



Association between *Helicobacter pylori* infection and autoimmune thyroid disease

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Abstract

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Aim: *Helicobacter Pylori* (HP) is the most common bacteria that cause chronic bacterial infections in humans. We aimed to investigate the possible relationship between HP infection and autoimmune thyroid diseases, as well as the possible relationship between HP density and platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR).

Materials and Methods: A total of 3,380 patients who underwent upper gastro intestinal system endoscopy in the our tertiary hospital endoscopy unit between 2010 and 2018 were scanned, and 250 patients who met the inclusion criteria were included in our retrospective study.

Results: The study was examined under 2 groups: 104 (41.6%) were HP negative and 146 (58.4%) were positive. While TPOAb was positive in 63 (25.2%) patients, 61 (24.4%) patients were found to be TgAb positive. Atrophy was detected in 11 (4.4%) patients and metaplasia in 20 (8%). There was no statistically significant difference between HP-positive and HP-negative patients in terms of age, gender, Wbc, Hg, Neu, Lymp, Plt, PLR, and NLR ($P > 0.05$). There was no significant concordance between HP positivity and TPOAb and TgAb positivity. There was no statistically significant relationship between HP density and PLR and NLR (Spearman's rho correlation analysis, $P > 0.05$).

Conclusion: In conclusion, no relationship was found between HP infection and autoimmune thyroid disease in our study. Similarly, there was no significant relationship between HP density and PLR and NLR.



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Introduction

Helicobacter pylori (HP) is a gram-negative, catalase oxidase- and urease-positive bacteria. It is the most common bacteria that causes chronic bacterial infections in humans [1, 2]. It protects itself by neutralizing gastric acid with the urease it secretes and localizes to the gastric epithelium. The prevalence of chronic HP infection is 80% in adults in developing countries, whereas it is 50% in adults in developed countries [2, 3]. The risk of peptic ulcer and gastric cancer is reduced by eradicating HP, which has been identified as one of the causes of these diseases. 4 It is thought that HP might be associated not only with peptic ulcer and gastric cancer but also with extra-gastric diseases [4]. Recent studies have suggested that there is a relationship between autoimmune thyroid diseases and HP infection [5]. On the other hand, the relationship between HP density and platelet-to-lymphocyte ratio (PLR) and

neutrophil-to-lymphocyte ratio (NLR), which are accepted as inflammation markers, is one of the issues of interest. In this study, we aimed primarily to investigate the possible relationship between HP infection and autoimmune thyroid diseases, and secondarily, the possible relationship between HP density and PLR and NLR.

Materials and Methods

Our study was designed as a retrospective analytical study. Ethical approval for study was obtained from Fatih Sultan Mehmet Training and Research Hospital (Decision numbered 17073117-050.06 and dated April 30, 2019). A total of 3380 patients who underwent upper gastrointestinal system endoscopy in our tertiary hospital endoscopy unit between 2010 and 2018 were scanned, and 250 patients who met the inclusion criteria were included in our study. The inclusion criteria were being over the age of 18, presence of available upper gastrointestinal endoscopic biopsy results, and availability of other medical data examined closer to biopsies such as hemogram parameters, thyroid peroxidase

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antibody (TPOAb), and thyroglobulin antibody (TgAb). Patients under the age of 18, patients diagnosed with cancer, and patients with inadequate biopsy results were excluded from the study.

Hemogram parameters such as white blood cell (Wbc), hemoglobin (Hg), neutrophil (Neu), lymphocyte (Lymp), and platelets (Plt) were analyzed by an automated blood counter (Cell Dyne 3700, Abbott Diagnostics). TPOAb and TgAb were measured by the chemiluminescent microparticle immunoassay (CMIA) method (Architect i2000, Abbott Laboratories). Values above 5.6 IU/mL for TPOAb and 10 IU/mL for TgAb were considered positive. If any of the thyroid autoantibodies were positive, it was accepted that there was an autoimmune thyroid disease. Stomach biopsy reports, evaluated by expert pathologists, were examined in terms of gastric atrophy, metaplasia, HP positivity, and HP density. It was learned that the preparations were stained with modified Giemsa dye for the evaluation of HP density and evaluated as mild (1), moderate (2), and severe (3). Other endoscopic findings are not included in the study. Scientific research permission was obtained from the scientific board of our hospital (Fatih Sultan Mehmet Training and Research Hospital) with the decision numbered 17073117-050.06 and dated April 30, 2019.

IBM SPSS Statistics 22 was used for the statistical analysis of the findings obtained in the study. The suitability of the parameters to the normal distribution was evaluated with the Shapiro–Wilk test. In addition to descriptive statistical methods (mean, standard deviation, frequency), the t test was used to compare normally distributed parameters between two groups in comparisons of quantitative data, and the Mann–Whitney U test was used for comparisons of non-normally distributed parameters. The χ^2 test, Fisher’s exact test, and Yates correction for continuity test were used to compare qualitative data. McNemar’s test was used to compare intragroup rates in qualitative data. Spearman’s rho correlation analysis was used to examine the relationships between parameters that did not conform to normal distribution. A P value < 0.05 was considered significant.

Results

A total of 250 patients who met the inclusion criteria were included in the study. The patients’ ages ranged from 20 to 87, with a mean age of 51.4 (14.4). Of the patients, 191 (76.4%) were female and 59 (23.6%) were male. The study was examined under 2 groups: 104 (41.6%) were HP negative and 146 (58.4%) were positive. While TPOAb was positive in 63 (25.2%) patients, 61 (24.4%) patients were found to be TgAb positive. Atrophy was detected in 11 (4.4%) patients and metaplasia in 20 (8%). Mild, moderate, and high-intensity HP were detected in 92, 25, and 29 patients, respectively. Basic characteristics of the study population are shown in Table 1. There was no statistically significant difference between HP-positive and HP-negative patients in terms of age, gender, Wbc, Hg, Neu, Lymp, Plt, PLR, and NLR ($P > 0.05$). The incidence of atrophy in HP-positive patients was found to be statistically significantly higher (7.5%) than in HP-negative (0%) ones ($P = 0.002$; Fisher’s exact test). There was no signif-

Table 1. Basic characteristics of the study population.

		Min-Max	Mean±SD
Age		20-87	51.44(14.4)
		n	%
Gender	Female	191	76.4
	Male	59	23.6
HP	Negative	104	41.6
	Positive	146	58.4
TPOAb	Negative	187	74.8
	Positive	63	25.2
TgAb	Negative	189	75.6
	Positive	61	24.4
Atrophy	No	239	95.6
	Yes	11	4.4
Metaplasia	No	230	92
	Yes	20	8
HP density	0	104	41.6
	1	92	36.8
	2	25	10
	3	29	11.6

HP: Helicobacter pylori, TgAb: Thyroglobuline antibody, TPOAb: Thyroid peroxidase antibody.

icant difference between the groups in terms of presence of metaplasia. The evaluation of study parameters according to HP positivity is shown in Table 2.

Examination of the discrepancy between HP positivity and TPOAb and TgAb positivity (Table 3) indicated a statistically significant discrepancy between the variables (McNemar’s test, $P < 0.05$). There was no statistically significant relationship between HP density and PLR and NLR (Spearman’s rho correlation analysis, $P > 0.05$). The evaluation of the correlation between HP density and PLR and NLR is shown in Table 4.

Discussion

HP causes chronic inflammation in the stomach. This inflammation is thought to cause autoimmune diseases. The relationship between HP and autoimmune thyroid diseases has been a topic that scientists have been curious about and studied for the last 20 years. However, there are studies in the literature with contradictory results. Because of this need, we felt the need to do such a study.

The main autoimmune thyroid diseases are Hashimoto’s thyroiditis and Graves’ disease. Hashimoto’s thyroiditis is also the most common autoimmune disease [6]. Blood levels of TPOAb and TgAb, which are thyroid antibodies, increase in autoimmune thyroid disease. Even TPOAb levels can be detected at higher concentrations in untreated Hashimoto’s patients [7]. The primary goal of our study was to investigate the relationship between HP and autoimmune thyroid diseases. For this purpose, we separated the patients as HP positive and HP negative, and we performed our analysis by comparing TPOAb and TgAb levels, which are frequently detected to be positive primarily

Table 2. Evaluation of study parameters according to HP positivity.

	HP positivity		P	
	Negative	Positive		
	Mean±SD n:104	Mean±SD n:146		
Age years	52.25±15.43	50.87±13.64	¹ 0.456	
WBC 10 ³ /uL (median)	7.26±1.99 (7)	7.55±2.67 (7.1)	² 0.441	
Hg g/dL (median)	12.69±1.72 (12.7)	12.65±1.85 (12.8)	² 0.659	
Neu 10 ³ /uL (median)	4.35±1.52 (4.1)	4.57±2.41 (4.1)	² 0.755	
Lymp 10 ³ /uL (median)	2.2±0.82 (2.2)	2.26±0.75 (2.2)	² 0.409	
Plt 10 ³ /uL (median)	269.32±80.13 (255)	269.45±78.02 (258)	² 0.919	
PLR (median)	137.04±71.64 (122.1)	131.3±58.31 (115.7)	² 0.386	
NLR (median)	2.3±1.63 (1.9)	2.28±2.01 (1.9)	² 0.783	
	n (%)	n (%)		
Gender	Female	84 (80.8%)	107 (73.3%)	³ 0.170
	Male	20 (19.2%)	39 (26.7%)	
Atrophy	No	104 (100%)	135 (92.5%)	⁵ 0.002*
	Yes	0 (0%)	11 (7.5%)	
Metaplasia	No	100 (96.2%)	130 (89%)	⁴ 0.071
	Yes	4 (3.8%)	16 (11%)	

WBC: White blood cell, Hg: Hemoglobin, Neu: Neutrophil, Lymp: Lymphocyte, Plt: Platelets, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio.

¹:t test, ²:Mann-Whitney U test, ³: χ^2 test, ⁴:Continuity (Yates) correction, ⁵:Fisher's exact test, *P < 0.05.

Table 3. Evaluation of the discrepancy between HP positivity and TPOAb and TgAb positivity.

	HP positivity			P	
	Negative	Positive	Total		
	n (%)	n (%)	n (%)		
TPOAb	Negative	83 (33.2%)	104 (41.6%)	187 (74.8%)	0.000*
	Positive	21 (8.4%)	42 (16.8%)	63 (25.2%)	
	Total	104 (41.6%)	146 (58.4%)	250 (100%)	
TgAb	Negative	83 (33.2%)	106 (42.4%)	189 (75.6%)	0.000*
	Positive	21 (8.4%)	40 (16%)	61 (24.4%)	
	Total	104 (41.6%)	146 (58.4%)	250 (100%)	

TgAb: Thyroglobuline antibody, TPOAb: Thyroid peroxidase antibody McNemar's test, *P < 0.05.

Table 4. Evaluation of the Correlation Between HP Density and PLR and NLR

		HP density
PLR	r	-0.124
	p	0.055
NLR	r	-0.075
	p	0.240

PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio Spearman's rho correlation analysis (P > 0.05).

in Hashimoto's patients, in these groups.

In our primary analysis for the study, we did not find a

significant correlation between HP positivity and thyroid autoantibodies. Regarding previous studies published on the subject in English, some publications claim that HP positivity and thyroid autoantibodies are related [8-14], and some did not report a significant relationship between them [15,16].

Figura et al [13] found a significant relationship between Cag-A-positive HP infection and Graves' disease and Hashimoto's thyroiditis in their study involving 76 patients with Hashimoto's thyroiditis, 39 Graves' patients, and 136 control patients. Choi et al [9] found that TPOAb positivity was more frequent in those who were IgG positive against HP in their study conducted with 5502 patients. In a case control study, Aghili et al [12], by investigating the TPOAb and anti HP IgG antibody in 40 healthy individuals and 43 patients diagnosed with Hashimoto's, found a significant relationship between Hashimoto's and HP. However, the sample size in this study was very small. In a meta-analysis of 3046 patients by Hou et al [14], HP was found to be associated with Graves' and Hashimoto's diseases. However, none of the studies included in the meta-analysis were based on histological examination of biopsy preparations taken directly from the gastric mucosa.

No significant relationship was found between HP IgG and TPOAb and TgAb in a study conducted by Shmueli et al [15] involving 101 women with a diagnosis of Hashimoto's and a control group of 111 women. In another similar study, using a urea breath test with 302 patients, Tomasi et al [16] found no significant relationship between autoimmune thyroiditis and HP. The results of our study are consistent with those of these 2 studies.

Looking at the methods used in all studies for HP detection, we see that tests such as HP antibody determination in serum, antigen determination in stool, and urea breath tests are used. The difference between our study from these studies is that it is based on the direct demonstration of bacteria in gastric biopsy preparations in the determination of HP infection.

The second goal of our study was to investigate the relationship between HP density and PLR and NLR, which are considered inflammation indicators. We did not find a significant relationship between HP density and PLR and NLR. The rates of PLR and NLR are expected to increase in inflammatory processes. Contrary to what was expected, although mean PLR was found to be lower in the HP-positive group, it was not statistically significant (Table 2). There are not many studies on this subject in the literature. Kaplan et al [17] found PLR-NLR combination to be a good predictor of HP presence in their study conducted with 1289 patients who underwent esophagogastroduodenoscopic biopsy. In another study involving 17 028 asymptomatic participants in Korea, Kim et al [18] found that HP infection was not associated with C reactive protein, NLR, and PLR. They had a large sample size, but they evaluated HP infection status only based on serum IgG results from enzyme-linked immunosorbent assay [18]. In our study, we found similar results to those obtained by Kim et al. Although we cannot determine a relationship on the subject, it might not be accurate to conclude that HP infection does not cause inflammatory processes. HP infection could constitute a much more limited inflammatory process than rheumatological or oncological conditions.

Another finding not overlooked in our study is that gastric atrophy was significantly higher in the HP-positive group. HP, which is one of the causes of atrophic gastritis, [19] is already expected to be high in this group. One of the weaknesses of our study is its retrospective design. It is not known whether the patients included in the study were diagnosed and treated for thyroid disease. On the other hand, we did not analyze another group in which both thyroid autoantibodies were positive. It should also be kept in mind that a different result can be obtained with such an analysis. Its strengths are the reliability of the method used for HP determination and the adequate number of patients.

Conclusion

In conclusion, no relationship was found between HP infection and autoimmune thyroid disease in our study. Similarly, there was no significant relationship between HP density and PLR and NLR. However, further studies especially which has a prospective design on this subject will lead scientists to more generalizable results. If a relationship between HP and thyroid autoantibodies is found in future larger and more comprehensive studies, it may enable clinicians to be more careful in the follow-up of patients with HP positivity in terms of autoimmune thyroid diseases.

Ethics approval

Ethical approval for this study was obtained from Fatih Sultan Mehmet Training and Research Hospital (Decision numbered 17073117-050.06 and dated April 30, 2019).

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