Thyroid function related symptoms during levothyroxine monotherapy in athyreotic patients

Mitsuru Ito, Akira Miyauchi, Mako Hisakado, Waka Yoshioka, Takumi Kudo, Eijun Nishihara, Minoru Kihara, Yasuhiro Ito, Akihiro Miya, Shuji Fukata, Mitsushige Nishikawa and Hirotoshi Nakamura

Center for Excellence in Thyroid Care, Kuma Hospital, Kobe 650-0011, Japan

Abstract. Previous reports by us and other investigators showed that among athyreotic patients on levothyroxine (LT4) following total thyroidectomy patients with normal serum thyroid-stimulating hormone (TSH) levels had mildly low serum free triiodothyronine (FT3) levels, whereas patients with mildly suppressed serum TSH levels had normal serum FT3 levels and patients with strongly suppressed serum TSH had elevated serum FT3 levels. The objective of this study was to clarify which of these three patient groups are closer to their preoperative euthyroid condition based on reported subjective symptoms. We prospectively studied 148 consecutive euthyroid patients with papillary thyroid carcinoma who underwent a total thyroidectomy. Symptoms reflecting thyroid function documented preoperatively and following 12 months of LT4 after thyroidectomy were compared. In 65 patients with strongly suppressed TSH levels significant changes in symptoms with tendencies towards thyrotoxicosis (p < 0.01), bowel movements (p < 0.05), and hand tremors (p < 0.05). In 33 patients with normal TSH levels, significant changes in symptoms with tendencies towards hypothyroidism were seen with regards to heat and cold tolerance (p < 0.05) and activity (p < 0.05). Lastly, in 50 patients with mildly suppressed TSH levels and FT3 levels equivalent to preoperative levels, all symptom items remained equivalent to their preoperative levels. Symptoms reflecting thyroid function in patients on LT4 following total thyroidectomy suggested that patients with mildly suppressed TSH levels were closest to a euthyroid status. These data provide useful findings regarding the management of patients following total thyroidectomy.

Key words: Thyrotropin, Triiodothyronine, Thyroidectomy, Levothyroxine, Athyreotic patients

THYROXINE (T4) and triiodothyronine (T3) are the two thyroid hormones, and T3 is the biologically active form. In normal subjects, 100% of T4 is secreted by the thyroid, approximately 20% of T3 is secreted from the thyroid gland, and approximately 80% of T3 is derived from the conversion of T4 to T3 in extra-thyroidal peripheral tissues [1]. As a result, a relative T3 deficiency may be present in athyreotic patients during T4 monotherapy. We and other investigators [2-5] have compared pre and postoperative T3 levels in patients on LT4 therapy with those of euthyroid controls. These studies showed that in the athyreotic condition following total thyroidectomy during LT4 therapy patients with normal serum TSH levels had mildly lower serum FT3 levels, and patients with suppressed serum TSH levels had normal serum FT3 levels. It remains to be determined from these findings which of the two patient groups were in the euthyroid status.

The objective of the present study was to compare thyroid function preoperatively and during LT4 therapy in patients who underwent total thyroidectomy to determine whether a mild T3 deficiency affects thyroid function in postoperative athyreotic patients on LT4 therapy. The subset of patients with papillary thyroid carcinoma unrelated to thyroidal conversion of T4 to T3 [6] were selected for the present study.

Materials and Methods

Patients

This nonrandomized, controlled, prospective cohort study recruited euthyroid patients who underwent a total thyroidectomy for papillary thyroid carcinoma between...
October 2011 and February 2013 at Kuma Hospital in Kobe, Japan. Study exclusion criteria were as follows: (i) patients with thyroid malignancies other than papillary carcinoma; (ii) patients with thyroid dysfunction, such as Graves’ disease, thyroid dysormogenogenesis, autonomously functioning thyroid nodules, or hypothyroidism; (iii) patients taking drugs known to affect thyroid function or thyroid hormone metabolism, such as a steroid, estrogen, amiodarone, lithium, β-blocker, sucralfate, iron or iodine-containing drug; (iv) patients with chronic or serious diseases such as cardiac, pulmonary, hepatic, renal, or pancreatic diseases, diabetes or hyperparathyroidism; (v) patients with psychiatric disease; (vi) pregnant, lactating, or perimenopausal patients; (vii) patients with a body mass index (BMI) <18 or >30 kg/m²; and (viii) patients with a physical disability or those participating in a competitive sport.

In addition to the above exclusion criteria, patients who developed metastasis, and those who failed to achieve the target TSH levels were also excluded from analysis. The papillary thyroid carcinoma patients underwent total thyroidectomy with euthyroid Hashimoto’s disease included in this study. The present study was approved by the ethics committee at Kuma Hospital (No20110908-2, Sep 8, 2011), and all patients gave written informed consent to participate in the study.

**Study protocols**

This study initially recruited 165 patients (age range 18–78 years old) who underwent total thyroidectomy for papillary thyroid carcinoma. All patients also underwent central node and/or modified neck dissection. Attempts were made to preserve parathyroid glands in-situ with associated blood supply. However, if parathyroid glands were resected or devascularized, they were minced and autotransplanted into the sternocleidomastoid muscle. The patients were initially administered approximately 2.0 μg/kg of LT₄ daily after total thyroidectomy. Thyroid function tests were initially performed 1 month after surgery and continued every 1–2 month interval until stabilization, and every 3 months after stabilization. The LT₄ dosage was adjusted to achieve the target TSH levels determined by risk of recurrence based on the three-level stratification in ATA guidelines [7].

The target serum TSH levels were strongly suppressed TSH levels (≤0.03 μIU/mL) for 72 high-risk patients, mildly suppressed TSH levels (0.03 < TSH ≤ 0.3 μIU/mL) for 55 intermediate-risk patients, and normal TSH levels (0.3 < TSH ≤ 5 μIU/mL) for 38 low-risk patients. The dosage of LT₄ were unchanged for the last 3 months before postoperative evaluation, as described below. Patient metabolic profiles and thyroid function tests were evaluated 12 months after thyroidectomy.

Of the initially recruited study population 148 patients completed the study (Fig. 1). Study discontinuation during the observation period were due to failure to follow up (n = 7), failure to achieve the target TSH levels (n = 5), menopause (n = 4), and the initiation of glucocorticoid (n = 1). The clinical features of the three patient groups in the study are given in Table 1. Age, body weight, BMI, gender ratio, and menopausal status was similar among the groups.

**Laboratory serum tests**

Patient preoperative thyroid profiles were obtained 2 days prior to surgery. The postoperative thyroid profiles were obtained following stabilization 12 months after thyroidectomy. Blood samples were obtained in the morning following an overnight fast and after ingestion of LT₄. Patient serum levels of TSH, FT₄, and FT₃ were
measured using chemiluminescent immunoassays (ARCHITECT i2000; Abbott Japan, Tokyo). Intra-assay and inter-assay coefficients of variation were 1.1%–5.0% and 1.7%–5.3% for the TSH assay, 2.3%–5.3% and 3.6%–7.8% for the FT4 assay, and 1.4%–4.2% and 2.3%–5.0% for the FT3 assay, respectively. The reference ranges in our hospital are 0.3–5.0 μIU/mL for TSH, 0.7–1.6 ng/dL for FT4, 1.7–3.7 pg/mL for FT3, and 1.8–3.3 [(pg/mL)/(ng/dL)] for the FT3/FT4 ratio.

### Symptoms reflecting thyroid function

Preoperative symptoms questionnaires were obtained 2 days prior to surgery. Symptoms were expected to be affected by the season in which conducting the questionnaire, so in the present study postoperative questionnaires were obtained 12 months after thyroidectomy. Symptoms reflecting thyroid function were assessed by questionnaire as shown in Fig. 2. Questionnaire items were based on widely used previously published rating scores developed by Billewicz et al. for hypothyroid symptoms [8], the score developed by Zulewski et al. for hypothyroid symptoms [9], and the score developed by Klein et al. for hyperthyroid symptoms [10]. The questionnaire included 8 questions based on common symptoms reflecting thyroid function: (i) sweating; (ii) heat and cold tolerance; (iii) activity; (iv) bowel movements; (v) appetite; (vi) dryness and wetness of skin; (vii) temperature of hands and feet; (viii) tremor of hands. Answers to symptom questionnaires were recorded on the Likert scale from −2 to +2. Items regarding tremor symptoms were recorded on Likert scale from 0 to +2.

### Statistical analysis

Grouped data are expressed as the mean ± SD. Postoperative three group comparisons were analyzed by unpaired t-test in cases of normal distribution and by Mann-Whitney U test in cases of nonparametric distribution, using Bonferroni corrections for multiple comparisons. Values are mean (SD), ns is not significant. Win, winter; Spr, spring; Fal, fall; Sum, summer

**Results**

**Thyroid function tests**

Preoperative serum levels of TSH, FT4, and FT3 were within the normal ranges for all patients. Table 2 shows the TSH, FT4, and FT3 levels before and after total thyroidectomy in the three patient groups. The 65 patients with strongly suppressed TSH levels at ≤0.03 μIU/mL postoperatively had postoperative serum FT3 levels that were significantly higher compared to preoperative values (p < 0.001). However, only three of the 65 patients had serum FT3 levels higher than the normal upper limit.

The 50 patients with mildly suppressed TSH levels at 0.03 < TSH ≤ 0.3 μIU/mL postoperatively had postoperative serum FT3 levels equivalent to preoperative levels (p = 0.284). The 33 patients with normal TSH levels (0.3 < TSH ≤ 5 μIU/mL) postoperatively had postoperative serum FT3 levels significantly lower than preoperative levels (p < 0.05), although both were within the normal range.

The postoperative FT3 levels in each group stratified by TSH level were significantly different from those in the other two groups. The serum FT3 levels were significantly increased postoperatively in all three groups. However, the magnitude of increase varied according to the TSH levels.

### Table 1  Clinical characteristics of the three patient groups

<table>
<thead>
<tr>
<th>Patient subgroup:</th>
<th>TSH ≤ 0.03 μIU/mL</th>
<th>0.03 &lt; TSH ≤ 0.3 μIU/mL</th>
<th>0.3 &lt; TSH ≤ 5 μIU/mL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>65</td>
<td>50</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 13</td>
<td>47 ± 13</td>
<td>54 ± 15</td>
<td>*ns</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>56.5 ± 11.7</td>
<td>61.2 ± 11.6</td>
<td>58.4 ± 9.9</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 3.6</td>
<td>23.3 ± 3.3</td>
<td>23.7 ± 3.3</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>55/10</td>
<td>36/14</td>
<td>29/4</td>
<td>ns</td>
</tr>
<tr>
<td>Menopause status (pre/post)</td>
<td>18/37</td>
<td>19/17</td>
<td>11/18</td>
<td>ns</td>
</tr>
<tr>
<td>Season (Win/Spr + Fal/Sum)</td>
<td>21/40/4</td>
<td>20/25/4</td>
<td>14/16/3</td>
<td>ns</td>
</tr>
<tr>
<td>LT4 dose (μg/kg per day)</td>
<td>2.22 ± 0.55</td>
<td>2.14 ± 0.43</td>
<td>1.99 ± 0.59</td>
<td>ns</td>
</tr>
</tbody>
</table>

Statistical significance was analyzed by the χ² test (gender, menopausal status), unpaired t-test, or *Mann–Whitney U test using Bonferroni corrections for multiple comparisons. Significance was defined as a corresponding p-value <0.05/3 (two-sided). Treatment effects (pre- vs. post-T3 replacement) were analyzed by the paired t-test for normal distribution and by the Wilcoxon signed rank test for nonparametric distribution. Significance was defined as a corresponding p-value <0.05 (two-sided). Statistical analyses were performed using R package (ver. 3.0.2, R Core Team, Vienna, Austria).
A questionnaire to assess symptoms reflecting thyroid function

The seasons at the time of conducting the questionnaire in the 3 groups were similar, and were in the order of spring and autumn, winter and summer (Table 1). The correlations between each symptom and age were exam-
The changes in the patient symptoms reflecting thyroid function before and after total thyroidectomy are shown in Fig. 3. Comparison of before and after survey values in patients with strongly suppressed TSH levels showed significant changes with tendencies towards thyrotoxicosis with regards to heat and cold tolerance (–0.29 ± 1.09 vs. 0.00 ± 0.88, p < 0.01), bowel movements (–0.31 ± 0.76 vs. –0.08 ± 0.75, p < 0.05), and tremor of hands (0.01 ± 0.02 vs. 0.14 ± 0.43, p < 0.05).

In the patients with mildly suppressed TSH levels, all postoperative scores across all symptom categories in the present study were not significantly different from pre-treatment levels. Comparison of before and after survey values in patients with normal TSH levels showed significant changes with tendencies towards hypothyroidism with regards to heat and cold tolerance (0.15 ± 0.93 vs. –0.30 ± 0.83, p < 0.05), and activity (0.27 ± 0.86 vs. –0.12 ± 0.59, p < 0.05).

Table 3 indicated the number of patients who changed their symptoms by 2 points or more in each symptoms. Overall, the postoperative symptoms in the group of mild TSH suppression were equivalent to those before thyroidectomy, while in each case, there were some who had drastic scale changes in their symptoms.

**Discussion**

In the present study, patients with normal TSH levels had serum FT$_3$ levels that were significantly lower than preoperative levels. Patients with mildly suppressed TSH levels had serum FT$_3$ levels equivalent to preoperative levels, and patients with strongly suppressed TSH levels had significantly higher serum FT$_3$ levels. Results obtained for the present cohort of patients who underwent a total thyroidectomy during LT$_4$ therapy were consistent with those of our previous studies [2, 11] as well as studies by Gullo et al. [4] and Hoermann et al. [5].
These findings suggest that the reason for the observed decreased serum T₄ levels in these patients is due to lack of intra-thyroidal T₃ production caused by absence of the thyroid gland.

An animal study has shown that LT₄ alone administered to thyroidectomized rats at doses to normalize plasma TSH levels does not normalize T₃ levels in serum and some tissues [12]. A recent study reported that the combination of high serum T₄ and low serum T₃ levels in T₄-monotherapy athyreotic rats had consequences for thyroid hormone action reflected in brain, liver, and skeletal muscle, all of which were indicative of hypothyroidism despite normal serum TSH [13]. Moreover, we compared serum levels of peripheral markers for thyroid function (i.e. serum levels of lipoproteins, bone metabolic markers, and sex hormone-binding globulin [SHBG]) measured preoperatively and after LT₄ therapy in patients who underwent total thyroidectomy to determine whether a mild T₃ deficiency affects thyroid function in the postoperative athyreotic patients on LT₄ therapy [14]. Postoperative serum SHBG and bone alkaline phosphatase (BAP) levels were significantly increased in the patients with strongly suppressed TSH levels. Postoperative serum low-density lipoprotein cholesterol (LDL-C) levels were significantly increased and serum tartrate-resistant acid phosphatase (TRACP)-5b levels were significantly decreased in patients with normal TSH. In patients with mildly suppressed TSH and FT₃ levels equivalent to their preoperative levels, all metabolic markers remained equivalent to their preoperative levels, which was in agreement with the results of the study examining thyroidectomized rats.

There are only a few limited reports regarding signs and symptoms in athyreotic patients on LT₄ monotherapy. Larisch et al. conducted a retrospective study including 319 patients with differentiated thyroid carcinoma on LT₄ (median TSH 0.07 mIU/L) and analyzed the association of reported complaints during follow-up with changes in thyroid parameters. Hypothyroid complaints were expressed by 26% of patients and 9.7% expressed hyperthyroid complaints during their visits. The relationship between hypothyroid symptoms with FT₃ levels extended to below reference TSH ranges. Hypothyroid symptom relief was associated with both a LT₄ dose giving TSH-suppression below the lower reference limit and FT₃ elevated further into the upper half of its reference range. In multivariate analysis, relationships between complaints and FT₃ concentrations remained significant after adjusting for gender, age and BMI. Residual hypothyroid complaints in LT₄-treated patients were specifically related to low FT₃ concentrations which supports an important role of FT₃ in clinical decision making on dose adequacy, particularly in symptomatic athyreotic patients [15]. Hirata et al. reported the association with body temperature and serum T₃ levels in LT₄ treated hypothyroid patients. They studied four patient groups with central hypothyroidism, total thyroidectomy, primary hypothyroidism, and control benign thyroid nodules. Groups were stratified according to serum FT₄ level (≧1.10 or <1.10 ng/dL) and body temperature, serum FT₃ levels, and lipid profiles were compared. In patients with FT₄ <1.10 ng/dL, body temperature and FT₃ levels were significantly lower in patients with central hypothyroidism and total thyroidectomy than in patients with primary hypothyroidism, whereas no differences were found in patients with FT₄≧1.10 ng/dL. In central hypothyroidism and total thyroidectomy, patients with median-lower normal levels of serum FT₄ exhibited lower serum FT₃ levels and lower body temperature. These results support the association with body temperature and serum T₃ levels to T₃ in patients with central hypothyroidism and total thyroidectomy [16].

Table 3 The number of patients showing drastic scale change in each symptoms

<table>
<thead>
<tr>
<th>Patient subgroups: symptom</th>
<th>TSH ≤ 0.03 μIU/mL (n = 65)</th>
<th>0.03 &lt; TSH ≤ 0.3 μIU/mL (n = 50)</th>
<th>0.3 &lt; TSH ≤ 5 μIU/mL (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat and cold tolerance</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Activity</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bowel movement</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Appetite</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dryness or wetness of skin</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Temperature of hands and feet</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tremor of hands</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Increase; number of patients whose symptom score increased by 2 points or more.
Decrease; number of patients whose symptom score decreased by 2 points or more.
Athyreotic patients who have undergone a total thyroidectomy live in a chronic state of abnormal thyroid hormone status for the remainder of their lives. Therefore, even if thyroid dysfunction may be subtle, its long-term effects cannot be overlooked. The American Thyroid Association (ATA) stated in its guidelines for the treatment of hypothyroidism that there is insufficient evidence of benefit to recommend that treatment with LT₄ be targeted to achieve low-normal TSH values or high-normal T₃ values in patients with hypothyroidism who are athyreotic [17]. The results of the present study suggest that mild TSH suppression of LT₄ can be recommended to achieve preoperative native FT₃ levels and euthyroid status in athyreotic patients who have mild TSH suppression undergone a total thyroidectomy. The ATA guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (DTC) state that serum TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications in patients with persistent disease in long-term follow-up of DTC [18]. Our present findings suggest that a mildly TSH-suppressive treatment (approximately 0.1 mU/L LT₄) may not necessarily cause thyrotoxicosis. Rather, it may result in euthyroid status in patients who have undergone a total thyroidectomy for DTC. On the other hand, in each case with mild TSH suppression, there were some who had an increase or decrease in FT₃ levels and some who had drastic scale changes in their symptoms. In each case, it is considered necessary to adjust the LT₄ dose comprehensively using not only serum TSH levels but also serum thyroid hormone levels, physical symptoms, and metabolic markers.

There are some possible limitations in the present study. First, the limited number of study patients, unequal group distributions, and single study timepoint reduced the internal validity of the study. In particular, the number of male patients was so small that it was impossible to examine differences in symptoms according to gender. Further well-designed studies are necessary to clarify the long-term effect at multiple centers. In addition, we did not evaluate patient quality of life or monitor 24-h heart rates. Future studies including measures of these clinical parameters are also needed to clarify the best method of managing postoperative patient thyroid function.

In conclusion, both serum biochemical markers and symptoms reflecting thyroid function in patients on LT₄ following total thyroidectomy demonstrated that patients with mildly suppressed TSH levels were closest to euthyroid status, whereas those with normal TSH levels had mild hypothyroidism and those with strongly suppressed TSH levels had mild hyperthyroidism. These data provide useful findings that are directly applicable to management of patients following total thyroidectomy for thyroid cancer or benign thyroid disease.

Acknowledgements

Author contributions

A. Miyauchi and M. Ito constructed the study design, M. Ito analyzed the data, and the other coauthors contributed by performing surgery and/or caring for the patients.

Disclosure Statement

The authors declare that there are no relevant disclosures or conflicts of interest with regards to this study.

References


