Volume changes in remnant thyroid tissue after thyroidectomy in Graves disease

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Background/Purpose: Surgery is one of the treatment choices for Graves disease. The residual thyroid tissue may shrink or become larger. The object of this study was trying to find out what factors affect the residual thyroid gland volume change after thyroidectomy in Graves disease. Methods: We followed thyroid volume changes by ultrasonography in 101 patients with Graves disease who underwent one side lobectomy and another side subtotal thyroidectomy from 1996 to 2006. These patients were divided into three groups according to the residual thyroid size increasing, no change in size, and shrinking. We checked the factors as follows: age, body weight, thyroid-stimulating hormone (TSH) level, TSH-receptor antibody level, anti-thyroid peroxidase (TPO) antibody level, total thyroid volume before and after thyroidectomy, and degree of lymphocyte infiltration. Results: We found that young age and lower residual volume ratio were the most powerful two factors affecting remnant thyroid gland volume changing. We also found that there is no significant correlation between TSH levels and thyroid volume change, nor TSH-receptor antibody titer or thyroid volume change. Conclusion: Age and residual volume ratio were the most powerful two factors in this study. Copyright © 2012, Elsevier Taiwan LLC & Formosan Medical Association. All rights reserved.
Introduction

The prevalence of hyperthyroidism is approximately 1%–2% in women and 0.1% in men. Treatments for Graves disease include antithyroid drugs, radioactive iodine ablation, and surgery. It is unclear which of these therapies is optimal. For patients with intractable hyperthyroidism or large goiters, surgery is the favored means of treatment.

In clinical practice, residual thyroid gland volume may vary. Ultrasonography is a useful tool for thyroid examination and is widely used to assess thyroid gland size. To date, there have been no reports published describing serial residual thyroid changes as determined by neck ultrasound following thyroidectomy.

Thyroid-stimulating hormone (TSH)-receptor antibody (TSHRAb) and TSH are potent goitrogenic factors. Physiologically, TSH affects thyrocyte function and can promote cellular hypertrophy. The majority of TSHRAbs have TSH-like effects, while TSHRAbs exert stimulatory, neutralizing, and antagonistic effects. Few investigations have focused on the hyperplastic thyroid cell in studies pertaining to the involvement of growth factors in the development of thyroid cancer. The aim of this study was to determine if any clinical, biochemical, or histological factors are related to changes in residual thyroid volume in patients with Graves disease after thyroidectomy.

Materials and methods

A total of 101 patients with Graves disease who underwent one side lobectomy and another side subtotal thyroidectomy were studied from 1996 to 2006. There were 88 women and 13 men with a mean overall age of 39 ± 12.4 years (range: 18–73 years). The TSH, TSHRAb, and antithyroid peroxidase antibody (ATPO) levels were all measured postoperatively. We measured TSHRAb concentrations by radioreceptor assay using the porcine TSH receptor by electrochemiluminescence immunoassay (ECLIA) with the Roche Elecsys® 2010 assay (Roche Diagnostic Systems, Mannheim, Germany). We reviewed the surgical specimens and assessed the degree of lymphocyte infiltration subjectively with a classification of slight, moderate, and severe. The volume of residual thyroid tissue was determined by ultrasonography every 3 to 6 months for 1 to 10 years. The mean follow-up duration was 2.5 years, and the mean number of thyroid ultrasonography performed was 11.2 times. All thyroid remnants weighed less <3 g after thyroidectomy. Fifty percent patients had subclinical hypothyroidism during follow-up, and ten percent developed clinical hypothyroidism. There was no patient have recurrent thyrotoxicosis. During the follow-up period, no patients received antithyroid medication or thyroxin supplement. For those 10% of patients who later developed clinical hypothyroidism, we started eltroxin supplement and stopped collecting their TSH level and other laboratory data.

All measurements were made by the same operator to reduce interobserver error (intraobserver error was <2.5%). The rate of volume change was defined as follows: Vn/V1, where V1 is the initial examination volume, and Vn is the final examination volume. The year-volume change rate was defined as the volume change rate over time.

Other variables assessed included age at the time of surgery, body weight, surface area, TSHRAb level (expressed as times of upper normal limit), TSH level (expressed as the log value), anti-TPO antibody (ATPO), duration of follow-up, total thyroid volume before thyroidectomy, residual volume ratio (residual volume/total volume), and degree of lymphocyte infiltration. Thyroid volume was calculated as follows: (length × width × height)/2. A volume change rate of less than 7% was defined as no volume change in this study. This study was reviewed and approved by the Institutional Review Board committee and informed consent was obtained from all patients.

Statistical analysis

Data are reported as mean ± standard deviation. Analysis was performed with the statistical package SPSS 17.0 (IBM Software). Differences between parameters were compared with the Chi-square test (Cramer V), two-way analysis of variance (ANOVA). Relationships among parameters were tested by the Pearson correlation coefficient. Study parameters that had non-Gaussian distributions were transformed to log values. Results were considered statistically significant at p < 0.05.

Results

There were significant inverse correlations between the rate of volume increase and patient age (r = −0.230, p = 0.030; Fig. 1) and residual volume ratio (r = −0.249, p = 0.015; Fig. 2). There was no significant relationship
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between volume change rate or year volume change and the other variables assessed.

Of the 101 patients, 16 (15.7%) had no change in thyroid volume (Group A: rate of volume change ≤7% and ≥–7%), 59 patients (57.8%) had increased thyroid volume (Group B: rate of volume change >7%), while 26 patients (25.5%) had decreased thyroid volume (Group C: rate of volume change <–7%). There were significantly more TSHRAb-negative patients in Group C compared with both other groups (31% in Group A vs. 24% in Group B vs. 46% in Group C; p = 0.048; Fig. 3). There were no between group differences in the ATPO-positive rate (76% in Group A vs. 82% in Group B vs. 80% in Group C).

The rate of volume change was not related with mean TSHRAb in any group of patients. Similarly, TSHRAb titer was not correlated with the rate of volume increase.

In the present study it was found that there were more TSHRAb-negative patients amongst those who exhibited a decrease in residual thyroid volume. Bojarska-Szymynśka et al.3,13 reported that TSHRAb level was correlated with thyroid volume change post-thyroidectomy in Graves disease, and the TSHRAb-positive Group C patients to be inversely related with TSHRAb titer (p = 0.09) (Fig. 4).

Discussion

There are many known factors associated with thyroid gland size, such as iodine status, TSH level, TSHRAb, smoking, lithium treatment, and cytokines. In this study, we focus on clinical factors including age, thyroid function status, serum TSH and autoantibodies levels, pre- and postoperative thyroid volume, and lymphocyte infiltration.

We found that there was a negative correlation between the rate of residual thyroid volume increase and patient age. This finding suggests that the size of remnant thyroid tissue is more likely to increase in patients who are younger at the time of surgery. In a previous study, Orgiazzi et al10–11 found that young age was one of the major variables related to the subsequent risk of relapse after withdrawal of medical therapy in patients with Graves disease. Does this imply the juvenile Graves disease is more aggressive?

Maiorano and colleagues12 findings suggest that insulin-like growth factor 1 (IGF-1) and the IGF-1 receptor may be actively involved in the pathogenesis of Graves disease. The known decrease in IGF-1 levels with age may explain the link between young age and thyroid proliferation.

Although both TSHRAb and TSH levels are known to be potent goitrogenic factors,4–6 we found no significant correlation between TSH levels and thyroid volume change in any group of patients. Similarly, TSHRAb titer was not correlated with the rate of volume increase.

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size. Hence, low TSHRAb levels presumably contribute to thyroid tissue shrinkage. In these patients, there was a tendency for the decrease in volume to be inversely related with the TSHRAb titer. An increase in the proportion of TSHR blocking antibody may underlie this finding. It has previously been found that anti-TPOAb levels are related with Hashimoto destructive action. No such relationship was found in the present study. Similar to the result of the study from Rieu et al, TPOAb may play less of a role in modifying remnant thyroid volume change in patients with Graves disease.

The lymphocyte infiltration was hypothetically related to postoperative hypothyroidism. In Olsen et al, they found the there was some correlation between the degree of lymphocyte infiltration and the development of postoperative hypothyroidism, but it did not indicate a markedly increased tendency to hypothyroidism. But in Hargreaves et al, surgical treated thyrotoxicosis showed postoperative hypothyroidism occurred exclusively in those moderate or severe focal lymphocyte infiltration. When it comes to postoperative thyroid volume change, our result showed there was no change.

In 1995, Takai performed a study to evaluate clinical factors in subtotal thyroidectomy in Graves disease. He found that postoperative thyroid volume and weight were larger in patients with relapse than in patients in remission and in hypothyroid status. He also found a significant correlation between serum thyroglobulin level and the postoperative thyroid volume, and also thyroglobulin level in patients with relapse was significantly higher than others. We know that larger remnant thyroid weight is related to higher risk for relapse, and thyroglobulin level may reflect the thyroid volume. In our study, we did not check thyroglobulin level routinely, thus we did not find these clues.

Cytokines are known to related to thyroid cell proliferation. In Matsunaga et al, interferon-gamma induces human leukocyte antigen (HLA)-DR antigen expression on thyrocytes from patients with Graves disease, and these cells induce proliferation of autologous T cells, which may, in turn, act on thyrocytes to perpetuate the process. Genes have been shown to contribute to the etiology of Graves disease, and the substitution of the amino acid Ala or Gln with arginine at position beta 74 in the HLA-DR peptide binding pocket is the recently found specific sequence change causing Graves disease. However, among to Asian people, prevalence and many clinical presentations are much different from Caucasians. The recently study even identified distinct Graves disease-associated alleles. If available, further investigation in genes may answer more details about thyroid volume change in Graves disease.

Although we did not find any correlation between preoperative thyroid size and remnant thyroid volume change, a negative correlation between the rate of thyroid volume increase and the residual volume ratio was found. This implies that thyroid proliferation may be induced postoperatively in patients with larger preoperative goiters.

Excessive thyroid tissue removal may induce transient hypothyroidism and provoke TSH release, but we found no significant correlation between TSH levels and thyroid volume change. Furthermore, there were no instances of recurrent hyperthyroidism in this series (30% of patients received thyroxin supplement postoperatively after this study). The small amount of remnant thyroid (mostly 2.0–2.5 g) may explain the lack of recurrence. The relationship between thyroid function and thyroid volume change warrants further investigation in a cohort study of longer duration.

There are limitations in our study. First, we know there are two types of TSHRAbs with distinct functions. Stimulating antibodies promote thyroid growth and secretion, while blocking antibodies show inhibitory function. In our study, we used ECLIA method to measure TSHRAb concentrations, but we cannot distinguish these TSHRAb functions. Second, we used ultrasonography to measure thyroid gland size. Although all the measurements were made by the same operator to reduce interobserver error, the ultrasonography cannot completely represent real thyroid remnant sizes. We look forward to new studies that can provide more information about thyroid remnant volume change.

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References


