

The Serological and Biochemical Markers of Adrenal Cortex and Endocrine Pancreas Dysfunction in Patients with Hashimoto's Thyroiditis: A Hospital-based Pilot Study

Jaya Prakash Sahoo, Jayakumar Selviambigapathy, Sadishkumar Kamalanathan, V. S. Negi¹, M. G. Sridhar², Sitanshu Sekhar Kar³, Muthupillai Vivekanandan

Departments of Endocrinology and Metabolism, ¹Clinical Immunology, ²Biochemistry and ³Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Abstract

Background: The prevalence of both islet cell and adrenal autoimmunity among Asian Indian hypothyroidism patients with Hashimoto's thyroiditis (HT) is lacking in literature. **Objectives:** The objective of this study was to assess the proportion of Addison's disease (AD) and type 1 diabetes mellitus (T1DM) in patients with HT. **Materials and Methods:** The patients with hypothyroidism due to HT were included in this study over 2 years. Primary hypothyroidism was defined as high serum thyroid-stimulating hormone (>5.5 mIU/L) with or without low thyroxine level. HT was defined by the presence of high thyroid peroxidase antibody (Ab) titer (>35 IU/ml). Autoimmune markers of AD and T1DM, i.e., adrenal (21-hydroxylase) Ab, glutamic acid decarboxylase (GAD) Ab, and insulinoma-associated antigen-2 (IA-2) Ab were measured among them. In addition, 250 µg adrenocorticotropic hormone (ACTH) stimulation test was done in patients with adrenal Ab. Similarly, beta cell function was assessed in patients with GAD and/or IA-2 Ab. **Results:** Out of 150 patients screened, 136 patients were included in this study. Seven patients had adrenal Ab while 15 had IA-2 Ab. The GAD Ab was not present in any of the patients in the study. ACTH stimulation test was done in four of seven patients with adrenal Ab and beta cell function was assessed in 8 of 15 patients with islet cell Ab. All patients with adrenal Ab had normal adrenal function and 1 out of 15 with IA-2 Ab developed diabetes mellitus during follow-up. **Conclusions:** Either adrenal or islet cell Ab was found in 16% Asian Indian hypothyroidism patients with HT.

Keywords: Addison's disease, diabetes, hypothyroidism, thyroid

INTRODUCTION

Hashimoto's thyroiditis (HT) is a common autoimmune disorder with the prevalence of 5% to 10% in general population.^[1] It is responsible for most of the hypothyroidism cases in iodine sufficient areas. It may be the part of an autoimmune polyglandular syndrome, which includes multiple endocrine organ-specific autoimmune diseases such as Addison's disease (AD) and type 1 diabetes mellitus (T1DM). These diseases are diagnosed by detection of their respective antibody (Ab) in blood: Thyroid peroxidase (TPO) Ab in HT, adrenal (21-hydroxylase) Ab in AD, and glutamic acid decarboxylase (GAD)/insulinoma-associated antigen-2 (IA-2) Ab in T1DM. Biochemically, AD is associated with low serum cortisol (basal and/or post-adrenocorticotropic hormone [ACTH] stimulation). Similarly, hyperglycemia is seen in diabetes patients. The clinical features of these

associated autoimmune disorders may be indistinguishable from that of hypothyroidism due to HT. Sometimes, missing the diseases such as AD and T1DM may have adverse consequences in these patients. Limited experience is available in the literature which shows the prevalence of AD and T1DM together in up to 20% of patients with HT.^[2,3] Therefore, various guidelines recommend that preclinical screening for Ab should be performed in patients with autoimmune thyroid diseases such as HT.^[4] The clustering of other organ-specific autoimmunity also depends on the type of autoimmune thyroid disorder (HT vs. Graves' disease).^[2]

Address for correspondence: Dr. Jaya Prakash Sahoo,
House No. 28, Lane-B, VVP Nagar, Puducherry - 605 009, India.
E-mail: jppgi@yahoo.com

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Most of the studies assessed the beta cell autoimmunity by measuring only GAD Ab except few, where both GAD and IA-2 Ab were estimated.^[5-11] The presence of Ab against beta cells in HT patients put them at the risk of development of latent autoimmune diabetes in adults (LADA) in the future. The sensitivity of IA-2 Ab is better than GAD Ab for the diagnosis of LADA in some ethnicities.^[12-14] Hence, the findings of earlier studies would have underestimated the prevalence of beta cell autoimmunity in adult patients with HT. This study was planned to find the prevalence of both islet cell (GAD and IA-2) and adrenal (21-hydroxylase) Ab among hypothyroidism patients with HT in an Asian Indian population.

MATERIALS AND METHODS

The study was done in the Endocrinology Department of a tertiary care institute in South India over 2 years (from January 2014 to December 2015) after getting approval from the Institutional Ethics Committee. This was a pilot study involving screening of 150 primary hypothyroid patients with HT aged between 18 and 45 years. Only 136 patients were finally included after obtaining their informed consent [Figure 1]. Primary hypothyroidism was defined as a high serum thyroid-stimulating hormone (TSH) (>5.5 mIU/L) with or without low serum free T4 level. HT was defined as patients having high TPO Ab titer (>35 IU/ml). The exclusion criteria were hypothyroidism of other etiology, glucocorticoid therapy during the last 2 months, pregnancy, lactation, oral contraceptive use, chronic kidney disease, chronic liver disease, chronic infection, and malignancy.

Detailed clinical examination including anthropometry was done in all patients. Body weight was measured using the electronic scale to the nearest 0.1 kg. A wall-mounted stadiometer was used to measure standing height to the nearest 0.1 cm. The body mass index was calculated as weight/height² (kg/m²). Waist circumference was measured

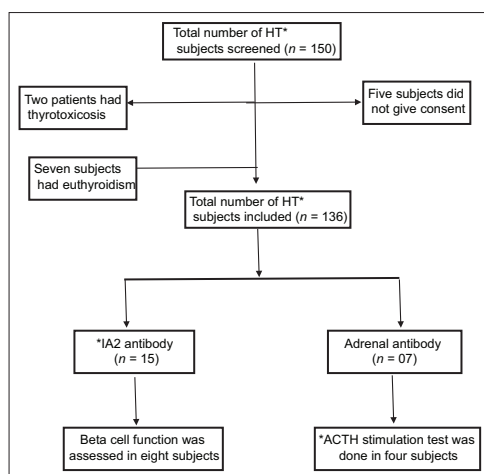


Figure 1: The diagram showing the design of the study. *HT: Hashimoto's thyroiditis, IA-2: Insulinoma associated antigen-2, ACTH: Adrenocorticotrophic hormone

at the midpoint of the inferior costal margin and the superior border of the iliac crest on the midaxillary line level at the end of expiration. It was measured using a flexible plastic tape with a graduated scale to the nearest 0.1 cm. Blood pressure measurements were taken according to the Joint National Committee VII recommendations.^[15]

The venous blood sample was collected between 8:00 and 10:00 h after overnight fasting. The samples were quickly centrifuged at 4000 rpm for 5 min to separate the serum, which was stored at -80°C till assay of Ab (21-hydroxylase, GAD, and IA-2). In addition, serum cortisol was collected at 0 min (8 am), 30 min, and 60 min following intramuscular injection of 250 μg ACTH in patients with adrenal Ab.^[16] Adrenal insufficiency (AI) was defined as either low basal cortisol <83 nmol/L and/or poststimulation serum cortisol <497 nmol/L.^[17] The insulin sensitivity and beta cell function were calculated from plasma glucose and insulin values (0, 30, 60, and 120 min) during oral glucose tolerance test (OGTT) with 75-g anhydrous glucose. The whole-body insulin sensitivity was measured by the Matsuda Index (MI) ($n > 2.50$).^[18,19] The beta cell function in patients with GAD and/or IA-2 Ab. was assessed with homeostasis model assessment beta (HOMA-B) ($n > 100\%$), insulinogenic index (IGI) ($n > 0.4$), and oral disposition index (oDI) ($n > 1$).^[19,20] IGI was defined by Δ insulin (I_{30-0} mIU/L)/ Δ glucose (G_{30-0} mg/dl), which is a surrogate measure of the acute insulin response. oDI is the product of the MI and IGI obtained during the OGTT.

Thyroid function tests, serum cortisol, and insulin were measured using ADVIA Centaur XP Immunoassay System, Siemens Healthcare Global, USA. The reference values for the normal TSH, free T4, and TPO-Ab in our laboratory are 0.35–5.5 mIU/L, 11.12–22 pmol/L, and <35 IU/ml, respectively. Both 21-hydroxylase and GAD Ab were estimated by qualitative enzyme-linked immunosorbent assay (ELISA) kits (Cusabio Biotechnology Company, Hubei, China). The positive cutoff values of 21-hydroxylase and GAD Ab were taken as 0.25 and 0.105, respectively. Both the intra- and inter-assay coefficient of variation (CV) for 21-hydroxylase Ab were <15%. The intra- and inter-assay CV for GAD Ab were <15% and <20%, respectively. The IA-2 Ab was measured by quantitative ELISA kits (NovaTec Immundiagnostica GmbH, Dietzenbach, Germany). The sensitivity of this kit was 0.37 IU/ml and Ab titer >7.5 IU/ml was considered as positive. The intra-assay CV was <4.6% and the inter-assay CV was <4.5%.

The statistical analysis was done using SPSS version 16 (IBM company, Chicago, IL, USA). Kolmogorov–Smirnov test was used to verify the data distribution. The continuous variables with normal distribution were expressed as the mean with standard deviation, and the variables without normal distribution were presented as the median with interquartile range. Mann–Whitney *U*-test and Student's *t*-test were used to find the difference in continuous variables. The $P < 0.05$ was considered statistically significant.

RESULTS

Out of 136 patients, 130 were females. The mean age was 33 years, and the median duration of hypothyroidism was 12 months [Table 1]. The median serum TSH was 29.2 mIU/L. Seven (5%) patients had adrenal Ab, and 15 (11%) had IA-2 Ab. However, none of these patients was symptomatic for either AI or diabetes mellitus (DM). None had both adrenal and IA-2 Ab. The GAD Ab was not present in any of the study patients. Those with IA-2 Ab had the higher titer of other two Ab compared to those with negative serology [Table 2].

ACTH stimulation test was done in four of seven patients with adrenal Ab [Figure 1]. All four patients had basal cortisol >83 nmol/L and stimulated serum cortisol >497 nmol/L ruling out AI. The whole-body insulin sensitivity and beta cell function were assessed in 8 of 15 patients with islet cell Ab [Figure 1]. The median MI was 2.30 (1.66–2.59). All of them had HOMA-B >100% except one. The beta cell function of that particular patient was low (HOMA-B - 60%) as his whole-body insulin sensitivity was very high (MI - 7.44). However, all of

them had normal acute insulin response during first 30 min of OGTT, for example, IGI: 0.83–6.28 and oDI: 2.59–7.88. One patient with IA-2 Ab developed DM during follow-up.

DISCUSSION

Eleven percentage of HT patients had either GAD and/or IA-2 Ab in our study in contrast to the prevalence of 3.6%–8% in the literature.^[10,11] IA-2 Ab was present in 3 (0.6%) patients among 441 nondiabetic HT patients in a study by Lethagen *et al.*^[10] Two of the three patients with IA-2 Ab also had GAD Ab, and one of them developed DM during follow-up. IA-2 Ab was detected in 8 (3.39%) out of 236 HT patients in a study by Pilia *et al.*^[11] One of them had also GAD Ab who developed DM during 2-year follow-up. The patients with IA-2 Ab also had a higher titer of other two Ab compared to those with negative serology in this study. Epitope spreading could be one of the possible mechanisms for this occurrence. A self-directed immune response induced by a single epitope could spread to include other epitopes on other self-molecules.^[21] Our study patients with Ab may have autoimmune susceptible human leukocyte antigen (HLA) and non-HLA alleles, for example, cytotoxic T-lymphocyte-associated protein 4 which led to the development of Ab to multiple endocrine organs.^[5] However, this aspect was not evaluated in our study.

The prevalence of GAD Ab among HT patients varied from 0% to 13.8% in different studies.^[5-11] The GAD Ab was present in 3.4% (15/441) of nondiabetic HT patients compared to 1.1% prevalence among Swedish adult population in a study by Lethagen *et al.*^[10] The GAD Ab was associated with a decreased insulin secretion capacity, and two of them developed DM during follow-up. However, another study among nondiabetic HT patients by Aksoy *et al.*^[8] did not show the association between the GAD Ab and decreased beta cell function. However, one out of 11 patients with GAD Ab developed DM in their study. Eleven out of 320 (3.4%) HT patients had GAD Ab in the study by Moriguchi *et al.*^[5] The prevalence of GAD Ab positivity was slightly, but not significantly, higher than

Table 1: Demographics, anthropometry, and biochemical profiles of all subjects

Parameters	Total (n=136)
Age (years)*	33 (11.1)
Duration of hypothyroidism (months)	12 (4–24)
Body weight (kg)*	54.1 (12.4)
BMI (kg/m ²)*	22.8 (4.8)
Waist circumference (cm)*	79.1 (10.9)
Systolic blood pressure (mmHg)*	112.5 (15.8)
Diastolic blood pressure (mmHg)*	75.8 (9.7)
Serum thyroid-stimulating hormone (mIU/L)	29.2 (10.4-109)
Glutamic acid decarboxylase Ab	0.005 (0.001-0.009)
IA2 Ab (IU/mL)	0.066 (0-2.424)
Adrenal Ab	0.073 (0.04-0.108)

*Parameters were presented as mean with standard deviation and others were expressed as median with IQR. BMI: Body mass index, IQR: Interquartile range, IA2: Insulinoma-associated antigen-2, Ab: Antibody

Table 2: Comparison between patients with positive insulinoma-associated antigen-2 antibodies and patients without any antibody

Parameters	Patients with positive IA2 Ab (n=15)	Patients without any Ab (n=114)	P
Age (years)*	34.4 (14.2)	32.8 (10.7)	0.613
Duration of hypothyroidism (months)	15 (3-36)	12 (4-24)	0.920
Body weight (kg)*	52.7 (9.2)	54.2 (12.8)	0.649
BMI (kg/m ²)*	22.4 (3.9)	22.8 (4.9)	0.725
Waist circumference (cm)*	78.7 (9.5)	79.1 (11.1)	0.915
Systolic blood pressure (mmHg)*	111.3 (13.6)	112.6 (16.1)	0.771
Diastolic blood pressure (mmHg)*	75.3 (8.3)	75.8 (9.9)	0.861
Serum thyroid-stimulating hormone (mIU/L)	98 (8.2-150)	26.9 (10.5-100)	0.334
Glutamic acid decarboxylase Ab	0.008 (0.005-0.012)	0.004 (0.001-0.008)	0.023
IA2 Ab (IU/mL)	11.9 (10.5-13.2)	0.066 (0-0.352)	<0.0001
Adrenal Ab	0.103 (0.073-0.171)	0.071 (0.035-0.099)	0.003

*Parameters were presented as mean with standard deviation and others were expressed as median with IQR. Ab: Antibody, IA2: Insulinoma-associated antigen-2, BMI: Body mass index, IQR: Interquartile range

that in healthy control patients (3.4% vs. 2.1%). Similar result was found in a study involving 236 Sardinian children and adolescents with HT.^[11] GAD Ab was detectable in 12 (5.09%) patients with HT and in 36 (4.11%, $P = \text{NS}$) control patients, while IA-2 Ab was detected in eight patients with HT (3.39%) and in 11 control patients (1.16%, $P = 0.012$). However, none of 47 HT patients had GAD Ab in a study by Silva *et al.* similar to our findings.^[9] These different prevalence rates can be attributed to the differences in study design, patient characteristics, and sensitivity of the assays used for Ab measurements.

Although 11% of patients had IA-2 Ab, none had GAD Ab in our study. This is similar to the Ab profile of LADA patients from India reported by Kanungo and Sanjeevi.^[12] The above study compared the frequency of GAD and IA-2 Ab among 120 healthy controls and 214 type 2 DM patients. The positivity of GAD Ab was not significantly different between patients and controls (7% vs. 4%). However, IA-2 Ab was predominant in LADA patients compared to controls (36% vs. 2%). All of our patients except one with IA-2 Ab had euglycemia due to adequate beta cell function. These patients may later present as LADA due to progressive destruction of beta cell mass. The positive predictive value (PPV) and sensitivity of IA-2 Ab for the future development of DM (median follow-up, 9.1 years) were 55% and 69%, respectively, in a study by Kulmala *et al.*^[22]

The prevalence of adrenal Ab among HT patients varied from 2% to 5.7% in different studies.^[2,9,23,24] Ten patients had adrenal Ab in a cohort of 200 HT patients as reported by Scherbaum *et al.*^[24] Six patients with adrenal Ab had normal adrenal function and four had AI. Out of 47 patients with HT, only one had 21-hydroxylase Ab in a study by Silva *et al.*^[9] That patient had normal basal cortisol and normal cortisol response after ACTH stimulation but high plasma renin activity suggestive of subclinical AI. The overt AD was developed in five patients and subclinical hypoadrenalism in seven patients, while 24 maintained normal adrenal functions in 50-month follow-up study of 36 patients with adrenal Ab.^[25] The shortest period for progression from normal adrenal function to clinical disease was 23 months in that study. It was concluded that high levels of 21-hydroxylase Ab, initial impaired adrenal function, and HLA-DR3 status were associated with the highest progression toward clinical AD. Overall, the PPV of adrenal Ab for the future development of AI is 70%.^[26] Hence, our patients with adrenal Ab need longer follow-up to detect AI at the earliest.

To the best of our knowledge, this is the first study evaluating the biochemical and autoimmune markers of AD and T1DM in Asian Indian hypothyroidism patients with HT. However, there were few limitations in this study. The sample size was small and healthy controls were not included in the study. The evaluation for the functional reserve of endocrine organs was not done in all patients with Ab.

CONCLUSIONS

Either adrenal or islet cell Ab was found in 16% hypothyroidism patients with HT. These patients with different endocrine

organ-specific Ab need long-term follow-up to look for the future development of DM or AI.

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Conflicts of interest

There are no conflicts of interest.

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