

Anti-thyroid antibodies, parietal cell antibodies and tissue transglutaminase antibodies in patients with autoimmune thyroid disease

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Abstract

Introduction: The co-existence of tissue-specific autoantibodies in autoimmune thyroid disease (ATD) is well established. The published prevalence of anti-parietal cell antibodies (PC-Ab) is 20–25%, and that of celiac antibodies is 2–5%. The goal of this study was to determine the prevalence of PC-Ab and anti-tissue transglutaminase antibodies (tTG-Ab) in patients with ATD and to evaluate the correlation between anti-thyroid antibodies and the other antibodies.

Material and methods: The files of 120 Israeli Jews and Arabs with ATD were evaluated for anti-thyroglobulin antibodies (Tg-Ab), anti-thyroid peroxidase antibodies (TPO-Ab), PC-Ab and tTG-Ab. For patients with positive PC-Ab and/or tTG-Ab, upper gastrointestinal (GI) endoscopy results were recorded. Gastrin levels were collected in patients with positive PC-Ab.

Results: Twelve (10%) males and 108 (90%) females were evaluated, of whom 93.33% had Hashimoto's thyroiditis. Thirty-four (28.3%) subjects had positive PC-Ab. This rate was not affected by gender, ethnicity or thyroid disease. Abnormal gastroscopy findings were documented in 95.2% of the upper GI endoscopies. The mean gastrin level in this subgroup was 660.4 pg/ml. Five of 114 tTG-Ab tests were positive (4.4%). All were females with Hashimoto's thyroiditis. Rates were equal among Jews and Arabs. Higher TPO-Ab levels were associated with higher risk for PC-Ab positivity ($p = 0.027$), but not tTG-positivity. Higher Tg-Ab levels were not associated with higher levels of other antibodies.

Conclusions: Considering the frequency of PC-Ab and tTG-Ab positivity in ATD, checking for the presence of these two entities should be an integral part of the workup of this disease.

Key words: autoimmune thyroid disease, anti-thyroid antibodies, parietal cell antibodies, celiac disease.

Introduction

The association of autoimmune thyroid disease (ATD) with other autoimmune disorders is well established.

Autoimmune thyroid disease and autoimmune gastritis

Anti-parietal cell antibodies (PC-Ab) are associated with the development of autoimmune gastritis, usually limited to the fundus and body of the stomach [1]. The presence of PC-Ab in patients with ATD predicts the development of autoimmune gastritis [2] and correlates with biopsy-proven fundal gastritis [3]. Autoimmune gastritis can lead to vitamin B₁₂ deficiency, iron deficiency anemia and, in rare cases, type I gastric neuroendocrine tumors [1, 4]. The prevalence of PC-Ab in patients with ATD is 20–29% [2, 5, 6], and 28% have vitamin B₁₂ deficiency [7]. The prevalence of PC-Ab in subjects with ATD in Israel is unknown.

Autoimmune thyroid disease and celiac disease

The classic malabsorption syndrome presentation of celiac disease is not common in the adult population. Adult celiac disease usually presents with mild gastrointestinal symptoms, anemia or osteoporosis. Prompt treatment is associated with symptomatic improvement, reduced risk of malignancy and lower mortality rate [8]. Tissue transglutaminase (tTG) is a calcium-dependent enzyme that plays a crucial role in celiac disease pathogenesis. During gluten consumption anti-tissue transglutaminase antibodies (tTG-Ab) are produced by the mucosa of the small intestine. Immunoglobulin A (IgA) tTG-Ab has high sensitivity and specificity for the detection of celiac disease in adults [9]. The prevalence of celiac antibodies in patients with ATD is 2–5% [10, 11]: much higher than the estimated prevalence in the general population, which is 0.3–1.4% in most countries [12]. The prevalence of tTG-Ab in patients with ATD in Israel is unknown.

The aim of this study was to determine the prevalence of PC-Ab and tTG-Ab in patients with ATD in a heterogeneous urban population in Israel and to identify the correlation between anti-thyroid antibody levels and the other antibodies tested.

Material and methods

Patients and methods

The files of 120 consecutive patients with ATD from a community endocrinology clinic were reviewed. These patients were diagnosed with either Hashimoto's thyroiditis or Graves' disease. Data collected included anti-thyroglobulin antibodies (Tg-Ab), anti-thyroid peroxidase antibodies (TPO-Ab), PC-Ab and tTG-Ab. For patients with positive PC-Ab and/or tTG-Ab, results of upper gastrointestinal (GI) endoscopy were recorded. Gastrin levels were collected in patients with positive PC-Ab.

Anti-thyroid peroxidase antibodies and Tg-Ab were measured using a solid phase, enzyme-labeled, chemiluminescent sequential immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Inc., UK). TPO-Ab and Tg-Ab levels were expressed in IU/ml. IgA tTG-Ab were measured by multiplex flow immunoassay (Bioplex 2200, Bio-Rad Laboratories, Inc.). Anti-tissue transglutaminase antibodies levels were measured in U/ml, and expressed by positivity. PC-Ab were measured by immunofluorescence antibody assay. Gastrin levels were measured by a chemiluminescent, enzyme-labeled immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Inc., UK). The normal reference range for serum gastrin is 13–115 pg/ml.

Ethical consideration

This study was approved by the local institution review board. Informed consent was not required.

Statistical analysis

A binary logistic regression model was used to estimate the association between positive PC-Ab and demographic data in multivariate analyses. Interaction terms for statistically significant effect modifiers were added to the multivariate model when appropriate.

T-test for equality of means was used for comparison of the means of TPO-Ab and Tg-Ab titers. Statistical analysis was performed using SPSS software, version 20.

Results

Patient population

A total of 120 patients at a mean age of 50.4 ± 16.1 years (range: 15–79 years) were included in the study. Twelve (10%) males and 108 (90%) females were evaluated; 112 (93.3%) had Hashimoto's thyroiditis and the other 8 (6.7%) had Graves' disease. Twenty-four (20%) patients were Arabs and 96 (80%) were Jews.

Incidence of positive PC-Ab in different groups

Thirty-four (28.3%) subjects had positive PC-Ab. The rate of positive PC-Ab was associated with older age (54.8 vs. 48.5, $p < 0.05$), but not with gender (33.3% in males vs. 28.7% in females, $p > 0.05$), ethnicity (30.2% in Jews vs. 25% in Arabs, $p > 0.05$) or thyroid disease (29.4% in Hashimoto's thyroiditis vs. 25% in Graves' disease, $p > 0.05$).

Results of GI endoscopy

Twenty-six of the PC-Ab positive patients underwent an upper GI endoscopy, with abnormal

results in all but 1 (95.5%). Atrophic gastritis was documented in 19 (73.1%) patients. Six (23.1%) patients presented with intestinal metaplasia in addition to the atrophy, and 1 (3.8%) had gastric neuroendocrine tumor type I on a background of atrophic gastritis. Six (23.1%) patients were diagnosed with non-specific gastritis.

Serum gastrin levels

Gastrin serum levels were measured in 23 of the 34 patients with positive PC-Ab. Hypergastrinemia was documented in 18 (78.3%). Mean gastrin level in this subgroup was 688.7 pg/ml, ranging from 38 to 2800 pg/ml (normal reference values: 13–115 pg/ml). Gastrin levels above 1000 pg/ml were observed in 6 (26.1%) patients.

Incidence of positive tTG-Ab in different groups

Five of 114 tTG-Ab tests were positive (4.2%). All were females with Hashimoto's thyroiditis. Rates were equal among Jews and Arabs. One patient, a 61-year-old woman, was both PC-Ab and tTG-Ab positive.

Relationship between thyroid antibodies, PC-Ab and tTG-AB

The TPO-Ab level was significantly higher in patients with positive PC-Ab compared to those without positive PC-Ab (967 ±1371 vs. 600.2 ±373 respectively, $p = 0.027$). Tg-Ab levels were similar in patients with or without PC-Ab (Table I). Anti-thyroid antibody levels were not associated with positive tTG-Ab (Table II).

Discussion

The association of ATD with other autoimmune disorders is well established and is clinical-

ly significant. However, routine measurement of PC-Ab and tTG-Ab is still not included in the clinical guidelines for evaluation and treatment of patients with ATD [13, 14].

ATD and autoimmune gastritis

This study demonstrates a 28.3% prevalence of PC-Ab in subjects with ATD, which is compatible with the published prevalence of 20–29% [2, 5, 6]. PC-Ab positivity is predictive of pathologic disturbances in gastric mucosa. PC-Ab predicted the development of chronic atrophic gastritis in a 5-year, prospective study of 208 adults with ATD [2]. In our series, 95.5% of the patients with positive PC-Ab who underwent an upper GI endoscopy had abnormal results. Atrophic gastritis was the major finding, documented in 73.1% of the endoscopies. A subgroup of 23.1% presented with intestinal metaplasia in addition to the atrophy, and 1 (3.8%) patient presented with gastric NET type I. The other abnormal pathology results (23.1%) were consistent with non-specific gastritis.

The loss of HCl-secreting cells in the stomach secondary to the autoimmune process results in hypergastrinemia. Hypergastrinemia was documented in the majority of subjects with positive PC-Ab (78.3%). Gastrin level was extremely elevated in some of these patients, measuring as high as 2800 pg/ml (normal reference values: 13–115 pg/ml). Six of the 23 gastrin measurements were above 1000 pg/ml, a level compatible with gastrin-secreting tumor (Zollinger-Ellison syndrome). Clinical judgment and other confirmatory procedures are necessary to differentiate between gastrin-secreting tumor and hypergastrinemia secondary to autoimmune gastritis [15].

Hypergastrinemia stimulates enterochromaffin cell hyperplasia in the gastric mucosa in ATD patients, which can develop into type I gastric NET [4, 16]. Although type I gastric NET is considered

Table I. Association between anti-thyroid auto-antibody levels and positive PC-Ab

PC-Ab	TPO-Ab level, ± SD [IU/ml]	Tg-Ab level, ±SD [IU/ml]
Positive	967.06 ±1371.97 (n = 33)	355.57 ±767.06 (n = 30)
Negative	600.24 ±373.80 (n = 82)	552.2 ±1032.34 (n = 83)
P-value (t-test for equality of means)	0.027	0.343

PC-Ab – anti-parietal cell antibodies, TPO-Ab – anti-thyroid peroxidase antibodies, Tg-Ab – anti-thyroglobulin antibodies.

Table II. Association between anti-thyroid auto-antibody levels and positive tTG-Ab

tTG-Ab	TPO Ab level, ±SD [IU/ml]	Tg-Ab level, ±SD [IU/ml]
Positive	463.50 ±353.77 (n = 4)	785.5 ±1476.84 (n = 4)
Negative	646.1 ±375.02 (n = 106)	501.54 ±971.64 (n = 104)
P-value (t-test for equality of means)	0.340	0.574

tTG-Ab – anti-tissue transglutaminase IgA antibodies, TPO-Ab – anti-thyroid peroxidase antibodies.

a benign lesion, recent data suggest that up to 8% metastasize to local lymph nodes and even to the liver [17].

Nevertheless, PC-Ab are predictors of autoimmune gastritis, as well as predictive markers of subsequent metabolic and hematologic manifestations. Autoimmune atrophic gastritis may manifest as vitamin B₁₂ deficiency, pernicious anemia or iron deficiency anemia. Vitamin B₁₂ deficiency was detected in 28% of subjects with ATD [7] and was defined as the causative agent for anemia in 10% of subjects with hypothyroidism [18]. In addition to the aforementioned effects of autoimmune gastritis, PC-Ab positivity is associated with increased L-thyroxine requirements in hypothyroid subjects [19].

ATD and celiac disease

In this cohort, 4.2% of the subjects with ATD showed tTG-Ab positivity. This rate is compatible with that published in the literature [10, 11] and is much higher than the estimated prevalence in the general population, which is 0.3–1.4% in most countries [12]. Immunoglobulin A (IgA) tTG-Ab has high specificity and sensitivity for detection of celiac disease in adults and its level correlates closely with disease activity [20]. Early recognition of celiac disease enables prompt treatment with a gluten-free diet, which is associated with symptomatic improvement, reduced malignancy risk and a reduced mortality rate [11].

The study population included Arabs (20%) and Jews (80%). The rates of PC-Ab positivity and tTG-Ab positivity in these ethnic groups were similar.

Anti-thyroid antibodies, PC-Ab and tTG-Ab

Another interesting finding was the relation between anti-thyroid Ab levels, PC-Ab and tTG-Ab. The TPO-Ab level was significantly higher in patients with positive PC-Ab, but not in those with positive tTG-Ab. Tg-Ab level was not associated with higher levels of other antibodies. Interestingly, the TPO-Ab/Tg-Ab ratio in PC-Ab positive patients was 2.71, while the ratio in tTG-Ab positive patients was 0.59. The small sample size of tTG-Ab positive patients ($n = 4$) does not allow statistical analysis of these results. We are not aware of a specific role of the thyroid autoantibodies in the pathogenesis of either atrophic gastritis or celiac disease.

Although this study underscores the importance of PC-Ab and tTG-Ab measurements in patients with ATD, it has several potential limitations that should be considered. First, the data were collected retrospectively. However, the rates of PC-Ab and tTG-Ab positivity are similar to those published in other studies. Second, the study is

lacking long-term patient follow-up and data concerning hematologic and metabolic status. Nevertheless, information about the prevalence of anemia and vitamin B₁₂ deficiency in this population has already been published [7].

In conclusion, the results of this study, combined with previously published data, support routine screening for PC-Ab and tTG-Ab in patients with ATD, especially those with high TPO-Ab levels.

Conflict of interest

The authors declare no conflict of interest.

References

- Toh BH. Diagnosis and classification of autoimmune gastritis. *Autoimmun Rev* 2014; 13: 459-62.
- Tozzoli R, Kodermaz G, Perosa AR, et al. Autoantibodies to parietal cells as predictors of atrophic body gastritis: a five-year prospective study in patients with autoimmune thyroid diseases. *Autoimmun Rev* 2010; 10: 80-3.
- Uibo R, Krohn K, Villako K, Tammur R, Tamm A. The relationship of parietal cell, gastrin cell, and thyroid autoantibodies to the state of the gastric mucosa in a population sample. *Scand J Gastroenterol* 1984; 19: 1075-80.
- Alexandraki KI, Nikolaou A, Thomas D, et al. Are patients with autoimmune thyroid disease and autoimmune gastritis at risk of gastric neuroendocrine neoplasms type 1? *Clin Endocrinol (Oxf)* 2014; 80: 685-90.
- Checchi S, Montanaro A, Ciulli C, et al. Prevalence of parietal cell antibodies in a large cohort of patients with autoimmune thyroiditis. *Thyroid* 2010; 20: 1385-9.
- García García B, Gimeno Orna JA, Aguillo Gutiérrez E, et al. Prevalence and predictive factors of parietal cell antibody positivity in autoimmune thyroid disease [Spanish]. *Endocrinol Nutr* 2010; 57: 49-53.
- Ness-Abramof R, Nabriski DA, Braverman LE, et al. Prevalence and evaluation of B12 deficiency in patients with autoimmune thyroid disease. *Am J Med Sci* 2006; 332: 119-22.
- Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. *Am J Med* 2006; 119: 355.e9-14.
- Di Sabatino A, Vanoli A, Giuffrida P, Luinetti O, Solcia E, Corazza GR. The function of tissue transglutaminase in celiac disease. *Autoimmun Rev* 2012; 11: 746-53.
- Meloni GF, Tomasi PA, Bertocelli A, Fanciulli G, Delitala G, Meloni T. Prevalence of silent celiac disease in patients with autoimmune thyroiditis from Northern Sardinia. *J Endocrinol Invest* 2001; 24: 298-302.
- Spadaccino AC, Basso D, Chiarelli S, et al. Celiac disease in North Italian patients with autoimmune thyroid diseases. *Autoimmunity* 2008; 41: 116-21.
- Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol* 2012; 18: 6036-59.
- Garber JR, Cobin RH, Gharib H, et al.; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract* 2012; 18: 988-1028.

14. Bahn Chair RS, Burch HB, Cooper DS, et al.; American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011; 21: 593-646. Erratum in: *Thyroid* 2011; 21: 1169. *Thyroid* 2012; 22: 1195.
15. Berna MJ, Hoffmann KM, Long SH, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. Evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine (Baltimore)* 2006; 85: 331-64.
16. Nicolaou A, Thomas D, Alexandraki KI, Sougioultzis S, Tsolakis AV, Kaltsas G. Predictive value of gastrin levels for the diagnosis of gastric enterochromaffin-like cell hyperplasia in patients with Hashimoto's thyroiditis. *Neuroendocrinology* 2014; 99: 118-22.
17. Grozinsky-Glasberg S, Thomas D, Strosberg JR, et al.; Metastatic type 1 gastric carcinoid: a real threat or just a myth? *World J Gastroenterol* 2013; 19: 8687-95.
18. Das C, Sahana PK, Sengupta N, Giri D, Roy M, Mukhopadhyay P. Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India. *Indian J Endocrinol Metab* 2012; 16 (Suppl. 2): S361-3.
19. Checchi S, Montanaro A, Pasqui L, et al. L-thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies. *J Clin Endocrinol Metab* 2008; 93: 465-9.
20. Osman M, Taha B, Al Duboni G. Assessment of the response to gluten-free diet in an Iraqi population with coeliac disease. A histological and serological follow-up study. *Arch Med Sci* 2014; 10: 294-9.