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Thymic Involution After Radioiodine Therapy for Graves Disease: Relationships With Serum Thyroid Hormones and TRAb

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Context: The mechanisms of thymic hyperplasia in Graves disease and its involution after radioiodine (I-131) therapy remain unknown.

Objective: To examine whether computed tomography (CT) findings of the thymus in patients with Graves disease change before and 6 months after I-131 therapy and to elucidate factors that affect these changes.

Design, Setting: A retrospective, single-center study was conducted. Thymic and thyroid volumes and thymic density were measured on CT. The associations of thymic volume or density with the following factors before I-131 therapy were examined: age; serum triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone receptor antibody (TRAb) levels; and thyroid volume. The changes in thymic volume and density and TRAb levels before and after I-131 therapy, and the correlations of thymic volume with T3 and T4 decline rates and TRAb changing rate and age were examined.

Patients: We studied 40 consecutive patients with Graves disease who underwent neck and chest CT before and 6 months after I-131 therapy.

Intervention: Observational study.

Results: A significant negative correlation was observed only between thymic density and age before I-131 therapy. Thymic volume and density decreased and TRAb levels increased significantly after I-131 therapy. The thymic volume decline rate significantly positively correlated with serum T3 and thyroid volume decline rates. No significant correlation was found between thymic volume decline and TRAb changing rates.

Conclusions: Significant thymic involution occurs after I-131 therapy in patients with Graves disease. Serum T3, but not TRAb, may be related to thymic hyperplasia and involution following I-131 therapy.

Freeform/Key Words: thymus, Graves disease, thymic hyperplasia, thymic involution, thyroid hormones, TRAb

Graves disease is an autoimmune condition characterized by the presence of circulating thyroid-stimulating hormone receptor antibody (TRAb), which overstimulates thyroid cells to

Abbreviations: CT, computed tomography; HU, Hounsfield unit; I-131, radioiodine; ROI, region of interest; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid stimulating hormone.

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result in hyperthyroidism [1]. Thymic hyperplasia in patients with Graves disease has been known for almost a century [2], and the important association between thymic medullary lymphoid follicles and Graves disease has been noted already by pathological examinations of the biopsied thymic specimens obtained at thyroidectomy in the 1960s [3]. Extreme enlargement of the thymus mimicking a mediastinal mass has been rarely reported previously. Presently, along with the development of imaging modalities, such as X-ray computed tomography (CT) and magnetic resonance imaging, many cases have been examined by CT or magnetic resonance imaging and the involution of thymic hyperplasia after antithyroid drug treatment of Graves disease has been reported [4–9]. Although the mechanism for thymic hyperplasia in patients with Graves disease has been postulated, namely, immunological reaction [4, 5, 10] and thyroid hormone stimulation [11–13] or both [4, 6, 7], the exact underlying mechanism remains to be established. Furthermore, thymic changes after radioiodine (I-131) therapy for Graves disease are poorly understood, although, to our knowledge, only one case of thymic involution after I-131 therapy for Graves disease has been reported [6].

The purpose of this study was to examine whether the volume and CT attenuation of the thymus in patients with Graves disease change after I-131 therapy and to elucidate factors that affect these changes.

1. Material and Methods

The institutional review board of our institution approved this retrospective study (Approval No. 27-26), and the need to obtain informed consent for this study was waived.

A. Patients

This retrospective study population consisted of 40 consecutive patients with Graves disease (7 male and 33 female patients; mean age, 49.6 ± 13.0 years; age range, 20 to 73 years) who underwent neck and chest CT before and 6 months after I-131 therapy at our institution from March 2007 to February 2012. Neck and chest CT has been used to estimate thyroid volume for the determination of the I-131 oral dose [14] and to evaluate the therapeutic results in the thyroid gland and thymus. Six patients received I-131 therapy as an initial therapy, and the other 34 patients received I-131 therapy due to inadequate control or side effects by antithyroid drug therapy. These 34 patients had received antithyroid drug (thiamazole and/or propylthiouracil) therapies for various durations (more than 30 years to 2 weeks) before therapy. No patient was included who received I-131 therapy two or more times.

At 6 months after I-131 therapy, 15 patients were euthyroid, 11 were hyperthyroid, and 14 were hypothyroid. To maintain a euthyroid state, 14 patients who became hypothyroid received a thyroid drug (levothyroxine sodium hydrate) and two who still were hyperthyroid received an antithyroid drug (thiamazole).

B. Image Analysis

CT was performed with 16- or 64-detector row CT scanners using either of two CT units (Aquilion; Toshiba Medical Systems, Tokyo, Japan). Imaging parameters for all phases were as follows: tube voltage, 120 kVp; gantry rotation speed, 0.5 seconds; maximum allowable tube current, 300 mA for 16-detector row CT or 400 mA for 64-detector row CT; detector row configuration, 16 × 1 mm for 16-detector row CT or 64 × 0.5 mm for 64-detector row CT; and table increment, 15 mm/rotation for 16-detector row CT or 63 mm/rotation for 64-detector row CT. Thymic and thyroid volumes were measured using the freehand region of interest (ROI) tracing of the outer contour of each thymus and thyroid on axial CT slices, at every 9- and 5-mm widths, respectively. The cross-sectional slice areas of each thymus and thyroid were automatically calculated by a workstation (SYNAPSE; Fujifilm Medical System, Tokyo, Japan) and recorded. The sum of these slice areas was subsequently multiplied by 9 mm for thymus and 5 mm for thyroid to obtain thymic and thyroid volumes (cm^3). Thymic density was

measured as averaged CT attenuation value [Hounsfield unit (HU)] at the level where the thymus appeared most prominently. The ROI for thymic density was traced manually as large as possible, taking care not to include the attenuation by air in the lung and sternum (Fig. 1).

C. Measurements of Serum Thyroxine, Triiodothyronine, Thyroid-Stimulating Hormone, and TRAb Levels

Before and 6 months after I-131 therapy, serum thyroxine (T4; μg/dL), triiodothyronine (T3; ng/mL), and thyroid-stimulating hormone (TSH; μIU/mL) levels were obtained in all 40 patients, and TRAb (IU/L) levels were obtained in 34 of 40 patients.

Serum T4, T3, and TSH levels were measured by the electrochemiluminescence immunoassay kit (Roche, Tokyo, Japan). TRAb levels were measured by a radioreceptor assay kit (Cosmic Corp., Tokyo, Japan). The normal ranges were 6.3 to 12.4 for serum T4, 0.80 to 1.60 for T3, 0.50 to 5.00 for TSH, and <1 for TRAb.

D. Examined Items and Statistical Analyses

First, we examined the associations between thymic volume or density and each of the following factors using the Spearman rank correlation test: age; serum T3, T4, and TRAb levels; and thyroid volume before I-131 therapy. When the measured values were above the upper limit values, we used the upper limit values, *i.e.* 24.8 for T4, 6.51 for T3, and 30 for TRAb.

Second, thymic volume and density; serum T3, T4, TSH, and TRAb levels; and thyroid volume were compared before and after therapy using the Wilcoxon signed-rank test. When the TSH value was < 0.01, the TSH value was assumed to be 0.

Third, we examined correlations between the thymic volume changing rate and each of the following factors using the Spearman rank correlation test: serum T3, T4, TRAb, and thyroid volume changing rates and age. These changing rates were calculated according to the following formula: (value before I-131 therapy − value 6 months after I-131 therapy) × 100% / value before I-131 therapy. We also performed partial correlation analysis using age as a control variable.

Data were expressed as means ± standard deviations (SDs) and/or ranges. Two-tailed P values of less than 0.05 were considered statistically significant. The statistical program SPSS statistics 23 (IBM, Inc., Chicago, IL) was used.

2. Results

Before I-131 therapy, there were no significant correlations of thymic volume with age ($\rho = -0.209$, $P = 0.196$); serum T3 ($\rho = -0.120$, $P = 0.461$), T4 ($\rho = -0.119$, $P = 0.463$), and TRAb

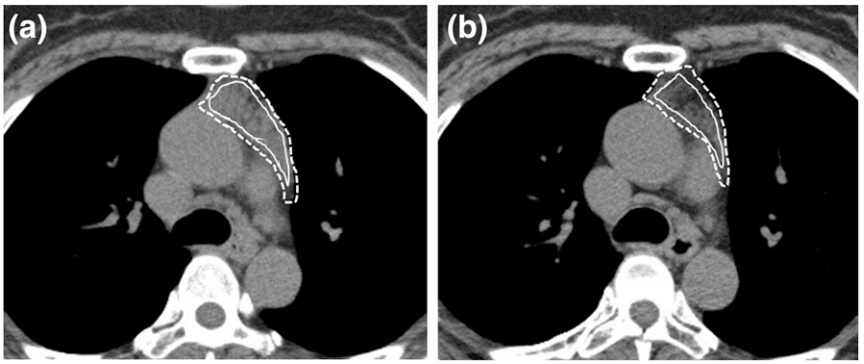

Figure 1. Axial CT images of a patient at the level where the thymus appears most prominently before (a) and after (b) I-131 therapy. The thymic area (dotted line) of each slice and density (solid line) were measured by the freehand ROI method.

($\rho = 0.109$, $P = 0.540$) levels and thyroid volume ($\rho = 0.175$, $P = 0.280$). A significant correlation was observed only between thymic density and age [ρ (correlation coefficient)] = −0.650, $P < 0.001$; Fig. 2). There were no significant correlations of thymic density with serum T3 ($\rho = 0.250$, $P = 0.120$), T4 ($\rho = 0.196$, $P = 0.225$), and TRAb ($\rho = -0.003$, $P = 0.986$) levels and thyroid volume ($\rho = 0.041$, $P = 0.802$).

The following parameters decreased significantly 6 months after I-131 therapy: thymic volume [before, 29.2 ± 19.3 (range, 5.7 to 83.8) and after, 22.7 ± 15.1 (range, 2.1 to 61.4)] and density [before, −26.4 ± 43.4 (range, −107.2 to 58.7) and after, −46.6 ± 38.7 (range, −107.6 to 38.8); $P < 0.001$ for both; Figs. 3 and 4]; serum T3 [before, 3.98 ± 1.33 (range, 1.87 to 6.51) and after, 1.41 ± 0.72 (range, 0.50 to 3.75)] and T4 [before, 17.0 ± 3.8 (range, 9.9 to 24.8) and after, 7.9 ± 2.8 (range, 3.1 to 14.1); $P < 0.001$ for both; Fig. 5(a) and 5(b)]. The following parameters increased significantly: serum TSH [before, 0 (range, 0.0 to 0.0) and after, 12.45 ± 30.89 (range, 0.0 to 139.8); $P < 0.001$; Fig. 5(c)] and TRAb [before, 9.3 ± 8.6 (range, 1 to 30) and after, 17.0 ± 11.6 (range, 1 to 30); $P = 0.002$; Fig. 5(d)].

There were significant positive correlations between thymic and thyroid volume decline rates ($\rho = 0.422$, $P = 0.007$) and thymic volume and T3 decline rates [$\rho = 0.345$, $P = 0.029$; Fig. 6(a)] and a negative correlation between thymic volume decline rate and age [$\rho = -0.644$, $P < 0.001$; Fig. 6(b)]. The correlation between thymic volume and T3 decline rates was significant even when age was adjusted ($\rho = 0.377$, $P = 0.018$).

There were no significant correlations of thymic volume decline rate with T4 decline rate ($\rho = 0.213$, $P = 0.187$) or TRAb changing rate ($\rho = 0.052$, $P = 0.772$).

3. Discussion

Thymic hyperplasia consists of two subtypes, true hyperplasia and lymphoid hyperplasia [14]. True thymic hyperplasia is defined as enlargement of the thymus (as defined by weight and volume), which remains normally organized, beyond the upper limit of normal for a given patient age. True hyperplasia is observed in patients who are recovering from recent stress, including chemotherapy for neoplasm, corticosteroid therapy, irradiation, or thermal burns [15]. Lymphoid hyperplasia refers to the presence of more lymphoid follicles and germinal centers, which may or may not be associated with the enlargement of the thymus [15]. Lymphoid hyperplasia of the thymus is observed in a number of immunologically mediated disorders, including myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, and Graves disease [15]. Pathologically, thymic medullary lymphoid follicle formation, lymphoid hyperplasia, was found in 32% (16/50) of thyrotoxicosis cases [3]. In contrast, true thymic hyperplasia, which is usually detected by chest X-ray or CT, is also known to

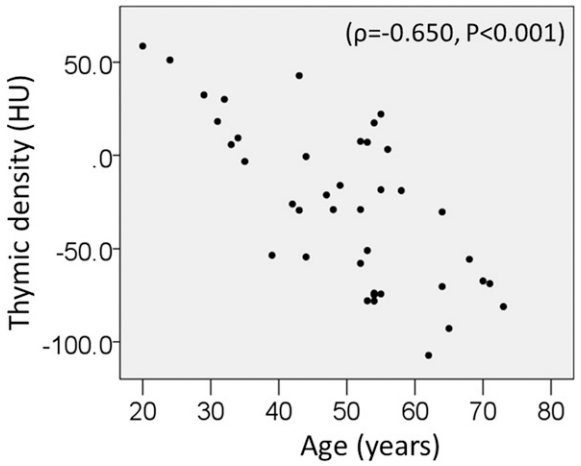

Figure 2. The correlation between thymic density (HU) and age before I-131 therapy.

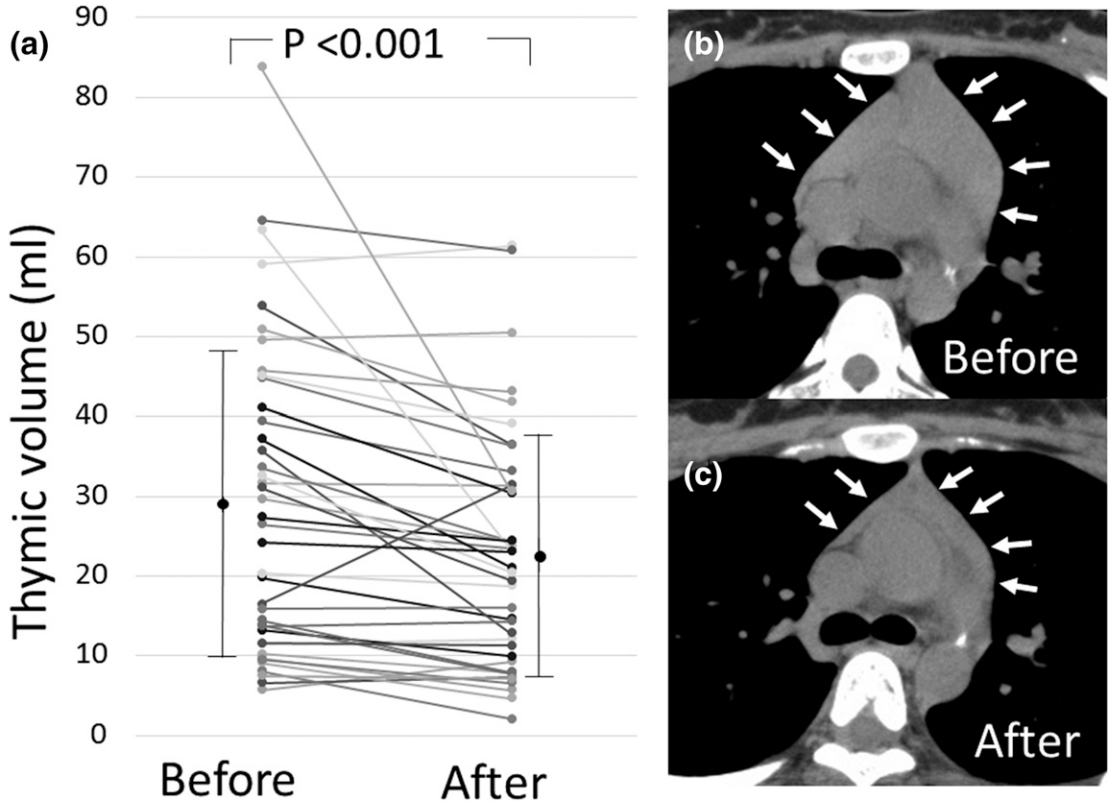

Figure 3. The change in thymic volume before and after I-131 therapy (a). Axial CT images of a 20-year-old woman before (b) and after (c) I-131 therapy. Her thymic volume decreased from 83.8 to 30.7 mL before and after I-131 therapy. The thymus of each slice was shown by white arrows.

complicate Graves disease [4–9, 16]. Judd *et al.* [17] reported that true and lymphoid thymic hyperplasia can be combined in Graves disease. In our study, thymic biopsy was not performed in any patient. Therefore, we do not know the ratio of lymphoid thymic hyperplasia to true hyperplasia. Young and Turnbull [18] pathologically calculated the mean thymic weights and SD for various age groups, and Lack [19] and Judd *et al.* [17] have suggested using two SDs above mean weights for age as a criterion for significant thymic enlargement. Comparing the previously-mentioned criterion and the results of thymic CT volumetry, at least 40% (16/40) of our patients seemed to have true thymic hyperplasia before I-131 therapy.

The mechanisms for producing thymic hyperplasia in Graves disease have not yet been clearly elucidated. Thymic hyperplasia in patients with Graves disease is more likely to be the result, rather than the cause, of their Graves disease because thymectomy did not improve hyperthyroidism, unlike myasthenia gravis [20]. Thymic hyperplasia seems to be caused by hyperthyroid states; however, it was not understood whether autoimmune or thyroid hormone itself contributed more deeply. Murakami *et al.* [4] investigated the thymic size and density of 23 patients with Graves disease, of whom 13 were evaluated before and after treatment with antithyroid drugs for 5 to 24 months. The thymic size and density were significantly reduced with a concomitant decrease in TRAb levels under the euthyroid state. The presence of TSH receptors in the nonneoplastic human thymic tissue was also clearly shown by polymerase chain reaction amplification, Northern and Western blot analysis, and immunohistochemistry [4, 5]. After I-131 therapy, autoimmunity is known to frequently worsen transiently after I-131 therapy [21]. In our study, we showed that thymic size and density were significantly reduced after I-131 therapy for Graves disease despite a concomitant increase in serum TRAb levels. These results appeared to be inconsistent with the posttreatment thymic size reduction with a concomitant reduction of TRAb levels reported by

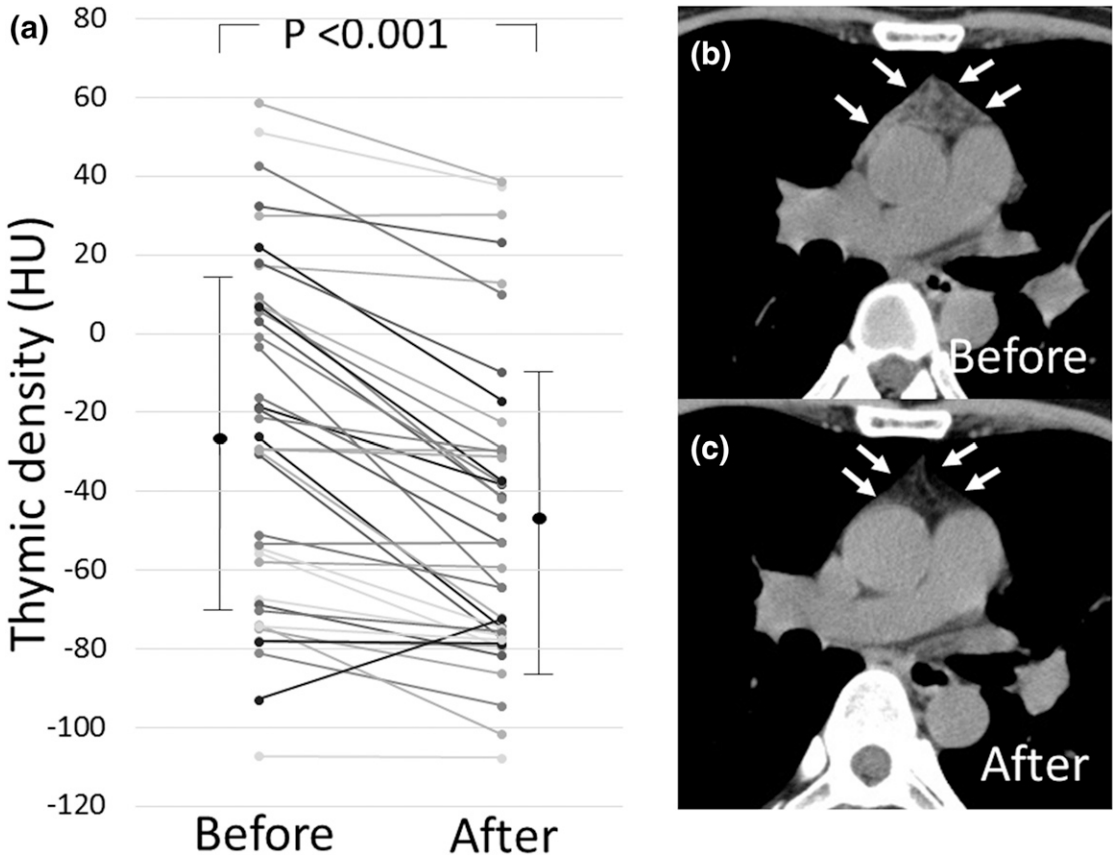

Figure 4. The change in thymic density before and after I-131 therapy (a). Axial CT images of a 42-year-old woman before (b) and after (c) I-131 therapy. Her thymic density decreased from −26.2 to −74.5 HU before and after I-131 therapy. The thymus of each slice was shown by white arrows.

Murakami *et al.* [4]. However, in our study, the T3 decline rate was significantly correlated with the thymic volume reduction rate. Villa-Verde *et al.* [22] demonstrated the expression of functional nuclear T3 receptors in thymic epithelial cells and discussed the pleiotropic effect of T3 upon thymus physiology, with its indirect stimulation of thymocyte differentiation [12].

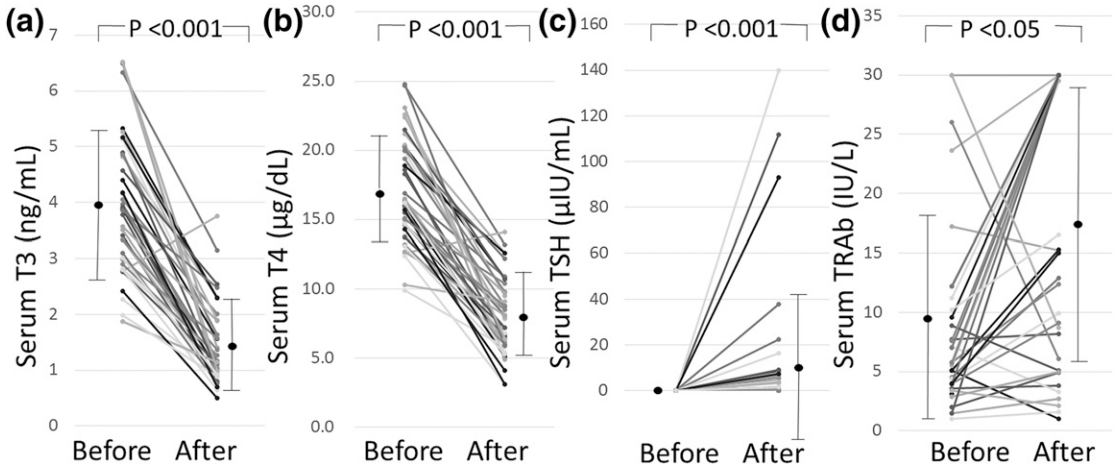

Figure 5. The changes in serum T3 (a), T4 (b), TSH (c), and TRAb (d) levels before and after I-131 therapy.

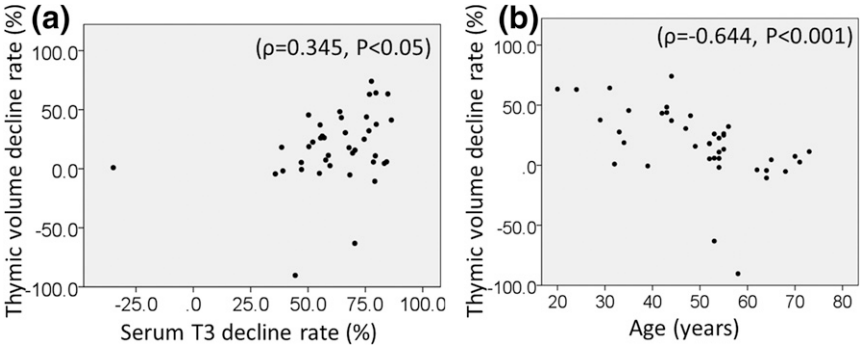

Figure 6. The correlations between thymic volume and T3 decline rates (a) and between thymic volume decline rate and age (b).

Moreover, administration of T3 in animals induced thymic hyperplasia [13, 23]. Therefore, T3 levels may influence considerably thymic hyperplasia and involution.

In our study, the obvious negative thymic volume decline rate was observed in two cases (−63.2% and −90.3%; Fig. 6). Both of them had a high T3 decline rate, and the former T3 value became normal, but the latter T3 value remained high 6 months after I-131 therapy. Even when these two cases were excluded as outliers, the correlation between the thymic volume decline rate and T3 decline rate remained significant (ρ = 0.330, P = 0.043).

Some cases of thymic visualization with I-131 in patients with differentiated thyroid cancer after total or near total thyroidectomy were reported [24–26]. Although the human sodium iodide symporter is present in the thymus, the iodine uptake ability of the thymus is far less compared with that of the thyroid [27]. In addition, the rare cases of visualization of the thymus were after the higher oral I-131 dose (3700 MBq or more dose) than after the oral I-131 dose for Graves disease [214.8 ± 152.6 (range, 48.1 to 479.5) MBq] in our study under conditions, such as postablation of the thyroid remnant and absence of metastatic spread and very high serum TSH levels [24–26]. In our patients, the mean serum TSH level 6 months after I-131 therapy was 12.45 ± 30.89 (0.0 to 139.8). Before I-131 therapy, thyroids were imaged to confirm diffuse goiter by a pinhole collimator 24 hours after oral diagnostic 3.7 MBq of I-131. In addition to this imaging, the 24-hour mediastinal imaging has been done by a high-energy multiparallel hole collimator to examine the thymic uptake in 26 patients. However, the thymus was visualized in none of them. Thus, thymic involution by the I-131 direct damage to thymic cells is unlikely.

Murakami *et al.* [4] reported that thymic volume and density decreased with increasing age in patients with Graves disease and control subjects. In our study, only thymic density was significantly correlated with age before I-131 therapy. Although, thymic volume was not correlated with age before I-131 therapy, the thymic volume decline rate was higher in younger patients. Age seemed to be one of the important factors affecting the thymic appearance.

Before I-131 therapy, none of the serum T3, T4, and TRAb values showed significant correlations with thymic volume or density in our study. In addition to the effect of age before I-131 therapy, the degree and duration of the hyperthyroid state and the amount and duration of previously used antithyroid drugs or other factors, for example, other medicines and complications, also might be related to the thymic appearance.

The limitations of our study include possible biases in patient selection due to the retrospective nature of the study. Other factors than those taken into consideration here might have affected the thyroid volume/density. A small study population is another major limitation. To further clarify the mechanisms of thymic hyperplasia in Graves disease and its involution after treatment, future studies with larger numbers of patients would be needed.

4. Conclusion

After I-131 therapy in patients with Graves disease, thymic volume and density on CT were significantly decreased. Thymic involution before and 6 months after I-131 therapy

significantly correlated with age, thyroid volume decline rate, and T3 decline rate despite a significant increase in serum TRAb levels. These results suggest that serum T3, but not TRAb, may be related to thymic hyperplasia and involution following I-131 therapy for Graves disease.

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Author contributions: M.J. collected and interpreted data, performed statistical analysis and drafted the manuscript. MY.N. interpreted the data and contributed to editing the discussion and manuscript. MT.N. collected and interpreted the data, C.K. provided statistical advice, and T.Y. reviewed and edited the manuscript.

Disclosure Summary: The authors have nothing to disclose.

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