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Helicobacter pylori CagA antibodies and thyroid function in latent autoimmune diabetes in adults

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Abstract. – OBJECTIVE: *H. pylori* infection is reportedly associated with autoimmune diseases such as chronic thyroiditis and autoimmune diabetes. The aim of this study is to determine the association between *H. pylori* infection and its virulent strain CagA with antibodies against thyroperoxidase (TPO Ab) and thyrotropin (TSH) in a cohort of latent autoimmune diabetes in adult (LADA) patients.

PATIENTS AND METHODS: We included 234 LADA patients (53.8% women). Antibodies against *H. pylori* whole antigens and CagA, TPO Ab and TSH were assessed in all patients.

RESULTS: Prevalence of IgG against *H. pylori* and GagA was 52.1% and 20.9% respectively. Antibodies against *H. pylori* were not associated with TPO Ab and TSH (rho = 0.067, *p* = 0.620 and rho = 0.156, *p* = 0.099, respectively). Antibodies against CagA showed a positive association with TSH and TPO Ab (respectively rho = 0.309, *p* = 0.036 and rho = 0.419, *p* = 0.037). Subjects with hypothyroidism (TSH ≥ 3.5 μU/ml) had an increased frequency of Ab anti CagA (*p* = 0.059).

CONCLUSIONS: The infection by *H. pylori* strains expressing CagA is associated with increased TPO Ab and TSH levels in LADA patients, suggesting a possible mechanism involved in thyroid autoimmunity and dysfunction of the gland. Further research is needed to test this hypothesis.

Key Words:
Latent autoimmune diabetes in adults, CagA, Antibodies against thyroperoxidase, Thyrotropin.

Introduction

Autoimmune thyroid disease (AITD) is characterized by the presence of circulating antibodies (Ab) against thyroid antigens, such as thyroglobulin, thyroid peroxidase, and thyrotropin (TSH) receptor, the latter being pathognomonic of Grave's disease[1,2]. The prevalence of AITD is high in the general population, especially in specific geographic areas[3,4]. The mechanisms involved in AITD pathogenesis are not completely understood but an interplay between genetic and environmental factors is generally accepted. Among these, infections caused by different microorganisms have been implicated in the pathogenesis of AITD[5]. Infection by *Yersinia enterocolitica* and hepatitis virus C were found to be highly prevalent in patients with AITD[6-9], but a clear evidence is still lacking.

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium which colonizes the gastric mucosa and is widely accepted as a major cause of gastritis, gastric and duodenal ulcers[10-12]. A possible association between *H. pylori* with lymphoid tissue lymphoma and gastric cancer has also been proposed[13-17]. In addition, *H. pylori was* found to be linked also with extra-gastric manifestations such as autoimmune thrombocytopenic purpura[18], type 1 and type 2 diabetes mellitus[19-21], and a number of other conditions[22-24]. The relationship between AITD and *H. pylori* is controversial and conflicting results are reported in the literature.

Latent autoimmune diabetes in adults (LADA) is a type of autoimmune diabetes characterized by the presence of antibodies against glutamic acid decarboxylase 65 (GAD65 Ab) with a clinical picture very similar to type 2 diabetes at diagnosis. As other autoimmune diseases, LADA pa-

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tients show an increased frequency of extrapancreatic organ-specific autoantibodies, such as antibodies against thyroperoxidase (TPO Ab)[25], antibody against gastric parietal cell[26], and antibody against tissue tranglutaminase[27]. The role of *H. pylori* in LADA patients is poorly investigated. Recently, we reported that antibodies against *H. pylori* were more prevalent in LADA patients as well in subjects with late-onset type 1 diabetes than in the general population[28].

The aim of this study was to investigate the association between AITD and *H. pylori* infection in a cohort of LADA patients.

Patients and Methods

Since the end of 2005, patients with type 2 diabetes at diagnosis were screened for the presence of pancreatic islet autoantibodies. These patients have been referred as a part of a multicentric study, from five Diabetic Units of the island of Sardinia, Italy. The clinical features, autoimmune markers, and progression toward insulin dependence in these patients have been reported elsewhere[29,30]. From the original cohort of 251[29], patients whose sera were no longer available were excluded. A total of 234 serum samples (126 women) were analyzed. Diagnostic criteria for LADA were: (1) presence of circulating GAD65 Ab; (2) age at onset of diabetes above 30 years, and (3) lack of insulin requirement for at least 8 months after diagnosis and absence ketoacidosis and/or significant weight loss. Mean age at onset of diabetes 52.9 ± 10.4 yrs.

Serologic Methods

Blood venous samples were collected between 7 and 8 a.m., after an overnight fasting. Serum samples were stored at -80°C until use. *H. pylori* status was evaluated by an enzyme-linked immunosorbent assay (ELISA) for anti *H. pylori* immunoglobulin G (Helicobacter pylori IgG, ELISA kit, Genesis Diagnostics Ltd, Littleport, UK), with a reported sensitivity and specificity of 99.2% and 90.9% respectively[31]. In addition, the presence of putative *H. pylori* virulence factor was assessed by a specific serological ELISA test for IgG antibodies against CagA (CagA IgG ELISA Kit, Genesis Diagnostics, Littleport, UK), with a sensitivity of 96%, specificity 97%, and inter-assay coefficient of variation < 12%[31]. TPO Ab were measured by immunoradiometric assays, commercial kits (Immunotech, Prague, normal range 0-12 IU/ml; DIASorin, Saluggia, Italy, reference range 0-50 U/ml). Serum TSH was measured with ultra sensitive Immunoradiometric assay kit (RADIM, Pomezia, Italy). As alredy reported in a previous paper[25]. We defined hypothryoidism subjects with TSH level ≥ 3.5 μU/ml.

Statistical Analysis

Normality was assessed by using the Kolmogorov-Smirnov test. The variables not normally distributed were log transformated before analysis. Differences in mean values of continuous variables were tested by the Mann-Whitney U test. Frequencies between groups were tested by the Pearson chi-square test. The association between two variables was measured by calculating the Spearman's rank correlation coefficient.

Statistical analysis was performed with SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Significance level of $p < 0.05$ was set for all calculations.

Results

The main characteristics of the patients' cohort are shown in Table I. The mean value of TPO Ab titer was 239 ± 310 U/ml and the frequency of TPO Ab positivity was 38.9% (91/234). Mean value of TSH was 2.20 ± 1.96 μU/ml and the frequency of subjects with TSH ≥ 3.5 μU/ml was 26.9% (62/234).

The prevalence of IgG against *H. pylori* was 52.1% (122/234). The mean value of IgG titer

Table I. Anthropometric parameters and clinical data of LADA patients. Values are expressed as mean and standard deviations or percentage.

Variables	
No. of patients	234
Gender (M:F)	108:126
Insulin dependence within 4 years (%)	37.9%
Body mass index (kg/m²)	28.1 ± 5.3
TPO Ab (U/ml)	233 ± 310
TPO Ab, % positive	38.9%
TSH (μU/ml)	2.22 ± 1.94
TSH ≥ 3.5 μU/ml, % positive	26.9%
IgG anti H. pylori titer (U/ml)	55 ± 34
IgG anti H. pylori, % positive	52.1%
anti CagA Ab titer (U/ml)	66 ± 36
anti CagA Ab, % positive	20.9%

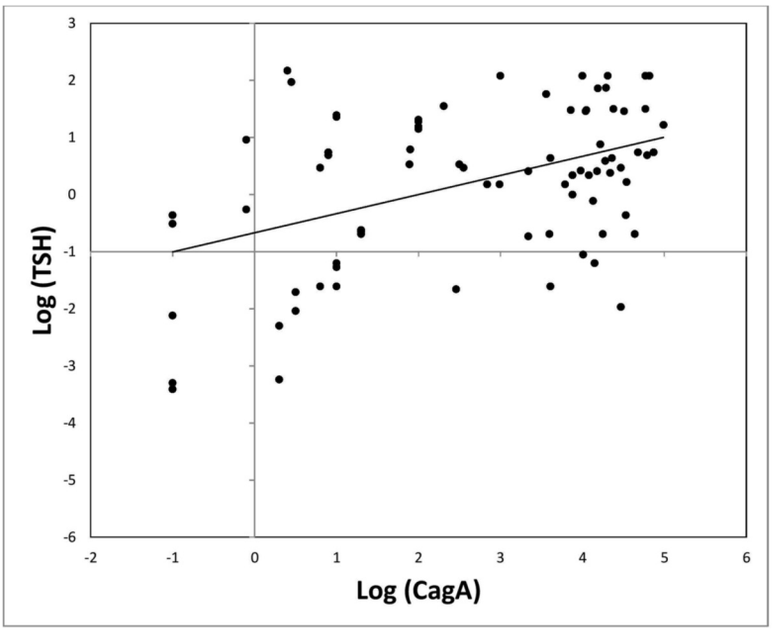

Figure 1. Correlation between TSH and antibodies against CagA.

anti *H. pylori* was 55 ± 34 U/ml. The presence of antibodies against CagA was 20.9% (49/234) and the mean concentration was 66 ± 36 U/ml.

Antibodies against *H. pylori* were not associated with TPO Ab and TSH (rho = 0.067, p = 0.620 and rho = 0.156, p = 0.099, respectively). The correlation between antibodies against CagA and TSH was significant (rho = 0.309, p = 0.036) as well as the correlation between anti-CagA antibodies and TPO Ab (rho = 0.419, p = 0.037), as reported in the scatter plot of Figures 1 and 2.

Therefore, we compared the frequency of LADA patients with TSH ≥ 3.5 μU/ml according to Ab anti CagA. Subjects with hypothryoidism had

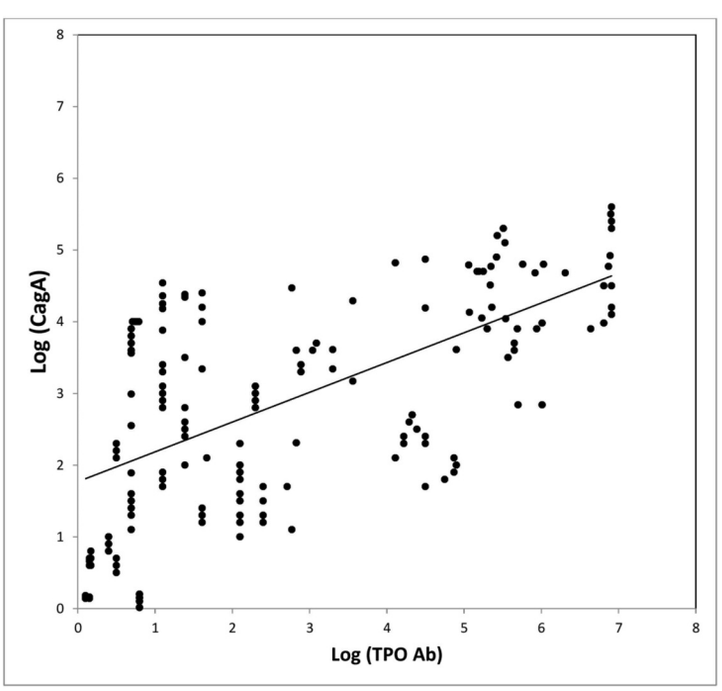

Figure 2. Correlation between antibodies against thyroperoxidase (TPO Ab) and antibodies against CagA.

an increased frequency of Ab anti CagA with a bordeline statistical significance ($\chi^2 = 3.56$; $p = 0.059$), as shown in Table II.

Table II. Frequency of TSH ≥ 3.5 according to CagA Ab positivity among patients with circulating IgG anti *H. Pylori.*

	Ab anti CagA negative	Ab anti CagA positive
TSH < 3.5	60 (64.5%)	33 (35.5%)
TSH ≥ 3.5	13 (44.8%)	16 (55.2%)

*$\chi^2 = 3.56$; $p = 0.059$.

Discussion

Patients with autoimmune diabetes have an increased risk to develop extra-pancreatic autoimmune disease, in particular AITD. Various potential causative mechanisms have been proposed: infectious agents or other cross-reactive environmental triggers activating immune mechanisms in genetically susceptible individuals[5]. However, none has been definitely implicated in the pathogenesis.

In the present study, we showed that both TPO Ab and TSH levels were directly and significantly correlated with CagA Ab titer. Subgroup analyses also reveled that patients with hypothyroidism (defined as TSH ≥ 3.5 μU/ml) had an increased frequency of antibodies against CagA. Our findings are similar to those reported by other studies. For instance, Bassi et al[32] were able to detect an increased prevalence of *H. pylori* antigens in stool samples and Larizza et al[33] and others authors found *H. pylori* antibodies in serum of patients affected by AITD[34-36]. de Luis et al[32] also demonstrated that the titer of TPO Ab was postively and significantly associated with IgG anti *H. pylori*. Further, the titer of TPO Ab and antibodies against thyroglobulin (TG Ab) decreased in a small sample of patients treated for *H. pylori* infection[37]. Other studies found a correlation only with the presence of CagA-positive strain[38]. This is consistent with the finding that the nucleotide sequence of CagA-positive *H. pylori* had a partial homology with the coding sequence of thyroperoxidase gene[39]. However, other reports failed to find any relationship between *H. pylori* and AITD. In particular, the frequency of *H. pylori* infection was comparable between patients with AITD and adult healthy controls[40] regardless of the presence of CagA virulent strain[41]. A recent meta-analysis, which analyzed 7 studies involving a total of 662 patients, showed that the prevalence of *H. pylori* infection and CagA-positive strains were both associated with AITD[42]. These discrepancies might be explained by several reasons. First, the detection methods of *H. Pylori* infection through IgG against *H. Pylori* with ELISA do not differentiate between the past and current infection. Other tests, such as urea breath test and stool antigen test detect only current infection. Other potentially confounding factors are sample size and gender, as AITD is most commonly found in female than in male. Finally, the presence of other pathogens sharing similar epitopes can cause a false positive results, thus interfering with the interpretation of the findings[43]. It is also unclear whether a particular genetic background may have a role in the association between AITD and *H. pylori* infection. Larizza et al[33] showed that *H. pylori* may trigger an immune response against thyroid cell in subjects carrying HLA-DBR1*0301 allele although their findings have not yet been confirmed by other authors[44].

The role of *H. pylori* on LADA susceptibility is unclear. However, according to these results, in a previous study we showed that the frequency of antibodies against CagA was increased in autoimmune diabetes (LADA and late-onset type 1 diabetes) in comparison to type 2 diabetes, suggesting that more virulent *H. pylori* strains might act as a trigger for immune mechanisms involved in the pathogenesis of autoimmune diabetes[28]. The association between *H. pylori* and AITD in autoimmune diabetes has been studied by El-Eshmawy et al[45] who analyzed the titer of TPO Ab, TG Ab, and IgG anti *H. pylori* in 162 euthyroid patients with type 1 diabetes mellitus. Their results supported the hypothesis of a possible relationship between *H. pylori* infection and the occurrence of anti-thyroid antibodies, suggesting that *H. pylori* might be the trigger for the development of AITD in patients with autoimmune diabetes.

Most of the authors suggested a cross-reactivity between the bacteria and some antigen of thyoid gland[5]. Alternatively, *H. pylori* might induce the expression of major histocompatibility complex molecules on thyrocytes or mimiking self-molecules[46]. However, it has also been speculated also that *H. pylori* might be an important trigger factor for the onset of Graves' disease because

the infection is usually present before disease onset[47]. Furthermore, an increased recurrence of *H. pylori* infection in patients affected by Graves' disease, could predispose to AITD whereas hyperthyrodism might lead to an increased susceptibility of *H. pylori* infection[48].

We acknowledge some limitations of our study. The cross-sectional design of the study precluded temporality ascertainment. In addition, we tested only TPO Ab and not TG Ab, thus causing a possible underestimation of AITD. Finally, the IgG anti *H. pylori* could not allow to differentiate between the past and current infection.

Conclusions

We showed that titers of TPO Ab and CagA were related, suggesting that the presence of most virulent *H. pylori* could be a risk factor for the presence of thyroid autoimmunity and a functional impairment of the thyroid gland, as demonstrated by the association between anti GagA Ab and TSH. Taken together these data might suggest that *H. pylori* had a role in thyroid dysfunction, an interesting hypothesis that deserved to be tested in further research.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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