

## 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.

## 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  $51 \pm 16$  years (mean  $\pm$  s.d.)). The patients were initially administered  $2.0 \mu\text{g}/\text{kg}$   $L\text{-T}_4$  daily after total thyroidectomy. The  $L\text{-T}_4$  dose was adjusted to achieve the target TSH levels determined according to the prognostic evaluations. Patients with very low-risk cancer were administered  $L\text{-T}_4$  with the goal of achieving a normal TSH level. Patients with middle or high-risk cancer were administered  $L\text{-T}_4$  with the goal of achieving a suppressed TSH level. The dose of  $L\text{-T}_4$  was unchanged for the last 3 months before measurement. The ultimate mean daily dose of  $L\text{-T}_4$  administered was  $2.03 \mu\text{g}/\text{kg}$  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,  $\beta$ -blocker, sucralfate, and iron- or iodine-containing drugs. Among the participants, there were four patients ( $\beta$ -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  $L\text{-T}_4$ , usually 6 and 12 months after thyroidectomy. Blood samples were drawn 2–4 h after ingestion of usual morning  $L\text{-T}_4$  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 (ARCHTEC 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  $\mu\text{IU}/\text{ml}$  for TSH, 0.7–1.6  $\text{ng}/\text{dl}$  for  $FT_4$ , 1.7–3.7  $\text{pg}/\text{ml}$  for  $FT_3$ , and 1.8–3.3 ( $\text{pg}/\text{ml}$  per  $\text{ng}$  per  $\text{dl}$ ) for the  $FT_3$ -to- $FT_4$  ratio.

### Statistical analysis

Statistical significance was analyzed by the paired  $t$ -test in normal distributed data (mean  $\pm$  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.

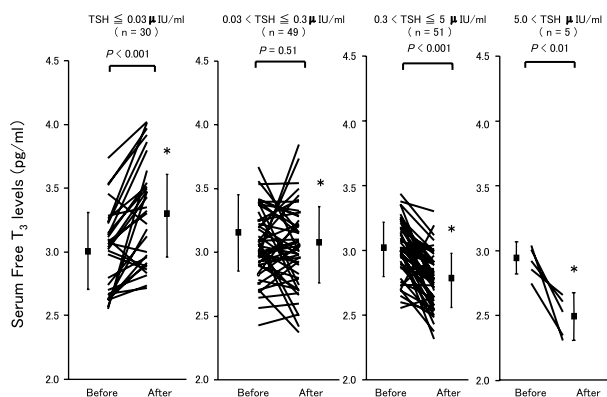
## Results

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	<i>P</i> value
TSH, median (IQR) ( $\mu\text{IU}/\text{ml}$ )	1.65 (0.99–2.48)	0.21 (0.04–1.02)	$< 0.001^a$
$FT_4$ , mean (s.d.) ( $\text{ng}/\text{dl}$ )	1.01 (0.11)	1.39 (0.18)	$< 0.001$
$FT_3$ , median (IQR) ( $\text{pg}/\text{ml}$ )	3.01 (2.87–3.19)	2.92 (2.71–3.19)	0.029 <sup>a</sup>
$FT_3/FT_4$ , 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 <sup>a</sup>Wilcoxon signed-rank test.



**Figure 1** Individual changes in the serum FT<sub>3</sub> 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<sub>3</sub> 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<sub>4</sub> levels were significantly increased ( $P < 0.001$ ). However, postoperative serum FT<sub>3</sub> levels were significantly decreased ( $P = 0.029$ ), although they were within the normal ranges. The postoperative serum FT<sub>3</sub>/FT<sub>4</sub> ratios were significantly decreased ( $P < 0.001$ ).

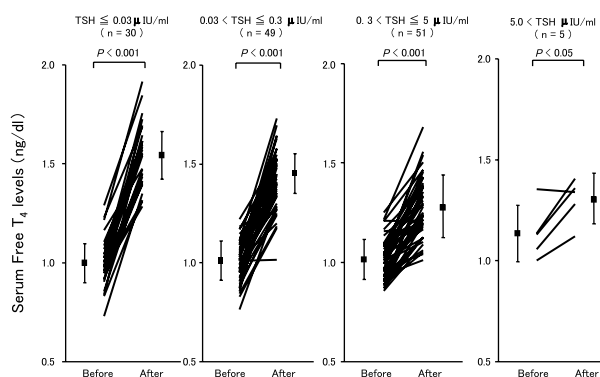
Individual changes in serum FT<sub>3</sub> levels before and after total thyroidectomy are shown in Fig. 1. Patients were divided into four groups according to postoperative serum TSH levels: those with TSH  $< 0.03$   $\mu\text{IU/ml}$ ; those with TSH levels between  $0.03$  and  $0.3$   $\mu\text{IU/ml}$ ; those with TSH levels between  $0.3$  and  $5$   $\mu\text{IU/ml}$ ; and those with TSH levels more than  $5$   $\mu\text{IU/ml}$ . In patients with TSH levels  $< 0.03$   $\mu\text{IU/ml}$ , the postoperative serum FT<sub>3</sub> levels significantly increased ( $3.01 \pm 0.32$  vs  $3.31 \pm 0.41$  pg/ml, before and after thyroidectomy respectively;  $P < 0.001$ ). Six of 30 patients had serum FT<sub>3</sub> levels higher than the normal upper limit. In patients with TSH levels between  $0.03$  and  $0.3$   $\mu\text{IU/ml}$ , postoperative serum FT<sub>3</sub> levels were equivalent to the preoperative levels ( $3.06 \pm 0.27$  vs  $3.03 \pm 0.32$  pg/ml, before and after thyroidectomy respectively;  $P = 0.51$ ). In patients with TSH levels between  $0.3$  and  $5$   $\mu\text{IU/ml}$ , the serum FT<sub>3</sub> levels were significantly decreased postoperatively ( $3.01 \pm 0.21$  vs  $2.77 \pm 0.21$  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  $5$   $\mu\text{IU/ml}$  also had decreased serum FT<sub>3</sub> levels ( $2.92 \pm 0.12$  vs  $2.49 \pm 0.16$  pg/ml, before and after thyroidectomy respectively;  $P < 0.01$ ). Postoperative FT<sub>3</sub> levels in each group stratified by TSH level were significantly different from those in the other groups (Fig. 1). Serum FT<sub>4</sub> 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<sub>3</sub> levels before and after thyroidectomy and postoperative serum TSH level. The changes in both FT<sub>3</sub> levels showed a significant negative correlation with postoperative TSH levels ( $r = -0.334$ ,  $P < 0.0001$ ). The postoperative FT<sub>3</sub> levels in patients treated with L-T<sub>4</sub> were equivalent to the preoperative native levels when the postoperative serum TSH level was about  $0.1$   $\mu\text{IU/ml}$ . This finding suggests that a TSH-suppressive dose of L-T<sub>4</sub> is required for the preoperative native serum FT<sub>3</sub> level to be achieved by postoperative L-T<sub>4</sub> therapy.

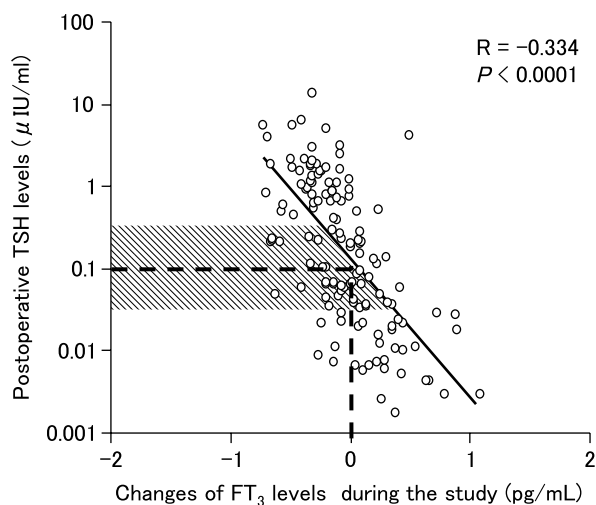
We stratified patients into three groups based on the changes in FT<sub>3</sub> levels (below 1 s.d., within  $\pm 1$  s.d., and above 1 s.d.) before and after thyroidectomy (Table 2). Patients in the increased FT<sub>3</sub> group (Group 1;  $n = 21$ ) had strongly suppressed TSH levels during postoperative L-T<sub>4</sub> therapy. Patients in the similar FT<sub>3</sub> group (Group 2;  $n = 81$ ) had moderately suppressed TSH levels. Patients in the decreased FT<sub>3</sub> group (Group 3;  $n = 33$ ) had normal TSH levels equivalent to the native levels. Serum FT<sub>4</sub> 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<sub>4</sub> therapy. As the negative feedback relationship between serum T<sub>4</sub> (and T<sub>3</sub>) 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<sub>4</sub> 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<sub>3</sub> 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<sub>3</sub> level equal to the preoperative level (change of FT<sub>3</sub> level = 0 pg/ml) was achieved when the postoperative serum TSH level was about 0.1 μIU/ml (broken line).

regulated primarily by T<sub>3</sub> produced locally via the conversion of T<sub>4</sub> transported from the peripheral blood, which is keeping with the view that serum T<sub>4</sub> rather than T<sub>3</sub> has a dominant role in regulating TSH secretion (13). On the other hand, T<sub>3</sub> 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<sub>3</sub> levels in patients on L-T<sub>4</sub> compared with their preoperative T<sub>3</sub> levels, although their FT<sub>4</sub> 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<sub>3</sub> levels via postoperative L-T<sub>4</sub> 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<sub>3</sub> 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<sub>3</sub> 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<sub>4</sub> levels and lower serum FT<sub>3</sub> levels compared with their native levels.

Higher FT<sub>4</sub> levels in individuals taking L-T<sub>4</sub> 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<sub>4</sub> level was needed to normalize the serum TSH level, possibly in order to compensate for the absence of circulating T<sub>3</sub> secreted by the thyroid. Therefore, several investigators have advocated monitoring the dosage of L-T<sub>4</sub> based on the serum levels of T<sub>3</sub> rather than T<sub>4</sub> (4, 5). Such a relative deficiency of T<sub>3</sub> in athyreotic patients on L-T<sub>4</sub> may be overlooked if only serum TSH and T<sub>4</sub> levels are determined. Indeed, some studies showed that hypothyroid patients treated with L-T<sub>4</sub> had impaired well-being despite their normal TSH levels (15, 16). Meanwhile, patients with moderately suppressed TSH levels postoperatively had higher serum FT<sub>4</sub> levels and unchanged serum FT<sub>3</sub> 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<sub>4</sub> therapy who have serum T<sub>4</sub> levels higher than the normal upper limit and normal T<sub>3</sub> 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<sub>4</sub> and FT<sub>3</sub> levels increased transiently after ingestion of L-T<sub>4</sub> (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<sub>4</sub> intake. As a result, a postoperative decrease of the serum FT<sub>3</sub> levels

**Table 2** Serum TSH, FT<sub>4</sub>, and FT<sub>3</sub> levels in three patient groups stratified by changes in serum FT<sub>3</sub> levels before and after thyroidectomy. TSH; median (IQR), FT<sub>4</sub>, and FT<sub>3</sub>; mean  $\pm$  s.d.

	Group 1 ( $n=21$ )		Group 2 ( $n=81$ )		Group 3 ( $n=33$ )	
	Before	After	Before	After	Before	After
TSH ( $\mu$ IU/ml)	1.80 (0.68)	0.02 (0.01) <sup>*,a</sup>	1.65 (0.72)	0.12 (0.37) <sup>*,a</sup>	1.55 (0.93)	1.24 (0.97) <sup>†,a</sup>
FT <sub>4</sub> (ng/dl)	0.95 $\pm$ 0.10	1.50 $\pm$ 0.17 <sup>*</sup>	1.01 $\pm$ 0.10	1.39 $\pm$ 0.17 <sup>*</sup>	1.06 $\pm$ 0.11	1.30 $\pm$ 0.15 <sup>*</sup>
FT <sub>3</sub> (pg/ml)	2.96 $\pm$ 0.28	3.50 $\pm$ 0.33 <sup>*</sup>	3.01 $\pm$ 0.26	2.98 $\pm$ 0.27 <sup>†</sup>	3.09 $\pm$ 0.22	2.62 $\pm$ 0.20 <sup>*</sup>

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



was observed. FT<sub>3</sub> levels after L-T<sub>4</sub> intake are supposed to be relatively high. Thus, the fact that the FT<sub>3</sub> levels were lower than the preoperative FT<sub>3</sub> levels suggests that postoperative FT<sub>3</sub> levels in serum remained relatively low for most of the day. On the other hand, the serum FT<sub>4</sub> level is higher than the preoperative level, and this could be affected by blood sampling after taking L-T<sub>4</sub>. In addition, our study did not examine patients' satisfaction or well-being. It is not until serum T<sub>3</sub> levels are correlated with patients' satisfaction or well-being that this question will be resolved and moderately TSH-suppressive doses of L-T<sub>4</sub> can be recommended to achieve euthyroid status.

In conclusion, this study showed that moderate TSH-suppressive doses of L-T<sub>4</sub> were required for postoperative athyreotic patients to achieve their preoperative native serum FT<sub>3</sub> levels. They must take L-T<sub>4</sub> 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<sub>3</sub> or those with serum FT<sub>3</sub> levels equivalent to their preoperative native serum FT<sub>3</sub> levels and mildly suppressed TSH. An animal study has shown that L-T<sub>4</sub> alone administered to thyroidectomized rats at doses to normalize plasma TSH levels does not normalize T<sub>3</sub> 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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