared. In one study, in which the doses were much higher than those used in this study, the patients preferred thyroxine alone, because it was somewhat less toxic.[18] In the other, an open trial involving nine depressed patients who were receiving thyroxine-replacement therapy but were responding poorly to an antidepressant drug, the addition of triiodothyronine (15 to 50 μg daily) to thyroxine (rather than the substitution of triiodothyronine) resulted in a marked decrease in depression in seven patients.[19]

There are at least two ways in which the use of thyroxine alone for replacement therapy might deprive the brain of triiodothyronine. First, delivery of triiodothyronine through the circulation, the source of about 20 percent of the triiodothyronine in the rat brain,[20] is deficient to the extent that thyroid glandular secretion is deficient unless compensated for by production in peripheral tissues. Second, circulating thyroxine, and presumably thyroxine in the brain, will be increased, and in the brain thyroxine down-regulates its own conversion to triiodothyronine.[21] However, the two hormones are differently bound to plasma proteins and may be differently delivered to the brain.[22]

The daily production of triiodothyronine by the human thyroid gland is about 6 μg[23]; the rate of absorption of ingested triiodothyronine is almost 100 percent.[24] Thus, the dose of triiodothyronine given in the present study somewhat exceeded the normal glandular production. The ideal replacement regimen when thyroid-gland function is absent or nearly

absent might consist of 10 μg of triiodothyronine daily in sustained-release form (because the hormone is rapidly absorbed and metabolized), along with enough thyroxine to ensure euthyroidism.

We conclude that in patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may have more salutary effects on the brain and perhaps other tissues than those of an equivalent amount of thyroxine, as determined by their effects on thyrotropin secretion. This finding suggests that thyroidal secretion of triiodothyronine is physiologically important.

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