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Thyroid Volume Measured by ^{99m}Tc-Pertechnetate Scintigraphy and Its Relationship with Clinical Parameters in Korean Patients with Autoimmune Thyroiditis

Sang Ah Lee[1,2], Seong Man Lee[1], So-Yeon Yoo[2], Young Hwan Kim[3] and Gwanpyo Koh[1,2]

Department of Internal Medicine, Jeju National University School of Medicine[1] and Jeju National University Hospital[2], Jeju, Department of Nuclear Medicine and Molecular Imaging, Kangbuk Samsung Medical Center[3], Seoul, Korea

Background and Objectives: Autoimmune thyroiditis (AIT) is a form of thyroiditis associated with autoimmune antibodies. Few studies have measured thyroid volume in Asians. This study was undertaken to determine the distribution of thyroid volume and to explore possible correlations between thyroid volume and other factors in a Korean cohort. **Materials and Methods:** Two hundred eleven patients who underwent ^{99m}Tc-pertechnetate thyroid scintigraphy between 2009 and 2011 were recruited and their thyroid volume was measured. AIT was defined as having thyroperoxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb) positivity and TRAb negativity, regardless of thyroid function. **Results:** The mean thyroid volume was 32.1 mL in AIT patients. The distribution of thyroid volume was normal after log transformation. Thyroid volume was larger in patients with both autoantibodies than in patients with only one antibody ($p<0.001$). The first quartile of patients grouped according to thyroid volume were older (52.1 years, $p=0.037$) than the patients in other quartile groups. Thyroid volume correlated independently with TPOAb titer, and TgAb titer adjusted for other factors in a multivariate analysis. **Conclusion:** Thyroid volume in Korean AIT patients had an unimodal distribution and correlated with autoantibody titer.

Key Words: Autoimmune thyroiditis, Antithyroid peroxidase antibody, Antithyroglobulin antibody

Introduction

Autoimmune thyroiditis (AIT) is a form of thyroiditis associated with autoimmune antibodies such as antithyroperoxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). Hyperthyroidism, hypothyroidism, subclinical hypothyroidism, and euthyroid status can be detected in AIT. The clinical diagnosis of AIT is reached by measuring thyroid hormone, thyroid-stimulating hormone (TSH), and autoantibody levels. AIT includes Hashimoto's thyroiditis, primary myxedema, painless thyroiditis, and others, but in most cases, AIT is understood as Hashimoto's thyroiditis because it is the most common form. Conventionally, AIT is known to have two forms: atrophic and hypertrophic thyroiditis. Atrophic AIT is called Ord's disease, and hypertrophic AIT is called Hashimoto's thyroiditis.[1)]

Although AIT is a well-studied disease entity, some controversy remains regarding the distribution of thy-

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Correspondence: Gwanpyo Koh, MD, PhD, Department of Internal Medicine, Jeju National University School of Medicine, 15 Aranl 3-gil, Jeju 63241, Korea
Tel: 82-64-754-8163, Fax: 82-64-717-1131, E-mail: okdom@jejunu.ac.kr

roid volumes; some researchers have reported a two-peak distribution as a evidence for different disease entity, whereas others have found only one peak.[2,3] Atrophic AIT is usually detected in older patients with AIT, whereas hypertrophic AIT is usually detected in younger patients. This suggests that atrophic AIT represents an end stage of a broad spectrum of hypertrophic AIT. One study, however, has suggested that atrophic AIT is not the same disease as hypertrophic AIT through follow-up thyroid biopsy data showed no change over a long time.[2] Considering these previous studies, we didn't have clear evidence to determine whether the two forms of AIT are the same disease located at two ends of a large spectrum or are different diseases.

Some studies measuring thyroid volume in AIT using ultrasonography[4-7] have shown that thyroid volume in Hashimoto's thyroiditis is increased, normal, or decreased, and that thyroid volume in Ord's disease is normal or decreased. Several studies have been conducted in the West to measure thyroid volume in AIT appearing in children to adults.[8,9] However, few studies have measured thyroid volume in Asians.[10] Although one study has described thyroid length as determined by ultrasonography in Koreans,[11] no evidence has been presented on thyroid volume distribution in Korean with AIT. Thyroid hormone treatment affects thyroid volume in people with AIT.[12,13] Therefore, we aimed to determine the distribution of thyroid volume in treatment-naive patients with AIT and to explore the relationships between clinical parameters and thyroid volume measured by ^{99m}Tc-pertechnetate scintigraphy.

Materials and Methods

Subjects

This was cross-sectional study, and the population was selected from patients diagnosed with AIT who visited the outpatient clinic between December 2005 and December 2011. Two hundred eleven patients diagnosed with AIT who underwent ^{99m}Tc-pertechnetate thyroid scintigraphy were enrolled, and their information was obtained through chart review. We retrospectively reviewed the records of patients diagnosed with AIT according to the following criteria: (1) TPOAb positive (>34 IU/mL) or TgAb positive (>115 IU/mL); (2) thyroid-stimulating homone receptor antibody (TRAb) negative (<1.75 IU/L); and (3) any status of thyroid function such as euthyroid status, subclinical hypothyroidism, or overt hypothyroidism. We excluded hyperthyroidism because TRAb-negative Graves' disease could not be excluded. The other exclusion criteria were a history of thyroid disease or taking thyroid medication, hyperthyroidism, thyroid-associated ophthalmopathy, pregnancy, or increased uptake in a thyroid scan (>6%). Weight and height were routinely measured for all patients during the first visit.

^{99m}Tc-Pertechnetate Thyroid Scintigraphy

^{99m}Tc-pertechnetate thyroid scintigraphy was performed using a gamma camera (Vertex V60; ADAC, CA, USA) equipped with a low-energy high-resolution parallel-hole collimator. Thyroid scan images were acquired 20 min after administration of 111 MBq (3 mCi, i.v.) of ^{99m}Tc-pertechnetate. All patients were positioned supine with the neck hyperextended. Anterior neck and left and right anterior oblique neck images were acquired (over 300,000 counts), and a 20% symmetric window was centered at the 140 keV peak of ^{99m}Tc. The lengths of the thyroid lobes were measured manually. The lengths of the three main axes (longest craniocaudal axis [length], medial-lateral axis [width], and posterior-anterior axis [thickness]) were measured for each thyroid lobe. The craniocaudal and medial-lateral axes were measured on anterior images, and the posterior-anterior axes were measured on bilateral oblique images. Thyroid volumes was calculated as previously described[14] by a nuclear radiologist using the following equation:

Thyroid volume (mL)=anterior-posterior diameter (cm)×medial-lateral diameter (cm)×craniocaudal diameter (cm)×0.479

Blood Analyses

Thyroid testing included measurement of the levels of T3, freeT4, TSH (RIA, SPAC-S TSH kit; Daiichi,

Tokyo; normal range 0.5–5.0 mU/L), TPOAb, TgAb, and TRAb. TgAb and TPOAb were measured using a luminescence assay (BRAHMS Diagnostica, Berlin, Germany). A TgAb titer >115 IU/mL and a TPOAb titer >34 IU/mL were considered positive. TRAb was measured using a radioreceptor assay, and a value of >1.75 IU/L was considered positive.

Statistics

The data are presented as mean±standard error of the mean (SEMs). The Statistical Package for the Social Sciences (version 14; SPSS, Chicago, IL, USA) was used to calculate means and quartile ranges. Histograms and Q–Q plots were used to determine thyroid volume distribution. Groups of subjects were compared using ANOVA and Pearson's chi-square test. Correlation coefficient analysis was used to identify factors associated with thyroid volume, and linear regression analysis was used to identify factors independently related to thyroid volume. Values of $p < 0.05$ were considered significant.

Results

Subject Characteristics

We selected 211 patients with drug-naive AIT who satisfied all inclusion criteria. Their mean age was 46.7 years (range, 16–88 years) and 84.1% were women (Table 1). The thyroid functions were classified as euthyroid in 61.6%, subclinical hypothyroidism in 22.3%, and overt hypothyroidism in 16.1% (data not shown). The mean thyroid function test results were as follows: T3, 1.21 ng/dL; free T4, 1.26 ng/dL; and TSH 5.13 μU/mL. The mean autoantibody concentrations were TgAb, 414.15 IU/mL and TPOAb, 787.19 IU/mL. The mean thyroid uptake measured using ^{99m}Tc-pertechnetate thyroid scintigraphy was 4.28%.

Thyroid Volume Distribution

The mean thyroid volume was 16.77 mL for the right lobe, 15.32 mL for the left lobe, and 32.10 mL for total thyroid volume (Table 1). The right and left

Table 1. Basal characteristics of AIT patients

Factor	
Age (years)	46.70±1.40
Sex (female, %)	84.1
Height (cm)	160.75±0.94
Weight (kg)	59.13±1.37
Goiter (yes, %)	36.6
T3 (ng/dL)	1.21±0.04
Free T4 (ng/dL)	1.26±0.04
TSH (μU/mL)	5.13±1.32
TgAb (IU/mL)	414.15±51.89
TPOAb (IU/mL)	787.19±103.91
Right volume (mL)	16.77±0.78
Left volume (mL)	15.32±0.68
Total volume (mL)	32.10±1.03
Tc-99m uptake (%)	4.28±0.19

Tc: technetium, TgAb: thyroglobulin antibody, TPOAb: thyroid peroxidase antibody, TSH: thyroid-stimulating hormone

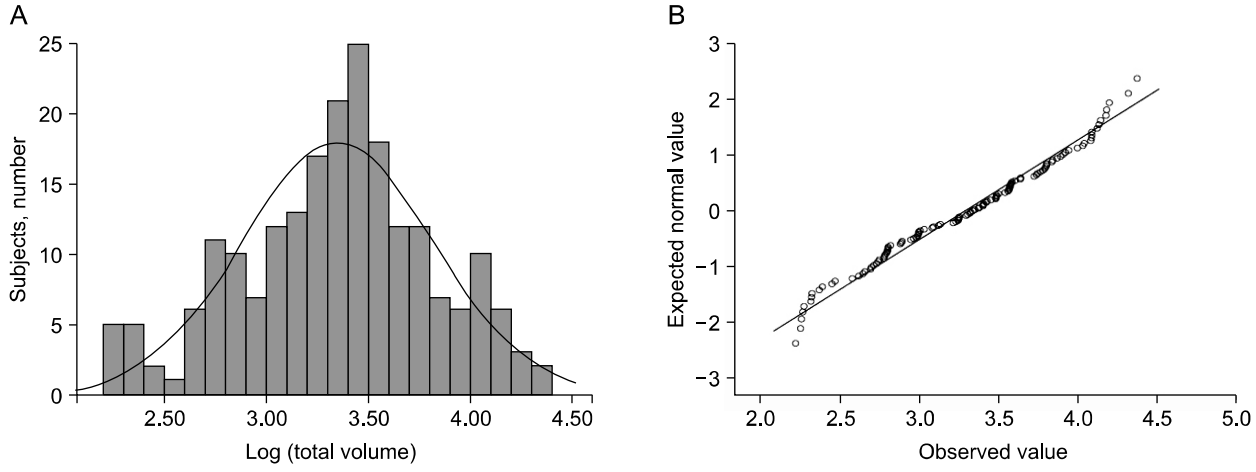

Fig. 1. Distribution of thyroid volume in AIT patients (A), histogram (B) Q–Q plots.

lobe volumes did not differ significantly. The thyroid volume distribution was skewed to the right (data not shown); therefore, we log transformed the thyroid volume data to obtain a normal distribution (Fig. 1A). A Q-Q plot of the log-transformed thyroid volume in the patients was normally distributed (Fig. 1B). The maximum thyroid volume was 79.03 mL, minimum thyroid volume was 4.62 mL, and median thyroid volume was 29.99 mL. The mean thyroid volume was 28.6 mL for patients with euthyroid status, 35.3 mL for those with subclinical hypothyroidism, and 37.1 mL for those with overt hypothyroidism. Thyroid volume correlated positively with thyroid function (data not shown, r=0.215, p=0.033).

Number and Titers of Thyroid Antibodies Related to Thyroid Volume

Patients enrolled in this study were positive for TPOAb and/or TgAb. Of the 211 patients with AIT, 70.6% (n=149) were positive for TPO Ab and 72.9% (n=154) for TgAb (Fig. 2A). We classified the patients with antibodies into three groups: those positive for TPOAb only, TgAb only, or both. We used ANOVA to compare thyroid volume between these three groups. The mean thyroid volume was significantly smaller in patients positive for only TPOAb or TgAb compared with patients positive for both antibodies (Fig. 2A). We also used correlation analysis to examine the association between thyroid antibody titer and thyroid volume

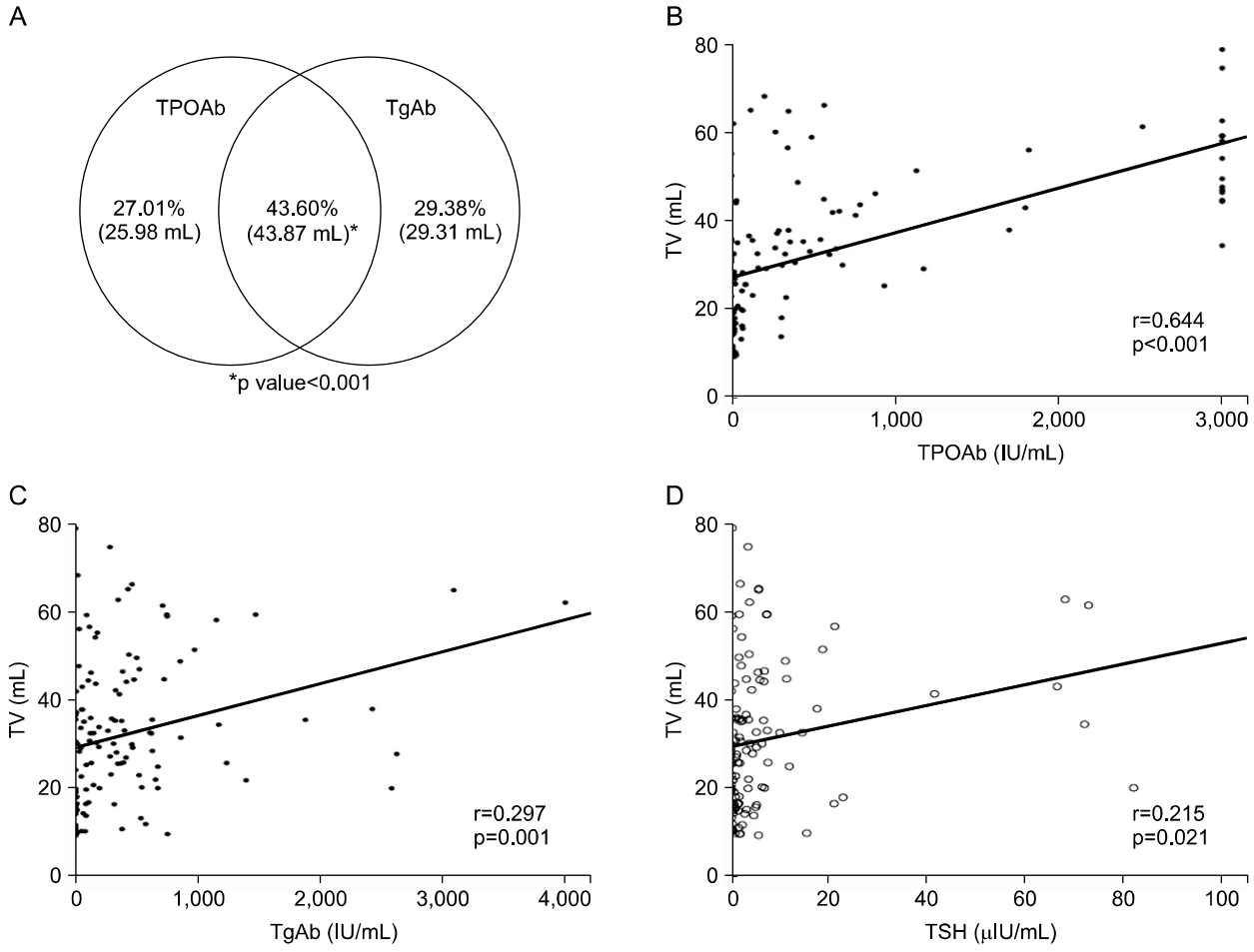

Fig. 2. Association between thyroid volume and clinical characteristics (A) thyroid volume related with number of autoantibody (B) correlation between thyroid volume and titer of TPOAb (C) correlation between thyroid volume and titer of TgAb (D) correlation between thyroid volume and serum TSH levels. TgAb: antithyroglobulin antibody, TPOAb: antithyroperoxidase antibody, TV: thyroid volume.

(Fig. 2B, C). Both TPOAb and TgAb titers correlated significantly with thyroid volume: r=0.644, p<0.001 (Fig. 2B) and r=0.297, p<0.01, respectively (Fig. 2C). Patients with both thyroid autoantibodies had higher TSH levels than those with only one of the antibodies (data not shown, p=0.032). TSH level also correlated with thyroid volume: r=0.215, p=0.021 (Fig. 2D).

Factors Associated with Thyroid Volume

We stratified the patients into quartiles based on their thyroid volume. The characteristics of the four quartiles are presented in Table 2. The 1st quartile patients were significantly older, had lower autoantibody titers, and were more likely to be euthyroid compared with the other quartiles. Nearly all (96.2%, n=50) patients in the 1st quartile had a single autoantibody. The other quartiles had similar mean ages. The percentage of patients with both autoantibodies increased significantly in the quartile groups classified according to thyroid volume. More patients in the 4th quartile 33 (66%) had both autoantibodies compared with the other quartile groups with smaller thyroid volumes. TSH level was significantly lower in the 1st quartile than in the other three quartiles, with a significant linear trend. Multivariate analysis showed that TPOAb (β=0.700, p<0.001), and TgAb (β=0.239, p=0.046) titers were independently associated with thyroid volume in patients with AIT after adjusting for age (β=−0.196, p=0.258), sex (β=0.066, p=0.707), body mass index (β=0.163, p=0.350), scan uptake (β=−0.166, p=0.343), free T4 (β=−0.170, p=0.328), and TSH (β=0.112, p=0.524).

Discussion

In this Korean study, the mean thyroid volume in treatment-naive AIT patients was 32 mL as determined by ^{99m}Tc-pertechnetate thyroid scintigraphy, and thyroid volume exhibited a normal distribution after log transformation and unimodal distribution. Thyroid volume was related to the number and titers of autoantibodies, and TSH level correlated positively with thyroid volume. However, TPOAb and TgAb titers were only independently associated with thyroid volume after adjusting for other clinical factors.

The mean thyroid volume in our AIT patients measured using ^{99m}Tc-pertechnetate thyroid scintigraphy was 32 mL. The normal thyroid volume in Koreans is 15.3 mL for men and 11.3 mL for women when determined by MRI,[15] which is similar to that reported in the West.[6,16,17] Therefore, the thyroid volume was larger in these AIT patients than in the normal

Table 2. Clinical characteristic of stratified quartiles groups based on thyroid volume

Factor	Thyroid volume				p value (ANOVA)	p value (linear trend)
	1st quartile (n=52)	2nd quartile (n=53)	3rd quartile (n=53)	4th quartile (n=53)		
Age (years)	52.07±3.01	46.80±2.99	42.59±2.58	42.59±2.48	0.037†*	0.044*
Sex (female, %)	77.78	90.00	82.14	93.33	0.271	0.251
Height (cm)	157.66±2.42	16.35±3.43	164.20±1.60	162.17±1.74	0.195	0.083
Weight (kg)	59.91±2.49	60.80±5.38	63.15±3.23	62.7±2.21	0.890	0.474
T3 (ng/dL)	1.12±0.06	1.25±0.08	1.11±0.05	1.09±0.06	0.298	0.407
Free T4 (ng/dL)	1.19±0.07	1.29±0.07	1.16±0.07	1.03±0.07	0.306	0.264
TSH (μU/mL)	1.72±0.34	2.01±0.55	7.38±2.76	12.06±2.77	0.010†*	0.001*
TgAb (IU/mL)	122.64±41.31	488.39±111.15	376.44±93.34	644.58±154.43	0.005†*	0.007*
TPOAb (IU/mL)	29.59±10.77	157.02±53.66	488.48±117.97	1591.60±230.53	<0.001†*	0.001*
Antibody number (both, %)	3.8	7.5	30.2	66.0	<0.001†*	0.001*
Total volume (mL)	13.72±0.50	24.24±0.63	34.90±0.60	55.69±1.62	–	–

TgAb: thyroglobulin antibody, TPOAb: thyroid peroxidase antibody, TSH: thyroid-stimulating hormone
*p value<0.05
†1st quartile vs. 2nd, 3rd, 4th quartile groups
‡1st and 2nd quartile vs. 3rd and 4th quartile groups

population. In previous Western studies, the mean thyroid volume in AIT patients was 12.8–50.4 mL,[7,8,18] which includes the range found in our study. Therefore, we suggest that the thyroid volumes of Korean AIT patients are similar to those of Western and Asian AIT patients. However, we note that different methods were used to measure thyroid volume in these studies. Most previous studies used ultrasonography to measure thyroid volume. Therefore, we cannot directly compare the results of our study with those of previous studies. However, no differences were found in the measurement of thyroid volume in diffuse goiter using scintigraphy compared with ultrasonography.[19,20] Therefore, we believe that our results are valid despite the use of a different method to measure thyroid volume in AIT patients.

AIT has been suggested to comprise two clinical subtypes, although this remains controversial among clinicians because of the overlapping of clinical manifestations and pathogenesis.[1–3,21] In the present study, we found that after log transformation, the distribution of thyroid volume was normal and had a unimodal distribution in treatment-naive Korean AIT patients. In 2009, Carle et al.[3] reported that thyroid volume follows a normal distribution in primary autoimmune hypothyroidism. To examine the relationships between thyroid volume and other clinical characteristics, we classified patients into four quartiles according to thyroid volume. Patients in the 1st quartile were significantly older (52.07 years) than those in the other quartiles and a higher percentage were euthyroid (TSH 1.72 μU/mL). Considering these two results, we propose that AIT may be one disease and that the small size of the thyroid in older patients is a result of mild disease. The patients in 1st quartile showed the higher percentage of euthyroid patients, the lower percentage of patients with both autoantibodies, and lower antibody concentrations, which were evidences of mild disease on elderly onset AIT.

We found that autoantibody titer correlated strongly with thyroid volume and that TSH concentration tended to be related to thyroid volume. These findings concur with that of the other study, which was conducted on 4168 patients with subclinical hypothyroidism.[22] In that study, TPOAb and TgAb concentrations were found to increase the risk of a large thyroid volume by 9.5 times. This phenomenon was also seen in a study of children and in a follow-up study of these children.[23,24] These findings indicate that thyroid autoantibody levels are related to thyroid volume.[25,26] The patients enrolled in the present study had a variety of thyroid statuses-euthyroid, subclinical hypothyroidism, and overt hypothyroidism. We found relationship between a larger thyroid volume and the number of autoantibodies such as TPOAb and TgAb. We also found that autoantibody titers were related to thyroid volume, which has been reported in other studies of AIT.[3,22,27,28] Therefore, we conclude that the factors most related to thyroid volume in AIT is autoantibody concentration.

This study had some limitations. First, thyroid volume was measured using ^{99m}Tc-pertechnetate thyroid scintigraphy; therefore, the values cannot be compared directly with those obtained using other modalities. Second, we selected patients who had undergone ^{99m}Tc-pertechnetate thyroid scintigraphy to identify those with suspicious or definite goiter. However, we found that thyroid volume showed a normal distribution in this study, which may reflect minimized selection bias. Finally, the assays to measure autoantibody titers were not repeated to minimize the risk of false positives. However, the prevalence of TPOAb and TgAb in AIT patients did not differ from the range in the Korean population, which is known to be lower than that of Western populations.[29]

In conclusion, a larger thyroid volume measured by thyroid scintigraphy was related to elevated autoantibody titers in Korean patients with AIT. Thyroid volume showed a unimodal distribution, which suggests that AIT might be a single disease entity.

Conflicts of Interest

The authors report no potential conflict of interest relevant to this article.

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