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Association of *Helicobacter pylori* Infection with Autoimmune Thyroid Disease in the Female Gender

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Abstract: Background. Helicobacter pylori infection has been associated with an increased risk of thyroid diseases (TDs), although scientific evidence is conflicting. In the present study the relationship between TDs, including both autoimmune (AI) and non-autoimmune TD, and H. pylori infection was investigated. Methods: Data from records of patients undergoing upper endoscopy and histologically evaluated for H. pylori infection were retrieved. In addition to demographic information, the features of gastritis based on non-targeted biopsies collected from the antrum, angulus, and corpus were analyzed. The presence of H. pylori infection and atrophy and/or metaplasia and/or dysplasia in at least one gastric specimen was defined as a long-lasting H. pylori infection and the presence of a chronic active gastritis as a current infection. Hashimoto's and Graves' diseases were included in AITD and thyroid nodules, goiter, iatrogenic thyroid hypo/hyper function, and thyroidectomy in the non-autoimmune TD group. Results: A total of 8322 records from adult patients aged 18–93 years were analyzed: 562 had a diagnosis of AITD and 448 of non-autoimmune TD. A significant association between long-lasting H. pylori and AITD (OR 1.34; 95%CI 1.13–1.60) was found irrespective of age, sex, body mass index, and smoke, while it was not associated with non-autoimmune TD. The H. pylori current infection did not show significant ORs for AITD (OR 0.99; 95%CI 0.64–1.57) and non-autoimmune TD (OR 0.86; 95%CI 0.66–1.15). Conclusions. Our results indicate that long-lasting H. pylori infection is associated with AITD in the adult population of Northern Sardinia.

Keywords: autoimmune thyroid disease; hashimoto's thyroiditis; graves' disease; helicobacter pylori

1. Introduction

Helicobacter pylori (H. pylori), is a flagellated Gram-negative bacterium mainly transmitted via the fecal-oral route and colonizing approximately half of the world's population [1]. The pathogen is adapted to the gastric environment, which represents the main target of the infection. Unlike other Gram-negative bacteria, which elicit an acute reaction in the host capable to contain the infection and clearing the bacterium, the 60,000 years evolution-driven adaptation strategy of H. pylori to the host's environment [2] relies on the attenuation of the host's innate and adaptive immune response, resulting in latent and long-lasting infection, if otherwise not treated [3,4]. For this reason, most infection carriers are asymptomatic or paucisymptomatic [5,6], and only a minority of cases presents with dyspepsia-like complaints and, in the long run, may develop peptic ulcer, gastric cancer, and MALT lymphoma [7]. During the past decades, research on H. pylori has indicated that, despite being confined to the stomach, the infection may cause extraintestinal manifestations. Several investigations tried to identify key pathogenetic mechanisms suggesting the microorganism as a systemic pathogen [8]. Specifically, the remodeling of the host's immune response enabling H. pylori to escape early clearance promoting its survival in the host environment may enhance, as a side effect, the risk of developing organ-specific autoimmune manifestations such as Behçet disease [9], type 1 diabetes mellitus [10], rheumatoid arthritis [11], and systemic lupus erythematosus [12], among others [13]. In particular, H. pylori has been implicated in AITD [14] as well as in a number of non-

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autoimmune TD. This seems confirmed by the reduced anti-thyroid antibody titer following the eradication therapy for H. pylori [15]. In the past twenty years, the potential of H. pylori infection in increasing the risk of AITD was explored in several studies, obtaining mixed results. Most cross-sectional studies support the association between H. pylori infection and increased AITD risk across Western [16–20], Middle-Eastern [21] and Asian populations [22]. More importantly, prospective studies investigating AITD over time in carriers of H. pylori infection [23], as well as two meta-analyses [24,25], have furnished evidence for a positive association. However, other studies did not find any significant association [26]. Several methodological issues could explain these discrepancies including the cohort's small size [14] and the lack of adjustment for potential confounds. Notably, the majority of studies considered only H. pylori infection in general without separating short and long-standing infection, although the pathogenetic underpinnings are quite different in the two conditions. Taking these premises into account, in the present study the association between TDs, both AITD and non-autoimmune TD, and H. pylori infection was explored in a cohort of subjects undergoing endoscopic examinations of the upper tract, and in whom the presence or absence of an H. pylori infection was ascertained, as well as the histopathological features of gastritis.

2. Materials and Methods

2.1. Study Design and Data Collection

This was a retrospective case-control study. Data were collected from clinical records of patients undergoing upper endoscopy for dyspeptic symptoms at the Gastroenterology Unit of the teaching hospital Clinica Medica of the University of Sassari, Italy. For patients undergoing multiple endoscopies, only the index case was considered for the analysis. Information retrieved included demographic and anthropometric parameters, a medical history comprehensive of all defined diagnoses, and ongoing treatments.

Due to the observational design of the study according to the Italian law (GU No. 76 31/Mar/2008), ethical review and approval were waived.

2.2. Helicobacter Pylori Status

In each patient, at least four non-targeted biopsies were collected, if not contraindicated during endoscopy, and more specifically two from the antrum, one from the angulus, and one from the corpus. As previously described [27], gastric specimens were evaluated for morphology by a dedicated GI pathologist. The presence of H. pylori associated with areas of atrophy and/or metaplasia and/or dysplasia in at least one gastric sample was defined as a long-lasting H. pylori infection. Detection of chronic-active gastritis characterized by the presence of granulocytes and lymphocytes, in addition to the bacteria on specimens, was defined as a current infection.

Diagnosis of thyroid disorders

The diagnosis of the TD was made by the endocrinologist according to national and international guidelines/expert consensus used in the clinical setting and classified into AITDs (Hashimoto thyroiditis and Graves' disease) and non-autoimmune TDs (goiter, nodules, cancer, and others) [28].

2.3. Statistical Analysis

SPSS statistical package was used to conduct the statistical analyses (SPSS 22, Chicago, IL, USA). Patients with TDs (cases) were compared with patients without TDs (controls) according to the H. pylori status. Multivariable logistic regression analysis was used to estimate the risk of AITD and non-autoimmune TD, and long-lasting or current H. pylori infection, independently of confounding factors (i.e., sex, age, body mass index (BMI), and smoke). Patients with celiac disease, with a well-known increased risk of developing AITD [29], were excluded from the analysis. A two-tailed p-value <0.05 was considered as the threshold for statistical significance.

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3. Results

A total of 8322 records from patients aged 18 – 93 years were examined. Table 1 illustrates the overall characteristics of the cohort investigated. Briefly, the mean age of the cohort was 52.33 ± 16.91 years, and the percentage of females was greater than that of males (60.9% and 39.1%, respectively). Among 1010 patients with a diagnosis of TD, 562 patients had more specifically an AITD.

Table 1. Descriptive statistics in 8322 study participants according to the presence of autoimmune thyroid disease (AITD) and non-autoimmune thyroid disease (TD).

Variables	No TD (n=7312)	AITD § (n=562)	Non AITD (n=448)
Sex, *n* (%)			
Female	4437 (60.7)	511 (90.9)	391 (87.3)
Male	2875 (39.3)	51 (9.1) **	57 (12.7) **
Age, *n* (%)			
< 30	956 (13.1)	36 (6.4)	14 (3.1) **
30–39	1089 (14.9)	65 (11.6)	44 (9.8) **
40–49	1226 (16.8)	86 (15.3)	81 (18.0)
50–59	1301 (17.8)	137 (24.4)	101 (22.5) **
60–69	1432 (19.6)	132 (23.5)	127 (28.3) **
70–79	1025 (14.0)	88 (15.7)	64 (14.3)
≥80	283 (3.9)	18 (3.2)	17 (4.0)
Body mass index, n (%)			
<25 kg/m²	4219 (57.7)	320 (56.9)	214 (47.8) **
25–29 kg/m²	2244 (30.7)	167 (29.7)	174 (38.8) **
≥30 kg/m²	849 (11.6)	75 (13.3)	60 (13.4)
Smoke, *n* (%)			
Never smoker	3882 (53.1)	294 (52.3)	1094 (53.7)
Former smoker	314 (4.3)	25 (4.4)	111 (5.4) *
Current smoker	3116 (42.6)	243 (43.2)	834 (40.9)
H. pylori infection, *n* (%)			
No	3583 (53.2)	303 (51.8)	1977 (97.0)
Yes	3158 (46.8)	282 (48.2)	62 (3.0)
H. pylori status, *n* (%)			
No infection	4082 (55.8)	293 (52.1)	246 (54.9)
Long-lasting *H. pylori* infection	1519 (20.8)	149 (26.5) **	95 (21.2)
Current *H. pylori* infection	1456 (19.9)	93 (16.5)	83 (18.5)
Past *H. pylori* infection	255 (3.5)	27 (4.8)	24 (5.4)

* $p < 0.05$; ** $p < 0.001$ §TD=thyroid disease.

As expected, the proportion of individuals with TD showed a slightly increasing trend with age. Although mildly, excess weight was observed among patients with TD, while the percentage of current or former smokers did not differ between the three groups. Each H. pylori infection was confirmed in 3395 patients among a total of over 30000 gastric specimens analyzed: 1763 had a diagnosis of long-lasting and 1632 current H. pylori infections. A past H. pylori infection—successfully eradicated—was present in the clinical history of 316 patients. The proportion of subjects with long-lasting infection was significantly greater in the subgroup of patients with AITD (26.5% vs 20.8%, p<0.001), whereas no statistical difference was found regarding the current (16.5% vs 19.9%, n.s.) and past infection (4.8% vs 3.5%, n.s.).

Figure 1 illustrates the proportion of AITD as a function of age and H. pylori status. It can be noticed that AITD is clearly more frequent in patients with long-lasting H. pylori infection than in patients with current or no infection.

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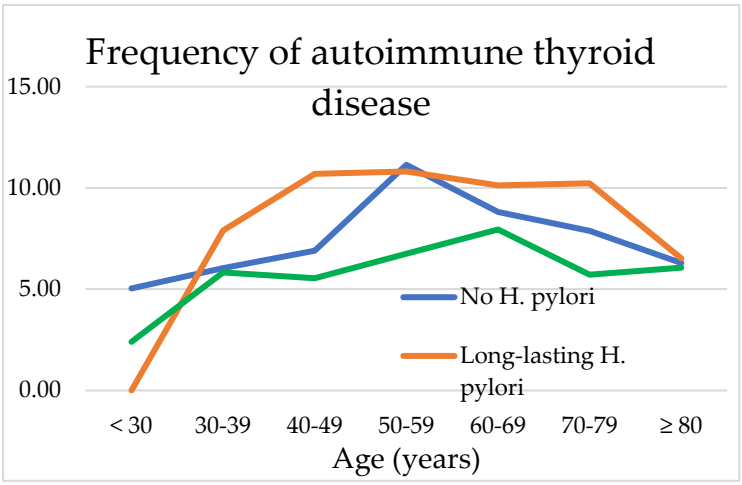

Figure 1. Frequency of autoimmune thyroid disease (AITD) according to age and Helicobacter pylori status.

Results of the logistic regression analysis, after excluding the 306 patients with the past H. pylori infection successfully eradicated, are shown in Table 2. After adjusting for age, sex, BMI, and smoking, the analysis revealed a positive association of long-lasting H. pylori infection with AITD (OR 1.34; 95%CI 1.13–1.60). The association was not significant for the current H. pylori infection (OR 0.99; 95%CI 0.64–1.57). Considering the overall H. pylori infection (without stratifying for gastritis subtypes) no significant risk difference was found.

When the analysis was conducted in patients with non-autoimmune TD, the association with H. pylori infection was neither observed in the case of long-lasting infection (OR 0.97; 95%CI 0.74–1.28) nor for the current infection (OR 0.86; 95%CI 0.66–1.15).

Patients with AITD were separated into those with Hashimoto's thyroiditis and Graves' disease. In both subgroups, the regression analysis showed a significant association with long-lasting H. pylori infection, but the effect size was greater in the latter (OR 1.94; 95%CI 1.20–3.15) than in the former (OR 1.32; 95%CI 1.06–1.64). On the contrary, the analysis did not highlight a significant association between H. pylori infection—either acute or chronic—with non-autoimmune TD.

Interestingly, after categorizing patients according to sex, the association between long-lasting H. pylori infection and AITD was detected as significant only among females (OR 1.39; 95%CI 1.12–1.72) while in males was observed only a trend albeit non-significant (OR 1.19; 95%CI 0.63–2.23).

An additional subanalysis with AITD patients stratified into those with functionally compromised thyroid (maintained via levothyroxine therapy or methimazole) and those in euthyroid status, the association with long-lasting H. pylori infection remained in both groups (ORs 1.31 and 1.29, respectively).

Table 2. Logistic regression analysis for autoimmune thyroid disease in 8016 study participants.

Variables	**AITD** § **Unadjusted OR (95%CI)**	**AITD Adjusted OR 95%CI**	**Non AITD** # **Adjusted OR 95%CI**
Sex			
Male	Ref.	Ref.	Ref.
Female	6.59 (4.94–8.81) **	6.81 (5.09–9.11) **	4.99 (3.60–6.92) **
Age			
< 60	Ref.	Ref.	Ref.
≥ 60	1.17 (0.98–1.39)	1.18 (0.98–1.42)	1.40 (1.12–1.75)
Body mass index			
<25 kg/m²	Ref.	Ref.	Ref.
25–29 kg/m²	0.92 (0.76–1.12)	1.02 (0.84–1.25)	1.69 (1.33–2.15) *

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≥30 kg/m²	1.13 (0.87–1.47)	1.18 (0.90–1.55)	1.61 (1.15–2.25) *
Smoke			
Never smoker	Ref.	Ref.	Ref.
Former or current smoker	1.03 (0.87–1.22)	1.15 (0.97–1.38)	1.03 (0.82–1.29)
H. pylori infection			
No	Ref.	Ref.	Ref.
Yes	1.15 (0.96–1.36)	1.12 (0.94–1.34)	0.91 (0.73–1.14)
H. pylori status, *n* (%)			
No infection	Ref.	Ref.	Ref.
LL *H. pylori* infection §	1.36 (1.11–1.67) **	1.34 (1.13–1.60) **	0.97 (0.74–1.28)
Current *H. pylori* infection	0.92 (0.72–1.17)	0.99 (0.64–1.57)	0.86 (0.66–1.15)

* $p < 0.05$; ** $p < 0.01$.

4. Discussion

A number of studies have hinted that microorganisms play a significant etiological role in autoimmune disorders [13] including thyroid autoimmunity [30]. In the last decade, a growing literature identified several bacterial taxa able to trigger Hashimoto's thyroiditis and Graves' disease [31]. Among microorganisms, also H. pylori is thought to increase the risk of developing AITD, however, there is a lack of definite consensus among endocrinologists about the robustness of this association and the possible interfering role of additional factors. The present study, conducted in a cohort of patients from Northern Sardinia, Italy, undergoing upper endoscopy for dyspepsia, tried to shed light on the role played by H. pylori infection according to gastritis phenotype and provides a number of interesting findings. First, a significant association was found between long-lasting H. pylori infection and AITD among female patients, independently of the functional status. The association was confirmed also adjusting for age, sex, BMI, and smoking. When patients were categorized based on the etiology of TD, the association was maintained only for AITD which represented the majority of our cases (56%). More specifically, the association was observed with both Hashimoto's and Graves' diseases but not for non-autoimmune TD. Although the association was restricted to females, a trend was noted in males; however, we cannot exclude that the lower percentage of male patients in our cohort and the consequent weak statistical power could be at the origin of this finding. Remarkably, only long-lasting H. pylori and not H. pylori infection as a whole did show an association with AITD. Current H. pylori infection did not show any significant association with TDs.

Overall, our results are partially in accord with literature data [14,17,19,22,23] supporting the claim that H. pylori infection is an independent risk factor for AITD. In particular, our results could help interpret the negative results obtained in other studies, owing to the fact that the acute or chronic type of infection was never taken into account.

The H. pylori/AITD association was generally corroborated by most case-control studies [16,21] although in other studies the association was confirmed only for patients infected by strains positive for the virulence CagA cytotoxic factor [19]. Instead, the large prospective study by Arslan clearly showed that the association does not depend on the mere presence of CagA positive strains [23], a finding further confirmed by two metanalyses [24,25]. Even though in the present study the association with virulence factors could not be tested—owing to the unavailability of CagA typing—in a previous study we reported that patients infected by H. pylori strains expressing CagA showed increased thyroid peroxidase (TPO) Ab titers, despite the lack of a significant correlation between anti-H. pylori and anti-thyroid antibody titers. Vice versa, patients with hypothyroidism (TSH ≥ 3.5 μU/ml) had an increased frequency of anti-CagA Ab ($p = 0.059$) [32]. In the study by Bassi et al., the association between H. pylori infection and AITD was confined to Graves' disease [33], whereas in our cohort the association was found for both Graves' disease and Hashimoto's thyroiditis, although the effect size was greater in the former. The association of H. pylori infection and AITD has also been described in Asian populations [22,24] and even in children [18], but whether the infection was current or long-lasting was not specified.

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While most studies point to a positive association, two cross-sectional studies—based on H. pylori seropositivity—did not find any association [26,34].

Detection of serum IgG against H. pylori (or against H. pylori CagA) provides a reliable assessment of current, or prior, H. pylori infection. Because the antibody tests remain positive long after successful treatment of the infection a positive test result cannot be used to ascertain whether the patient is infected or not. Last of all, the presence of antibodies against H. pylori can discern between a current or long-lasting infection [35]. Similarly, the urea breath test (UBT) and stool antigen test, although characterized by a very high accuracy in detecting the active infection, again cannot distinguish between a chronic-active infection from the presence of metaplasia/dysplasia/atrophy [35]. For example, in a previous study, the prevalence of hypothyroidism, or hyperthyroidism, was similar in H. pylori positive and negative subjects, where the infection was ascertained by UBT [36]. According to diagnostic methods used to detect H. pylori infection in the present study, we would have had a prevalence of AITD in H. pylori-positive patients and in H. pylori-negative patients of 49.6% vs 50.4% ($p > 0.05$) by serology, and of 39.7% vs 45.3% ($p > 0.05$) by UBT/stool antigen test. The different tests used to detect H. pylori infection and the lack of adjusting for the gastritis phenotype may justify discrepancies among study findings. Our results indicate that the immune dysregulation determining the loss of specific tolerance for the thyroid, as a target organ, requires a long-lasting interaction between the microorganism and the host.

Mechanisms that could explain the association between H. pylori and AITD have been described by Cellini et al. [37]. The stomach and the thyroid gland are embryologically related [38] and similarity between H. pylori and thyroid epitopes has been reported [34]. The damage of gastric cells by H. pylori infection exposes epitopes to the immune system, as demonstrated by the frequent association of anti-gastric parietal cell antibodies with AITD [39] thus potentially triggering an autoimmune response via molecular mimicry. However, while the acute infection by H. pylori induces a strong proinflammatory immune process, the persistent infection induces instead a relatively weak type-2 immune reaction driving the reprogramming of macrophage and dendritic cell function [40] as well as expansion of the T regulatory cell compartment [41]. In addition, T cells recognize H. pylori epitopes structurally similar to H/K/ATPase on the stomach parietal cells. This promotes the survival of H. pylori in the host but results in an increased probability of immunotolerance impairment.

This study has some limitations including the retrospective design per se unable to assess a causal effect. In addition, in retrospective studies, the exposure to factors is not well controlled. However, the major exposure factor considered in this study for AITD occurrence, i.e., H. pylori infection, was ascertained by histology on at least four gastric specimens and the presence of metaplasia/dysplasia/atrophy used as a proxy of gastritis duration. Moreover, a number of patients undergoing upper endoscopy may have had a still undiagnosed AITD, especially the ones without clinical evidence, although this kind of patients could be missed in H. pylori-positive or negative groups, respectively. Nonetheless, the large size of the cohort studied minimizes the interference of these potential biases, making our findings reliable.

5. Conclusions

In conclusion, our results confirm an association between a long-lasting H. pylori infection and AITD regardless of age, smoke, and BMI in a population with a high prevalence of both conditions investigated for gastrointestinal symptoms. The association was restricted to female patients, although in males a trend for association was observed in aged participants.

Author Contributions: Conceptualization, Maria Pina Dore; Data curation, Maria Pina Dore, Alessandra Manca and Giovanni Mario Pes; Formal analysis, Giuseppe Fanciulli and Giovanni Mario Pes; Investigation, Maria Pina Dore, Giuseppe Fanciulli and Alessandra Manca; Methodology, Maria Pina Dore and Giovanni Mario Pes; Validation, Maria Pina Dore; Writing – original draft, Maria Pina Dore, Giuseppe Fanciulli and Giovanni Mario Pes; Writing – review & editing, Maria Pina Dore, Giuseppe Fanciulli, Alessandra Manca and Giovanni Mario Pes. **A**ll authors will be informed about each step of manuscript processing including submission, revision, revision reminder, etc. via emails from our system or assigned Assistant Editor.

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Conflicts of Interest: The authors declare no conflict of interest.

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