TSH and Prolactin Secretions in Hashimoto's Thyroiditis Following Withdrawal of Thyroid Hormone Therapy

NATSUKO OHSAWA, ISAO KOBAYASHI, KUNIHiko SUWA, NOBUYUKI KAMIO, SAKAE MARUTA, KIHACHI OHSHIMA, HITOSHI FUKUDA AND SETSUO KOBAYASHI

Division of Endocrinology, Department of Medicine and First Department of Internal Medicine, School of Medicine, Gunma University, Maebashi 371, Japan

Abstract

Changes in the pituitary-thyroid axis in patients with Hashimoto's thyroiditis following withdrawal of thyroid suppressive therapy were analyzed. The group of patients with thyroid adenoma served as control (group I). Patients with Hashimoto's thyroiditis were divided into 2 groups on the basis of serum TSH levels 8 weeks after discontinuing the exogenous thyroid hormone (group II, less than 10 \( \mu \text{U/ml} \); group III, more than 10 \( \mu \text{U/ml} \)).

During withdrawal of L-T4 (200 \( \mu \text{g/day} \) or L-T3 (50 \( \mu \text{g/day} \)), there was no significant difference in serum T4-I and T3 levels among the three groups. Following L-T4 withdrawal, basal serum TSH levels were higher at 2 to 8 weeks in groups II and III than in group I. Serum TSH response to TRH was greater at 4 to 8 weeks in groups II and III than in group I. Following L-T3 withdrawal, basal serum TSH levels were higher at 1 and 2 weeks in group II than in group I, while those of group III were consistently higher during the study. Higher TSH responses to TRH were observed at 1 to 8 weeks in groups II and III. Neither basal nor TRH-induced prolactin (PRL) secretion differed significantly among the three groups.

We have demonstrated that pituitary TSH secretion in patients with Hashimoto's thyroiditis is affected more by withdrawal of thyroid hormone therapy than in patients with thyroid adenoma. In addition, the present findings suggest a difference between the sensitivity of thyrotrophs and lactotrophs in Hashimoto's thyroiditis after prolonged thyroid therapy is discontinued.

Vagenakis et al., (1975) reported decreased TSH reserve in euthyroid subjects at 2 to 5 weeks after prolonged thyroid suppressive therapy. Krugman et al. (1975) also mentioned that basal serum TSH may be used to differentiate euthyroid from hypothyroid patients approximately 5 weeks after withdrawal of thyroid medication. Their studies were conducted in normal subjects, euthyroid goitrous patients and hypothyroid patients who had been receiving various thyroid preparations including desiccated thyroid, synthetic L-T4 and mixtures of L-T4 and L-T3. On the other hand, abnormalities in the pituitary-thyroid axis in patients with Hashimoto's thyroiditis have been reported by many investigators (Mayberry et al., 1971; Gordin et al., 1974; Takeda et al., 1975). However, little is known of the pituitary-thyroid axis in patients with Hashimoto's thyroiditis as a group following the discontinuation of thyroid medication.

The present investigation was undertaken to determine patterns of the pituitary-thyroid axis in patients with Hashimoto's thyroiditis after withdrawal of prolonged thyroid therapy. In addition, basal and TRH-induced prolactin secretion was measured. The results indicate that the pituitary TSH response to TRH is increased in patients with Hashimoto's thyroiditis following withdrawal of thyroid hormone therapy compared to patients with thyroid adenoma. These findings suggest a difference in the sensitivity of thyrotrophs and lactotrophs in Hashimoto's thyroiditis after prolonged thyroid therapy is discontinued.
prolactin (PRL) secretions in such patients also were examined.

Materials and Methods

The study group consisted of 24 patients with Hashimoto's thyroiditis and 12 patients with thyroid adenoma. All of the patients were women who had been receiving either L-T₄ (100 μg orally twice a day) or L-T₃ (25 μg orally twice a day) for varying periods (1-60 months). Some patients were initially treated with L-T₃ or desicated thyroid and then switched to L-T₄ 4 weeks before withdrawal of L-T₄. Clinical and laboratory data, including the age of the patients, the mode and duration of treatment, and drugs employed, are shown in Table I. The diagnosis of Hashimoto's thyroiditis was based on enlarged and hard goiter with elevated circulating thyroid antibody titers. All patients had normal levels of serum T₄-iodine (T₄-I), T₃ resin uptake, thyroidal 24-hr ¹³¹I uptake and basal metabolic rate (BMR) before the administration of thyroid hormone. None of the patients had definite clinical hypothyroidism prior to treatment. The group of patients with thyroid adenoma served as control (group I). Patients with Hashimoto's thyroiditis were divided into 2 groups, as suggested previously (Krugman et al., 1975). Group III had elevated serum TSH (more than 10 μU/ml) 8 weeks after withdrawal of thyroid hormone, while serum TSH levels in group II were within the normal range (less than 10 μU/ml).

Serum TSH and PRL responses to 500 μg synthetic TRH were determined before and after withdrawal of thyroid hormone. Relative changes in the peak TSH and PRL above the mean basal concentrations were shown in the present study. The serum T₄ and TSH were determined by radioimmunoassay (RIA), as reported previously (Kobayashi et al., 1980). Serum T₄-I was measured by Oxford-T₄ manual methods (Oxford Lab., California). The normal ranges of serum T₃, T₄-I and TSH were 80-180 ng/100 ml, 2.8-6.8 μg/100 ml and less than 10 μU/ml, respectively. Serum PRL was measured by RIA using CEA-IRE-SORIN's PRL kit. Statistical evaluation was made by the Student's t-test.

Results

L-T₄ withdrawal

Changes in serum T₄-I, T₃, TSH and PRL levels are shown in Fig. 1. During L-T₄ administration, there was no significant difference in these parameters among the three groups. Following withdrawal of L-T₄, changes in the pituitary-thyroid axis for the group displayed a distinct pattern. Serum T₃ showed a pattern similar to that observed in serum T₄-I. The lowest values for serum T₃-I and T₃ were obtained at 2 weeks in all groups. Serum T₄-I tended to be lower in groups II and III than in group I, although these differences were not significant (p>0.05). Serum T₄ was significantly lower at 2 week in group II than in group I (p<0.05). At 8 weeks, serum T₄-I and
Fig. 2. Serum TSH and PRL responses to TRH in Hashimoto’s thyroiditis and thyroid adenoma before and after L-T₄ withdrawal.

ΔTSH or ΔPRL refers to the maximum increase in serum hormone concentration above the respective basal level after administration of TRH.

*p<0.05, **p<0.01 vs. group I.

Table 1. Summary of laboratory data in patients with Hashimoto’s thyroiditis and thyroid adenoma before and 8 weeks after withdrawal of thyroid suppressive therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>T₃ (μg/dL)</th>
<th>T₄ (μg/dL)</th>
<th>TSH (mIU/mL)</th>
<th>PRL (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>19±2</td>
<td>3.2±0.2</td>
<td>4.9±0.3</td>
<td>148±12</td>
<td>161±16</td>
</tr>
<tr>
<td>II</td>
<td>21±3</td>
<td>3.7±0.4</td>
<td>4.5±0.4</td>
<td>171±25</td>
<td>43±0.2</td>
</tr>
<tr>
<td>III</td>
<td>24±4</td>
<td>3.8±0.9</td>
<td>4.5±0.4</td>
<td>149±12</td>
<td>42±0.1</td>
</tr>
</tbody>
</table>

**p<0.01 vs. group I.

T₃ concentrations in the three groups were within normal ranges (Table 1).

In group I, there was no significant change in serum TSH levels during the study. By contrast, basal TSH levels from groups II and III were higher at 2 to 8 weeks than those of group I. There was no change in serum PRL levels.

The TRH-induced serum TSH and PRL responses are shown in Fig. 2. Serum TSH
response to TRH was almost completely suppressed at 1–2 weeks in groups I and II. Higher TSH responses were observed at 4 and 8 weeks in groups II and III than in group I. There was no significant change in serum PRL response to TRH.

**L-T₃ withdrawal**

Changes in serum T₄-I, T₃, TSH and PRL levels are shown in Fig. 3. Before L-T₃ withdrawal, there was no significant change in these parameters among the three groups. Following L-T₃ withdrawal, serum T₃ decreased abruptly, while serum T₄-I increased gradually. The lowest values for serum T₃ were obtained at 1–2 weeks. Serum T₄-I tended to be lower at 1–2 weeks in group III than in group I, although the differences were not significant (p>0.05). At 8 weeks, serum T₄-I and T₃ concentrations in the three groups were within normal ranges (Table 1). The basal serum TSH levels were significantly higher at 2 and 4 weeks in groups II and III than in group I. However, there was no change in serum PRL during the study.

As shown in Fig. 4, a significant rise
in the serum TSH level after TRH administration was observed at 1 week in group I. However, serum TSH responses were higher at 1 to 8 weeks in groups II and III than in group I. By contrast, there was no significant difference in the PRL response to TRH among the three groups.

Discussion

The patterns of the pituitary-thyroid axis in patients with Hashimoto's thyroiditis following withdrawal of prolonged thyroid therapy have been demonstrated. In addition, there was a dissociation between TSH and PRL secretion in patients with Hashimoto's thyroiditis.

Following L-T₄ withdrawal, serum TSH levels were significantly higher at 2 to 8 weeks in groups II and III than in group I (Fig. 1). A similar result was also obtained following L-T₃ withdrawal (Fig. 3). Thus, we have demonstrated that pituitary TSH secretion in patients with Hashimoto's thyroiditis is affected more by withdrawal of thyroid hormone than in thyroid adenoma.

TSH secretion in patients with Hashimoto's thyroiditis may be explained by decreased feedback inhibition of thyroid hormone at the pituitary level. This suggests intrinsically impaired biosynthesis of thyroid hormone in patients with Hashimoto's thyroiditis (Mayberry et al., 1971; Gordin et al., 1974; Takeda et al., 1975). However, changes in serum T₄-I and T₃ levels in the three groups following L-T₄ or T₃ withdrawal did not differ significantly, although these values appeared to be somewhat lower in groups II and III than in group I (Fig. 1, 3). It is postulated that elevated basal serum TSH may occur without a reduction of serum T₄ and T₃ concentrations into the hypothyroid range in clinically euthyroid patients with Hashimoto's thyroiditis (Greenberg et al., 1970). Serum T₄ and T₃ are presumably maintained at a nearly normal level in such patients, by the rapid rate of synthesis and secretion of thyroid hormones through the augmented TSH secretion.

Vagenakis et al. (1975) reported that decreased TSH reserve persisted for 2 to 5 weeks in euthyroid subjects after withdrawal of thyroid hormones. Krugman et al. (1975) also described how basal TSH may be used to differentiate euthyroid from hypothyroid patients 35 days after withdrawal of thyroid hormones. On the basis of our data, it took 2 week for L-T₄ withdrawal to draw a sharp line between Hashimoto's thyroiditis and thyroid adenoma, while this was 1 week for L-T₃ withdrawal, when basal TSH was compared (Fig. 1, 3). On the other hand, it seems that the TRH test is more sensitive for the detection of mild thyroid failure than the basal TSH alone (Takeda et al., 1975). Krugman et al. (1975) reported that the mean duration of suppressed TSH response to TRH in euthyroid subjects was 12 day after stopping thyroid hormones. In accordance with their data, we have observed that serum TSH response to TRH was suppressed by the end of the second week in group I after L-T₄ withdrawal (Fig. 2). No potentiation by TRH response was observed at 1–2 weeks after L-T₄ withdrawal (Fig. 2), in agreement with the data of of Krugman et al. (1975). However, serum TSH response to TRH was evident at 1 week in group I after L-T₃ withdrawal (Fig. 4), suggesting a rapid disappearance of the L-T₃ effect on pituitary TSH response.

Finally, there was a striking difference in serum TSH and PRL secretion. Neither basal nor TRH-induced PRL secretion differed between patients with Hashimoto's thyroiditis and thyroid adenoma significantly. Since TRH directly stimulates TSH and PRL secretion from the pituitary (Jacobs et al., 1971), our demonstration of differential sensitivity of thyrotrophs and lactotrophs following withdrawal of thyroid
hormones is consistent with the concept that
TRH and thyroid hormone receptors in these
two cell types may be independent (Sachson
et al., 1972; Refetoff et al., 1974; Yamaji,
1974).

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