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Original Research

A study of serum IgG4 levels in the clinical metamorphosis of autoimmune thyroid disease

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ABSTRACT

Background: Measurement of serum IgG4 had been suggested to distinguish the unique subtypes of autoimmune thyroid disease (AITD) which demonstrated patterns of fluctuating between hyperthyroidism and hypothyroidism. However, the clinical utility of serum IgG4 measurement is inconclusive due to few studies having addressed these unusual patients compared with the specificity of serum IgG4 in healthy patients.

Aim: To investigate whether elevated serum IgG4 levels could be used as a marker to identify fluctuating AITD patients.

Materials and Methods: 20 AITD patients who evolved from hyperthyroid Graves' disease to spontaneous hypothyroidism or vice versa were compared with 40 healthy subjects, 40 patients with hyperthyroid Graves' disease (GD) and 40 patients with subclinical or overt hypothyroid Hashimoto's thyroiditis (HT). Serum levels of total IgG and IgG4 were measured and the proportion of elevated serum IgG4 levels (defined by serum IgG4 levels $\geq$ 135 mg/dL) was compared with control patients.

Results: A series of 20 Thai patients with clinical evolution of AITD was analyzed with a median follow-up at 92 months (range 3–380 months). Elevated serum IgG4 levels were not found in fluctuating AITD patients but were found in 5% of the control GD patients, 2.5% of the control HT, and 2.5% of healthy subjects which were not statistically significant between each group.

Conclusion: Our results contrasted with those of previous studies from Japan which reported elevated serum IgG4 as a marker to identify subset of AITD patients. At present, the clinical utility of serum IgG4 measurements in AITD is inconclusive and requires further investigation.

Introduction

Patients with AITD may have both stimulating and blocking TSH receptor antibodies (TRAbs) in their sera, the clinical manifestation will depend on either way which TRAbs attached to [1]. Hyperthyroidism in Graves' disease (GD) is caused by thyroid-stimulating autoantibodies to the TSH receptor, whereas hypothyroidism in Hashimoto's thyroiditis (HT) is associated with thyroid peroxidase (Anti-TPO) and thyroglobulin autoantibodies (Anti-Tg). Anti-TPO antibody activates complement and is involved in thyroid dysfunction and the pathogenesis of Hashimoto's thyroiditis. Whether anti-Tg plays a role in the pathogenesis of AITD or it is merely a disease marker is more controversial than anti-TPO. Graves' disease patients who had been treated with anti-thyroid medications may develop eventual hypothyroidism in 5–20% of patients [2–3]. Therefore, hyperthyroid Graves' disease patients require lifelong follow-up after remission from anti-thyroid medications. Conversely, several studies reported the transformation from hypothyroid phase of Hashimoto's thyroiditis into hyperthyroid Graves' disease [4–5]. Moreover, some exceptional patients underwent three cycles of transition from hypo- to hyperthyroidism and back to hypothyroidism, with corresponding changes in stimulating and blocking TSH receptor antibodies. This fluctuation leads to a difficulty in clinical care [6]. Only few studies have addressed the clinical evolution of AITD which switches between hyperthyroidism and hypothyroidism in these unusual patients. Of particular importance is the issue of whether this unique type of AITD can be recognized based on a biomarker at an earlier stage, and if an early treatment could be initiated to avoid transformation of the disease. Recently, a Japanese study found that elevated serum

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immunoglobulin G, subclass 4 (IgG4) concentrations which is the least abundant subclass of immunoglobulin G (IgG) tended to be higher in hyperthyroid Graves' disease patients who were prone to hypothyroid after anti-thyroid medications [7]. Measurements of serum IgG4 levels have been suggested to distinguish this novel subtype of Graves' disease who will progress to overt hypothyroidism. In normal subjects, serum IgG4 levels generally range from less than 10 mg/dL to 140 mg/dL, with levels over 200 mg/dL noted in a very few healthy individuals [8].

The role of IgG4 antibodies had been also demonstrated in the pathogenesis of Hashimoto's thyroiditis and IgG4-related systemic disease (IgG4-RSD) which represents a diverse group of clinical disorders unified by the elevated IgG4 levels and specific histolopathologic findings [9]. IgG4-RSD can affect the thyroid in two different ways: a subset of Hashimoto's thyroiditis referred to as a 'fibrosing variant' and Riedel's thyroiditis [10]. Responsiveness to high dose steroid is a characteristic found early in the disease course, before the onset of significant tissue fibrosis. Because fibrous variant of Hashimoto's thyroiditis also had been reported in a previous series of hypothyroidism, in Graves' disease in 1980s [11], these group of patients offer valuable opportunities for studying the predictive value of elevated IgG4 levels in this interesting entity.

Herein, we reported the clinical features of Thai patients with clinical metamorphosis in the spectrum of AITD and the proportion of elevated serum IgG4 levels in these patients compared with typical cases of hyperthyroid Graves' disease and hypothyroid Hashimoto's thyroiditis patients. The aim of our study was to investigate whether elevated serum IgG4 levels could be used as a marker to identify fluctuating AITD patients.

Material and methods

Patients

A series of cases was collected by recruiting 20 AITD patients who evidenced changes from hyperthyroid Graves' disease to spontaneous hypothyroidism or vice versa in Theptarin hospital, Bangkok, Thailand. Clinical characteristics, laboratory findings at the time of transformation, and outcomes were recorded retrospectively from chart review. Serum total IgG and IgG4 levels were measured at time of recruitment. The results of serum IgG4 levels were compared with the control groups which composed of 40 healthy subjects, 40 patients with hyperthyroid Graves' disease and 40 patients with subclinical or overt hypothyroid Hashimoto's thyroiditis.

The inclusion criteria of fluctuating AITD patients included Graves' disease patients who developed a spontaneous change from hyperthyroidism to hypothyroidism (without ablative intervention with radioactive iodine or overtreatment with antithyroid medications) and autoimmune hypothyroidism patients (subclinical hypothyroidism or overt hypothyroidism) who later developed hyperthyroidism associated with the appearance of TRAbs or with increased titers of serum Anti-Tg and/or Anti-TPO. In patients with subclinical hypothyroidism after remission from hyperthyroid Graves' disease, subclinical hypothyroidism was ascertained by re-evaluation of thyroid function tests at 3 months after the first diagnosis. In the control group of hyperthyroid Graves' disease, the diagnosis was based on the presence of hyperthyroidism (clinical presentation and laboratory tests), positive thyroid auto-immunities, increased radioiodine uptake and/or the presence of TRAbs. All cases of Graves' disease patients required anti-thyroid medications at the time of study and none of the patients underwent previous treatment with surgery or radioiodine treatment. In the control group of Hashimoto's thyroiditis, the diagnosis was based on the diffuse thyroid enlargement with positive Anti-Tg and/or Anti-TPO and/or hypoechogenic pattern from ultrasound findings. All cases of the Hashimoto's thyroiditis must exhibit a biochemical picture of either subclinical or overt hypothyroidism at the time of diagnosis. In the healthy control patients, participants had been recruited from hospital staffs who did not have any confounding factors which might interfere the serum IgG4 level measurements. Age and gender did not require to be matched because these factors did not affect serum IgG4 level measurements.

The exclusion criteria included patients who had previous treatment with surgery or radioiodine treatment, confounding conditions which might cause elevated serum IgG4 levels including severe infections, allergic disorders, parasite infestations, pemphigus, autoimmune pancreatitis, chronic pancreatitis, pancreatic cancer, primary biliary cirrhosis, primary sclerosing cholangitis, and Sjogren's syndrome [12]. Written informed consent was obtained from all patients, and the study protocol was approved by Theptarin hospital ethics committee.

Data collection and laboratory analysis

Clinical data including the following variables were obtained: age, gender, family history of AITD, duration of AITD, duration of anti-thyroid medications, symptoms at the time of transformation, estimated thyroid gland size by palpation, ultrasonographic evaluation (if available), thyroid function tests at the initial diagnosis of AITD and at the time of transformation.

The total T3 (TT3) concentrations, free T4 (FT4) concentrations and thyroid-stimulating hormone (TSH) levels were measured by using electrochemiluminescent immunoassays (Roche Diagnostics, Indianapolis, USA). The reference ranges used for serum TSH, FT4 and TT3 were 0.30–5.00 mIU/l, 1.70–3.70 pg/ml and 0.70–1.60 ng/dl, respectively. Thyroglobulin autoantibodies (Anti-Tg) and thyroid peroxidase antibodies (anti-TPO) were measured with an electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, USA). Normal values were defined as follows: Anti-Tg < 115 IU/mL and Anti-TPO < 34 IU/mL.

The levels of total IgG and IgG4 were measured by immunonephelometry, using a commercial assay (Siemens Diagnostics Inc., Newark, U.S.A.). The measurements of serum IgG4 were performed in duplicate with coefficient variables of 5.2%. Because the differences in calibration of the binding site (as used in Japanese literatures) and Siemens reagents used in the IgG4 assays in our study had been estimated at the 2-fold differences [13]. The levels of IgG4 analyses has been divided by two from the results obtained from Siemens reagents in order to comparison with the criteria of elevated serum IgG4 levels (>135 mg/dL) according to the comprehensive clinical diagnostic criteria of IgG4-RSD [14].

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or median and range, as appropriate. Differences between three or more unpaired groups were analyzed by the Kruskal Wallis test and between two unpaired groups by the Mann-Whitney test to compare two groups. A Chi-square test or Fisher's exact test was used to compare the qualitative variables. Quantitative variables were analyzed by one-way ANOVA (normal distribution) or Wilcoxon test (abnormal distribution). The data were analyzed using an SPSS software program (version 18.0; SPSS, Inc.). Values of $p < 0.05$ were considered to indicate statistical significance.

Sample size calculation

Because no previous study about association of serum IgG4 concentrations and fluctuating AITD patients were available, we multiplied control samples from each spectrum of AITD patients (Hyperthyroid Graves' disease and Hypothyroid Hashimoto's thyroiditis patients) by two corresponding to the case-control ratio at 1:2. Control cases had been selected randomly from routine out-patients clinic without pre-defined age/sex-matched subjects with index cases of fluctuating AITD patients. Power of the study was set at 80%.

Results

Twenty Thai patients with clinical evolution of AITD were recruited with a median follow-up time of 92 months (range 3–380 months). There were 18 cases of evolved GD to HT and 2 cases of evolved HT to GD. In the patients of hyperthyroid GD who transformed into HT (16 women and 2 men, age 45.8 ± 9.6 years), the median interval duration after discontinuation of anti-thyroid drugs was 8 years (range 0.5–22 years). At the time of HT diagnosis, 12 patients developed subclinical hypothyroidism and 6 patients developed overt hypothyroidism. The hypothyroidism did not represent a hypothyroid phase of an episode of thyroiditis since the patients had consistent elevation of TSH levels over several years. Nine patients in the subclinical hypothyroid group were treated with levothyroxine (LT4) at the mean dose of 60.7 ± 24.4 μg/day and 3 patients were observed without medication. No cases of subclinical hypothyroidism recovered a normal thyroid function in this group of patients. In the group of overt hypothyroid patients, an average dose of LT4 was 91.7 ± 25.8 μg/day. Goiter size was estimated by palpation with the same physician and showed marked reductions in goiter size by more than 50% reduction in two-thirds of patients between the time hyperthyroidism was diagnosed and the time of hypothyroidism was diagnosed.

Ultrasonography was performed in only 3 patients with overt hypothyroidism and revealed thyroid atrophy with hypoechogenicity characteristics of autoimmune thyroiditis. In the patients with HT who transformed into hyperthyroid GD (2 women, age 42.5 ± 12.0 years), one patient was euthyroid and another patient had overt hypothyroidism before transformation. At the time of transformation, both of these patients had been treated with levothyroxine at the dosage of 100 μg/day. After transformation to hyperthyroid GD, one patient was treated with oral methimazole 15 mg/day while another patient had been given radioiodine therapy to treat hyperthyroidism. The clinical characteristics and laboratory data of index fluctuating AITD patients were summarized in Table 1.

For control cases, 40 healthy subjects, 40 cases of hyperthyroid Graves's disease and 40 cases of hypothyroid Hashimoto's thyroiditis were recruited. The demographic data, thyroid function tests at the time of recruitment, serum total IgG levels and serum IgG4 levels of the study subjects were summarized in Table 2. None of the index patients or control subjects had evidence of other organs affected by IgG4-RD or other autoimmune diseases or history of neoplastic diseases, allergic disorders, chronic rhinosinusitis, active infections, or kidney failure. As shown in Fig. 1, there is a considerable overlap of serum IgG4 between the index AITD patients and the control groups. There was no statistical difference of serum IgG4 concentrations between the three groups ($p = 0.589$) by the Kruskal Wallis test. Despite this, the median value of IgG4 levels appeared to be higher in index patients (median 60 mg/dL, range 2–122 mg/dL) than the controls (GD: median 39 mg/dL, range 6–173 mg/dL and HT: median 40 mg/dL, range 8–371 mg/dL). When elevated serum IgG4 were defined by comprehensive clinical diagnostic criteria of IgG4-RSD (serum IgG4 levels $\geq$ 135 mg/dL), none was found in the index fluctuating AITD patients, 5% of the control GD patients, 2.5% of the control HT, and 2.5% of healthy subjects which were not statistically significant in each group. None of the factors including age, sex, duration of AITD, smoking status, the presence of ophthalmopathy, or thyroid auto-antibodies had an association with elevated serum IgG4 levels.

Discussion

Although autoimmune thyroid disease (AITD) is now better understood than in the past, there are still several unexplored areas especially regarding its of pathogenesis and potential benefits of future alternative treatments. Anti-thyroid drug therapy is one of the main medical treatments for GD. One major problem with medical therapy is the high recurrence rate which is estimated to be 50–60% [15]. Therefore, radioactive iodine has been used commonly to treat hyperthyroid GD in United States since the 1940s. However, in China, as well as in Europe and Japan, the majority of patients with the first episode of GD are initially trea-

Table 1
Clinical characteristics and laboratory data of fluctuating AITD patients.

	GD to HT (N = 18)		HT to GD (N = 2)
	Subclinical Hypothyroid (N = 12)	Overt Hypothyroid (N = 6)	
Age (years)	48.5 ± 10.0	42.7 ± 5.5	42.5 ± 12.0
Sex (M/F)	1/11	1/5	0/2
Age at AITD diagnosis (years)	35.2 ± 10.4	34.3 ± 4.0	37.0 ± 12.7
Duration of follow-up (months)*	190 (66–380)	36 (6–280)	32 (6–60)
Time interval before transformation (years)*	10.5 (2.0–22.0)	3.5 (0.5–9.0)	NA
Family history of AITD (cases)	2	0	2
Presence of goiter at the time of fluctuation (cases)	4	2	1
Presence of ophthalmopathy (cases)	4	2	1
Total T3 (61–177 ng/dL)#	95 ± 15	51 ± 31	121 ± 72
Free T4 (0.93–1.70 ng/dL)#	1.02 ± 0.25	0.58 ± 0.35	2.66 ± 1.10
TSH (0.27–4.20 μIU/mL)#	10.67 ± 10.31	54.82 ± 39.51	0.01 ± 0.02
Total IgG (mg/dL)	1373 ± 187	1538 ± 174	1610 ± 170
Serum IgG4 (mg/dL)	55 ± 28	68 ± 39	36 ± 50
IgG4/Total IgG ratio (%)	4.0 ± 2.3	4.4 ± 2.5	2.0 ± 2.9
Anti-TPO (0–34 IU/mL)*	542 (6–600)	435 (0–600)	574 (0–600)
Anti-Tg (0–115 IU/mL)*	435 (0–1191)	560 (0–963)	421 (0–691)

* Data were expressed in median (range).
\# Thyroid function test at the time of transformation.

Table 2
Clinical characteristics and laboratory data of fluctuating AITD cases and control groups.

	AITD cases (N = 20)	Graves' disease (N = 40)	Hashimoto's thyroiditis (N = 40)	Healthy Subjects (N = 40)	*p-value*
Age (years)	46.2 ± 9.0	36.4 ± 10.5	50.7 ± 14.0	44.0 ± 11.8	<0.001
Sex (M/F)	2/18	4/36	6/34	10/30	0.753
Age at diagnosis (years)	35.1 ± 8.7	33.6 ± 10.0	42.6 ± 15.7	–	0.004
Duration of AITD (years)*	10.4 (0.5–32)	1.6 (0–11)	4.5 (0–37)	–	<0.001
Family history of AITD (%)	20.0%	40.0%	22.5%	25%	0.138
Smoking (%)	0%	12.7%	8.5%	5%	0.021
Total T3 (61–177 ng/dL)#	89 ± 26	235 ± 144	97 ± 40	86 ± 12	<0.001
Free T4 (0.93–1.70 ng/dL)#	1.14 ± 0.81	2.86 ± 2.11	1.09 ± 0.39	1.31 ± 0.21	< 0.001
TSH (0.27–4.20 μIU/mL)*,#	6.10 (0.00–100.00)	0.01 (0.00–19.50)	5.07 (2.24–116.70)	2.14 (00.0.44–3.20)	< 0.001
Total IgG (mg/dL)	1447 ± 196	1299 ± 327	1441 ± 320	1254 ± 430	0.143
Serum IgG4 (mg/dL)*					
– Mean value (±SD)	57 ± 32	58 ± 44	54 ± 60	72 ± 44	
– Median value (range)	60 (2–122)	39 (6–173)	40 (8–371)	49 (2–216)	0.589
Anti-TPO (0–34 IU/mL)*	512 (0–600)	152 (0–600)	263 (0–600)	0	0.321
Anti-Tg (0–115 IU/mL)*	220 (0–1191)	175 (0–1942)	88 (0–1130)	0	0.466
Elevated serum IgG4 (%)	0%	5.0%	2.5%	2.5%	0.331

* Data were expressed in median (range).
\# Thyroid function test at the time of recruitment.

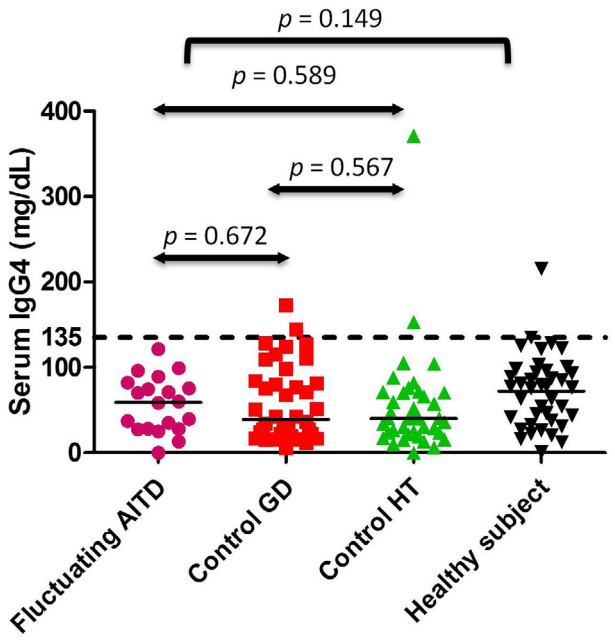

Fig. 1. Comparison of serum IgG4 levels between fluctuating AITD patients and control groups (GD and HT patients) and healthy subjects. Elevated serum IgG4 levels were not statistically significant between each group.

ted with medications [16]. Despite some patients remaining euthyroid for a long period after treatment, spontaneous hypothyroidism could develop in 5–20% of patients [2]. As a result, lifetime follow-up is indicated for all patients with Graves' disease.

In the early 2000s, Hamano et al. [17] found that there was an elevation in serum immunoglobulin G, subclass 4 (IgG4) concentrations, a minor component of immunoglobulin G (IgG) subclasses, in patients with "sclerosing pancreatitis" and recognized the novel entity of 'autoimmune pancreatitis (AIP)'. Hypothyroidism has been reported as a complication of autoimmune pancreatitis [18] and similar histopathological features have been noted with the fibrosing variant of Hashimoto Thyroiditis [19]. Recently, Li et al. reported that immunostaining of IgG4 can help to subclassify IgG4-related thyroiditis and non-IgG4-related thyroiditis, the former of which may have a close relationship with IgG4-RSD [20]. As a result of this, a proposed classification of patients with Hashimoto's thyroiditis as having IgG4 thyroiditis and non-IgG4 thyroiditis, based on the immunostaining of IgG4. IgG4 thyroiditis subgroup of Hashimoto's thyroiditis is characterized by an abundance of IgG4-positive plasma cells and fibrosis in the thyroid tissue, lower female/male ratio, higher percentage of diffuse low echogenicity at ultrasonography, more rapid clinical progression, and higher serum levels of IgG4 and thyroid autoantibodies [21].

It should be noted that IgG4 is a unique antibody that does not have an ability to bind to C1q complement and therefore is unable to activate the classical complement pathway [22]. Theoretically, IgG4 has low affinity for the target antigen and should not be involved in the pathogenesis of autoimmune disorders. The lack of effector function of IgG4 and the phenomenon of half-antibody exchange (IgG4 is a dynamic molecule that exchange Fab arms by swapping a heavy chain and attached light chain with a heavy-light chain pair from another molecule) have raised many questions as to whether this subtype antibody is pathogenic or alternatively, mediate a counter-regulatory response to an ongoing immunologic disease [23]. However, serum IgG4 concentrations were found to be over 10-fold higher in patients with autoimmune pancreatitis (AIP).

The role of elevated serum IgG4 concentrations for the diagnosis of AIP had been evaluated worldwide, with varying sensitivity ranging from 50% to 92% and specificity of over 90% [24–25]. Therefore, serum IgG4 concentration is considered as a reliable marker for the diagnosis of AIP and hence included in the diagnostic criteria of IgG4-RSD. Serum IgG4 levels range from less than 10 mg/dL to 140 mg/dL, with levels over 200 mg/dL noted in a few individuals [26]. IgG4 accounts for 3–6% of the total IgG and does not vary with sex or age. Moreover, the amount of IgG4 and the ratio of IgG4/total IgG (less than 8%) tends to remain constant throughout a lifespan [8]. Elevated serum IgG4 could be found in about 5% of healthy individuals, 10% of patients with pancreatobiliary malignancy and other inflammatory disorders [26].

Recently, Japanese researchers also showed that elevated serum IgG4 concentrations (serum IgG4 concentrations $\geq$ 135 mg/dL) had been found in 7/109 (6.4%) of Graves' disease patients [7]. Among the patients with high serum IgG4 levels, the elevations were successfully controlled with a small dosage of anti-thyroidal medication, and these patients were prone to develop spontaneous hypothyroidism after withdrawal of medications. This subset of patients were significantly older than the patients without elevated levels (mean ages 54.7 and 43.4 years, respectively) which was different from studies on Hashimoto's thyroiditis, in which patients with elevated IgG4 were younger than those with non-

elevated serum IgG4 levels. Therefore, the utility of serum IgG4 as a simple tool to differentiate the unique subtype of AITD holds great promise for re-classification the new entity in spectrum of AITD. However, in the present study, we found that there was a substantial overlap of serum IgG4 levels between fluctuating AITD patients and control groups. This finding challenges the role of serum IgG4 as a biomarker to identify the clinical course of AITD patients. Nevertheless, these results also provided further evidence that autoimmune thyroiditis is a heterogeneous disease and suggested that a significant percentage of patients with Graves' disease and Hashimoto's thyroiditis showed elevated serum IgG4 levels. The difference in ages of fluctuating AITD patients with Graves' disease might be occurred by chance because the clinical metamorphosis of AITD in our present study and other reports revealed considerably interval period before transformation in each patient. It is unknown if the elevated blood levels of IgG4 still remained unknown whether it is a consequence of increased numbers of IgG4-positive plasma cells in the tissues or the cause of disease. Based on our data, none of the factors including age, sex, duration of AITD, smoking status, the presence of ophthalmopathy, and thyroid auto-antibodies have any association with the elevated serum IgG4 levels. This was different from previous studies which reported that elevated serum IgG4 were positively correlated with the titers of thyroid auto- antibodies [27–28]. It should be also noted from current study that the presence or absence of ophthalmopathy did not affect the levels of serum IgG4 which our findings were contrast with Bozkirli et al. [29] which found the positive correlation between serum IgG4 and severity of Graves' ophthalmopathy. The diagnostic utility of serum IgG4 levels in IgG4-RSD had also been questioned in the recent studies [30–31], a cutoff value of serum IgG4 ranging from 135 to 144 mg/dl modestly diagnosed IgG4-RSD and analysis of the serum IgG4/total IgG ratio did not improve the diagnostic utility.

From our perspective, elevated serum IgG4 levels seem to reflect the duration of the immune responses or non-specific findings rather than separate forms of autoimmune thyroid disease and did not help to identify subset of patients who had fluctuating thyroid function tests. We acknowledged that there are several limitations in our study. First, this is an observational study with cross-sectional design with a limited number of patients, therefore, we cannot rule out the presence of other possible confounding variables such as duration of the disease, the timing of serum IgG4 measurements in relation to disease activity and treatment, iodine status, etc. that might affect our serum IgG4 results. Serial monitoring of biomarkers is likely to reduce confounding "noise" and establish a temporal trend that may be more informative for prognosis. Secondly, our index fluctuating AITD cases did not have serial measurements of stimulating and blocking thyroid antibodies to correlate with thyroid function status and serum IgG4 results. However, it is likely that the alternating thyroid function was associated with an alternating pattern of antibodies from previous case reports which might not contribute more novel data in our study. In addition, bioassays of subtypes of TRAbs are very difficult to perform and these auto-antibodies are usually used in studies investigating the developmental mechanism of clinical evolution of AITD rather than clinical utility as a biomarker. Thirdly, the ultrasonographic findings to document echogenic area and precise estimation of thyroid gland size could not be obtained in most cases. Finally, questions have been raised whether the circulating IgG4 levels reflect tissue levels. Immuno-histochemistry staining studies of IgG4 should be done in patients who underwent thyroidectomy in order to verify the existence of IgG4-RSD in fluctuating AITD patients.

In conclusion, fluctuating AITD is a unique group of patients which one type of AITD transform into the opposite form of AITD within the same individual over time. Phenotypes probably differ because of the specific type of immunological response that occurs. We observed the shifting process from GD to HT took almost a decade in our cohort, therefore, a lifetime follow-up is required for all patients with Graves' disease. To the best of our knowledge, our study is the first study reporting that the measurement of serum IgG4 in these interesting group of AITD patients. In the present study, the rate of elevated serum IgG4 levels which had been proposed to be a marker to identify subset of AITD patients did not differ from control groups of AITD patients. These results suggested that serum IgG4 may be not as useful in predicting the development of clinical evolution of AITD patients once it is established and serum IgG4 levels might have incorrectly become a 'surrogate' marker for AITD patients. Further work is needed to confirm these findings and studies on biopsies in fluctuating AITD may help to give a better understanding in the nature of the IgG4 in AITD patients.

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Conflict of interest

No potential conflicts of interest relevant to this article have been reported.

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