TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy

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Abstract

Objective: Thyroidal production of triiodothyronine (T3) is absent in patients who have undergone total thyroidectomy. Therefore, relative T3 deficiency may occur during postoperative levothyroxine (L-T4) therapy. The objective of this study was to evaluate how the individual serum T3 level changes between preoperative native thyroid function and postoperative L-T4 therapy.

Methods: We retrospectively studied 135 consecutive patients with papillary thyroid carcinoma, who underwent total thyroidectomy. Serum free T4 (FT4), free T3 (FT3), and TSH levels measured preoperatively were compared with those levels measured on postoperative L-T4 therapy.

Results: Serum TSH levels during postoperative L-T4 therapy were significantly decreased compared with native TSH levels (P<0.001). Serum FT4 levels were significantly increased (P<0.001). Serum FT3 levels were significantly decreased (P=0.029). We divided the patients into four groups according to postoperative serum TSH levels: strongly suppressed (less than one-tenth of the lower limit); moderately suppressed (between one-tenth of the lower limit and the lower limit); normal limit; and more than upper limit. Patients with strongly suppressed TSH levels had serum FT3 levels significantly higher than the native levels (P<0.001). Patients with moderately suppressed TSH levels had serum FT3 levels equivalent to the native levels (P=0.51), and patients with normal TSH levels had significantly lower serum FT3 levels (P<0.001).

Conclusions: Serum FT3 levels during postoperative L-T4 therapy were equivalent to the preoperative levels in patients with moderately suppressed TSH levels. Our study indicated that a moderately TSH-suppressive dose of L-T4 is required to achieve the preoperative native serum T3 levels in postoperative L-T4 therapy.

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Introduction

There are two thyroid hormones, thyroxine (T4) and triiodothyronine (T3). In normal subjects, T4 is secreted by the thyroid (about 100%) and T3 as the active form is produced by the thyroid gland (about 20%) or is derived from the conversion of T4 to T3 in extra-thyroidal peripheral tissues (80%) (1). T4 therapy using synthetic levothyroxine (L-T4) is the standard of care for patients who had undergone total thyroidectomy (2, 3). Thyroidal production of T3 is absent in postoperative athyreotic patients. Therefore, relative T3 deficiency may be present during postoperative T4 therapy.

Several studies regarding the use of L-T4 therapy to treat hypothyroidism showed that when serum T4 levels are maintained at the upper limit of the normal ranges, serum T3 levels are within the normal ranges (4, 5, 6, 7, 8). However, there have been few studies that compared postoperative T3 levels in patients on L-T4 therapy with their own preoperative endogenous levels. Therefore, it is uncertain whether individuals have deficient T3 levels based on their own thyroid axis set point. Recently, Jonklaas et al. (9) evaluated 50 patients who underwent total thyroidectomy for various thyroid diseases and reported that there were no significant changes in T3 levels in patients undergoing l-T4 therapy compared with preoperative T3 levels. On the other hand, Gullo et al. (10) studied 1811 athyreotic subjects with normal TSH levels and 3875 euthyroid controls and found that serum free T3 (FT3) levels in the athyreotic subjects were significantly lower than those in the euthyroid controls.

The objective of this study was to compare the circulating levels of T4 and T3 produced by an individual’s own thyroid gland with those levels resulting from L-T4 therapy in the same individuals who underwent total thyroidectomy. Only patients with papillary thyroid carcinoma that did not affect the thyroidal conversion of T4 to T3 (11) were selected for this study. We investigated how to achieve the preoperative native serum T3 levels using postoperative L-T4 therapy.
Materials and methods

Patients

We retrospectively identified 135 consecutive patients who underwent total thyroidectomy for papillary thyroid carcinoma between January 2009 and July 2009 at Kuma Hospital. There were 113 females and 22 males (aged 51 ± 16 years (mean ± s.d.)). The patients were initially administered 2.0 μg/kg l-T4 daily after total thyroidectomy. The l-T4 dose was adjusted to achieve the target TSH levels determined according to the prognostic evaluations. Patients with very low-risk cancer were administered l-T4 with the goal of achieving a normal TSH level. Patients with middle or high-risk cancer were administered l-T4 with the goal of achieving a suppressed TSH level. The dose of l-T4 was unchanged for the last 3 months before measurement. The ultimate mean daily dose of l-T4 administered was 2.03 μg/kg per day.

Patients with preoperative thyroid profiles including thyroid dysfunction, thyroid dysfornogenensis, or autonomous functioning thyroid nodule were excluded from the study. Patients with thyroid malignancies other than papillary carcinoma were also excluded. Patients with chronic, serious diseases such as cardiac, pulmonary, hepatic, and renal disease were not eligible for study participation. We also excluded patients receiving drugs known to affect thyroid function or thyroid hormone metabolism, such as thyroid hormone, steroid, estrogen, amiodarone, lithium, β-blocker, sucralfate, and iron- or iodine-containing drugs. Among the participants, there were four patients (β-blocker (n = 2), steroid (n = 1), iodinated contrast material (n = 1)) taking medications that affected T₄-to-T₃ conversion, and 11 patients including these four were preliminarily excluded from the study because they were taking conflicting medications. This study was approved by the ethics committee at Kuma Hospital, and all patients gave informed consent.

Thyroid function tests

Two presurgical thyroid profiles were obtained, one at the first visit to our hospital and the other 2 days before thyroidectomy. Two postsurgical thyroid profiles for each patient were obtained after stabilization of the thyroid profiles while receiving maintenance doses of l-T₄, usually 6 and 12 months after thyroidectomy. Blood samples were drawn 2–4 h after ingestion of usual morning l-T₄ medication. TSH and free T₄ (FT₄) assays were performed when blood samples were collected for each patient. Small aliquots of the samples were stored frozen. FT₃ assays were performed simultaneously at the end of the study to avoid inter-assay variability. In order to minimize the effect of daily variation or measurement variation, we evaluated the mean of two preoperative thyroid profiles and the mean of two postoperative values for each patient.

Serum levels of TSH, FT₄, and FT₃ were measured by a chemiluminescent immunoassay (ARCHTECT i2000; Abbott Japan). TSH assay showed an intra-assay coefficient of variation (CV) of 1.1–5.0% and an inter-assay CV of 1.7–5.3%. FT₄ assay showed an intra-assay CV of 2.3–5.3% and an inter-assay CV of 3.6–7.8%. FT₃ assay showed an intra-assay CV of 1.4–4.2% and an inter-assay CV of 2.3–5.0%. The normal ranges were 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 per ng per dl) for the FT₃-to-FT₄ ratio.

Statistical analysis

Statistical significance was analyzed by the paired t-test in normal distributed data (mean ± s.d.), or by the Wilcoxon test in not-normal distributed data (median and inter-quartile range (IQR)). Significance was defined as P<0.05. Postoperative FT₃ levels in each group stratified by TSH level were analyzed by the Games–Howell test. Significance was defined as a corresponding P value of <0.05 (two-sided). Pearson’s correlation coefficient test was used to assess the correlation between the change in the levels of FT₃ during the study and postoperative serum TSH level.

Results

Table 1 shows the TSH, FT₄, and FT₃ levels before and after total thyroidectomy in the patients in this study. Before total thyroidectomy, the serum levels of TSH, FT₄, and FT₃ were within the normal range in all patients. The postoperative serum TSH levels were significantly decreased compared with the native preoperative TSH.
FT3 levels significantly increased (3.01 with TSH levels greater than 5 mIU/ml. The postoperative FT3 levels in patients treated with l-T4 were equivalent to the preoperative native levels when the postoperative serum TSH level was about 0.1 mIU/ml. This finding suggests that a TSH-suppressive dose of l-T4 is required for the preoperative native serum FT3 level to be achieved by postoperative l-T4 therapy.

We stratified patients into three groups based on the changes in FT3 levels (below 1 s.d., within ± 1 s.d., and above 1 s.d.) before and after thyroidectomy (Table 2). Patients in the increased FT3 group (Group 1; n = 21) had strongly suppressed TSH levels during postoperative l-T4 therapy. Patients in the similar FT3 group (Group 2; n = 81) had moderately suppressed TSH levels. Patients in the decreased FT3 group (Group 3; n = 33) had normal TSH levels equivalent to the native levels. Serum FT4 levels were significantly increased postoperatively in all three groups.

**Discussion**

Considerable controversy exists about the management of thyroid function status in patients who have undergone total thyroidectomy and are receiving postoperative l-T4 therapy. As the negative feedback relationship between serum T4 (and T3) levels and serum TSH levels is log-linear, most endocrinologists accept that serum TSH levels is a very sensitive indicator of thyroid function. However, serum TSH levels only reflect the feedback effect of thyroid hormones at the hypothalamic–pituitary level and, therefore, may not be an appropriate indicator of peripheral tissue euthyroidism (12). The TSH secretion from the pituitary is negatively

**Figure 1** Individual changes in the serum FT3 levels before and after thyroidectomy in patients who underwent total thyroidectomy. The patients were divided into four groups stratified by postoperative serum TSH levels. Closed squares represent means; bars represent the s.d. Postoperative FT3 levels in each group stratified by TSH level were significantly different from those in the other groups. *P < 0.05 vs other post-thyroidectomy TSH groups. Individual changes in serum FT3 levels before and after total thyroidectomy are shown in Fig. 1. Patients were divided into four groups according to postoperative serum TSH levels: those with TSH < 0.03 mIU/ml; those with TSH levels between 0.03 and 0.3 mIU/ml; those with TSH levels between 0.3 and 5 mIU/ml; and those with TSH levels more than 5 mIU/ml. In patients with TSH levels < 0.03 mIU/ml, the postoperative serum FT3 levels significantly increased (3.01 ± 0.32 vs 3.31 ± 0.41 pg/ml before and after thyroidectomy respectively; P < 0.001). Six of 30 patients had serum FT3 levels higher than the normal upper limit. In patients with TSH levels between 0.03 and 0.3 mIU/ml, postoperative serum FT3 levels were equivalent to the preoperative levels (3.06 ± 0.27 vs 3.03 ± 0.32 pg/ml before and after thyroidectomy respectively; P = 0.51). In patients with TSH levels between 0.3 and 5 mIU/ml, the serum FT3 levels were significantly decreased postoperatively (3.01 ± 0.21 vs 2.77 ± 0.21 pg/ml before and after thyroidectomy respectively; P < 0.001), although they were within the normal ranges. All the five patients with postoperative serum TSH levels more than 5 mIU/ml also had decreased serum FT3 levels (2.92 ± 0.12 vs 2.49 ± 0.16 pg/ml before and after thyroidectomy respectively; P < 0.01). Postoperative FT3 levels in each group stratified by TSH level were significantly different from those in the other groups (Fig. 1). Serum FT4 levels were significantly increased postoperatively in all four groups (Fig. 2). However, the magnitude of increase varied according to the TSH levels.

**Figure 2** Individual changes in the serum FT4 levels before and after thyroidectomy in patients who underwent total thyroidectomy. The patients were divided into four groups stratified by postoperative serum TSH levels. Closed squares represent means; bars represent s.d.

**Figure 3** shows the correlation between changes in FT3 levels before and after thyroidectomy and postoperative serum TSH level. The changes in both FT3 levels showed a significant negative correlation with postoperative TSH levels (r = −0.334, P < 0.0001). The postoperative FT3 levels in patients treated with l-T4 were equivalent to the preoperative native levels when the postoperative serum TSH level was about 0.1 mIU/ml. This finding suggests that a TSH-suppressive dose of l-T4 is required for the preoperative native serum FT3 level to be achieved by postoperative l-T4 therapy.
Figure 3 Correlation between changes in FT₃ levels before and after thyroidectomy and postoperative serum TSH levels. Open circles represent patients who underwent total thyroidectomy. The shaded area represents postoperative TSH levels from 0.03 to 0.3 μIU/ml. A postoperative FT₃ level equal to the preoperative level (change of FT₃ level = 0 pg/ml) was achieved when the postoperative serum TSH level was about 0.1 μIU/ml (broken line).

regulated primarily by T₃ produced locally via the conversion of T₄ transported from the peripheral blood, which is keeping with the view that serum T₄ rather than T₃ has a dominant role in regulating TSH secretion (13). On the other hand, T₃ transported from the peripheral blood also has a role in regulating TSH secretion by the pituitary (14).

Recently, Jonklaas et al. reported that there were no significant decreases in T₃ levels in patients on l-T₄ compared with their preoperative T₃ levels, although their FT₃ levels were significantly higher than their native levels. However, Jonklaas et al. did not indicate in detail how to achieve the preoperative individual native serum T₃ levels via postoperative l-T₄ therapy. Their results came from compound data from all cases, including cases in various thyroid states. They also stratified their study patients by postoperative TSH level and found that the mean T₃ levels in the group with postoperative TSH levels over 4.5 μIU/ml were lower than those in the other group. However, they did not demonstrate how the serum T₃ level changed from the preoperative native levels in each group stratified by TSH level. In addition, there were differences between their study and ours in the subject population and the number of patients. Jonklaas et al. included 50 patients with various thyroid diseases, while we studied 135 patients with papillary thyroid cancer only.

In this study, patients with normal TSH levels postoperatively had higher serum FT₄ levels and lower serum FT₃ levels compared with their native levels. Higher FT₄ levels in individuals taking l-T₄ have been shown in numerous previous studies (4, 5, 6, 7, 8). The same data were also obtained from our study and were in agreement with these studies. These findings also suggest that a supraphysiological serum T₄ level was needed to normalize the serum TSH level, possibly in order to compensate for the absence of circulating T₃ secreted by the thyroid. Therefore, several investigators have advocated monitoring the dosage of l-T₄ based on the serum levels of T₃ rather than T₄ (4, 5). Such a relative deficiency of T₃ in athyreotic patients on l-T₄ may be overlooked if only serum TSH and T₄ levels are determined. Indeed, some studies showed that hypothyroid patients treated with l-T₄ had impaired well-being despite their normal TSH levels (15, 16). Meanwhile, patients with moderately suppressed TSH levels postoperatively had higher serum FT₄ levels and unchanged serum FT₃ levels compared with their native levels, findings that are in agreement with those of Silva & Larsen (13). Indeed, most physicians encounter patients on TSH-suppressive doses of l-T₄ therapy who have serum T₄ levels higher than the normal upper limit and normal T₃ levels (2, 3, 5). In general, most clinicians believe that a low-serum TSH level indicates subclinical thyrotoxicosis and is a risk factor for cardiac dysfunction or osteoporosis (17). However, such clinical outcome in subclinical thyrotoxicosis seems to be unclear in patients with moderately low-TSH levels (18).

There were some possible limitations in this study. First, it has been reported that serum FT₃ and FT₄ levels increased transiently after ingestion of l-T₄ (19, 20). In consideration of such an increment, the evaluation of diurnal variation or area under the curve by repeated blood sampling may be the best; however, it is practically difficult to carry out such an examination in many patients (n = 135). In this study, we evaluated the blood sampling data 2–4 h after l-T₄ intake. As a result, a postoperative decrease of the serum FT₃ levels

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<th>Group 1 (n=21)</th>
<th>Group 2 (n=81)</th>
<th>Group 3 (n=33)</th>
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<tbody>
<tr>
<td>Before</td>
<td>After</td>
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<tr>
<td>TSH (μIU/ml)</td>
<td>1.80 (0.68)</td>
<td>0.02 (0.01)</td>
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<tr>
<td>FT₄ (ng/dl)</td>
<td>0.95 ± 0.10</td>
<td>1.50 ± 0.17</td>
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<tr>
<td>FT₃ (pg/ml)</td>
<td>2.96 ± 0.28</td>
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Statistical significance (pre- vs post-thyroidectomy) was analyzed by paired t-test or by Wilcoxon signed-rank test. *P < 0.001, †P > 0.05.
was observed. FT3 levels after l-T4 intake are supposed to be relatively high. Thus, the fact that the FT3 levels were lower than the preoperative FT3 levels suggests that postoperative FT3 levels in serum remained relatively low for most of the day. On the other hand, the serum FT4 level is higher than the preoperative level, and this could be affected by blood sampling after taking l-T4. In addition, our study did not examine patients’ satisfaction or well-being. It is not until serum T3 levels are correlated with patients’ satisfaction or well-being that this question will be resolved and moderately TSH-suppressive doses of l-T4 can be recommended to achieve euthyroid status.

In conclusion, this study showed that moderate TSH-suppressive doses of l-T4 were required for postoperative athyreotic patients to achieve their preoperative native serum FT3 levels. They must take l-T4 for the remainder of their lives. Therefore, even if thyroidal dysfunction may be subtle, its long-term effects cannot be overlooked. The question arises as to which of two patient groups is in euthyroid condition: those with normal serum TSH levels and mildly low FT3 or those with serum FT3 levels equivalent to their preoperative native serum FT3 levels and mildly suppressed TSH. An animal study has shown that l-T4 alone administered to thyroidectomized rats at doses to normalize plasma TSH levels does not normalize T3 contents in some tissues (21). Prospective, properly designed studies including well-being or a metabolic marker such as lipid or bone are needed to clarify the best method of managing thyroid function in postoperative athyreotic patients.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
A Miyauchi constructed the study design, S Morita was responsible for quality control of the thyroid function measurements, M Ito analyzed the data, and the other coauthors contributed by performing surgery and/or caring for the patients.

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