Correlation of Autoimmune Thyroid Diseases With Helicobacter pylori Infection

Zahra Heidari, Nima Shahriari

Department of Endocrinology and Metabolism, Zahedan University of Medical Sciences, Zahedan, Iran

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Abstract- Autoimmune thyroid diseases are multifactorial conditions caused by genetic and environmental factors. Among environmental factors, infectious agents include viruses, bacteria, and parasites acting as triggers. The current study intended to investigate the association between Helicobacter pylori infection and autoimmune thyroid diseases in a group of Iranian cases with Hashimoto's thyroiditis (HT) and Graves' disease (GD). This study included adult cases newly diagnosed with GD and HT and euthyroid controls. A number of clinical and biochemical factors were evaluated, including tests of thyroid function and serum Helicobacter Ab (IgG), and then inter-group comparisons were performed. Data from 404 patients with HT and 248 cases with GD were analyzed. Also, data from 480 healthy controls were analyzed. For those with HT, GD, and controls, the prevalence of Helicobacter pylori infection was 93.3%, 92.7%, and 88.8%, respectively. The prevalence of H. pylori infection in cases with HT and GD was significantly higher compared to controls. While concerning the prevalence of H. pylori infection, the two groups (HT and GD) were not significantly different. H. pylori antibody level was significantly correlated with FT4, FT3, Anti-TPO, and Anti-Tg in cases with HT. In the group of patients with GD, the H. pylori antibody had a significant positive correlation with Anti-TPO and Anti-Tg. According to the present results, H. pylori is associated with autoimmune thyroid diseases (both Hashimoto's and Graves' diseases).

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Keywords: Graves' disease; Hashimoto's disease; Helicobacter pylori

Introduction

Autoimmune thyroid diseases (AITD) include a wide spectrum of thyroid disorders, ranging from autoimmune hypothyroidism (Hashimoto's thyroiditis) to autoimmune hyperthyroidism (Graves' disease). These disorders are recognized as the most common autoimmune diseases in humans. The main characteristics of these diseases are the presence of circulating antibodies against thyroid antigens like thyroglobulin and thyroid peroxidase in Hashimoto's thyroiditis (HT) and antibodies against thyroid-stimulating hormone (TSH) receptors in Grave's disease (GD) (1).

Autoimmune thyroid diseases are multifactorial conditions caused by genetic and environmental factors. Among environmental factors, infections acting as triggers are widely investigated. Infectious agents like bacteria, viruses, and parasites can even be part of the normal flora in the body (2). Infectious agents, such as *Yersinia enterocolitica*, hepatitis C virus, and *Helicobacter pylori*, have been examined in autoimmune thyroid disorders (3-8).

Infection caused by *Helicobacter pylori (H. pylori)*, as an environmental factor, mimics the antigenic profile of the membrane of thyrocyte and, therefore, contributes to the initiation of the autoimmune process in the thyroid. *H. pylori* is a Gram-negative, microaerophilic, helical bacterium that can colonize gastric mucosa. This organism is responsible for some gastric problems like peptic ulcer disease, gastritis, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma (9-11).

Besides, *H. pylori* infection is connected with some extraintestinal disorders, such as autoimmune

Corresponding Author: Z. Heidari
Department of Endocrinology and Metabolism, Zahedan University of Medical Sciences, Zahedan, Iran
Tel: +98 5433430230, Fax: +98 5433445434, E-mail address: z.heidari10@yahoo.com

thrombocytopenic purpura (12), type I and II diabetes (13,14), primary biliary cirrhosis (15), migraine and primary Raynaud's phenomenon (16,17), and ischemic heart disease (18). The antibodies produced in response to *H. pylori* antigens can have cross-reactions with many antigens of soft tissues, including the thyroid tissue (19).

According to some studies, *H. pylori* infection and autoimmune thyroid disorders are correlated (19-28), whereas some studies have found no such correlation (29-31), making it a controversial topic. Therefore, the current case-control study intended to investigate the association between *H. pylori* infection and autoimmune thyroid disorders in a group of Iranians with HT and GD.

Materials and Methods

This research was conducted on new cases with HT and GD referring to endocrine clinics in Zahedan, Southeastern Iran, from January 2019 to November 2020. Following the consecutive sampling approach, those older than 18 years were continuously enrolled. The inclusion criteria were defined as suffering from Grave's disease: enhanced Free Tetraiodothyronin (FT4) and Free Triiodothyronine (FT3) due to suppressed Thyroid Stimulating Hormone (TSH) (normal FT4: 0.8-1.8 ng/dl, normal FT3: 2.3-4.2 pg/ml and normal TSH: 0.4-4.2 mIU/L) and positive TSH-Rec-Ab (normal: up to 1.75 IU/L) or Hashimoto's thyroiditis: decreased FT4 and FT3 in association with elevated TSH and positive Anti-TPO (normal: up to 16 Iu/ml) or Anti-Tg (normal: up to 100 Iu/ml). Those who had indications of suffering from other disorders (e.g., infectious disease or malignancies) were not considered eligible for inclusion in this study. Furthermore, those with any of the following criteria were also excluded: history of receiving thyroid medication, smoking, and women in pregnancy or lactation. Euthyroid-healthy cases who did not have thyroid disorders were considered as controls after evaluation against the inclusion and exclusion criteria. The participants did not suffer from any known acute or chronic disorder. Noteworthy, both controls and cases had a similar geographical origin. A digital scale was used to measure the body weight of participants while they were asked to wear no shoes. Also, a stadiometer was used to measure the height of participants, again, while they had no shoes. All blood samples were collected from 8 to 9 am and kept at -70° C until assay.

The tests of thyroid function and serum concentrations of *H. pylori* Ab (IgG) were assessed in cases with GD and HT and controls. An automated analyzer was used to evaluate FT4, FT3, and TSH using immunochemoluminescent assays. Antithyroid peroxidase (normal range< 16 Iu/ml), antithyroglobulin (normal range< 100 Iu/ml), and TSH-Rec-Ab (normal range:< 1.75 IU/L) were evaluated using immunochemoluminescent assays and commercial kits. Enzyme-linked immunoassay method was employed to measure IgG anti-H. pylori Ab (Values≥ 10 IU/ml were regarded as positive).

The study protocol is approved by the Ethics Committee for Human Studies of Zahedan University (code: IR.ZAUMS.REC.1398.407). All participants signed the written informed consent.

Data analyses

The results are provided using descriptive statistics, including frequency, percentage, and mean with standard deviation (SD). ANOVA test was applied to compare the mean difference of numerical variables among three study groups (i.e., those suffering from Hashimoto, Graves, and controls). In addition, Bonferroni correction was used for post hoc pairwise comparisons. The independent t-test was employed to analyze the mean difference of numerical variables in cases of either positive or negative for *H. Pylori* infection. Pearson chi-square or Fisher's exact test was used to investigating the association between categorical variables among study groups. The correlation between *H. Pylori* antibody titers and numerical variables was assessed using the Pearson correlation. Also, scatter plots, and quadratic fitting with a 95% confidence interval are used to present important correlations. Statistical significance was considered when the $P<0.05$. Data analysis was administered using Stata: Release 14.2 College Station, TX: StataCorp LP.

Results

A total of 404 cases with Hashimoto, 248 with Graves, and 480 healthy subjects (i.e., controls) were found eligible for data analysis. For all three groups, nearly 80% of cases were women, and the mean age was higher than 35 years. Those suffering from HT presented a higher mean of *H. pylori* antibody in comparison to those suffering from GD; however, it was lower than that of controls (Figure 1). Concerning the mean of the *H. pylori* antibody, the study groups were significantly different. In total, 93.3% of those with HT suffered from *H. pylori* infection, while it was 92.7% and 88.8% for those with GD and controls, respectively. For controls, the prevalence of *H. pylori* was significantly lower in comparison to those suffering from HT or GD ($P<0.05$), while it was not significantly different between those

suffering from HT and GD (Table 1).

A comparison of clinical and biochemical characteristics of those with positive and negative H. Pylori, separated by the study group, is provided in Table 2.

The mean of Anti-TPO in cases with H. pylori infection in all three study groups was significantly higher than in patients without infection. Similar to Anti-TPO findings, the mean of Anti-Tg was significantly higher in those suffering from H. pylori infection in all three study groups than in patients without it (Figure 2).

In patients with HT and GD, the mean of H. pylori antibody had the highest correlation with Anti-TPO and Anti-Tg titer. In patients with HT, H. pylori antibody and FT4, FT3, Anti-TPO, and Anti-Tg were significantly correlated. In the GD group, the H. pylori antibody was significantly correlated with Anti-TPO and Anti-Tg (Table 3).

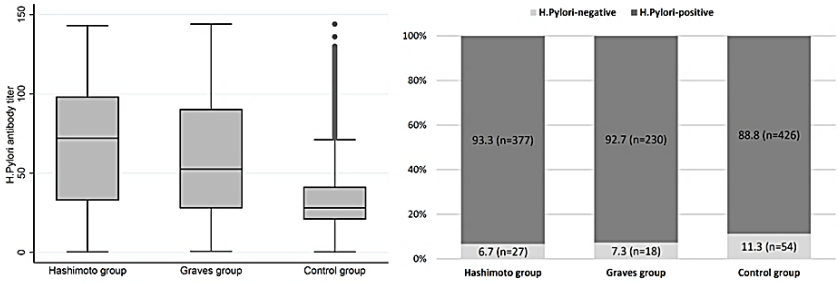

Figure 1. Distribution of *H. Pylori* antibody and prevalence of *H. Pylori* infection by Hashimoto, Graves, and control group

Table 1. Characteristics by study group

Variable	Hashimoto group (n=404)	Graves group (n=248)	Control group (n=480)	*P*
Age (years)	34.76±10.01	34.15±5.86	35.31±8.71	0.191
Sex (female)	328 (81.18)	198 (79.83)	377 (78.54)	0.599
Body mass index (Kg/m^2)	24.20±3.32 [a]	23.69±3.91 [a]	23.12±3.88 [b]	<0.001
TSH (mIu/L)	80.15±21.04 [a]	0.03±0.01 [b]	1.61±0.86 [b]	<0.001
FT3 (pg/ml)	1.65±0.48 [a]	1.65±0.48 [a]	3.59±0.42 [c]	<0.001
FT4 (ng/dl)	0.47±0.14 [a]	3.36±0.97 [b]	1.21±0.27 [c]	<0.001
Anti-TPO (Iu/ml)	469.49±658.09 [a]	339.80±598.21 [b]	13.23±18.98 [c]	<0.001
Positive anti-TPO (≥16)	359 (88.86) [a]	203 (81.85) [b]	57 (11.87) [c]	<0.001
Anti-Tg (Iu/ml)	874.1±1306.94 [a]	529.11±1028.49 [b]	53.97±48.98 [c]	<0.001
Positive anti-Tg (≥100)	346 (85.6) [a]	204 (82.25) [a]	57 (11.87) [b]	<0.001
***H. Pylori*-Ab titer (Iu/ml)**	68.45±38.49 [a]	60.82±39.18 [b]	36.85±29.52 [c]	<0.001
Positive *H. Pylori* (≥10)	377 (93.3) [a]	230 (92.7) [a, b]	426 (88.8) [b]	0.037

-Data are presented as mean±SD or number (%). *P* was determined by one-way ANOVA or Pearson $\chi 2$ test.
a, b, c: in the same row of variables reflect significant ($P< 0.05$) difference between the means while the same superscript letters in one row reflect a non-significant difference between the means of three group

Table 2. Clinical and laboratory variables comparison in patients with positive and negative *H. Pylori* infection by Hashimoto, Graves, and control group

		Hashimoto group			Graves group			Control group		
		Negative *H. Pylori*	**Positive *H. Pylori***	***P***	**Negative *H. Pylori***	**Positive *H. Pylori***	***P***	**Negative *H. pylori***	**Positive *H. pylori***	***P***
Sex	**Male**	2 (2.6)	75 (97.4)	0.111	2 (4.1)	47 (95.9)	0.339	14 (13.5)	90 (86.5)	0.420
	Female	25 (7.6)	302 (92.4)		16 (8.0)	183 (92.0)		40 (10.6)	336 (89.4)	
Age (years)		32.70±9.02	34.49±10.26	0.378	31.89±8.68	34.22±5.70	0.276	33.81±9.20	35.43±8.78	0.206
BMI (Kg/m^2)		25.80±3.02	24.08±3.54	0.014	24.78±3.68	23.68±3.68	0.235	22.84±4.08	23.05±3.97	0.721
FT4 (ng/dl)		0.38±0.18	0.45±0.16	0.032	2.94±0.82	3.31±0.91	0.097	1.27±0.21	1.27±0.20	0.848
FT3 (pg/ml)		1.35±0.55	1.65±0.49	0.012	6.14±1.34	6.71±1.55	0.133	3.64±0.40	3.61±0.46	0.617
TSH (mIu/L)		88.07±16.10	78.89±20.56	0.008	0.02±0.01	0.02±0.01	0.760	1.39±0.70	1.57±0.79	0.112
Anti-TPO		12.78±5.52	510.75±674.19	<0.001	7.56±4.18	370.12±626.05	<0.001	6.80±4.17	14.36±19.99	<0.001
Positive anti-TPO (≥16)	**No**	22 (51.2)	21(48.8)	<0.001	18 (39.1)	28 (60.9)	<0.001	54 (12.7)	370 (87.3)	<0.001
	Yes	5 (1.4)	356 (98.6)		0 (0.0)	202 (100)		0 (0.0)	56 (100)	
Anti-Tg		54.48±14.49	932.80±1333.81	<0.001	51.17±28.56	574.38±1165.55	<0.001	30.65±26.88	57.78±2.47	<0.001
Positive anti-Tg (≥100)	**No**	27 (46.6)	31 (53.4)	<0.001	18 (39.1)	28 (60.9)	<0.001	54 (12.7)	370 (87.3)	<0.001
	Yes	0 (0.0)	346 (100.0)		0 (0.0)	202 (100.0)		0 (0.0)	56 (100.0)	

Data are shown as mean±SD or number (%). *P* were determined by independent t-test, Pearson Chi-square, or Fisher exact test

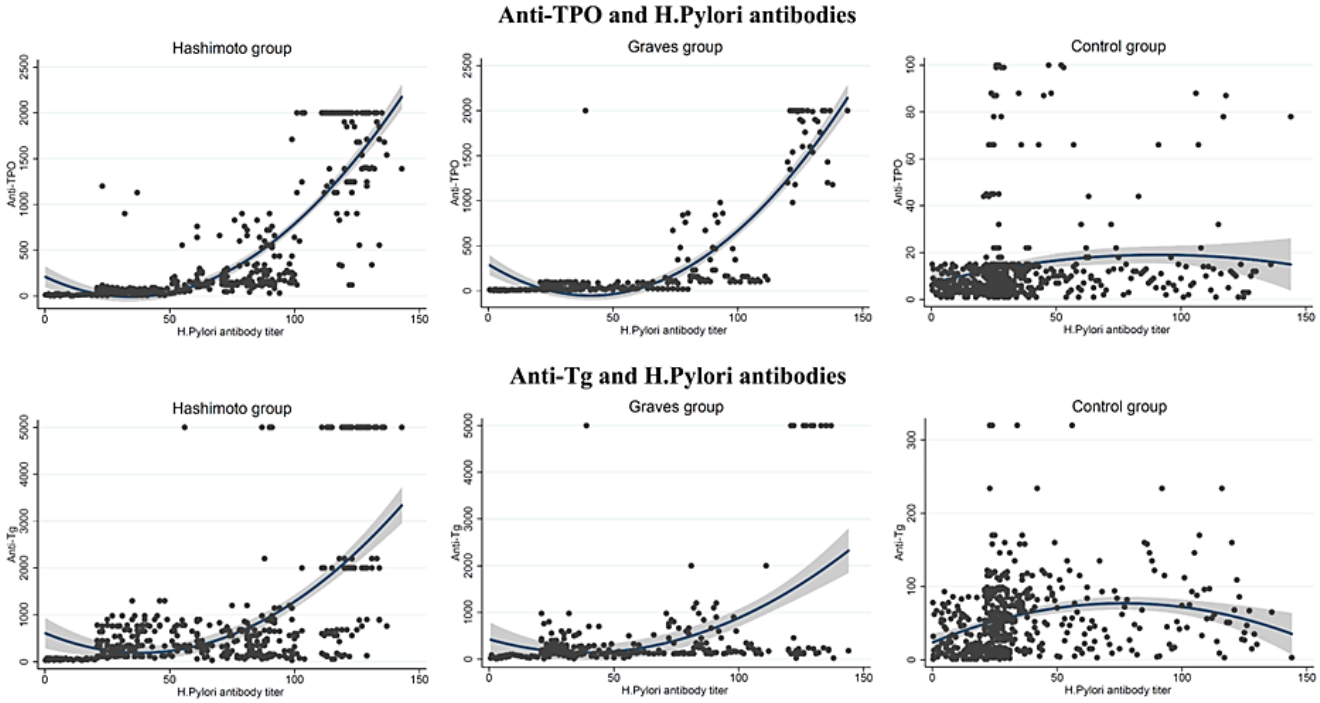

Figure 2. The scatter plot with the quadratic fitting with 95% confidence interval of serum *H. Pylori* antibody and thyroid antibodies titer correlation by Hashimoto, Graves, and control group

Table 3. Correlation between serum *H. Pylori* antibody titer and variables in Hashimoto, Graves, and control group

		***H. Pylori* antibody titer in**		
		Hashimoto group	**Graves group**	**Control group**
Age	r	0.037	-0.057	0.058
	P	0.461	0.373	0.207
BMI	r	-.189**	-0.095	0.034
	P	<0.001	0.138	0.455
FT4	r	.120*	-0.062	-0.016
	P	0.016	0.330	0.720
FT3	r	.190**	-0.023	0.009
	P	<0.001	0.721	0.840
TSH	r	-.262**	0.059	-0.010
	P	<0.001	0.355	0.829
Anti-TPO	r	.739**	.736**	.138**
	P	<0.001	<0.001	0.002
Anti-Tg	r	.515**	.412**	.176**
	P	<0.001	<0.001	<0.001

.**Correlation is significant at the 0.01 level (2-tailed)
*. Correlation is significant at the 0.05 level (2-tailed)

Discussion

According to the present findings, there was a correlation between *H. pylori* infection and newly diagnosed Hashimoto's thyroiditis and Graves' diseases. This study is consistent with previous studies that reported a significant relationship between *H. pylori* infection and AITD (19-28). In this regard, De Luis *et al.*, showed that in HT and GD, the antithyroid antibody titer has a significant positive relationship with the IgG antibody titer against *H. pylori* (19). A number of studies found a significant correlation between *H. pylori* infection and autoimmune thyroid diseases (20,25). Bassi and colleagues evaluated the correlation between *H. pylori* infection and AITD in 112 newly diagnosed cases. According to their results, 83.7% of patients with GD

were positive for *H. pylori* infection. However, they reported that *H. pylori* infection and HT were not associated (21). The association between *H. pylori* infection and autoimmune thyroid diseases has been confirmed in other studies (25,26). However, there are some studies indicating no significant relationship between *H. pylori* infection and autoimmune thyroid disorders (29-31).

As the embryonic origin of the thyroid gland, stomach, and digestive systems is the same, thyroid cells can be considered gastrointestinal cells that absorb, accumulate, and concentrate iodine. It is known that both the thyroid gland and the stomach can concentrate on iodine. Also, thyroid cells, similar to gastrointestinal cells, contain microvilli on the apical surface and can synthesize and inhibit glycoproteins. The surface parietal cell antigens of the stomach and the protein portion of thyroid peroxidase enzymes are homologous. It has been confirmed that *H. pylori* infection can trigger autoimmune thyroid reactions (32).

H. pylori is a bacterium colonizing the stomach of 50% of people worldwide (33). In Iran, the prevalence of *H. pylori* infection ranges from 36% to 90% in different geographical regions (34). This type of infection leads to the acute infiltration of polymorphonuclear cells into the gastric mucosa. In cases where effective treatment is not provided, this acute cellular infiltration gradually progresses into chronic infiltration of mononuclear cells (35), resulting in the local production and systemic propagation of proinflammatory cytokines that may affect other distant tissues and organs (36). Therefore, *H pylori* infection has been epidemiologically connected with a number of extra-digestive conditions (e.g., autoimmune thyroid disorder) (37).

Several mechanisms are developed to describe how *H. pylori* can cause autoimmune thyroid diseases. These mechanisms include molecular mimicry (38,39), epitopic release, bystander activation (40,41), microbial superantigens, formation of immune complexes (42), MHC class II expression on immune cells (43), direct inflammatory damage (42), high concentrations of proinflammatory cytokines, like interferon-gamma, and imbalance of regulatory T cells and T-helper cells (44).

In this study, antithyroid antibodies and anti-*H pylori* IgG antibodies were significantly correlated, which is consistent with the findings of some previous research that supports molecular mimicry theory in the pathogenesis of AITD (45).

This research suffered from some limitations. First, *H. pylori* infection was defined, according to serological tests, not tissue samples, although the sensitivity and specificity of *Helicobacter* antibodies to diagnose *H. pylori* infection have been estimated at 88.4% and 93.4%, respectively (46). There are also some concerns about the false-positive results of *H. pylori* infections in people with positive anti-TPO titers (47). The strengths of the current study were the inclusion of a euthyroid control group, matched based on age and BMI with the case group, and a relatively acceptable number of participants.

Based on the findings, *H. pylori* infection and autoimmune thyroid disorders (both Hashimoto's and Graves' diseases) are associated. Nevertheless, further studies with more subjects and more accurate detection of *H. pylori* species, considering the host genetic polymorphisms and environmental factors, are necessary to confirm these findings.

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