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The effect of *helicobacter pylori* infection on thyroid function tests in diabetic patients and its relationship with autoimmune thyroiditis

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ABSTRACT

Introduction: In this study, we aimed to show the effect of *Helicobacter pylori* presence on thyroid function tests and its relationship with autoimmune thyroiditis in patients with Type 2 diabetes mellitus (DM) with dyspeptic complaints.

Materials and Methods: Our randomized and retrospective study was planned with 136 Type 2 patients with DM who were followed up from our gastroenterology outpatient clinic and diabetes unit between January 2019 and January 2020. Biopsy samples of patients undergoing gastroscopy due to dyspepsia are evaluated pathologically. The relationship between the presence of *H. pylori* and autoimmune thyroiditis is investigated by looking at demographic and laboratory findings and thyroid function tests.

Results: 136 diabetic patients between the ages of 31–85, with a mean age of 60.03±9.82 years, 43 of whom male (31.6%) and 93 female (68.4%), were considered. *H. pylori* positivity was detected in 41.9% (n=57) of the cases. In *H. pylori* positive cases, the body mass index (BMI) value was found to be significantly higher (p<0.01). There was no significant relationship between *H. pylori* positivity and thyroid function test level or gender (p>0.05). In addition, gastroesophageal reflux and atrophy were higher in patients with *H. pylori* (p=0.001; p<0.01). The ODDS ratio of the presence of atrophy in anti-TPO positive cases was 5,409 (95% CI: 1,962–14,900) and no relationship was found between Anti-TPO positivity and *H. pylori* positivity (p>0.05).

Conclusion: Although *H. pylori* positivity is common in Type 2 DM patients, no relationship was found between thyroid function test level and anti-TPO positivity (autoimmune thyroiditis). Meanwhile, the BMI value, acid reflux, and gastric atrophy were found to be more common in case of *H. pylori* positivity and autoimmune thyroiditis to be associated with atrophic gastritis. It can thus be recommended for obese, diabetic patients with dyspeptic mellitus disease to be evaluated in terms of thyroid function.

Keywords: Anti-TPO, Atrophic gastritis, Diabetes, *Helicobacter pylori*, Obesity, Thyroid

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Introduction

Diabetes mellitus (DM), the frequency of which is increasing globally, is a disease that shows an increase in morbidity and mortality when left untreated.[1] The prevalence of thyroid disease in DM patients is more common than in the normal population, and changes in the thyroid hormones are known to affect glycemic regulation. *Helicobacter pylori* is associated with many metabolic diseases, chief among them stomach diseases. It can cause the development of ulcers, gastritis, atrophy, and malignancy in the stomach. If left untreated, *H. pylori* continues to multiply in the stomach, causing progressive loss of stomach glands and developing atrophic gastritis.[2] In pathogenesis, especially cytotoxin-associated gene A (CagA) is affected and *H. pylori* and CagA antibodies cause atrophic gastritis.[3] The frequency of helicobacter increases with reduced immune tolerance in diabetic patients.[4]

Türkiye is the first in the prevalence of overweight and obese adults in the 2022 WHO European Region Obesity Report, with 21% of its adult population classified as obese and 66.8% (including obese population) as overweight.[5] Diabetes risk shows a 3-to-7-fold increase in obese people and obesity is quite common in Type 2 DM patients at a rate of 54–59%.[6,7] Increased body mass index (BMI) is also associated with the frequency of *H. pylori*.[8] It has been shown that the risk of *H. pylori* is increased in autoimmune thyroiditis and may be associated with thyroid autoantibodies.[9] Approximately 10–40% of patients with Hashimoto's thyroiditis have stomach disorders. Similarly, approximately 40% of patients with autoimmune atrophic gastritis have Hashimoto's thyroiditis.[10] This study was planned to investigate the relationship between *H. pylori* infection and autoimmune thyroiditis and thyroid function tests in Type 2 DM patients.

Materials and Methods

Our study was conducted between January 2019 and January 2020 among 136 Type 2 DM patients with dyspeptic complaints who applied to Kartal Dr. Lütfi Kırdar City Hospital gastroenterology and diabetes unit policlinic. Those over 18 years of age, requiring no emergency care, diagnosed with Type 2 DM and without any neuropsychiatric disease, who underwent gastroscopy due to dyspepsia complaints are included in the study. Type 1 DM, pregnant women, those who have undergone *H. pylori* eradication therapy, those with solid organ malignancy and those with advanced neuropsychiatric disease are excluded.

Height and body weight measurements were made on the same measuring instrument in the policlinic examination room. BMI was calculated with the formula BMI=-body weight/height^2 (kg/m^2) and BMI 25 and above were considered overweight. Gastroscopy was performed by the same gastroenterologist using a Fujinon endoscopy instrument. *H. pylori* was evaluated pathologically according to Sydney protocol by gastroscopic biopsy. The approval for the study was obtained from the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Decision No: 2020/514/188/5).

Statistical Analysis

Number cruncher statistical system program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to evaluate the data. The suitability of quantitative data to normal distribution was tested by Shapiro–Wilk test and graphical examinations. Student-t test was used for comparisons of normally distributed quantitative variables between two groups, and Mann–Whitney U test was used for comparisons of quantitative variables with non-normal distribution between two groups. Pearson Chi-square test, Fisher's exact test, and Fisher-Freeman-Halton test were used to compare qualitative data. Logistic Regression (Backward) analysis was used to determine the effects on anti-TPO. Statistical significance criterion is defined as $p<0.05$.

Results

In this study, conducted at Kartal Dr. Lütfi Kırdar City Hospital between January 2019 and January 2020, a total of 136 Type 2 DM cases were evaluated, of which 31.6% (n=43) were male and 68.4% (n=93) female. They range in age from 31 to 85 years old, with an average age of 60.03±9.82 years. BMI measurements ranged from 22 to 42 kg/m^2 and its mean was 28.79±3.16 kg/m^2. The duration since DM diagnosis was between 2 and 31 years with a mean of 13.43±6.68 years. Gastritis was observed in 97.1% (n=132), ulcer in 7.4% (n=10), varicose veins in 0.7% (n=1), and reflux in 39.7% (n=54) of the patients. In the pathologies of the biopsy samples taken, inflammation was observed in 91.9% (n=125), atrophy in 19.9% (n=27), intestinal metaplasia in 22.1% (n=30), and *H. pylori* in 41.9% (n=57) (Table 1).

Table 1. Demographic features and distribution of endoscopic data

Min-Max (Median)	31–85 (60.5)
Age	
Mean±SD	60.03±9.82
Sex	
Male	43 (31.6)
Female	93 (68.4)
BMI	
Min-max (median)	22–42 (29)
Mean±SD	28.79±3.16
Diabetes duration	
Min-max (median)	2–31 (13)
Mean±SD	13.43±6.68
Gastritis n (%)	
No	4 (2.9)
Yes	132 (97.1)
Ulcer n (%)	
No	126 (92.6)
Yes	10 (7.4)
Varice n (%)	
No	135 (99.3)
Yes	1 (0.7)
Reflux n (%)	
No	82 (60.3)
Yes	54 (39.7)
Inflamation n (%)	
No	11 (8.1)
Yes	125 (91.9)
Atrofia n(%)	
No	109 (80.1)
Yes	27 (19.9)
Intestinal metaplasia n (%)	
No	106 (77.9)
Yes	30 (22.1)
HP n (%)	
No	79 (58.1)
Yes	57 (41.9)

When *H. pylori* positivity was examined, there was no statistically significant difference between age, sex, and duration since diabetes diagnosis (p>0.05). The correlation between presence of *H. pylori* and thyroid function test results, thyroid-stimulating hormone (TSH), free T3, free T4, fT3/sT4 and hemoglobin, fasting blood glucose, HbA1c, total cholesterol, LDL, HDL, and triglyceride values was not statistically significant (p>0.05) (Table 2).

In the study, *H. pylori* was seen in 11% of the patients with BMI within the normal limit (BMI: 22–24.9), while *H. pylori* was positive in 63% of those who were obese (BMI: ≥ 25) and in 32% of the overweight group (BMI: 25–29.9). The BMI value of *H. pylori* positive cases was statistically significantly higher than negative cases (p=0.001; p<0.01) (Fig. 1).

The rate of acid reflux in *H. pylori* positive cases was statistically significantly higher than in negative cases (p=0.001; p<0.01). However, the incidence of gastritis, ulcers, and varicose veins does not show significant difference (p>0.05). When the pathological findings were evaluated, the rate of atrophy in *H. pylori* positive cases was also found to be significantly higher than in negative cases (p=0.001; p<0.01) (Table 3).

With respect to anti-TPO positivity, there was no statistically significant difference between the ages, genders, BMI measurements, and duration of diabetes (p>0.05). When the gastroscopic findings were evaluated, the incidence of gastritis, ulcers, varicose veins and acid reflux, inflammation, intestinal metaplasia and *H. pylori* positivity did not show a correlation with anti-TPO positivity. Meanwhile, the rate of atrophy in anti-TPO positive cases was found to be significantly higher than others (p=0.002; p<0.01) (Table 4).

Logistic Regression Analysis

Evaluation by logistic regression analysis (Backward Stepwise) of the risk factors affecting anti-TPO, including gender, BMI, TSH, st4, fT3/T4, *H. pylori*, and atrophy variables, ended in step 5 and the variables that are signifi-

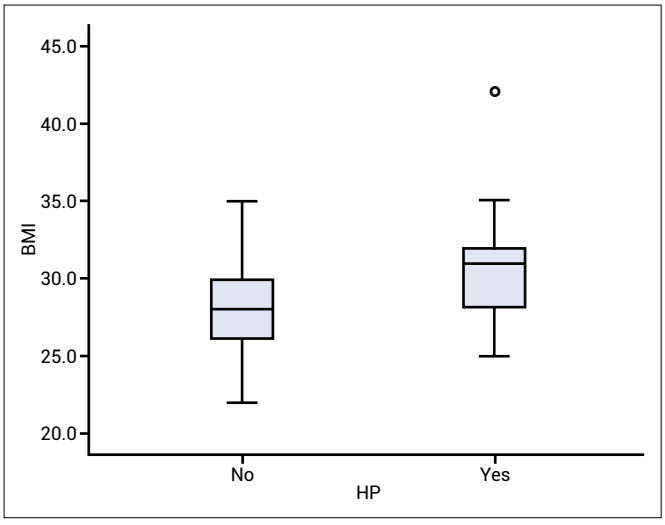

Figure 1. Distribution of the relationship between Helicobacter pylori and body mass index.

Table 2. Comparisons by presence of Helicobacter pylori

	H. pylori negative (n=79)	H. pylori pozitive (n=57)	P
TSH			
N	76	56	c0.130
Min-max (median)	0.1–12.2 (2.1)	0.5–7.3 (2.1)	
Mean±SD	3.05±2.5	2.2±1.35	
fT3			
N	79	56	a0.122
Min-max (median)	1–6.2 (4.1)	2.7–9.1 (4.3)	
Mean±SD	4.17±0.88	4.41±0.95	
fT4			
Min-max (median)	7.9–27 (12.5)	7.4–26.7 (15)	a0.092
Mean±SD	13.69±4.16	14.86±3.71	
fT3/T4			
Min-max (median)	0.1–0.7 (0.3)	0–0.6 (0.3)	a0.439
Mean±SD	0.33±0.11	0.31±0.12	
Hemoglobin			
Min-max (median)	8–15.4 (12.6)	6.4–17.4 (12.6)	a0.374
Mean±SD	12.22±1.78	12.5±1.82	
Fasting blood glucose			
Min-max (median)	51–344 (141)	74–298 (141)	a0.976
Mean±SD	152.68±62.62	152.39±50.75	
HbA1c			
Min-max (median)	5.2–19 (7.6)	5.4–19 (7.4)	c0.879
Mean±SD	7.93±2.11	8.03±2.26	
Total cholesterol			
Min-max (median)	89–285 (183)	99–281 (165)	a0.087
Mean±SD	185.48±43.04	172.81±41.1	
LDL			
N	77	55	a0.308
Min-max (median)	41–198 (101)	35–187 (97)	
Mean±SD	107.74±35.49	101.27±36.28	
HDL			
Min-max (median)	12–83 (48)	23–82 (43)	a0.098
Mean±SD	48.09±13.51	44.25±12.94	
Triglycerides			
Min-max (median)	53–496 (134)	47–400 (146)	c0.778
Mean±SD	158.85±84.46	152.32±76.32	
Age			
Min-max (median)	31–85 (60)	43–83 (62)	a0.842
Mean±SD	59.89±10.38	60.23±9.07	
Sex			
Male	20 (46.5)	23 (53.5)	b0.063
Female	59 (63.4)	34 (36.6)	
BMI			
N	75	56	a0.001**
Min-max (median)	22-35 (28)	25–2 (31)	
Mean±SD	27.69±2.76	30.27±3.08	
Diabetes duration			
Min-max (median)	2–30 (13)	2–31 (14)	a0.87

Table 3. Distribution of gastroscopy and pathology findings by Helicobacter pylori positivity

Gastritis	H. pylori negative (n=79) n (%)	H. pylori Pozitive (n=57) n (%)	P
No	2 (2.5)	2 (3.5)	d1.000
Yes	77 (97.5)	55 (96.5)	
Ulcer			
No	74 (93.7)	52 (91.2)	d0.742
Yes	5 (6.3)	5 (8.8)	
Varice			
No	78 (98.7)	57 (100.0)	d1.000
Yes	1 (1.3)	0 (0.0)	
Reflux			
No	66 (83.5)	16 (28.1)	b0.001**
Yes	13 (16.5)	41 (71.9)	
Inflamation			
No	9 (11.4)	2 (3.5)	d0.119
Yes	70 (88.6)	55 (96.5)	
Atrofia			
No	72 (91.1)	37 (64.9)	b0.001**
Yes	7 (8.9)	20 (35.1)	
Intestinal metaplasia			
No	63 (79.7)	43 (75.4)	b0.550
Yes	16 (20.3)	14 (24.6)	

bPearson Chi-square test; dFisher's exact test; **p<0.01.

cant are reported in Table 11. When we examine the effect of variables on Anti-TPO with Backward Stepwise: (Conditional) Logistic Regression, we see that the model is found to be pertinent, given the relatively good explanatory coefficient of the model (the correct prediction rate of non-anti-TPO cases is 84.2%; The correct prediction rate of cases with anti-TPO was 58.8%; the overall prediction rate was 74%). The ODDS ratio of the effect of the patient's being female on anti-TPO was 3,280 (95% CI:1,233–8,724%). The ODDS ratio of BMI measurement was 0.811 (95% CI:0.694–0.947), the ODDS ratio of st4 measurement was 1,299 (95% CI:1,142–1474), and the ODDS ratio of atrophy was 5409 (95% CI:1,962–14,900).

Discussion

H. pylori infection is an infection associated with metabolic diseases, most notably stomach diseases, affecting approximately 4.4 million people worldwide.[11] In obesity, there is a predisposition to infections as a result of deterioration of immune functions due to increased adipose tissue.[4] Looking at the literature, there are more studies that indicate a positive correlation between *H. pylori* infection and BMI elevation, and one study showed that participants with a high BMI had more *H. pylori* positivity.[5,12] In our study, it was also seen that there was a positive correlation between increased BMI and *H. pylori* infection and our findings agree with the literature.

In the previous studies, the incidence of *H. pylori* infection has been reported to be similar in both sexes.[13,14] In our study, no significant relationship between *H. pylori* and gender was detected and findings consistent with the literature were obtained.

The most affected organ in autoimmune diseases is the thyroid gland. The presence of a peroxidase-encoding gene in the *H. pylori* chromosome has been detected as well as a cross-reaction between anti-hp antibodies and thyroid follicles, resulting in an antigenic similarity between *H. pylori* and thyroid tissue.[15,16] Another study showed that *H. pylori* was more prevalent in individuals with autoimmune thyroid disease and particularly so in those who were CagA positive.[16] In our study, there was no significant relationship found between *H. pylori* positivity and thyroid autoantibodies, fT3, fT4 levels, fT3/fT4

Table 4. Evaluation of pathology and gastroscopy findings with respect to Anti-TPO

Gastritis	Anti-TPO negative (n=80) n (%)	Anti-TPO pozitive (n=56) n (%)	P
No	2 (2.5)	2 (3.6)	d1.000
Yes	79 (97.5)	53 (96.4)	
Ulcer			
No	73 (90.1)	53 (96.4)	d0.202
Yes	8 (9.9)	2 (3.6)	
Varice			
No	80 (98.8)	55 (100)	d1.000
Yes	1 (1.2)	0 (0)	
Reflux			
No	50 (61.7)	32 (58.2)	b0.678
Yes	31 (38.3)	23 (41.8)	
Inflamation			
No	7 (8.6)	4 (7.3)	d1.000
Yes	74 (91.4)	51 (92.7)	
Atrofia			
No	72 (88.9)	37 (67.3)	b0.002**
Yes	9 (11.1)	18 (32.7)	
Intestinal metaplasia			
No	65 (80.2)	41 (74.5)	b0.431
Yes	16 (19.8)	14 (25.5)	
Helicobacter pylori			
No	46 (56.8)	33 (60)	b0.710
Yes	35 (43.2)	22 (40)	

bPearson Chi-square test, dFisher's exact test, **P<0.01.

ratio. We think that this situation may be due to the inadequacy of the number of patients and the difference in the epidemiological distribution of *H. pylori*.

In a case-control study of the frequency of *H. pylori* with female patients diagnosed with Hashimoto's, no significant relationship was found between autoimmune thyroiditis and *H. pylori* positivity.[17] In our study, although autoimmune thyroiditis was more common in female patients, we observed no significant correlation between the frequency of *H. pylori* with autoimmune thyroiditis in female patients, in line with previous literature. In a meta-analysis considering polyimmunity in autoimmune thyroiditis, 17.45% of the patients had type 1 diabetes and autoimmune gastritis.[18] In addition, in another study where patients with atrophic gastritis were evaluated, it was seen that anti-TPO antibody positivity was high and the association of Hashimoto's disease and autoimmune atrophic gastritis was emphasized.[19]

H. pylori infection is a risk factor for the development of atrophic gastritis. Since atrophic gastritis increases the risk of gastric carcinoma, it is reported that *H. pylori* eradication reduces the risk of developing gastric carcinoma.[2,20,21] In our study, in line with the literature, atrophic gastritis was seen more in those with *H. pylori* infection. In a study conducted in Italy, a positive correlation between Hashimoto's thyroiditis and the occurrence of autoimmune gastritis was found.[7] In addition, in a study conducted in patients with atrophic gastritis, it was seen that Anti-TPO antibody positivity was high and the association of Hashimoto's disease and autoimmune atrophic gastritis was emphasized.[22] In our study, the incidence of atrophy was found to be significantly higher in patients who are Anti-TPO positive in accordance with the literature, so it can be said that Anti-TPO positivity is a risk factor for atrophic gastritis.

While *H. pylori* is a risk factor for atrophic gastritis, gastric carcinoma and peptic ulcer, its relationship with reflux

disease is still controversial.[21] Two separate studies in Iran and Türkiye have not found a significant relationship between *H. pylori* and reflux disease.[22,23] In our study, a positive relationship was found between *H. pylori* and reflux disease, which is different from the literature. This may be a consequence of many common risk factors such as increased BMI, diet, and lifestyle.

Conclusion

In diabetic patients, the relationship between *H. pylori* infection and thyroid function tests was observed and high BMI and the incidence of reflux disease and atrophy and gastritis increased in the majority of those who were *H. pylori* positive. We can say that autoimmune thyroiditis, due to the high rate of atrophic gastritis in those who are anti-TPO positive, is a risk factor for atrophic gastritis and that diabetic, obese patients should be evaluated in terms of thyroid function. Studies in larger groups are needed to explain the relationship between *H. pylori* infection and thyroid diseases.

Disclosures

Ethichs Committee Approval: The study was approved by the Clinical Research Ethics Committee of Istanbul Kartal Dr. Lutfi Kırdar City Hospital (Date: October 27, 2020; Decision No: 514/ 188/ 5).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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