Suppression of serum thyrotropin with thyroxine in patients with Graves’ disease: effects on recurrence of hyperthyroidism and thyroid volume

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Abstract

Based on findings that thyroxine may have a beneficial effect on the recurrence of Graves’ hyperthyroidism, we prospectively studied the effects of a TSH suppressive treatment with thyroxine on the course of Graves’ disease in fifty patients with recent onset of hyperthyroidism. After the normalization of serum tri-iodothyronine (T₃) and thyroxine (T₄) concentrations, one group of patients was randomly assigned to a combined treatment with carbimazole and a TSH suppressive dose of T₄ for 12 months, followed by another 12 months of TSH suppressive therapy alone. The other group of patients also received carbimazole for one year, but T₄ was only added as indicated to normalize elevated TSH serum concentrations, and patients received no therapy during the second year. By the end of the second year, a relapse of hyperthyroidism had occurred in 43% of the patients with and in 45% of the patients without suppressive T₄ treatment. In those patients without a relapse of hyperthyroidism, initial thyroid size significantly (P = 0.01) decreased with time in both treatment groups. However, patients on suppressive T₄ treatment tended to have a greater reduction in thyroid volume than patients with normal TSH serum concentrations (P = 0.05). In conclusion, we were unable to detect a preventive effect of exogenous TSH suppression on the recurrence of hyperthyroidism. However, our data suggest that TSH suppressive treatment may have a beneficial effect on thyroid enlargement in Graves’ disease.

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Introduction

Thionamide antithyroid drugs are the established initial treatment for patients with Graves’ disease in Europe (1). Some clinicians prefer single treatment, others combine these drugs with thyroxine (2–5). The primary intention of the combined therapy is to avoid drug-induced hypothyroidism during antithyroid treatment. However, it has been suggested that the continuous administration of thyroxine (T₄) and the associated decrease in thyrotropin (TSH) serum concentrations might have additional beneficial effects on the course of Graves’ disease. Thus, Japanese patients who received T₄ therapy during antithyroid drug treatment and the subsequent year had a strikingly lower relapse rate of hyperthyroidism than patients treated with thionamide drugs alone (6). In order to find out whether the suppression of serum TSH might be equally effective in an area with a low iodine supply, we prospectively examined the effects of a TSH suppressive treatment with T₄ on the recurrence rate of hyperthyroidism in patients with Graves’ disease living in the area of Heidelberg, Germany.

Materials and methods

Subjects

A total of 66 patients with newly diagnosed hyperthyroidism due to Graves’ disease were enrolled in the study from 1992 to 1993 at the Department of Endocrinology and Metabolism in Heidelberg. We only included patients who had received a pretreatment with carbimazole or methimazole for less than 3 months before being referred to our clinic. Twelve patients who were directly referred to us without pretreatment were also included in the study. The diagnosis of Graves’ hyperthyroidism was based on the findings of elevated thyroid hormone levels and suppressed TSH serum levels, the presence of thyroid-associated ophthalmopathy, detectable serum concentrations of TSH receptor antibodies, an elevated diffuse isotope uptake in thyroid radionuclide scans and/or a characteristic diffuse low echogenicity on sonographic examination. TSH receptor antibody concentrations were only assessed initially to confirm the diagnosis of Graves’ disease, but were not followed up during the course of the study. Patients with
Table 1 Characteristics of the patients at study entry (after T₃ and T₄ normalization). Data are shown as means ± s.d. Data from the patients who were assigned to a normal TSH are separately shown for patients who had received carbimazole (Carb.) + T₄ and patients who had only received carbimazole. The last two columns to the right show the average length of time and the estimated cumulative dose of carbimazole (or equivalent) from initiation of antithyroid treatment to normalization of T₃ and T₄ serum concentrations.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of patients</th>
<th>Sex (F/M)</th>
<th>Age (years)</th>
<th>Thyroid volume (ml)</th>
<th>Normalization of T₃ and T₄ (months)</th>
<th>Cumulative carbimazole dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>22</td>
<td>17/5</td>
<td>37.9 ± 13.9</td>
<td>33.8 ± 16.2</td>
<td>1.7 ± 1.1</td>
<td>693 ± 379</td>
</tr>
<tr>
<td>Normal TSH Carb. + T₄</td>
<td>10</td>
<td>8/2</td>
<td>36.0 ± 15.1</td>
<td>30.7 ± 17.0</td>
<td>1.7 ± 0.7</td>
<td>771 ± 570</td>
</tr>
<tr>
<td>Carb. alone</td>
<td>12</td>
<td>9/3</td>
<td>39.6 ± 13.3</td>
<td>36.4 ± 15.8</td>
<td>1.7 ± 1.3</td>
<td>633 ± 125</td>
</tr>
<tr>
<td>Suppressed TSH</td>
<td>28</td>
<td>21/7</td>
<td>41.1 ± 10.2</td>
<td>30.6 ± 17.2</td>
<td>2.3 ± 1.7</td>
<td>777 ± 490</td>
</tr>
</tbody>
</table>

a large goiter were excluded. We arbitrarily choose 80 ml on the initial ultrasound examination as the cutoff point for exclusion. All patients gave informed consent for their participation in the study. The study was approved by the ethics committee on clinical investigations at the University of Heidelberg.

**Study design**

Patients who were still hyperthyroid upon referral to our clinic received variable doses of carbimazole until they had become euthyroid. Thirteen of the fifty patients received beta blocker treatment during the initial treatment phase. Patients were then randomly assigned to two treatment groups. Randomization into the treatment groups was achieved by random numbers without further stratification. One group of patients was allocated to a TSH suppressive treatment. Following normalization of tri-iodothyronine (T₃) and T₄ serum concentrations, these patients received 10 mg carbimazole and a variable dose of T₄ for the following 12 months. The T₄ dose was individually titrated from 50 μg to 150 μg to suppress TSH serum concentrations to below 0.03 mU/l. The other group of patients was assigned to normal TSH serum levels. After normalization of T₃ and T₄ serum concentrations, these patients also received 10 mg carbimazole for another 12 months. However, T₄ was only added when TSH concentrations exceeded 4 mU/l, and was administered in a dose that was just sufficient to normalize TSH levels. Of the 22 patients who were assigned to this group, 12 patients received 10 mg carbimazole alone. In the remaining 10 patients, carbimazole treatment had to be combined with low doses of T₄ in order to avoid latent hypothyroidism. After one year of treatment on this schedule, antithyroid medication was discontinued in all patients. Patients assigned to the normal TSH group received no further treatment. Patients on suppressive T₄ doses continued on the suppressive doses of T₄ for another year. Clinical status and serum concentrations of TSH, T₃, T₄, and thyroxine-binding globulin were routinely assessed at three-month intervals. In addition, patients who experienced symptoms suggestive of a relapse of hyperthyroidism after cessation of carbimazole treatment had their thyroid hormone concentrations checked immediately. In 3 patients with a suppressive dose of T₄, T₃ concentrations were borderline or only slightly elevated during regular follow-up visits. In these patients, T₄ treatment was discontinued and patients were re-evaluated after four weeks. In all 3

**Figure 1** Mean (± S.E.M.) serum TSH, T₃ and T₄ concentrations in the patients assigned to (◼) normal TSH serum levels and (○) suppressed TSH serum levels. Month 0 indicates the time point at which the serum concentrations of T₃ and T₄ had normalized and at which treatment with T₄ was initiated in patients assigned to the TSH suppressed group. Carbimazole treatment was discontinued at the end of month 12. Data from patients who had a recurrence of hyperthyroidism are included up to the time point of the manifestation of the relapse. * P < 0.05, ** P < 0.005 significantly different from the TSH-suppressed group.
patients, clearly elevated T₁ serum concentrations were observed at the time of the second visit.

**Ultrasound examination of the thyroid**

Ultrasound scans of the thyroid gland were performed using a 7-5 MHz linear array transducer. The volume of each lobe was calculated by the ellipsoid formula (volume (ml) = 1/6 × anterior-posterior diameter (cm) × width (cm) × length (cm)). Examinations were performed at the initial visit, after the patient had become euthyroid, and from then on in 6-months intervals. None of the patients had a significant retrosternal extension of the thyroid which would have interfered with the volume measurements. To ensure consistency, all scans were performed by the same physician.

**Measurement of serum TSH, T₃, and T₄**

Serum TSH was measured by an immunoluminometric assay (Henning, Berlin, Germany). The assay has a detection limit of 0-03 mU/l and a normal reference range of 0-3-4 mU/l. Total serum T₃ and T₄ were measured by competitive binding assay (Magic Lite, Ciba Corning, Fernwald, Germany). The normal ranges were 0-77-3-23 nmol/l (0-5-2-1 ng/ml), and 68-4-162-5 nmol/l (53-126 ng/ml) respectively. Interassay coefficients of variation for all three assays were less than 10%.

**Statistical analysis**

Results are given as means ± S.D. unless otherwise stated. For values of continuous outcome, the Mann-Whitney U test was used to assess differences between groups. The Wilcoxon paired signed-rank test was used to assess differences within groups during follow-up. P values for the differences in thyroid volume between TSH suppressive and nonsuppressive treatment are given for one-sided tests; all other P values are for two-sided tests. Differences in the proportion of recurrences of hyperthyroidism between groups were compared by chi-square test. The impact of thyroid size and function on the recurrence rate of hyperthyroidism was analyzed by multiple logistic regression.

Analyses were performed with SAS software (Cary, NC, USA).

**Results**

Of the 66 initially recruited patients, 50 (76%) completed the two-year study. None of the patients withdrew from the study because of side effects from the T₄ therapy. Patients in the two treatment groups were similar with respect to age, initial thyroid volume, and the length of time and cumulative dose of antithyroid drugs that were required to normalize T₃ and T₄ serum concentrations (Table 1). During the initial phase of hyperthyroidism, 6 of the 22 patients assigned to the TSH normal group and 7 of the 28 patients assigned to the TSH suppressed group had received beta blocker treatment which was discontinued after the patients had become euthyroid.

Patients in the TSH normal group who required a combined treatment with T₄ and carbimazole did not significantly differ from the patients on carbimazole monotherapy with respect to age, sex, and the time and cumulative dose of antithyroid drugs that were required to restore thyroid function (Table 1). Figure 1 shows the actual TSH serum levels over the course of the two-year study. As intended, TSH levels were persistently lower in the patients assigned to the suppressed TSH group than in the patients assigned to the normal TSH group. Differences in TSH between the two groups were accompanied by inverse differences in serum T₄ concentrations. In contrast, serum concentrations of T₃ did not significantly differ between the two groups (Fig. 1). Resting pulse rates were not significantly different between the two groups at any of the visits (data not shown). None of the patients experienced atrial fibrillation or other clinically apparent cardiac symptoms during the two-year study period.

**Effect of TSH suppression on recurrence of hyperthyroidism**

Ten of the twenty-two (45%) patients who had been assigned to normal TSH serum levels had a relapse of hyperthyroidism within 12 months after discontinuation of carbimazole (Table 2). Of these 10 patients, 5 had

<table>
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<tr>
<th>Treatment group</th>
<th>% recurrence rate (number of patients)</th>
<th>Time interval until recurrence (months)</th>
</tr>
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<tbody>
<tr>
<td>All patients combined</td>
<td>45-4 (10/22)</td>
<td>6.4 ± 4.3</td>
</tr>
<tr>
<td>Normal TSH Carbimazole + T₄</td>
<td>50-0 (5/10)</td>
<td>6.0 ± 4.8</td>
</tr>
<tr>
<td>Carbimazole alone</td>
<td>41.7 (5/12)</td>
<td>6.8 ± 4.3</td>
</tr>
<tr>
<td>Suppressed TSH</td>
<td>42.8 (12/28)</td>
<td>3.3 ± 1.7*</td>
</tr>
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* P = 0.05 significantly different compared with the TSH normal group.
transiently received T₄ during the first year of treatment and 5 had not (Table 2). A similar percentage of recurrent hyperthyroidism (12/28, 43%) occurred in the patients on TSH suppressive treatment (relative risk: 1.061, 95% confidence interval: 0.562–2.000, \( P = 0.856 \)). Recurrence of hyperthyroidism was not related to age and gender, to the presence or absence of beta blocker pretreatment, or to the initial thyroid volume, nor was it explained by the length of time and the cumulative dose of antithyroid drugs that were required to restore euthyroid function, when the impact of these variables was evaluated by multiple logistic regression (Table 3). Recurrence of manifest hyperthyroidism was detected at an earlier time point in patients on TSH suppressive treatment (Table 2, Fig. 2). Thyroxine doses in these patients during the last three months and after cessation of carbimazole treatment were similar between the patients who suffered a relapse \((73 \pm 26 \mu g/day)\) and the patients who stayed in remission \((83 \pm 31 \mu g/day)\). Notably, those patients in the TSH normal group who eventually suffered a relapse, already had significantly higher T₃ and lower TSH concentrations at three months after discontinuation of carbimazole \((T_3: 2.5 \pm 0.5 \text{ nmol/l}, \text{TSH: } 0.33 \pm 0.45 \text{ mU/l})\) as compared with the patients who remained in remission at the end of the second year \((T_3: 1.8 \pm 0.4 \text{ nmol/l}, P = 0.03; \text{TSH: } 0.79 \pm 0.49 \text{ mU/l}, P = 0.05)\).

### Effect of TSH suppression on thyroid volume

Thyroid enlargement was observed by ultrasound examination in 70% of the patients at study entry (defined as a volume >18 ml in women and >25 ml in men (7)) (Table 1). There was no significant difference in the initial thyroid volume between the patients who suffered a relapse \((34.0 \pm 13.8 \text{ ml})\) and those who did not \((30.8 \pm 18.5 \text{ ml})\). When analyzed as percent reduction of the thyroid volume at study entry, volumes of the patients with an enlarged thyroid gland significantly decreased with time in both groups (Fig. 3). However, the extent of the regression significantly differed between the two groups: in the patients assigned to a normal serum TSH, the average thyroid size was still enlarged by the end of the second year. In contrast, thyroid size had almost normalized in the patients on suppressive TSH treatment (Fig. 3). In order to assess the changes in thyroid size over the entire two-year observation period, only patients who had remained in remission for 12 months after cessation of carbimazole treatment were included in this analysis. Thyroid volumes in patients without initial goiter did not significantly change with time, regardless of treatment (Fig. 3).

In eight patients with an initial goiter who remained in remission, we had the chance to repeat sonographic measurements one year after the end of our study. Despite the fact that they had discontinued T₄ therapy for one year by this time, all four patients on former TSH suppressive treatment had maintained a normal thyroid volume \((14.1 \pm 4.5 \text{ ml})\) and had experienced no increase in thyroid volume since discontinuation of the T₄ treatment \((-3 \pm 3.9 \text{ ml})\). In contrast, in the four patients on nonsuppressive treatment, thyroid volume had remained enlarged \((37.3 \pm 16.3 \text{ ml})\; P = 0.025\) compared with suppressive treatment and was unchanged compared with one year after cessation of the carbimazole therapy \((-0.6 \pm 8.5 \text{ ml})\).

### Discussion

Prompted by the findings of Hashizume et al. (6) that a continuous treatment with T₄ might have a beneficial effect on the recurrence rate of hyperthyroidism in Japanese patients with Graves' disease, the present study was designed to study whether TSH suppressive treatment with T₄ might have similar beneficial effects on the recurrence rate of hyperthyroidism in an area with a low dietary iodine supply. Recent studies had

![Figure 2](https://via.placeholder.com/150)
shown that the average iodine excretion in the Heidelberg area is well below 100 μg iodine/g creatinine in individuals with a normal thyroid function and in hyperthyroid patients (8, 9). Although suppressive TSH serum concentrations were not achieved in all patients at all times during the phase of the antithyroid drug treatment, average TSH levels during the second year of the study after discontinuation of carbimazole did not exceed 0.3 mU/L, demonstrating that the aim of the study to keep the TSH concentrations suppressed in these patients was essentially achieved.

We found that patients on TSH suppressive therapy experienced the same rate of recurrence of hyperthyroidism (43%) as the patients who did not undergo exogenous TSH suppression (45%). We thus failed to reproduce the striking reduction (by more than 90%) in the recurrence rate with T4 treatment that had been observed by Hashizume and coworkers in Japan (6). Our findings are in agreement with the results from several other European studies with a similar design that have been conducted while our study was in progress (10–12). There has been much speculation as to why T4 treatment might work better in Japan than in Europe. Differences in the genetic background and the obvious differences in dietary iodine supply have been implicated (13, 14), but the exact reasons remain unclear. We should, however, point out that because of the limited number of patients, our study is not able to exclude a less than 50% reduction in the recurrence rate by TSH suppressive treatment. In order to exclude the possibility that a less substantial, but still clinically relevant, effect of TSH suppression on the recurrence rate can be achieved in Europe, further studies with a larger number of patients are warranted.

In contrast to the study by Mclver and co-workers (12), recurrence of hyperthyroidism in our patients on suppressive T4 doses tended to be diagnosed at an earlier time point than in the patients assigned to normal TSH serum levels. None of the patients in the TSH suppressed group suffered a relapse later than 6 months after the discontinuation of the antithyroid drug therapy. It is likely that the administration of exogenous thyroid hormones facilitated the manifestation of hyperthyroidism in patients with a persistent disease activity. Interestingly, however, the doses of T4 required to suppress TSH levels during carbimazole treatment did not differ between the patients who eventually suffered a relapse and those who did not.

Graves’ hyperthyroidism is often accompanied by an increase in thyroid size that may range from a slight enlargement to a large increase in gland size (15, 16). In our study, 70% of the patients had a sonographically enlarged thyroid before they were assigned to one of the two treatment schedules. Thyroid size decreased with time in all patients with an increased thyroid volume who had remained euthyroid by the end of the first year without carbimazole. However, the average thyroid size in patients assigned to normal TSH serum levels was still enlarged at the end of the two-year study, whereas it had almost completely normalized in the patients on suppressive T4 treatment. This reduction in thyroid size was particularly appreciated by those patients who had experienced a visible or symptomatic increase in thyroid volume. Although an observer bias cannot be completely excluded since sonographic measurements were not performed blind, our data thus indicate that TSH suppressive doses of T4 may be useful for normalizing thyroid volume in patients with Graves’ disease with a slight or moderate increase in thyroid volume.

In four of the patients with an enlarged thyroid at study entry, we had the chance to repeat volume measurements two years after cessation of the carbimazole treatment and one year after the cessation of suppressive T4 treatment. Notably, all four patients had maintained a normal thyroid volume by this time and had not experienced a significant increase in thyroid volume.

**Figure 3** Mean (± SEM) sonographic thyroid volumes after normalization of TSH and T4 serum values, and 12 and 24 months later. Solid bars represent patients assigned to normal TSH serum levels and open bars represent patients assigned to suppressed TSH serum levels. Patients who suffered a relapse are not included in the analysis. When analyzed as percentage of the thyroid volume at study entry, there was a significant reduction in thyroid size by 24 months in patients with an enlarged thyroid (right panel) in both treatment groups ($P < 0.01, n = 6$ for both groups). Thyroid volumes at 24 months were significantly smaller in patients on suppressive T4 treatment than in patients assigned to a normal TSH ($P = 0.05$). No significant changes in thyroid volume were observed in the patients without a goiter at study entry (left panel) (normal TSH: $n = 6$, suppressed TSH: $n = 10$).
volume. In contrast, patients with an initial goiter who had been assigned to nonsuppressive treatment, had still retained an enlarged thyroid by the end of the second year following carbimazole withdrawal. Thus, there is some evidence that suppressive T4 treatment may be beneficial even beyond the actual time of T4 administration. However, the number of patients in our study was small and further studies are required to evaluate the clinical significance of our findings.

In summary, we did not observe any beneficial effect of long-term TSH suppressive treatment in patients with Graves’ disease on the relapse rate of hyperthyroidism. However, suppressive T4 treatment may have a beneficial effect on thyroid size when thyroid enlargement is present.

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References


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