Effect of the presence of remnant thyroid tissue on the serum thyroid hormone balance in thyroidectomized patients

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Abstract

Objective: We and others recently reported that in total thyroidectomy (TT), serum triiodothyronine (T₃) levels during levothyroxine (L-T₄) therapy were low compared to the preoperative levels, suggesting that the presence of the thyroid tissue affects the balances of serum thyroid hormone levels. However, the effects of remnant thyroid tissue on these balances in thyroidectomized patients have not been established.

Methods: We retrospectively studied 253 euthyroid patients with papillary thyroid carcinoma who underwent a TT or hemithyroidectomy (HT). We divided the cases into the TT+supplemental L-T₄ (+L-T₄) group (*n*=103); the HT+L-T₄ group (*n*=56); and the HT-alone group (*n*=94). We compared the postoperative serum levels of free T₄ (FT₄) and free T₃ (FT₃) and the FT₃/FT₄ ratio in individual patients with those of controls matched by serum TSH levels.

Results: The TT+L-T₄ group had significantly higher FT₄ (*P*<0.001), lower FT₃ (*P*<0.01) and lower FT₃/FT₄ (*P*<0.001) levels compared to the controls. The HT+L-T₄ group had FT₄, FT₃ and FT₃/FT₄ levels equivalent to those of the controls. The HT-alone group had significantly lower FT₄ (*P*<0.01), equivalent FT₃ (*P*=0.083), and significantly higher FT₃/FT₄ (*P*<0.001) ratios than the controls.

Conclusions: The presence of the remnant thyroid tissue was associated with different thyroid hormone balances in thyroidectomized patients, suggesting that T₃ production by remnant thyroid tissue has a substantial effect on the maintenance of postoperative serum T₃ levels.

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Introduction

There are two thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃). T₃ is the biologically active thyroid hormone. In normal subjects, 100% of T₄ is secreted by the thyroid, about 20% of T₃ is secreted from the thyroid gland, and about 80% of T₃ is derived from the conversion of T₄ to T₃ in extra-thyroidal peripheral tissues (1). A relative T₃ deficiency may thus be present in athyreotic patients during T₄ monotherapy. Several studies (2, 3, 4, 5) compared postoperative T₃ levels in patients on L-T₄ therapy with their own preoperative levels or those in

euthyroid controls. We reported that serum T₃ levels were inappropriately low in patients who had undergone a total thyroidectomy (TT) and were on L-T₄ supplementation and that a moderately thyroid-stimulating hormone (TSH)-suppressive dose of L-T₄ was required to achieve their preoperative native serum T₃ levels (2). Jonklaas *et al.* (3) reported that there were no significant decreases in T₃ levels in patients on L-T₄ supplementation compared with their preoperative T₃ levels within the group as a whole, although a higher ratio of free T₄ (FT₄) to T₃ ratio was

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necessary to achieve this. Gullo *et al.* (4) studied 1811 athyreotic subjects with normal TSH levels and 3875 euthyroid controls, and they found that serum free T₃ (FT₃) levels of the athyreotic subjects were lower than those of the euthyroid controls, whereas the athyreotic subjects' serum FT₄ levels were higher. Hoermann *et al.* (5) recently reported that in 50 carcinoma patients who underwent TT and showed normal TSH levels postoperatively, the FT₃ levels were lower than those of controls, whereas the FT₄ levels were higher than those of the controls. These findings suggest that the interrelation among serum T₄, T₃ and TSH levels might differ according to the postoperative presence or absence of thyroid tissue. However, to the best of our knowledge this hypothesis has not been investigated in detail.

Although hemithyroidectomy (HT) is associated with a risk of hypothyroidism, few studies have evaluated the thyroidal function including serum T₃ levels of HT patients, because patients who had normal serum TSH and FT₄ levels were generally considered to have euthyroidism (6). Some investigators reported that patients who underwent a HT had approximately the same serum T₃ levels compared to their preoperative native levels or those in controls (7, 8), but another group did not obtain such results (9). Most of the previous studies have some flaws such as the heterogeneity of patients or a small sample size ($n=28-35$). The cases in Lombardi *et al.* (7) and Toft Kristensen *et al.* (9) were only identified as euthyroid goiter; therefore, the cases in these studies may contain follicular tumor, thyroid dysmorphogenesis, or giant Hashimoto thyroiditis. These diseases reveal normal thyroid hormone levels but high T₃/T₄ ratio. In the present study, our cases were identified as papillary thyroid carcinoma that did not affect the thyroidal conversion of T₄ to T₃ (10). Moreover, in these reports, the postoperative serum TSH levels were increased compared to preoperative native levels or those of controls (7, 8, 9). It is possible that TSH stimulates both type 1 (D1) and type 2 (D2) deiodinases, which convert T₄ to T₃ mediated by a cAMP signaling pathway (11, 12, 13).

In the present study, we first measured serum TSH, FT₄, and FT₃ levels and the FT₃/FT₄ ratios on three groups of euthyroid patients who underwent a thyroidectomy for papillary thyroid carcinoma: the patients who underwent a TT and received supplemental L-T₄, the patients who underwent HT and received supplemental L-T₄, and the patients who underwent a HT alone, both before and after stabilization of the thyroid profiles 12 months after the thyroidectomy. We also compared gender, age, BMI, and serum thyroid parameters among the groups.

Postoperative TSH levels differed from the preoperative levels in two patient groups. Moreover, gender, age, and TSH levels differed among groups. Therefore, we further compared serum FT₄ and FT₃ levels and the FT₃/FT₄ ratio measured postoperatively in each patient group with those in a healthy control group matched by gender, age, and serum TSH level.

Subjects and methods

Patients

From their medical records, we identified 1012 consecutive patients who underwent a thyroidectomy for papillary thyroid carcinoma between October 2011 and February 2013 at Kuma Hospital and were followed at least for 18 months postoperatively. The inclusion criteria for the present study were as follows: the patient underwent a TT or HT; the patient had been diagnosed with papillary thyroid carcinoma; the patient had a preoperative TSH level within the laboratory reference range (0.3–5.0 µU/ml); and the patient had a final postoperative TSH level within the laboratory reference range.

The exclusion criteria were as follows: patients who underwent near-total or subtotal thyroidectomy; patients with thyroid malignancies other than papillary carcinoma; patients with Graves' disease, Hashimoto thyroiditis, thyroid dysfunction, thyroid dysmorphogenesis, or autonomously functioning thyroid nodules; patients with chronic or serious diseases such as cardiac, pulmonary, hepatic, and renal diseases; patients who were 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 drugs; patients who were pregnant or lactating; patients who were under 'suppressive' L-T₄ treatment for high-risk thyroid cancer; and patients who did not achieve normal serum TSH levels. Finally, 253 consecutive patients were enrolled in the present study.

The patients who underwent a TT were initially administered 2.0 µg/kg of L-T₄ daily after surgery. Thyroid function tests were performed 1 month after surgery and every 3–6 months thereafter. If necessary, L-T₄ was administered and doses were adjusted with the intention to maintain the patient's target serum TSH values. On the other hand, the patients who underwent a HT were initially followed up without L-T₄ after surgery. Thyroid function tests were performed 1 month after surgery and every 3–6 months thereafter. If a patient developed hypothyroidism, L-T₄ was administered and doses were

adjusted to maintain the patient's serum TSH values within the reference range. The ultimate mean daily doses of L-T₄ administered were 2.02 µg/kg per day for the patients who underwent a TT and received supplemental L-T₄ and 1.07 µg/kg per day for the patients who underwent a HT and received supplemental L-T₄.

Of the 253 patients, 103 patients underwent a TT and 150 patients underwent a HT. Among the latter, 56 patients (37%) developed hypothyroidism postoperatively and received supplemental L-T₄ treatment. Thus, the present patients were divided into three groups: 103 patients with TT+supplemental L-T₄ therapy, 56 patients with HT+supplemental L-T₄ therapy, and 94 patients with HT alone (Fig. 1).

Matched control subjects

A continuous series of 951 euthyroid subjects who were examined at Kuma Hospital during the same period and who did not have clinical or laboratory signs of thyroid diseases served as controls. Subjects with positive anti-thyroid peroxidase (TPO) or anti-thyroglobulin (Tg) antibody test results or with abnormal findings on an ultrasound examination were excluded. The other exclusion criteria were the same as those used for the selection of the present patients described above. To balance the covariates including age, sex, and serum TSH levels between the patients and controls, we used Mahalanobis-metric matching for choosing the control subjects for each patient group, as described by Rubin (14). Control

subjects for each group of patients were chosen from among the 951 subjects selected above by 1:1 matching.

The present study was approved by the Ethical Committee at Kuma Hospital, and all patients gave informed consent.

Thyroid function tests

Each patient's presurgical thyroid profile was obtained 2 days before the surgery. The postoperative thyroid profiles were obtained after stabilization of the thyroid profiles, usually 12 months after the thyroidectomy. For the patients who were taking L-T₄, blood samples were obtained in the morning and after the ingestion of L-T₄.

The patients' and controls' serum levels of TSH, FT₄, and FT₃ were measured with a chemiluminescent immunoassay (ARCHTECT i2000, Abbott Japan). The intra-assay coefficients of variation and the 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 2.3–5.0% for the FT₃ assay. The reference ranges in our hospital are 0.3–5.0 mU/l for TSH, 9.0–20.6 pmol/l for FT₄, 2.61–5.68 pmol/l for FT₃, and 0.21–0.39 for the FT₃/FT₄ ratio.

Statistical analysis

Treatment effects (pre-thyroidectomy or controls vs post-thyroidectomy) were analyzed by a paired *t*-test in case of normal distribution and by the Wilcoxon test in case of nonparametric distribution. The postoperative group comparisons were analyzed by an unpaired *t*-test in case of normal distribution and by the Mann–Whitney *U* test in case of nonparametric distribution, using Bonferroni corrections for multiple comparisons. Significance was accepted at *P* < 0.05. Mahalanobis-metric matching was performed using R package (version 3.0.2. R Core Team, Vienna, Austria). Other statistical analyses were performed using StatFlex (version 6.0. Artech Co., Ltd, Osaka, Japan).

Results

Postoperative vs preoperative thyroid function profiles in the three patient groups

Table 1 shows the TSH, FT₄, and FT₃ levels and the FT₃/FT₄ ratios before and after thyroidectomy in each patient group. In the TT+L-T₄ group, compared to their pre-operative values, the patients' postoperative serum TSH values were significantly decreased (*P* < 0.001), their postoperative FT₄ levels were significantly increased

Figure 1

Flow chart of study. PC, papillary carcinoma.

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Table 1 Pre- and post-thyroidectomy serum levels of TSH, FT₄, FT₃, and FT₃/FT₄ in the three patient groups. Statistical significance (pre- vs post-thyroidectomy) was analyzed by paired *t*-test or by Wilcoxon signed-rank test. Values indicate median (25th to 75th percentiles).

Patients groups	TSH (mU/l)	FT ₄ (pmol/l)	FT ₃ (pmol/l)	FT ₃ /FT ₄
Total thyroidectomy + L-T ₄ (n=103)				
Pre-thyroidectomy	1.52 (1.02–2.13)	14.4 (13.3–15.4)	4.45 (4.06–4.81)	0.31 (0.28–0.34)
Post-thyroidectomy	0.78 (0.49–1.50)	17.2 (15.7–18.9)	4.29 (3.96–4.65)	0.25 (0.22–0.28)
<i>P</i> value	<0.001	<0.001	0.023	<0.001
Hemithyroidectomy + L-T ₄ (n=56)				
Pre-thyroidectomy	1.84 (1.30–2.63)	13.8 (12.6–14.7)	4.38 (4.06–4.65)	0.32 (0.29–0.34)
Post-thyroidectomy	1.86 (1.16–2.75)	14.3 (13.2–15.4)	4.35 (3.98–4.61)	0.29 (0.27–0.33)
<i>P</i> value	0.136	0.024	0.498	0.017
Hemithyroidectomy alone (n=94)				
Pre-thyroidectomy	1.07 (0.73–1.51)	14.4 (13.1–15.3)	4.31 (3.89–4.77)	0.30 (0.27–0.33)
Post-thyroidectomy	2.41 (1.67–3.37)	12.9 (12.1–13.6)	4.43 (4.04–4.65)	0.34 (0.32–0.37)
<i>P</i> value	<0.001	<0.001	0.204	<0.001 ^a

TSH, thyroid-stimulating hormone; FT₄, free thyroxine; FT₃, free triiodothyronine.

^aWilcoxon signed-rank test.

($P<0.001$), and their postoperative FT₃ levels were significantly decreased ($P=0.023$), although all of these values were within their reference ranges (Table 1).

In the HT+L-T₄ group, the postoperative FT₃ levels and TSH levels did not show significant differences from their preoperative values, and the postoperative FT₄ levels were slightly and significantly increased ($P=0.024$), although all of these values were within their reference ranges (Table 1).

In the HT-alone group, the patients' postoperative FT₃ levels did not differ significantly from their preoperative values, whereas their postoperative serum TSH values were significantly increased ($P<0.001$) and the postoperative FT₄ levels were significantly decreased ($P<0.001$), although all of the values were within their reference ranges. Thus, the three groups of patients showed different

thyroid function profiles, although the values were all within their reference ranges (Table 1).

Regarding the FT₃/FT₄ ratio, the three groups showed different changes postoperatively: the TT+supplemental L-T₄ patients showed significant decreases in the ratio ($P<0.001$); the HT+L-T₄ patients had slight but significant decreases in the ratio ($P=0.017$), and the HT-alone patients showed increases in the ratio ($P<0.001$) (Table 1).

Clinical characteristics among the three patient groups

Characteristics among the three patient groups are given in Table 2. Gender ratios of the HT+L-T₄ group were significantly different from those of the other two groups ($P<0.001$). Ages of the HT+L-T₄ group were significantly higher than those of the HT alone group ($P<0.05$). BMI

Table 2 Clinical characteristics among the three patients groups. Statistical significance was analyzed by the χ^2 test (gender), unpaired *t*-test, or Mann–Whitney *U* test using Bonferroni corrections for multiple comparisons. Values indicate median and interquartile ranges.

Parameters	TT+L-T ₄	HT+L-T ₄	HT alone	<i>P</i> value		
				TT+L-T ₄ vs HT+L-T ₄	TT+L-T ₄ vs HT alone	HT+L-T ₄ vs HT alone
<i>n</i>	103	56	94			
Gender (M/F)	27/76	8/48	26/68	<0.001	0.96	<0.001
Age (years)	51 (40–63)	58 (43–65)	50 (41–60)	0.24	1.00	<0.05
BMI (kg/m ²)	23.0 (3.7)	23.1 (3.6)	23.6 (3.7)	0.84	1.00	1.00
TSH (mU/l)	0.78 (1.01)	1.86 (1.59)	2.41 (1.70)	<0.001	<0.001	0.07 ^a
FT ₄ (pmol/l)	17.2 (3.2)	14.3 (2.2)	12.9 (1.5)	<0.001	<0.001	<0.001
FT ₃ (pmol/l)	4.29 (0.68)	4.35 (0.63)	4.43 (0.61)	1.00	0.44	0.52
FT ₃ /FT ₄	0.25 (0.05)	0.29 (0.06)	0.34 (0.05)	<0.001	<0.001 ^a	<0.001

TSH, thyroid-stimulating hormone; FT₄, free thyroxine; FT₃, free triiodothyronine; TT, total thyroidectomy; HT, hemithyroidectomy.

^aMann–Whitney *U* test.

values of the three groups were similar among groups. Serum TSH levels in the TT+L-T₄ group were significantly lower than those of the other two groups ($P<0.001$). Serum FT₄ and FT₃/FT₄ levels of one of the three groups were different from those of the other two groups. Serum FT₃ levels of the three groups were not significantly different among groups.

Postoperative thyroid function profiles of the patients compared to those of the control subjects matched with the Mahalanobis-metric method

In the TT+L-T₄ group, the postoperative serum FT₄ levels were significantly higher than those of the matched controls (17.2 (15.7–18.9) vs 14.3 (13.3–15.2) pmol/l respectively, $P<0.001$ (median (25th to 75th percentiles)) and the postoperative serum FT₃ levels were significantly lower (4.29 (3.96–4.65) vs 4.42 (4.12–4.74) pmol/l respectively, $P=0.008$). The serum FT₃/FT₄ ratios were significantly lower than those of the matched controls (0.25 (0.22–0.28) vs 0.31 (0.28–0.34) respectively, $P<0.001$) (Fig. 2A).

In the HT+L-T₄ group, the postoperative serum FT₄ and FT₃ levels and FT₃/FT₄ ratios did not differ significantly from those of the matched controls (14.3 (13.2–15.4) vs 13.8 (12.7–14.9) pmol/l, $P=0.094$; 4.35 (3.98–4.61) vs 4.19 (3.77–4.47) pmol/l, $P=0.082$; and 0.29 (0.27–0.33) vs 0.32 (0.29–0.34) respectively, $P=0.978$) (Fig. 2B).

In the HT-alone group, the postoperative serum FT₄ levels were significantly lower than those of the controls (12.9 (12.1–13.6) vs 13.6 (12.3–14.5) pmol/l, $P=0.007$), but the postoperative serum FT₃ levels did not differ significantly from those of the matched controls (4.43 (4.04–4.65) vs 4.25 (3.92–4.56) pmol/l, $P=0.083$), and the serum FT₃/FT₄ ratios were significantly higher than those of the controls (0.34 (0.32–0.37) vs 0.32 (0.29–0.35), $P<0.001$) (Fig. 2C).

Discussion

The results of the present study demonstrate that in patients who underwent TT and showed normal TSH levels postoperatively, the postoperative serum FT₃ levels were lower than their preoperative native levels and those of the matched euthyroid controls despite the increased FT₄ levels. The results obtained for the patients with TT+supplemental L-T₄ in the present study were consistent with those of our previous report (2) and the reports by Gullo *et al.* (4) and Hoermann *et al.* (5). These findings suggest that the reason underlying the decreased serum T₃ levels in such patients is the lack of intra-thyroidal

Figure 2

Postoperative serum FT₄, FT₃, and FT₃/FT₄ levels of patients who underwent thyroidectomy and those of the euthyroid controls matched by age, sex, and serum TSH levels. (A) The total thyroidectomy + L-T₄ group ($n=103$). (B) The hemithyroidectomy + L-T₄ group ($n=56$). (C) The hemithyroidectomy-alone group ($n=94$). FT₄, free thyroxine; FT₃, free triiodothyronine. The top, bottom, and middle lines of the boxes correspond to the 75th, 25th, and 50th percentiles (median), respectively. The whiskers extend from the minimum to the maximum.

T₃ production caused by the absence of the thyroid gland. These data suggest that TSH-suppressive doses of L-T₄ are required to achieve normal T₃ levels in patients who have undergone TT not only for thyroid cancer but also for other diseases such as Graves' disease, multinodular disease, and Hashimoto thyroiditis.

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Here we studied a large number of patients with papillary thyroid cancer and observed that the postoperative serum FT₃ levels of the patients who underwent a HT alone were substantially equivalent to those of the controls matched by serum TSH level, although the patients' serum FT₄ levels were significantly lower, resulting in a higher FT₃/FT₄ ratio. The mechanism of this increased FT₃/FT₄ ratio in patients who have undergone a HT alone remains unknown. Lum *et al.* (15) reported that a non-thyroidal, non-TSH-mediated system exists for maintaining circulating T₃ levels in a state of T₄ deficiency.

Considered in conjunction with the decreased FT₃/FT₄ ratio in the present athyreotic patients who underwent a TT, this increased FT₃/FT₄ ratio in the patients who underwent HT seems to be caused by an increasing production of T₃ in the remnant thyroid tissue. Maia *et al.* (16) reported that D2 is expressed in the human thyroid gland and is postulated to play an important role as a source of plasma T₃. As a matter of fact, it has been suggested that the increased D2 in the thyroid gland may account for the status of a low FT₄ with relatively high or normal circulating T₃ levels in other thyroid diseases, such as follicular carcinoma (10), thyroglobulin gene abnormalities (17), and T₃-predominant Graves' disease (18). Very recently, Hoermann *et al.* reported the association between thyroid volume and deiodinase activity. They investigated deiodinase activity in L-T₄-treated patients from thyroid volume groups (cut-off 5 ml) and indicated that patients with a post-interventional lower residual volume (<5 ml) have significantly reduced deiodinase activity and lowered T₃ levels compared to patients with a higher residual thyroid volume (19). This result suggests that residual thyroid capacity plays a significant role in the physiological process of T₃ homeostasis in humans and is in good agreement with this study. A further proper study including the determination of D2 activity in the remnant thyroid tissue may be necessary to clarify the mechanism of the higher FT₃/FT₄ ratio in these patients.

In our patients who underwent a HT and were treated with L-T₄ therapy, the postoperative serum FT₄ and FT₃ levels and FT₃/FT₄ ratio were substantially equivalent to those of the matched controls. The present findings thus demonstrate that the serum thyroid hormone balances in these patients are similar to the preoperative levels in the physiological normal condition and to those of euthyroid controls. Because the dose of L-T₄ was less in the patients who underwent a HT than in the patients who underwent a TT, we speculate that the reason the decrease of T₃ levels was not observed in these patients was the production of T₃ in the remnant thyroid tissue.

Considerable controversy exists regarding the management of the thyroid function status in patients who have undergone a thyroidectomy and are receiving postoperative L-T₄ therapy. Since the negative feedback relationship between serum T₄ levels and serum TSH levels is a consistent inverse relationship, most endocrinologists consider the serum TSH level a very sensitive indicator of thyroid function. However, serum TSH levels only reflect the feedback effect of thyroid hormones at the hypothalamic-pituitary level. The TSH secretion from the pituitary is negatively regulated primarily by T₃ produced locally via the conversion of T₄ transported from the peripheral blood, which is in keeping with the view that serum T₄ rather than T₃ has a dominant role in regulating TSH secretion (20). On the other hand, T₃ transported from the peripheral blood also has a role in regulating TSH secretion by the pituitary. This has been well documented in patients acutely given large amounts of propylthiouracil, which inhibits the peripheral synthesis of T₃ (21).

L-T₄ alone administered to rats that had undergone a TT at doses to normalize the plasma TSH levels did not normalize the T₃ contents in some tissues (22). Alevizaki *et al.* (23) reported that athyreotic patients with T₄-treated hypothyroidism and normal TSH levels had lower T₃ and lower sex hormone-binding globulin (SHBG) levels than controls. These data suggest that normal TSH levels cannot guarantee euthyroidism in peripheral tissues in post-thyroidectomized athyreotic patients under L-T₄ therapy. Most clinicians generally believe that a low serum TSH level indicates subclinical thyrotoxicosis and is a risk factor for cardiac dysfunction or osteoporosis (24). However, such a clinical outcome in subclinical thyrotoxicosis seems to be unclear in patients with moderately low TSH levels (25). Thus, in patients who have undergone a TT, TSH-suppressive treatment by L-T₄ for high-risk thyroid cancer may not necessarily cause thyrotoxicosis.

The present study has some possible limitations. First, it has been reported that serum FT₄ and FT₃ levels increased transiently after the ingestion of L-T₄ (26, 27). In consideration of such an increment, the evaluation of diurnal variation or the area under the curve (AUC) by repeated blood sampling may be the best method; however, it is practically difficult to carry out such an examination in many patients. In the present study, we evaluated the blood sampling data after the ingestion of L-T₄. The result (i.e., the FT₃ levels were lower than the preoperative FT₃ levels) suggests that the postoperative FT₃ levels in the serum remained relatively low for most of the day. In contrast, the serum FT₄ levels were higher than the preoperative levels, and this could be affected by the blood sampling after the

consumption of L-T₄. Second, in this retrospective study, we did not measure the thyroid volumes. In general, it is believed that about 20% of the T₃ pool is secreted from the thyroid gland, while we found that a marked contribution that is attributed to the remnant would be at variance with this reported proportion in humans. It would be possible to put a rough quantitative estimate on thyroidal T₃ contributions by comparing pre- and postoperative levels and changes in volume. Properly designed studies including measures of the thyroid volumes are needed to clarify the quantitative estimate on thyroidal T₃ contributions in the postoperative patients. In addition, the present study is restricted to the patients with normal serum TSH levels. It might be interesting to get some additional comparisons with another large entity, thyroidectomized patients with advanced thyroid cancer maintained on a TSH-suppressive regimen.

In conclusion, the results of the present study showed that in thyroidectomized patients, the presence of thyroid tissue causes significant differences in the interrelation of FT₄, FT₃, and TSH levels. Our findings suggest that T₃ production by the remnant thyroid tissue has a substantial effect on the maintenance of serum T₃ levels in thyroidectomized patients. The question arises as to whether any of the patients in the three groups were in a euthyroid condition: those with normal TSH, mildly high FT₄, and mildly low FT₃ levels among the TT+L-T₄ patients, those with mildly suppressed TSH, mildly high FT₄, and mildly low FT₃ in the TT+supplemental L-T₄ group, or those with normal TSH, mildly low FT₄, and normal FT₃ among the HT-alone patients. These patients live in a chronic condition of abnormal thyroid hormone status for the remainder of their lives. Therefore, even if the thyroidal dysfunction may be subtle, its long-term effects cannot be overlooked.

In 2014, the American Thyroid Association stated in a guideline that patients with hypothyroidism treated with L-T₄ to achieve normal serum TSH values may have serum T₃ levels that are at the lower end of the reference range, or even below the reference range (28). The guideline also mentioned that there is insufficient beneficial evidence to recommend that treatment with L-T₄ be targeted to achieve low-normal TSH values or high-normal T₃ values in patients with hypothyroidism who are athyreotic (28). The major weakness of this study, and most of the studies like this, concerns its retrospective analysis that may eliminate the ability to obtain strong conclusions. Prospective studies including measures of the patients' well-being and/or metabolic markers such as lipid or bone markers are needed to clarify the best method of managing postoperative thyroid function in 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

M Ito and A Miyauchi constructed the study design. M Ito analyzed the data and wrote the manuscript. The other coauthors contributed by performing surgery and/or caring for the patients. All authors read and approved the final manuscript.

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Clinical Study	M Ito and others	T ₃ and T ₄ levels in thyroidectomized patients	173:3	340
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