Normal thyrotrophin response to intravenous thyrotrophin releasing hormone administration: the best index of optimal L-thyroxine therapy in primary hypothyroidism

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Summary: Normalization of basal thyrotrophin (TSH) level is used as the endpoint in L-thyroxine (L-T4) therapy of primary hypothyroidism. However, several reports have questioned the reliability of this index because of seasonal variation of TSH. Therefore, we studied 85 consecutive patients with primary hypothyroidism over a period of 3.5 y. In these patients, TSH response (ΔTSH) to intravenous thyrotrophin releasing hormone (TRH) administration was examined when basal TSH was normalized with L-T4 therapy. Eight patients showed a blunted response (ΔTSH < 5 μU), whereas 27 patients demonstrated an exaggerated response (ΔTSH > 25 μU). Thus, 42% of patients were apparently on inappropriate L-T4 dosage. These abnormal TSH responses normalized on adjusting the L-T4 dosage alone; prolonged therapy with the same dose failed to normalize TSH responses. Minor seasonal variations of basal TSH were observed in 30% of patients. However, TSH response to TRH remained normal. Hence, no adjustment of L-thyroxine dose was required. This study, therefore, demonstrates that normalization of TSH response to TRH administration rather than basal TSH may be the best index of adequate L-thyroxine therapy in primary hypothyroidism.

Introduction

Basal thyrotrophin (TSH) level is presently used as an index of the therapeutic adequacy of thyroid replacement therapy in primary hypothyroidism in conjunction with improvement in clinical manifestations (Evered et al., 1973; Stock et al., 1974). However, the reliability of this index has recently been questioned in the light of numerous studies reporting seasonal variations of basal TSH concentration (Konno & Morikawa, 1982; Hamada et al., 1984; Brajkovich et al., 1983). Furthermore, normal TSH levels may not be discriminated from low levels with the present available methodology in clinical practice. Therefore several hypothyroid patients with normal TSH levels during replacement therapy may not actually be euthyroid. Some of them may be hyperthyroid or overtreated; whereas others may be in a state of 'inadequate thyroid reserve', a state similar to a state of 'impending thyroid failure' or 'subclinical hypothyroidism' often seen in patients with Grave's disease following surgery or 131I therapy and Hashimoto's thyroiditis prior to onset of clinical et al., 1984). Both these noneuthyroid states can be discriminated from the euthyroid state by demonstration of altered TSH response to thyrotrophin releasing hormone (TRH) administration. Therefore, we examined TSH response to i.v. TRH administration in patients with primary hypothyroidism during replacement therapy with L-thyroxine when basal TSH level was normalized. This study also helped to examine the efficacy of several thyroid function tests in assessing adequacy of replacement therapy in primary hypothyroidism.

Material and methods

Eighty-five consecutive patients, 75 males and 10 females aged 36 to 84 y, with primary hypothyroidism were studied from September 1980 till March 1984. The diagnosis of primary hypothyroidism was established by the presence of several clinical features as well as low T4, low free T4 index and elevated basal TSH level. Patients with 'subclinical' or 'preclinical' hypothyroidism, and patients in whom the therapy with L-thyroxine was suppressive following thyroid surgery for cancer or nodule or for goitre were excluded. Serum levels of antithyroglobulin and antimicrosomal antibodies were determined.
Patients were started on L-thyroxine (Synthroid, Flint Laboratories, Deerfield, IN). The initiating dose was 100 μg/d in patients under 50 y and without previous history of 131I and/or surgical treatment for hyperthyroidism, external radiation therapy and/or neck surgery for other causes and ischaemic coronary artery disease. Patients aged 51–65 y without previous history of ischaemic heart disease and younger patients in whom hypothyroidism was secondary to either treatment of previous hyperthyroidism or radiation and/or neck surgery for other causes were begun on 50 μg/d. Finally, in all patients with known ischaemic heart disease and in patients over 65 y, the initial daily dose of L-thyroxine was 25 μg. Patients were examined at intervals of 2 to 4 weeks in the Endocrinology Clinic. In patients with initial doses of 50 μg and 25 μg, L-thyroxine was increased by 25 μg every 2 weeks in the absence of untoward symptoms such as chest pain, tachycardia, dyspnoea on exertion, until a dose of 100 μg was reached or patients were apparently clinically euthyroid or untoward symptoms recurred. In all patients, serum T3 resin uptake (T3RU), T4 triiodothyronine (T3) and TSH were reassessed after they had been on this dose of L-thyroxine for 4 weeks. Patients were then followed at intervals of 4 to 6 weeks and the daily dose of L-thyroxine was adjusted until basal serum TSH was normalized (<8 μU/ml). At this juncture, a TRH (Thyphinnone, Abbott Laboratories, North Chicago, IL) stimulation test was performed after an overnight fast. Serum TSH level was determined before as well as 30 and 60 min after intravenous bolus administration of 500 μg TRH. Serum T4, T3RU, T3 and TSH concentrations as well as serum TSH response to i.v. TRH administration observed in our patients were compared to the same parameters noted in 45 (37 male and 8 female) age matched (34–81 y) normal subjects. Patients with abnormal TSH responses were divided into 2 groups. In one group, the TRH stimulation test was repeated after the same dose of L-thyroxine was continued for 3 to 6 months; one patient was actually on the same dose of L-thyroxine (50 μg) for almost 1 y. In the other group, the L-thyroxine dose was increased or decreased respectively by 25 μg immediately and the TRH stimulation test was repeated after 6 weeks. Patients were then followed every 3 months. The TRH stimulation test was repeated if basal TSH altered by >4 μU from the previous clinic visit.

Serum T3 resin uptake was determined by a commercial kit (Tritab, Nuclear Medical, Irving, TX). Serum T4, T3, and TSH were assessed by previously well established radioimmunoassay methods (Premachandra & Ibrahim, 1976; Premachandra, 1976; Patel et al., 1971). Antithyroid antibodies were assessed by a commercial kit (Zeus, Inc., Raritan, NJ).

Statistical analyses were performed by Student’s t test and correlation coefficients.

Results

Patients were divided into 4 groups: (1) Hashimoto’s thyroiditis with diagnostic antithyroid antibody titres (1:100); (2) secondary to surgery and/or 131I therapy for hyperthyroidism; (3) secondary to neck surgery and/or external radiation for nonthyroidal disorders, and (4) idioopathic hypothyroidism.

TSH response (ΔTSH) to intravenous TRH administration ranged between 5–25 μU/ml in normal subjects (Table I). In hypothyroid patients with normal basal T4, T3RU, T3, and TSH levels on replacement therapy, blunted TSH response (ΔTSH < μU/ml) was noted in 8 patients whereas exaggerated TSH response (>25 μU/ml) was observed in 27 patients (Table I). In the remaining patients, TSH response to TRH was within normal limits. The abnormal TSH response to TRH administration was not related to either the age of the patient or the aetiology of hypothyroidism or

Table I Daily L-thyroxine dose (L-T4), serum T4, T3RU, T3, basal TSH and peak TSH response (ΔTSH) to TRH administration at the time of normalization of basal TSH with L-thyroxine replacement therapy in 82 hypothyroid patients (HypoT) and 45 normal subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>L-T4 (μg)</th>
<th>T4 (μg/dl)</th>
<th>T3RU (%)</th>
<th>T3 (ng/dl)</th>
<th>TSH (μU/ml)</th>
<th>ΔTSH (μU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HypoT I*</td>
<td>149 ± 3</td>
<td>9.6 ± 1.2</td>
<td>39 ± 3</td>
<td>136 ± 11</td>
<td>3.2 ± 0.8</td>
<td>17.0 ± 2.8</td>
</tr>
<tr>
<td>HypoT II</td>
<td>136 ± 5§</td>
<td>8.9 ± 1.3</td>
<td>38 ± 3</td>
<td>129 ± 8</td>
<td>4.4 ± 0.6</td>
<td>39.0 ± 6.0†</td>
</tr>
<tr>
<td>HypoT III</td>
<td>153 ± 6</td>
<td>9.9 ± 1.1</td>
<td>39 ± 3</td>
<td>134 ± 8</td>
<td>3.4 ± 0.8</td>
<td>2.1 ± 0.9‡</td>
</tr>
<tr>
<td>Normal</td>
<td>9.2 ± 0.9</td>
<td>40 ± 2</td>
<td>(5.5–11.3)†</td>
<td>143 ± 10</td>
<td>3.8 ± 0.6</td>
<td>15.1 ± 4.2</td>
</tr>
</tbody>
</table>

All values are mean ± s.e.m.

*Patients grouped according to ΔTSH: I. normal, 47 patients; II. > 25, 27 patients; III. < 5, 8 patients.
†Normal range is shown in parentheses.
‡Significantly different from normal, P < 0.01.
§Significantly different from other groups, P < 0.01.
the initial thyroid hormone concentrations. Daily L-thyroxine dose was significantly smaller in patients with exaggerated TSH response as compared to other groups (Table 1). In patients with blunted response, TSH response normalized on reducing L-thyroxine dose by 25 μg with a minimal decrease in T₄ and T₃ concentrations (Figure 1). Similarly, in patients with exaggerated response, TSH response normalized only on increasing the dose of L-thyroxine by 25 μg (Figure 2). Serum T₄ and T₃ increased slightly as well on increasing the L-thyroxine dose. However, the alteration in T₄ and T₃ in both these groups after adjustment of the L-thyroxine dose were not significant. Finally, prolonged duration of therapy with the same dose did not normalize altered TSH responses.

The optimal daily dose of L-thyroxine ranged from 100 to 200 μg with lower doses being adequate for patients showing blunted TSH response on first TRH stimulation test. It was reached and maintained without complications in 81 patients. In 3 patients (> 85 y) the optimal daily dose was not achieved due to worsening of angina pectoris despite concomitant therapy with propranolol. In the remaining patient, the dose of L-thyroxine had to be reduced after being maintained for 6 months due to the onset of recurrent atrial fibrillation.

The duration required for adjustment of L-thyroxine dosage to establish euthyroid status in 82 patients ranged from 6 weeks to 3 months; shorter duration with higher initial dose and vice versa. During the follow-up period, which ranged from 4 months to 3.5 y, 3 patients (> 80 y) died. They were on the optimal dose of L-thyroxine for 1 to 3 y before death. In 72 patients, the follow-up period covered at least one winter and one summer season. Only 22 of these patients demonstrated a significant rise in serum TSH concentrations (> 4 μU/ml) during the winter months, as compared to the summer. However, TSH response to TRH remained normal. This minor seasonal TSH alteration was not dependent on either the aetiology of hypothyroidism or the age of the patients.

**Discussion**

Assessment of the adequacy of therapy of primary hypothyroidism is often based on improvement in clinical manifestations and restoration of normal thyroid hormone concentrations as well as basal TSH level. However, disappearance of symptoms and signs appears to be an unreliable index of euthyroid state since the individual patient feels so much better on institution of replacement therapy that mild subjective symptoms often go unrecognized. Furthermore, the restoration of any normal T₄, T₃, and TSH concentrations may not be appropriate since the ranges of these levels are rather wide in normal subjects and optimal levels for an individual patient are not known (Utiger, 1979). Finally, these wide ranges may be due to varying sensitivity of target tissues to circulating thyroid hormones, and lack of simple reliable methodology has prevented the assessment of the effect of circulating thyroid hormones in most target tissues. Nevertheless, the TSH response to i.v. TRH administration is an extremely reliable indicator of effect of circulating thyroid hormones on pituitary thyrotrophs, a major target tissue for thyroid hormone action.

This study clearly demonstrates that improvement
in clinical manifestations with normal T₄, T₃, and TSH concentrations may not be reliable indices of euthyroid status in a significant patient population (42%) as documented by abnormal TSH response to i.v. TRH administration (Table I). Eight patients (10%) thought to be euthyroid by these indices were apparently hyperthyroid or overtreated as documented by blunted TSH response. Similar TSH responses have been described in patients with ‘euthyroid sick’ syndrome (Wartofsky & Burman, 1982). However, none of these patients suffered from acute or chronic illness at the time of the TRH stimulation test. Furthermore, 27 patients (32%) were in a state of ‘inadequate thyroid reserve’ as reflected by an exaggerated TSH response. Continuation of the same dose of L-thyroxine for several months failed to normalize these TSH responses as previously reported (Brajkovich et al., 1983). Normalization of TSH responses occurred only on adjusting the dose of L-thyroxine (Figures 1 and 2). Thus, this study indicates that normal basal TSH level may not be a reliable indicator of adequate thyroxine replacement therapy as recently reported (Konno & Morikawa 1982; Hamada et al., 1984; Brajkovich et al., 1983).

This study confirms recent reports (Konno & Morikawa, 1982; Hamada et al., 1984) that TSH levels may rise in the winter season with patients receiving the same dose of L-thyroxine. However, this finding was observed only in 30% of the patients and it was not clinically relevant since basal TSH did not rise above the normal upper limits as reported previously (Konno & Morikawa, 1982; Hamada et al., 1984). Furthermore, TSH response to TRH remained normal. This discrepancy in TSH regulation between the previous reports and our study may be because the adequacy of therapy was established by normal TSH response to TRH administration in this study rather than normalization of basal TSH alone. This finding is consistent with previous reports of lack of seasonal variation in TSH response to TRH administration in normal subjects (Konno, 1978; Konno, 1980).

In conclusion, this study demonstrates that normalization of TSH response to i.v. TRH administration may be the best index of adequate L-thyroxine replacement therapy in primary hypothyroidism along with remission from clinical manifestations.

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