CLINICAL STUDY

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 (T_3) is absent in patients who have undergone total thyroidectomy. Therefore, relative T_3 deficiency may occur during postoperative levothyroxine (L-T_4) therapy. The objective of this study was to evaluate how the individual serum T_3 level changes between preoperative native thyroid function and postoperative L-T_4 therapy.

Methods: We retrospectively studied 135 consecutive patients with papillary thyroid carcinoma, who underwent total thyroidectomy. Serum free T_4 (FT_4), free T_3 (FT_3), and TSH levels measured preoperatively were compared with those levels measured on postoperative L-T_4 therapy.

Results: Serum TSH levels during postoperative L-T_4 therapy were significantly decreased compared with native TSH levels ($P<0.001$). Serum FT_4 levels were significantly increased ($P<0.001$). Serum FT_3 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 FT_3 levels significantly higher than the native levels ($P<0.001$). Patients with moderately suppressed TSH levels had serum FT_3 levels equivalent to the native levels ($P=0.51$), and patients with normal TSH levels had significantly lower serum FT_3 levels ($P<0.001$).

Conclusions: Serum FT_3 levels during postoperative L-T_4 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-T_4 is required to achieve the preoperative native serum T_3 levels in postoperative L-T_4 therapy.

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Introduction

There are two thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). In normal subjects, T_4 is secreted by the thyroid (about 100%) and T_3 as the active form is produced by the thyroid gland (about 20%) or is derived from the conversion of T_4 to T_3 in extra-thyroidal peripheral tissues (80%) (1). T_4 therapy using synthetic levothyroxine (L-T_4) is the standard of care for patients who had undergone total thyroidectomy (2, 3). Thyroidal production of T_3 is absent in postoperative athyreotic patients. Therefore, relative T_3 deficiency may be present during postoperative T_4 therapy.

Several studies regarding the use of L-T_4 therapy to treat hypothyroidism showed that when serum T_4 levels are maintained at the upper limit of the normal ranges, serum T_3 levels are within the normal ranges (4, 5, 6, 7, 8). However, there have been few studies that compared postoperative T_3 levels in patients on L-T_4 therapy with their own preoperative endogenous levels. Therefore, it is uncertain whether individuals have deficient T_3 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 T_3 levels in patients undergoing L-T_4 therapy compared with preoperative T_3 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 T_3 (FT_3) 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 T_4 and T_3 produced by an individual's own thyroid gland with those levels resulting from L-T_4 therapy in the same individuals who underwent total thyroidectomy. Only patients with papillary thyroid carcinoma that did not affect the thyroidal conversion of T_4 to T_3 (11) were selected for this study. We investigated how to achieve the preoperative native serum T_3 levels using postoperative L-T_4 therapy.

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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-T_4 daily after total thyroidectomy. The L-T_4 dose was adjusted to achieve the target TSH levels determined according to the prognostic evaluations. Patients with very low-risk cancer were administered L-T_4 with the goal of achieving a normal TSH level. Patients with middle or high-risk cancer were administered L-T_4 with the goal of achieving a suppressed TSH level. The dose of L-T_4 was unchanged for the last 3 months before measurement. The ultimate mean daily dose of L-T_4 administered was 2.03 μg/kg per day.

Patients with preoperative thyroid profiles including thyroid dysfunction, thyroid dyshormonogenesis, 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 T_4-to-T_3 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-T_4, usually 6 and 12 months after thyroidectomy. Blood samples were drawn 2–4 h after ingestion of usual morning L-T_4 medication. TSH and free T_4 (FT_4) assays were performed when blood samples were collected for each patient. Small aliquots of the samples were stored frozen. FT_3 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, FT_4, and FT_3 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%. FT_4 assay showed an intra-assay CV of 2.3–5.3% and an inter-assay CV of 3.6–7.8%. FT_3 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 FT_4, 1.7–3.7 pg/ml for FT_3, and 1.8–3.3 (pg/ml per ng per dl) for the FT_3-to-FT_4 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 FT_3 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 FT_3 during the study and postoperative serum TSH level.

Results

Table 1 shows the TSH, FT_4, and FT_3 levels before and after total thyroidectomy in the patients in this study. Before total thyroidectomy, the serum levels of TSH, FT_4, and FT_3 were within the normal range in all patients. The postoperative serum TSH levels were significantly decreased compared with the native preoperative TSH

Table 1 Serum TSH, FT_4, and FT_3 levels in thyroidectomized patients ($n=135$).

	Pre-thyroidectomy	Post-thyroidectomy	*P* value
TSH, median (IQR) (μIU/ml)	1.65 (0.99–2.48)	0.21 (0.04–1.02)	<0.001[a]
FT_4, mean (S.D.) (ng/dl)	1.01 (0.11)	1.39 (0.18)	<0.001
FT_3, median (IQR) (pg/ml)	3.01 (2.87–3.19)	2.92 (2.71–3.19)	0.029[a]
FT_3/FT_4, mean (S.D.)	3.01 (0.35)	2.17 (0.31)	<0.001

Statistical significance (pre- vs post-thyroidectomy) was analyzed by paired *t*-test or by [a]Wilcoxon signed-rank test.

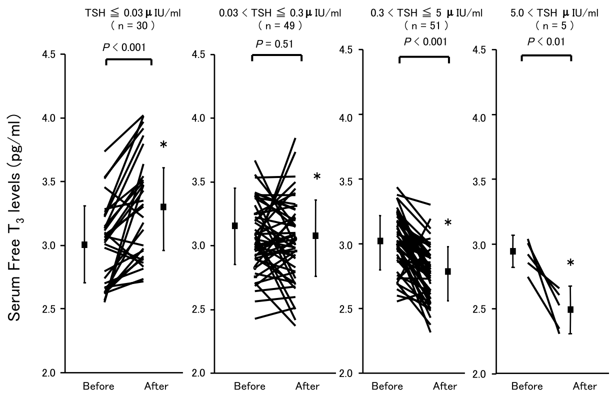

Figure 1 Individual changes in the serum FT_3 levels before and after thyroidectomy in patients who underwent total thyroidectomy. The patients were divided into four groups stratified by postoperative serum TSH levels. Closed squares represent means; bars represent the S.D. Postoperative FT_3 levels 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.

levels ($P<0.001$). The postoperative serum FT_4 levels were significantly increased ($P<0.001$). However, postoperative serum FT_3 levels were significantly decreased ($P=0.029$), although they were within the normal ranges. The postoperative serum FT_3/FT_4 ratios were significantly decreased ($P<0.001$).

Individual changes in serum FT_3 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 μIU/ml; those with TSH levels between 0.03 and 0.3 μIU/ml; those with TSH levels between 0.3 and 5 μIU/ml; and those with TSH levels more than 5 μIU/ml. In patients with TSH levels <0.03 μIU/ml, the postoperative serum FT_3 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 FT_3 levels higher than the normal upper limit. In patients with TSH levels between 0.03 and 0.3 μIU/ml, postoperative serum FT_3 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 μIU/ml, the serum FT_3 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 μIU/ml also had decreased serum FT_3 levels (2.92 ± 0.12 vs 2.49 ± 0.16 pg/ml, before and after thyroidectomy respectively; $P<0.01$). Postoperative FT_3 levels in each group stratified by TSH level were significantly different from those in the other groups (Fig. 1). Serum FT_4 levels were significantly increased postoperatively in all four groups (Fig. 2). However, the magnitude of increase varied according to the TSH levels.

Figure 3 shows the correlation between changes in FT_3 levels before and after thyroidectomy and postoperative serum TSH level. The changes in both FT_3 levels showed a significant negative correlation with postoperative TSH levels ($r=-0.334$, $P<0.0001$). The postoperative FT_3 levels in patients treated with L-T_4 were equivalent to the preoperative native levels when the postoperative serum TSH level was about 0.1 μIU/ml. This finding suggests that a TSH-suppressive dose of L-T_4 is required for the preoperative native serum FT_3 level to be achieved by postoperative L-T_4 therapy.

We stratified patients into three groups based on the changes in FT_3 levels (below 1 S.D., within ± 1 S.D., and above 1 S.D.) before and after thyroidectomy (Table 2). Patients in the increased FT_3 group (Group 1; $n=21$) had strongly suppressed TSH levels during postoperative L-T_4 therapy. Patients in the similar FT_3 group (Group 2; $n=81$) had moderately suppressed TSH levels. Patients in the decreased FT_3 group (Group 3; $n=33$) had normal TSH levels equivalent to the native levels. Serum FT_4 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-T_4 therapy. As the negative feedback relationship between serum T_4 (and T_3) levels and serum TSH levels is log-linear, most endocrinologists accept that serum TSH level 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

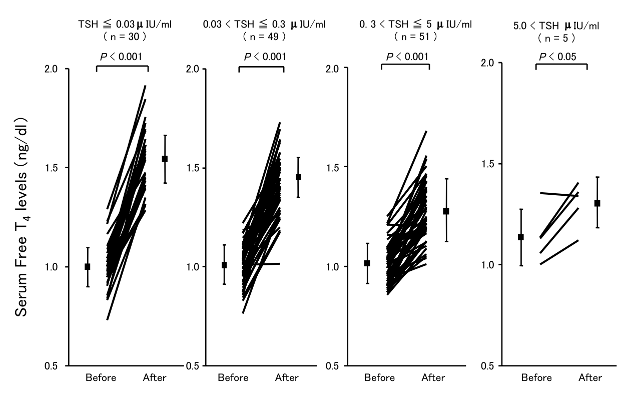

Figure 2 Individual changes in the serum FT_4 levels before and after thyroidectomy in patients who underwent total thyroidectomy. The patients were divided into four groups stratified by postoperative serum TSH levels. Closed squares represent means; bars represent S.D.

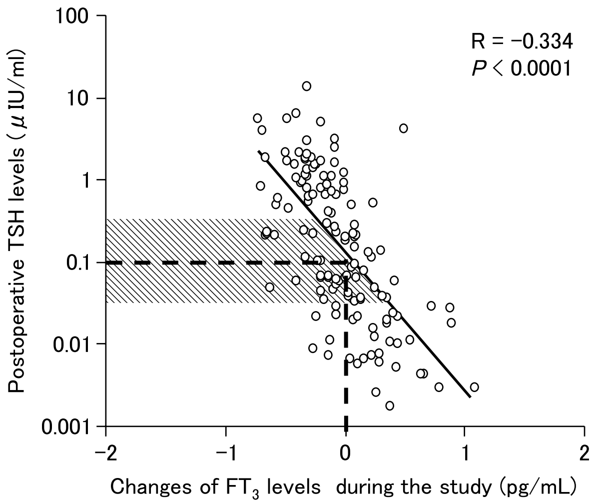

Figure 3 Correlation between changes in FT_3 levels before and after thyroidectomy and postoperative serum TSH levels. Open circles represent patients who underwent total thyroidectomy. The shaded area represents postoperative TSH levels from 0.03 to 0.3 μIU/ml. A postoperative FT_3 level equal to the preoperative level (change of FT_3 level=0 pg/ml) was achieved when the post-operative serum TSH level was about 0.1 μIU/ml (broken line).

regulated primarily by T_3 produced locally via the conversion of T_4 transported from the peripheral blood, which is keeping with the view that serum T_4 rather than T_3 has a dominant role in regulating TSH secretion (13). On the other hand, T_3 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 T_3 levels in patients on L-T_4 compared with their preoperative T_3 levels, although their FT_4 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 T_3 levels via postoperative L-T_4 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 T_3 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 T_3 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 FT_4 levels and lower serum FT_3 levels compared with their native levels.

Higher FT_4 levels in individuals taking L-T_4 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 T_4 level was needed to normalize the serum TSH level, possibly in order to compensate for the absence of circulating T_3 secreted by the thyroid. Therefore, several investigators have advocated monitoring the dosage of L-T_4 based on the serum levels of T_3 rather than T_4 (4, 5). Such a relative deficiency of T_3 in athyreotic patients on L-T_4 may be overlooked if only serum TSH and T_4 levels are determined. Indeed, some studies showed that hypothyroid patients treated with L-T_4 had impaired well-being despite their normal TSH levels (15, 16). Meanwhile, patients with moderately suppressed TSH levels postoperatively had higher serum FT_4 levels and unchanged serum FT_3 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-T_4 therapy who have serum T_4 levels higher than the normal upper limit and normal T_3 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 FT_4 and FT_3 levels increased transiently after ingestion of L-T_4 (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-T_4 intake. As a result, a postoperative decrease of the serum FT_3 levels

Table 2 Serum TSH, FT_4, and FT_3 levels in three patient groups stratified by changes in serum FT_3 levels before and after thyroidectomy. TSH; median (IQR), FT_4, and FT_3; mean±S.D.

	Group 1 ($n=21$)		**Group 2** ($n=81$)		**Group 3** ($n=33$)	
	Before	After	Before	After	Before	After
TSH (μIU/ml)	1.80 (0.68)	0.02 (0.01)*,a	1.65 (0.72)	0.12 (0.37)*,a	1.55 (0.93)	1.24 (0.97)†,a
FT_4 (ng/dl)	0.95±0.10	1.50±0.17*	1.01±0.10	1.39±0.17*	1.06±0.11	1.30±0.15*
FT_3 (pg/ml)	2.96±0.28	3.50±0.33*	3.01±0.26	2.98±0.27†	3.09±0.22	2.62±0.20*

Statistical significance (pre- vs post-thyroidectomy) was analyzed by paired *t*-test or by [a]Wilcoxon signed-rank test. *$P<0.001$, †$P>0.05$.

was observed. FT_3 levels after L-T_4 intake are supposed to be relatively high. Thus, the fact that the FT_3 levels were lower than the preoperative FT_3 levels suggests that postoperative FT_3 levels in serum remained relatively low for most of the day. On the other hand, the serum FT_4 level is higher than the preoperative level, and this could be affected by blood sampling after taking L-T_4. In addition, our study did not examine patients' satisfaction or well-being. It is not until serum T_3 levels are correlated with patients' satisfaction or well-being that this question will be resolved and moderately TSH-suppressive doses of L-T_4 can be recommended to achieve euthyroid status.

In conclusion, this study showed that moderate TSH-suppressive doses of L-T_4 were required for postoperative athyreotic patients to achieve their preoperative native serum FT_3 levels. They must take L-T_4 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 FT_3 or those with serum FT_3 levels equivalent to their preoperative native serum FT_3 levels and mildly suppressed TSH. An animal study has shown that L-T_4 alone administered to thyroidectomized rats at doses to normalize plasma TSH levels does not normalize T_3 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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