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Original Article

Higher serum thyroid autoantibody value is a risk factor of hypothyroidism in children and young adults with chronic thyroiditis

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Highlights

- The present retrospective cohort study aimed to predict the prognosis of thyroid function in children with anti-thyroid antibodies and found that a high TgAb and/or TPOAb level may predict hypothyroidism.
- Our study is the first to present cutoff values for anti-thyroid antibodies that may be useful for predicting thyroid function in Japanese children.

Abstract. Thyroid function in patients with chronic thyroiditis (CT) varies depending on the clinical course. Serum antithyroglobulin antibody (TgAb) and antithyroid peroxidase antibody (TPOAb) levels may be used to predict hypothyroidism in CT. In this retrospective cohort study, patients with CT, defined as having a high TgAb or TPOAb value, were divided into a hypothyroid group (HG) and euthyroid group (EG), after a mean follow-up of 2.5 years. The definitions of the two groups was based on the maximum TSH value from the initial measurement to the most recent follow-up: HG was defined as TSH 10.0 μIU/mL or higher, and EG was defined as TSH < 10.0 μIU/mL. There were 20 and 113 patients in the HG and EG, respectively. There were no significant differences in age, sex, underlying diseases, or TgAb and TPOAb levels between the groups. Receiver operating characteristic curve analyses of TgAb and TPOAb values for predicting thyroid function showed areas under the curve of 0.714 and 0.757, respectively. The value with the highest diagnostic accuracy was 106 IU/mL for TgAb and 16 IU/mL for TPOAb. Thus, TgAb > 106 IU/mL and TPOAb > 16 IU/mL may predict hypothyroidism in children and young adults with CT.

Key words: Antithyroid peroxidase antibody (TPOAb), antithyroglobulin antibody (TgAb), chronic thyroiditis, hypothyroidism

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Introduction

"Hashimoto's thyroiditis (HT)" is the most common cause of acquired hypothyroidism in children and young adults (1, 2). Although originally reported based on pathological findings, the diagnosis of HT in clinical practice is currently based on the presence of antithyroid peroxidase antibody (TPOAb) and antithyroglobulin antibody (TgAb) levels in the serum. In adult Japanese patients, the sensitivity and specificity of a test for detecting pathologically proven HT was reportedly 0.97 and 0.92 for TgAb and 0.72 and 0.88 for TPOAb, respectively. Approximately all patients with HT test positive for these antibodies in the early stages of the disease (3).

Patients with HT can be euthyroid, or have hypothyroidism or transient hyperthyroidism at the first diagnosis (4, 5). Hypothyroidism may develop if apoptosis and fibrosis of the thyroid follicles progress (6). Thus, the thyroid functions in patients with HT requires long-term follow-up even if they are normal at the initial evaluation.

Several reports have examined the value of thyroid autoantibodies in predicting future thyroid function in children and adults with HT. In children, the TSH value increased after five years of follow-up in 26% of patients positive for thyroid autoantibodies, and a high TPOAb value increased the risk of TSH increase by 3.5 times (7). A high TgAb value (> 10 times the upper normal limit) is a predictive factor for the development of hypothyroidism in children (8). Of the 459 adult patients aged over 65 years with subclinical hypothyroidism (SCH), 15% and 48% of TPOAb-positive patients and TPOAb-negative patients, respectively, were euthyroid after two years (9). In a study of patients with SCH aged > 55 yr, patients who were euthyroid for up to six years had a lower TSH value and tested negative for TPOAb (10).

To the best of our knowledge, no receiver operating characteristic (ROC) curve analysis of thyroid autoantibodies has been performed in children or young adults. We aimed to determine the thyroid autoantibody value that could predict hypothyroidism using ROC curve analysis in a cohort of pediatric and young adult patients with chronic thyroiditis (CT) defined as positivity for anti-thyroid autoantibodies. The subjects of this study were referred to as having "chronic thyroiditis," and, when HT was referred to in a previous paper, it was referred to as "Hashimoto's thyroiditis."

Materials and Methods

Patients

The subjects of this study were patients with CT, defined by the presence of serum TPOAb or TgAb at any time during the clinical follow-up period. Patients whose serum TPOAb and TgAb levels were measured between April 1, 2011, and March 31, 2017, at our hospital were initially included. The initial results were used to determine the predictive value of these antibodies in hypothyroidism. Patients who (1) later received an antithyroid drug, (2) had already received levothyroxine, (3) received fewer than two thyroid function measurements, (4) were older than 20 yr, or, (5) had 21 trisomy were excluded. Patients with trisomy 21 were excluded because their TSH values fluctuate independent of thyroiditis (11–13).

The enrolled patients were divided into a hypothyroid group (HG) and euthyroid group (EG) after the follow-up. The definitions of the two groups was based on the maximum TSH values during the study period. In the HG, the maximum TSH value reached 10.0 μIU/mL or more at least once during the study period, whereas in the EG, the TSH value was consistently below 10.0 μIU/mL. We also performed another set of analyses using a lower TSH value (6.0 μIU/mL) to differentiate between the HG and EG.

Study design

This was a retrospective cohort study based on patients' medical records. For baseline information, the following data were collected: date of birth, sex, age at the first visit, age at the final visit, and the presence of comorbidities, such as Turner syndrome, type 1 diabetes mellitus, and trisomy 21. After the initial visit, the TgAb, TPOAb, TSH, FT4, and FT3 levels of all patients were used.

Methods

Serum levels of FT4, FT3, TSH, TPOAb, and TgAb were measured by electrochemiluminescence immunoassay using Elecsys (Roche Diagnostics, USA). The detectable values of TPOAb ranged from 5–600 IU/mL. The detectable values of TgAb ranged from 11–4,000 IU/mL. The cutoff values for TgAb and TPOAb positivity were 28 and 16 IU/mL, respectively. The intra-CV of TgAb and TPOAb were within 15% and 10%, respectively.

Statistical analysis

The results of the statistical analyses are expressed as the mean ± SD or the median and range. Comparisons between groups were performed using Student's t-test (for normally distributed data) or the Mann–Whitney U test (for nonparametric data), as appropriate. Frequency rates were compared using the chi-squared test. Correlations between quantitative variables were assessed using Pearson correlation analysis. Statistical significance was set at $P < 0.05$. The cut-off values for the antibodies separating EG and HG were calculated using ROC curve analysis.

The study protocol was approved by the ethics committee of our hospital (approval number: H29b-50). The authors declare no conflicts of interest.

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Results

Patients' baseline data

We analyzed 133 patients (**Fig. 1**), 107 of whom were women. The mean age was 11.0 ± 5.5 (mean ± SD) yr, and the mean follow-up period after the TgAb and TPOAb measurements was 2.5 ± 1.4 (mean ± SD) yr.

There were 20 and 113 patients in the HG and EG, respectively. The two groups did not differ significantly in terms of age, sex, and frequency of underlying diseases (**Table 1**). In three patients in the EG who had received Levothyroxine (LT4) replacement therapy, the highest TSH values during their clinical course were 2.624–4.750 μIU/mL, which was not consistent with hypothyroidism. However, LT4 replacement was initiated at the discretion of the attending physician. One patient in the HG did not receive LT4 replacement therapy because his TSH value reached 10.061 μIU/mL once during the study period, but it improved immediately. In accordance with the definition of HG as TSH > 10 μIU/mL, the patient was placed in the HG.

Analysis of autoantibodies

The median, first quartile, and third quartile values for TgAb were 317.5 IU/mL, 109, and 619 IU/mL in the HG and 19, 12, and 308 IU/mL in the EG, respectively. The total TgAb levels differed significantly between the HG and EG groups ($P < 0.01$) (**Fig. 2**).

The median, first quartile, and third quartile values of the TPOAb were 120 IU/mL, 17 IU/mL, and 480.25 IU/mL in the HG and 10 IU/mL, 7 IU/mL, and 25 IU/mL in the EG, respectively. The total TPOAb level also differed significantly between the HG and EG groups ($P < 0.01$) (**Fig. 3**).

We obtained similar results on enrolling only patients with TSH > 6.0 μIU/mL (n = 43). The median values of TgAb in patients with TSH > 6 μIU/mL and in those with TSH < 6.0 μIU/mL were 262 IU/mL and 20 IU/mL, respectively ($P < 0.05$). The median TPOAb values in patients with TSH > 6.0 μIU/mL and TSH < 6.0 μIU/mL were 20 IU/mL and 10 IU/mL, respectively ($P < 0.05$).

ROC curve analysis

ROC curve analysis was performed to obtain the cut-off value of thyroid autoantibodies at the initial visit to predict the possibility of subsequent hypothyroidism. The ROC curve for TgAb had an area under the curve (AUC) of 0.714 (95% confidence interval [CI]: 0.605–0.822). The TgAb value with the highest diagnostic accuracy was 106 IU/mL, and the sensitivity and specificity were

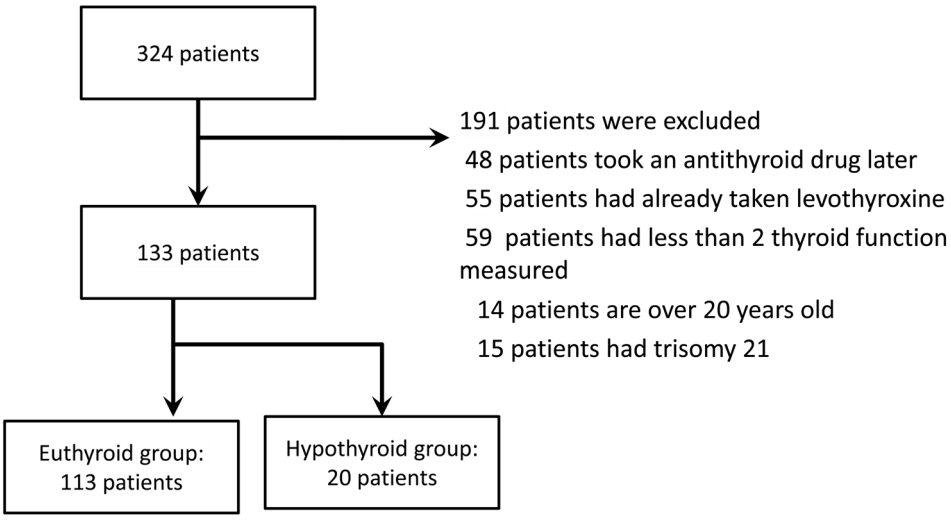

Fig. 1. Included and excluded subjects.

Table 1. Baseline data of the euthyroid group (EG) and hypothyroid group (HG)

	Euthyroid	Hypothyroid	P value
Number of patients (n)	113	20	
LT4 therapy (n)	3	19	
Female (n)	92	15	0.505
Turner syndrome (n)	20	1	0.151
Type 1 diabetes mellitus (n)	8	3	0.236
Age (yr: mean ± SD)	11.0 ± 4.0	12.3 ± 5.2	0.196
Median follow-up period (mo)	31.3	42.7	0.012

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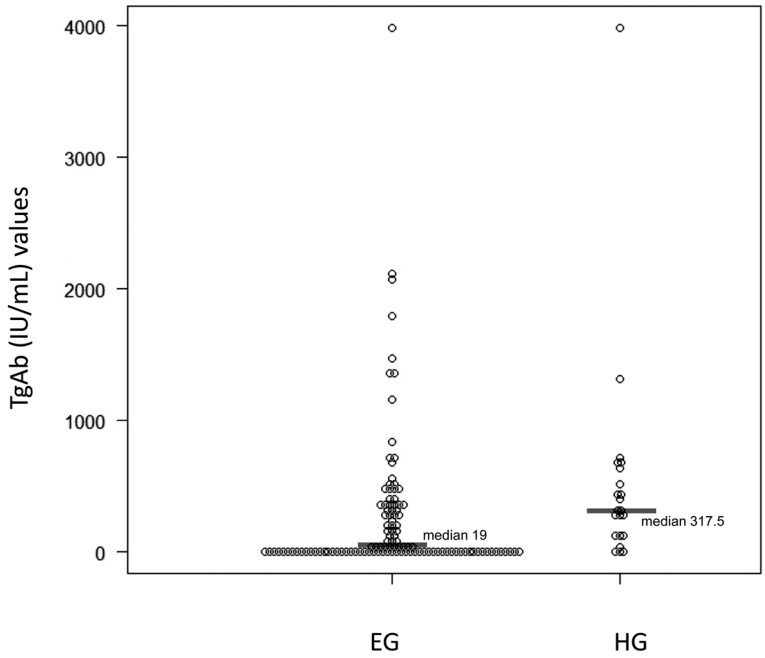

Fig. 2. Dot chart of TgAb values. The vertical axis indicates TgAb values. The chart on the left shows the EG and the chart on the right shows the HG. Horizontal bars represent the median of each group.

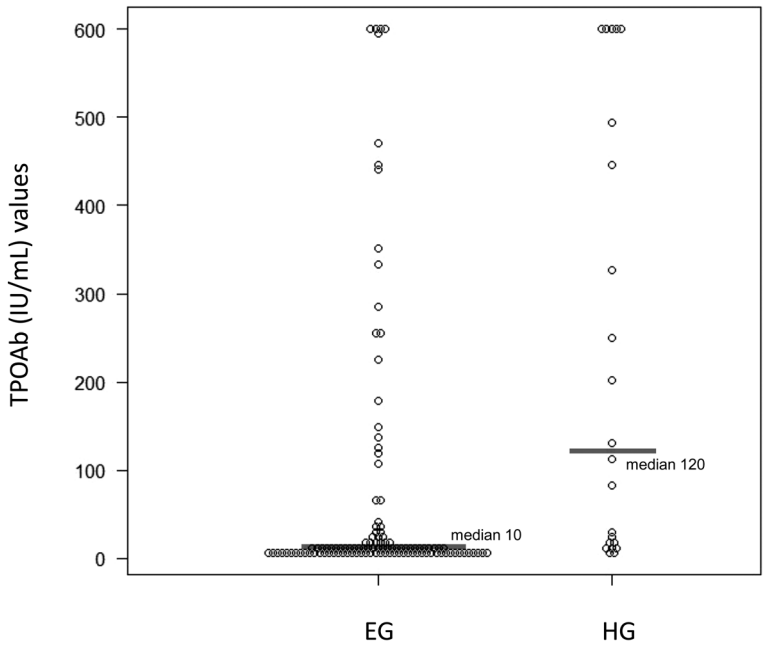

Fig. 3. Dot chart of TPOAb values. The vertical axis indicates TPOAb values. The chart on the left shows the EG and the chart on the right shows the HG. Horizontal bars represent the median of each group.

0.818 and 0.619, respectively (**Fig. 4**). The ROC curve for TPOAb had an AUC of 0.757 (95%CI, 0.640–0.874). The TPOAb value with the highest diagnostic accuracy was 16 IU/mL, and the sensitivity and specificity were 0.773 and 0.681, respectively (**Fig. 5**). When the TPOAb and TgAb values were above 16 IU/mL and 106 IU/mL, respectively, the sensitivity was 0.750, the specificity was 0.779, and the odds ratio of hypothyroidism was 10.56 (95% CI: 3.60–30.72).

Subgroup analysis

One of the limitations of this study was the heterogeneity of patient backgrounds. To address this issue, we analyzed three subgroups of the cohort: patients with an observation period exceeding two years (n = 83), those with an enlarged goiter (diagnosed on physical examination or ultrasonography, n = 84), and those older than 10 years (n = 88) (**Table 2**). Each subgroup

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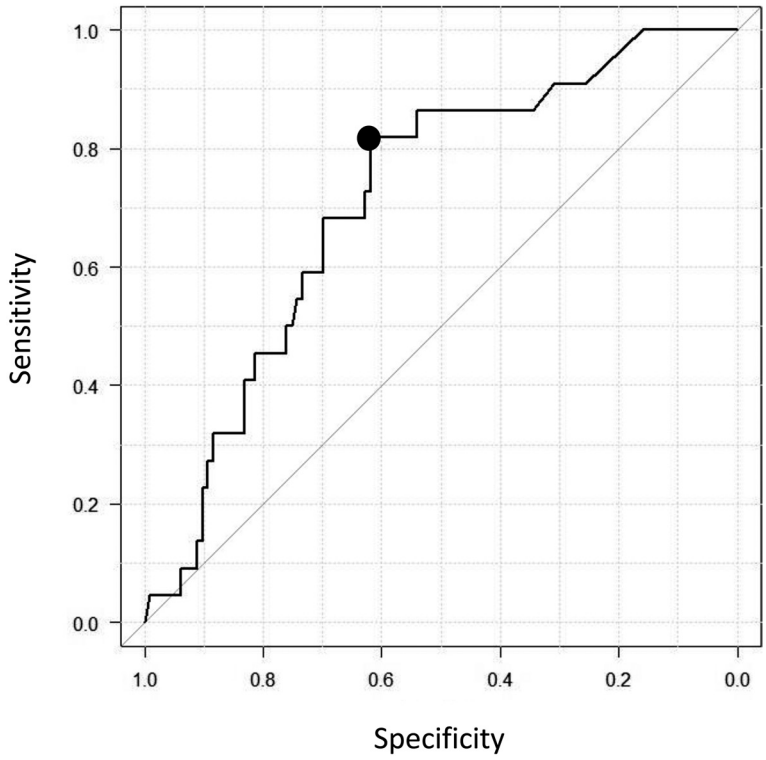

Fig. 4. ROC curve for TgAb for predicting hypothyroidism.

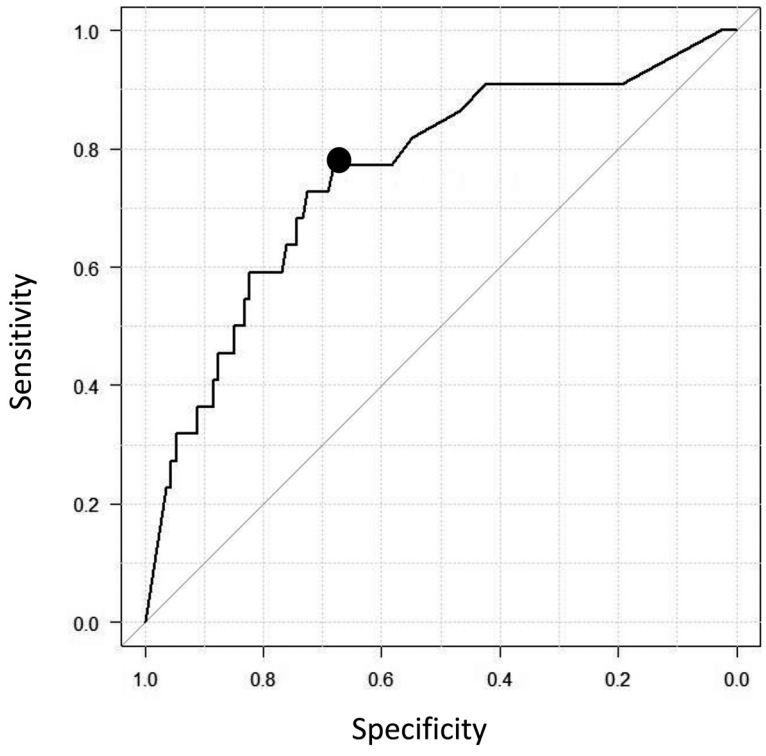

Fig. 5. ROC curve for TPOAb for predicting hypothyroidism.

analysis showed a significant difference in TPOAb levels between the HG and EG ($P < 0.05$). The TgAb values differed significantly between the groups only when the observation period exceeded two years ($P < 0.05$).

Discussion and Conclusion

The TPOAb and TgAb values with the highest accuracy for predicting hypothyroidism were 16 IU/mL and 106 IU/mL, respectively, according to the ROC

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Table 2. Sub-analysis of patients with observation periods exceeding 2 yr, enlarged goiter, or older than 10 yr

		Euthyroid	Hypothyroid	P value
Observation period exceeding 2 yr	n	67	16	
	TgAb (IU/mL)	21	355	0.011
	TPOAb (IU/mL)	10	120	0.001
With enlarged goiter	n	73	10	
	TgAb (IU/mL)	48	296	0.220
	TPOAb (IU/mL)	10	112	0.010
Older than 10 yr	n	77	11	
	TgAb (IU/mL)	79	327	0.139
	TPOAb (IU/mL)	10	112	0.018

TgAb and TPOAb shown here are the median levels for each group.

curve analysis of 133 patients with thyroid autoantibody measurements. Twenty patients showed elevated TSH levels during the average follow-up period of 2.5 yr.

Hypothyroidism, a feature of HG, was defined as TSH > 10.0 μIU/mL in this study. In adults, TSH > 10.0 μIU/mL is often used as an indicator for treatment (14–16). We obtained similar results while enrolling only patients with TSH > 6.0 μIU/mL (n = 43) in the HG. Regardless of the value used as a criterion for hypothyroidism, elevated TSH levels preceded a decrease in FT4 levels in progressive hypothyroidism.

TPOAb > 16 IU/mL, a marker of subsequent hypothyroidism according to our ROC analysis, was equal to the abnormal value (16 IU/mL) obtained in an analysis of adult Japanese patients with HT (3). The presence of TPOAb also reportedly predicts a higher risk of overt hypothyroidism development in adults (4.3% per year vs. 2.6% per year in antibody-negative individuals) (17, 18).

The TgAb value of 106 IU/mL obtained in this study was higher than the abnormal value (28 IU/mL) obtained in a previous analysis of adult Japanese patients with HT (3). However, Radetti *et al.* reported that in children, TgAb level > 10 times the upper normal limit is a predictive factor for the development of hypothyroidism (8). The difference between children and adults in terms of TgAb levels remains unclear.

In the present study, TgAb had a higher sensitivity and TPOAb had a higher specificity. This is consistent with results reported in adults (3), raising the possibility that the pathogenesis of CT is identical in adults and children. The reason for this difference in the utility of TgAb and TPOAb in predicting long-term prognosis remains to be clarified.

The present study used ROC analysis to determine the utility of thyroid autoantibody measurements in predicting hypothyroidism development in Japanese children. Our findings may enable the prediction of hypothyroidism development in patients with CT.

Our study has several limitations. The first was the wide heterogeneity in patient backgrounds, such as the length of the follow-up period and the presence or absence of goiter. However, to address this limitation, we performed a subgroup analysis of subjects with an observation period longer than two years, those with an enlarged goiter, and those aged > 10 yr. Another limitation was that it was a retrospective study, and crucial terms, such as treatment criteria and goiter, were not defined at the time of diagnosis.

Statements

Chronic thyroiditis with TgAb > 106 IU/mL and TPOAb > 16 IU/mL in children and young adults should be closely monitored for possible development of hypothyroidism.

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