

## Changes in Thyroid Stimulating Antibody Levels in Graves' Disease Patients: Methods to Prevent its Increase after Radioactive Iodine Therapy

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### ABSTRACT

**Background:** Although it is well-known that thyroid stimulating antibody levels usually increase after radioactive iodine therapy, we observed various changes in thyroid stimulating antibody levels.

**Methods:** We divided 47 patients who underwent radioactive iodine therapy into two groups based on thyroid stimulating antibody levels three months post-therapy, as follows: the D(3M) group with increasing levels and the I(3M) group with decreasing levels of the antibody. We compared the clinical characteristics of the two groups. In addition, the 47 patients were again divided into the following two groups, and their clinical characteristics were compared: the D(6M) and I(6M) groups, which consisted of patients with decreasing and increasing thyroid stimulating antibody levels, respectively, three to six months after radioactive iodine therapy.

**Results:** A significantly higher dose of Iodine-131(I-131) per gram of estimated thyroid weight was observed in the D(3M) group than in the I(3M) group, suggesting that the removal of intrathyroidal immune cells by  $\beta$ -rays may influence changes in thyroid stimulating antibody levels. The D(6M) group had significantly higher goiter shrinkage rates than did the I(6M) group, at three, six, and 12 months post-radioactive iodine therapy. Since the goiter shrinkage rate is equivalent to the decreasing rate of thyroid antigen levels, we speculate that the reduction in thyroid antigen led to a decrease in thyrotropin receptor antibody production mediated by peripheral blood immune cells.

**Conclusions:** Our study suggests that, in the short-term, thyroid stimulating antibody levels after radioactive iodine therapy were significantly associated with the receipt of radioactive iodine therapy, probably due to the reduction in the number of intrathyroidal immune cells, and, in the long-term, they were influenced by the immune response of peripheral blood cells associated with the reduction in thyroid antigen by I-131. Therefore, high-dosage I-131 therapy is recommended for Graves' patients who do not desire total thyroidectomy and are planning to become pregnant, or those with a risk of ophthalmopathy.

**Keywords:** Graves' disease; Radioactive iodine therapy; Thyroid stimulating antibody

### INTRODUCTION

Radioactive iodine therapy (RAIT) is a useful option in the treatment of Graves' disease; other treatment options include antithyroid drugs (ATDs) and surgery. Endocrinologists select appropriate therapies based on clinical characteristics such as age, thyroid volume, complications, and whether the patient is planning to become pregnant [1]. RAIT does not require hospitalization and can reliably correct hyperthyroidism; however, changes in thyrotropin receptor antibody (TRAb) and thyroid stimulating antibody (TSAb) levels significantly influence the course of pregnancy and the development or exacerbation of Graves' ophthalmopathy.

In a study by Laurberg et al. patients with Graves' disease were randomly assigned to ATD treatment, thyroidectomy, or RAIT group, and their clinical courses were reviewed prospectively. In the ATD and thyroidectomy groups, TRAb levels decreased gradually after treatment, and 70-80% of patients were observed to be TRAb-negative at 18 months; however, in the RAIT group, TRAb levels increased after treatment, reached a maximum at three months, and then decreased gradually to pre-treatment levels one year post-treatment. Laurberg et al. found that there were fewer TRAb-negative patients in the RAIT group than in the other groups [2]. In a retrospective study by Atkinson et al. 19 patients with Graves' disease treated by RAIT had TSAb- and TRAb-positivity rates of

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84% and 68%, respectively, before RAIT, but the positivity rates for both the antibodies had increased to 100% three months later. The TSAb-positivity rate decreased to 42% one to two years after RAIT; however, the TRAb-positivity rate remained high at 68% [3]. Therefore, it is thought that the levels of TRAb and TSAb after RAIT increase and do not readily decrease. However, we found that not all Graves' patients had increased TSAb levels, and some had decreased TSAb levels after RAIT. Further analysis of these patients showed that the TSAb levels continued to decrease in some patients, whereas in others, the TSAb levels started to decrease but then increased after RAIT. We also observed that some patients showed increased TSAb levels three months after RAIT followed by a decrease, whereas others showed a continued increase in TSAb levels. Understanding changes in TSAb levels after RAIT is important for patients who plan to become pregnant or are at a risk of developing Graves' ophthalmopathy. Therefore, in this study, we evaluated the clinical characteristics of cases in which TSAb tends to decrease or increase after RAIT for Graves' disease.

## MATERIALS AND METHODS

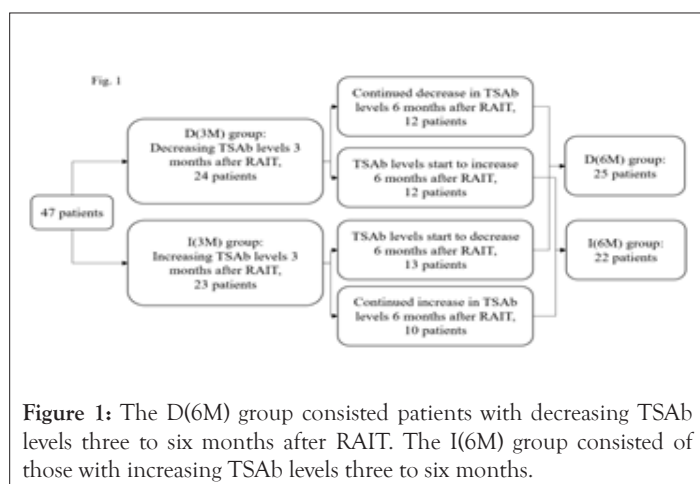
### Subjects

Of the 148 Graves' patients treated with RAIT at Yamashita Thyroid Hospital between June 2011 and May 2019, we were able to periodically collect data regarding TSAb levels in 47 patients. These 47 patients (three men, 44 women) were enrolled in the study.

Graves' disease was diagnosed based on thyrotoxicosis as per TRAb and/or TSAb. If these tests were not sufficient to diagnose Graves' disease, radioactive iodine uptake (RAIU) and scintigraphy were also performed to confirm the diagnosis. In addition, neck ultrasonography (US) was performed in all patients, and no thyroid nodules were found. Therefore, autonomously functioning thyroid nodule was not included in these patients.

### Methods

The 47 patients were divided into two groups. Those with decreasing and those with increasing TSAb levels three months after RAIT were categorized into the D(3M) and I(3M) groups, respectively. The clinical characteristics of the D(3M) and I(3M) groups are shown in Table 1a. Next, based on changes in TSAb levels three to six months after RAIT, we defined the following two groups: the D(6M) group, with decreasing TSAb levels, and the I(6M) group, with increasing TSAb levels (Figure 1). The clinical characteristics of the D(6M) and I(6M) groups are shown in Table 1b.



**Table 1a:** The characteristics of patients the comparison between D(3M) and I(3M) groups.

Only TSAb before RAIT of D(3M) group was significantly higher than that of I(3M) group. Other parameters did not show significant difference between D(3M) and I(3M) groups.

	D(3M)	I(3M)	p-value
Age (mean ± SD)	45.0 ± 13.5	41.1 ± 11.0	n.s.
Sex (male: female)	00: 24	03: 20	n.s.
Duration of GD treatment (25%-75% (median) months)	10.3-75.5 (38)	12.0-61.0 (40)	n.s.
Thyroid gland weight (25%-75% (median) g)	20.9-40.9 (31.6)	20.0-44.7 (34.9)	n.s.
TSAb before RAIT (25%-75% (median) %)	479.3-2131.8 (1275.5)	161.0-680.0 (219.0)	p<0.05
Drugs before RAIT (MMI : PTU : KI)*	12: 03: 10	13: 02: 09	

**Table 1b:** The comparison between D(6M) and I(6M) groups. All parameters did not show significant difference between D(3M) and I(3M) groups.

	D(6M)	I(6M)	p-value
Age (mean ± SD)	41.6 ± 9.87	44.8 ± 14.7	n.s.
Sex (male: female)	01: 24	02: 20	n.s.
Duration of GD treatment (25%-75% (median) months)	5.0-60.5 (36)	26.5-73.5 (46)	n.s.
Thyroid gland weight (25%-75% (median) g)	17.2-42.2 (31.7)	23.5-44.9 (33.2)	n.s.
TSAb before RAIT (25%-75% (median) %)	190.5-1644.0 (528)	210.8-1866.3 (630.5)	n.s.
Drugs before RAIT (MMI : PTU : KI)*	11: 04: 10	14: 01: 09	-

\* In some cases, both ATD and KI were administered at the same time. Therefore, the total number of this parameter does not match the number of patients. GD: Graves' Disease; TSAb: Thyroid Stimulating Antibody; RAIT: Radioactive Iodine Therapy; MMI: Thiamazole; PTU: Propylthiouracil; KI: Potassium Iodine.

The following factors were compared between the D(3M) and I(3M) groups: dose of Iodine-131 (I-131) per gram of estimated thyroid weight, administered dose of I-131, RAIU, thyroid gland weight, goiter shrinkage rate three, six, and 12 months after RAIT, smoking status, and postoperative recurrence of Graves' disease. Thyroid gland weight was calculated from the estimated volume of the thyroid by neck US. Based on the thyroid gland weight, the dose of I-131 per gram of estimated thyroid weight was calculated and expressed in units of  $\mu\text{Ci/g}$ . The goiter shrinkage rate was calculated by dividing the thyroid gland weight at the time of evaluation (three, six, and 12 months after RAIT) by the thyroid gland weight before RAIT, and expressed as a percentage. We compared the same parameters as above, between the D(6M) and I(6M) groups.

Serum levels of thyroid stimulating hormone (TSH) and free thyroxine (FT4) were assessed using an ECLusys kit (Roche Diagnostics, Penzberg, Germany), and the TSAb assay was performed using a Yamasa kit (Yamasa Corporation, Choshi, Japan). The reference ranges were as follows: TSH, 0.5-5.0 mIU/L; FT4, 0.9-1.7 ng/dL; and TSAb, 120%.

### RAIT Protocol

Before RAIU for RAIT, oral iodine intake was restricted for seven

days. Antithyroid drugs and/or potassium iodine were withdrawn three days before RAIU for RAIT. The duration of restriction of oral iodine intake and discontinuation of ATDs and potassium iodine (KI) was adopted according to the guidelines for RAIT, published by the Japan Thyroid Association in 2019. RAIU was evaluated three hours after intake of <sup>123</sup>I. The dose of administered I-131 was fixed at 13.0 mCi or was calculated as detailed below. The treatment method was determined based on the patient's clinical background. The calculated dose was determined using the following formula [4]: (calculated dose (mCi))=(thyroid gland weight (g)) × (80-160 μCi I-131/g of thyroid)/(RAIU (%)) × 10. The dose of I-131 per gram of estimated thyroid weight was between 80 and 160 μCi/g. The dose of I-131 per gram of estimated thyroid weight was assumed to be between 80-120 and 140-160 μCi/g to target euthyroidism and hypothyroidism, respectively, after RAIT. Discontinuation of ATDs and/or KI, and iodine restriction, was continued for three days after RAIT.

This study was conducted in accordance with the Declaration of Helsinki and current ethical codes, and was approved by the ethics committee at Yamashita Thyroid Hospital. This study was conducted as a part of standard clinical practice without intervention, and data were retrospectively retrieved from medical records. As this was not a clinical study, and the data were anonymized for retrospective analyses, written informed consent was not obtained from the study participants.

### Statistical analysis

Statistical analysis was performed by employing the Fisher's exact test and the Mann-Whitney U test, using JMP ver. 11.0 software (SAS Institute Inc.).

## RESULTS

As shown in Table 2, there were significant differences in the dose of I-131 per gram of estimated thyroid weight, thyroid gland weight, and goiter shrinkage rate 12 months after RAIT, between the D(3M) and I(3M) groups. The dose of I-131 per gram of estimated thyroid weight and thyroid gland weight were significantly higher and lower, respectively, in the D(3M) group than in the I(3M) group, 12 months after RAIT. Furthermore, the goiter shrinkage rate was significantly higher in the D(3M) group than in the I(3M) group.

**Table 2:** Results of the comparison between D(3M) and I(3M) groups. Dose of I-131 per gram of estimated thyroid weight and goiter shrinkage rate 12 months after RAIT of D(3M) group were significantly higher than those of I(3M) group. On the other hand, thyroid gland weight 12 months after RAIT of D(3M) group were significantly lower than that of I(3M) group. I-131: Iodine-131, RAIU: Radioactive Iodine Uptake, RAIT: Radioactive Iodine Therapy, GD: Graves' Disease.

	D(3M)	I(3M)	p-value
Dose of I-131 per gram of estimated thyroid weight (25%-75% (median) μCi/g)	113.1-175.0 (124.2)	84.1-143.0 (113.5)	0.0432*
Administered dose of I-131 (25%-75% (median) mCi)	6.6-11.9 (10)	7.5-10.9 (10)	n.s.
RAIU (25%-75% (median) %)	34.5-62.9 (49.1)	24.0-65.4 (47.3)	n.s.
Thyroid gland weight 3 months after RAIT (25%-75% (median) g)	9.2-16.8 (13.1)	9-23.5 (15.9)	n.s.

Thyroid gland weight 6 months after RAIT (25%-75% (median) g)	5.5-12.4 (9)	6.8-18.0 (13.5)	n.s.
Thyroid gland weight 12 months after RAIT (25%-75% (median) g)	4.3-7.8 (7)	5.0-13.6 (10.7)	0.0442*
Goiter shrinkage rate 3 months after RAIT (25%-75% (median) %)	48.3-66.3 (59.1)	36.6-62.5 (52.3)	n.s.
Goiter shrinkage rate 6 months after RAIT (25%-75% (median) %)	59.9-79.5 (72.8)	46.5-75.5 (64.1)	n.s.
Goiter shrinkage rate 12 months after RAIT (25%-75% (median) %)	70.5-86.4 (79.2)	64.6-82.3 (70.9)	0.0351*
Smoking status (yes : no)	01: 23	03: 20	n.s.
Postoperative recurrence of GD (yes : no)	03: 21	01: 22	n.s.

Although there was a significant difference in the dose of I-131 per gram of estimated thyroid weight between the D(3M) and I(3M) groups, there was no difference in this parameter between the D(6M) and I(6M) groups. However, goiter shrinkage rates at three, six, and 12 months after RAIT were significantly higher in the D(6M) group than in the I(6M) group. The number of patients who smoked was significantly higher in the D(6M) group than in the I(6M) group, and the number of patients who had postoperative recurrence was significantly higher in the I(6M) group than in the D(6M) group (Table 3).

**Table 3:** Results of the comparison between D(6M) and I(6M) groups. Goiter shrinkage rates at three, six, and 12 months after RAIT were significantly higher in the D(6M) group than in the I(6M) group. The number of patients who smoked was significantly higher in the D(6M) group than in the I(6M) group, and the number of patients who had postoperative recurrence was significantly higher in the I(6M) group than in the D(6M) group. I-131: Iodine-131, RAIU: Radioactive Iodine Uptake, RAIT: Radioactive Iodine Therapy, GD: Graves' Disease.

	D(6M)	I(6M)	p-value
dose of I-131 per gram of estimated thyroid weight (25%-75% (median) μCi/g)	103.7-167.5 (136.3)	91.8-145.1 (113.6)	n.s.
Administered dose of I-131 (25%-75% (median) mCi)	6.6-11.9 (10)	6.9-11.9 (10)	n.s.
RAIU (25%-75% (median) %)	28.9-65.7 (48.9)	30.0-57.6 (47.6)	n.s.
Thyroid gland weight 3 months after RAIT (25%-75% (median) g)	8.3-17.4 (13.4)	11.7-25.4 (15.6)	n.s.
Thyroid gland weight 6 months after RAIT (25%-75% (median) g)	4.9-13.7 (8.1)	7.6-16.7 (11.4)	n.s.
Thyroid gland weight 12 months after RAIT (25%-75% (median) g)	2.9-9.8 (7)	5.8-13.2 (8.5)	n.s.
Goiter shrinkage rate 3 months after RAIT (25%-75% (median) %)	51.0-67.0 (62.5)	32.3-59.2 (46.2)	0.0082*
Goiter shrinkage rate 6 months after RAIT (25%-75% (median) %)	62.9-78.2 (74)	51.0-72.6 (61.7)	0.0190*
Goiter shrinkage rate 12 months after RAIT (25%-75% (median) %)	69.5-86.1 (81.5)	60.9-80.0 (71.3)	0.0238*
Smoking status (yes : no)	04: 21	00: 22	0.0498*
Postoperative recurrence of GD (yes : no)	00: 25	04: 18	0.0258*

## DISCUSSION

According to Werner and Ingbar's *The Thyroid* 10th edition, approximately six months is required to stabilize thyroid function after RAIT, while 3-6 months is required for stabilization according to Kaplan et al. [5,6]. Pregnancy may be considered after this period; however, immunological disorders may continue in some patients. Graves' disease patients planning to become pregnant after RAIT should have low or decreasing TRAb and TSAb levels, as high levels after RAIT may lead to a risk of fetal or neonatal Graves' disease [7-12]. Furthermore, high TRAb and TSAb levels and elevated TRAb levels after RAIT are significant risk factors for Graves' ophthalmopathy [13,14]. Therefore, it is important to evaluate factors influencing changes in TRAb and TSAb levels to reduce the risk of Graves' ophthalmopathy after RAIT. From these perspectives, we focused on the changes in TSAb to evaluate the clinical characteristics of cases that showed a downward trend in TSAb after RAIT.

Our study suggests that TSAb levels three months after RAIT are less likely to increase with higher dose of I-131 per gram of estimated thyroid weight. In addition, the D(3M) group had a significantly lower thyroid gland weight and higher goiter shrinkage rate 12 months after RAIT, than did the I(3M) group. Various studies have shown the effect of I-131 dose on thyroid volume and thyroid function after RAIT [6,15-18], and patients who responded to RAIT had a rapid reduction in goiter size [19]. Therefore, a smaller goiter size and a higher goiter shrinkage rate in the D(3M) group were achieved with a higher dose of I-131 than in the I(3M) group.

Yoshioka et al. studied changes in TRAb levels in patients with Graves' disease after total thyroidectomy, and found that TRAb levels decreased rapidly after surgery [20]. They hypothesized that rapid decreases in TRAb levels over a 3-month postoperative period may be due to the removal of intrathyroidal B cells by thyroid gland resection, and that its gradual decrease between and 3-12 months may be associated with the production of TRAbs by peripheral memory lymphocytes [20-23]. Patients with decreased TSAb levels three months after RAIT received significantly higher dose of I-131 per gram of estimated thyroid weight than did those with increasing TSAb levels. We speculate that the removal of intrathyroidal B cells may be achieved by  $\beta$ -rays from I-131. This speculation is consistent with the fact that higher dose of I-131 per gram of estimated thyroid weight were associated with decreased TSAb levels three months post-therapy. Increased levels of TRAb and TSAb after RAIT are thought to be caused by the immune response triggered by antigen leakage induced by thyroid tissue destruction after RAIT [3]. Although antigen leakage may have occurred in cases with decreasing TSAb levels after RAIT, we speculate that the removal of intrathyroidal immune cells by  $\beta$ -rays, which may exceed the immune response induced by the leakage of antigen, did not cause an increase in TSAb levels.

Recently, rituximab, a monoclonal antibody to CD20-positive cells, has been found to be effective in the treatment of Graves' ophthalmopathy. Its mechanism of action is through selective impairment of CD20-positive B cells, and the depletion of intrathyroidal B cells is thought to be achieved in a manner similar to that by total thyroidectomy for Graves' disease. However, most studies found that TRAb levels were not significantly reduced with rituximab treatment [24,25]. Although these results may seem to contradict the statements included in the above discussion, there are some differences in the treatment of Graves' disease using the

rituximab regimen and that using other treatment strategies such as surgery and RAIT. Rituximab only removes intrathyroidal B cells, while RAIT and surgery also reduce other components of the thyroid tissue. Thyroid tissue reduction decreases the amount of antigen, which may affect the immune response. Therefore, rituximab may not significantly reduce TRAb levels because it does not reduce antigen levels. In addition, total thyroidectomy and RAIT affect not only intrathyroidal B cells but also all lymphocytes in the thyroid gland. Total thyroidectomy removes all immune cells along with the thyroid gland, and the  $\beta$ -rays from RAIT affect immune cells such as B cells. This is also different from rituximab, which selectively removes only B cells. Salvi M et al. showed that a single cycle of rituximab does not completely remove B cells from the thyroid tissue, and as a result, decreased TRAb levels may not be observed [26]. Therefore, although TRAb is not reduced during rituximab treatment, it does not negate our findings.

Six months after RAIT, we observed patients with varying patterns of increase and decrease in TSAb levels, which may be due to the activity of peripheral blood lymphocytes rather than due to the removal of intrathyroidal B cells. The effect of  $\beta$ -rays six months after RAIT is considered insignificant. Follicular helper T cells (Tfh cells) in the peripheral blood play an important role in the production of TRAb in Graves' disease, and a positive correlation between Tfh cells and serum TRAb level has been found [27]. We hypothesized that peripheral blood Tfh cells are not directly affected by RAIT-associated  $\beta$ -rays, and the presence of antigens after treatment leads to an immune response resulting in the production of a certain amount of TRAb. In our study, there was no significant difference in the dose of I-131 per gram of estimated thyroid weight between the D(6M) and I(6M) groups. However, the D(6M) group had a significantly higher goiter shrinkage rate than did the I(6M) group at three, six, and 12 months after RAIT. The goiter shrinkage rate may be equivalent to the rate of decrease in the amount of thyroid antigen. In our study, since RAIT reduced the amount of antigen more efficiently in the D(6M) group than in the I(6M) group, we hypothesized that it leads to the decreased production of TRAb through immune cells, such as Tfh cells, in peripheral blood.

Although a significant difference in smoking status and postoperative recurrence was found between the D(6M) and I(6M) groups, the sample size of these groups was too small to draw appropriate conclusions. However, the D(6M) group consisted of more patients who were smokers, which suggests that smoking may not have a significant effect on changes in TSAb levels when a sufficient dose of I-131 is administered. The frequency of postoperative recurrence was higher in the I(6M) group. Since Graves' patients with postoperative recurrence have higher disease activity, this factor may also influence changes in TSAb levels after RAIT.

## CONCLUSION

Based on the results of this study, we speculate that changes in TSAb levels after RAIT in patients with Graves' disease may be influenced in the short-term by the balance between the elimination of B cells and other immune cells in the thyroid gland by I-131, and the immune response due to antigen leakage induced by thyroid tissue destruction. Furthermore, in the long-term, we also speculate that TSAb levels may be influenced by the immune response of peripheral blood immune cells to the decreased amount of antigen. In conclusion, our study showed that efficient reduction of thyroid antigens by RAIT using a sufficient dose of I-131 may prevent

increases in TSAb levels and may promote its decrease relatively early, despite an initial increasing trend. We recommend a high dosage of I-131 therapy especially for Graves' patients who do not desire total thyroidectomy and plan to become pregnant or those with a risk of ophthalmopathy.

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## DISCLOSURE

None of the authors have any conflicts of interest associated with this research.

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