

## Dyspeptic Symptoms in Patients with Type 2 Diabetes Mellitus: *Helicobacter pylori* Infection and Its Associations with Metabolic Control

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### Abstract

**Aim:** *Helicobacter pylori* (Hp) is the causative agent of the most common chronic infection in the world. The close association of Hp with gastric and duodenal ulcer, gastric cancer and MALToma has been proven. Besides, there are numerous studies reporting the coexistence of Hp with diabetes mellitus, coronary artery disease, idiopathic thrombocytopenic purpura, and iron deficiency anemia.

**Material-Methods:** This study was conducted on 205 diabetic patients including 75 male and 130 female individual with dyspeptic complaints. The endoscopic biopsy specimens of these patients were investigated for the presence of Hp. Also, histochemical examinations were carried out. The patients were divided into two groups, namely, Hp-positive and Hp-negative group. The *Helicobacter pylori* positive group was divided into three subgroups as follows based on their bacterial intensity: Hp density-1, Hp density-2, Hp density-3 groups to compare metabolic parameters between subgroups.

**Results:** A total of 205 diabetic patients enrolled in the study. The mean HbA1c levels of the patients without Hp was  $7.59 \pm 1.66$  while that of the patients with Hp was found to be  $7.57 \pm 1.77$ . No statistically significant difference was detected between these two groups. Likewise, no statistically significant difference was observed in terms of HbA1c levels among the groups when they were classified according to Hp density.

**Conclusion:** In this study, we investigated metabolic outcomes of the coexistence of two commonly occurring entities, a chronic infection and a chronic disease. No relationship was detected regarding the presence of *Helicobacter pylori* and its intensity with the metabolic parameters mainly the HbA1c levels of diabetic people.

**Keywords:** *Helicobacter pylori*; HbA1c; Diabetes mellitus

### Introduction

*Helicobacter pylori* (Hp) is the culprit of one of the most common chronic infections in the world. It is estimated that this bacterium, which is transmitted by fecal-oral route and mostly acquired during childhood, affects approximately half of the world population. However, this number rises up to 80% in developing countries [1]. The only host in which Hp causes disease is human. Although it usually has an asymptomatic course during its life span, it is closely associated with gastroduodenal diseases such as gastritis, peptic ulcer, non-ulcer dyspepsia, gastric carcinoma, MALT-lymphoma, hypertrophic gastropathy [2]. Also, the association of Hp has been extensively investigated in relation to many diseases such as diabetes mellitus (DM), coronary artery disease, cerebrovascular diseases, idiopathic thrombocytopenic purpura (ITP) and iron deficiency anemia (DEA), urticaria and growth retardation [3].

The studies investigating the relationship between Hp and Diabetes Mellitus showed that Hp infection was more frequent in patients having diabetes [4,5]. Considering from another respect, DM was observed to be more prevalent in Hp-positive patients in the study by

Han et al. which included 30810 patients and was completed in 2015 in China (21.3% and 20.2%,  $p=0.026$ ) [6]. Also, numerous studies including large patient populations revealed that the HbA1c levels of Hp-positive diabetic patients were higher than that of Hp-negative diabetic patients, suggesting that bacterial infection may have had a negative effect on blood glucose regulation in infected patients [7,8]. We investigated whether there is any significant difference in metabolic control namely HbA1c levels among the patients having diabetes with dyspeptic complaints who underwent endoscopy.

### Materials and Methods

Our study was conducted on 205 patients having diabetes including 75 male and 130 female individual who were followed up in the internal medicine outpatient clinic of Gaziosmanpasa Taksim Education and Research Hospital between the years of 2014-2015. We, retrospectively, investigated the relationship between HbA1c levels and Hp density which was studied with histochemical examination in the patients out of those with the age range of 23 and 88 years who had dyspeptic complaints and underwent gastroscopy. Exclusion criteria are age of under 18, type 1 diabetes, pregnancy and history of Hp eradication therapy. The gastroscopies of the patients were performed in the endoscopy unit of our hospital. All patients signed informed

consent form before the procedure. Upper GIS endoscopy was performed using Olympus WM-N160 mobile workstation video endoscopy following at least 8 hours of fasting. Immediately before the procedure, topical anesthesia was applied to the oropharynx with lidocaine spray. Endoscopic findings of the procedure were recorded according to the Sydney classification. The punch biopsies taken from prepyloric antrum, incisura angularis and great curvature proximal to the antrum were sent to the pathology department within the formal liquid. The endoscopic biopsy specimens admitted to the pathology unit underwent through normal routine histopathological examination which was performed on the slides obtained from paraffin blocks and stained with Giemsa. Biopsy materials were examined for the presence of Hp and morphological changes. In our study, the patients were firstly divided into two groups, namely, Hp-negative and Hp-positive patients. Then, Hp-positive patients were grouped as Hp density-1, Hp density-2, Hp density-3 at histological level according to the Sydney classification (Mild, Moderate, Severe). The mean HbA1c levels were examined in both main groups and in the groups according to Hp density. Whether there was any significant difference in terms of mean HbA1c levels was also investigated among these groups.

### Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Oneway ANOVA test was used to compare descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as quantitative data while assessing the comparisons of three groups or more. For two group comparisons, the Student t test was used. The Kruskal Wallis test was used for the assessment of HbA1c levels according to Hp between genders due to the number of cases. The chi-square test was used for comparison of qualitative data. Significance level was accepted at  $p < 0.05$ .

### Results

Among 205 patients, 36.6% (n=75) were male and 63.4% (n=130) were female individual. Their ages range between 23 and 88 years with the mean of  $58.33 \pm 11.20$  years. The HbA1c measurements of the study participants were found to vary between 5-13.1 with the mean of  $7.58 \pm 1.72$ . Of the cases, 42.9% (n=88) were Hp-negative, 28.7% (n=59) were Hp density-1, 18.5% (n=38) were Hp density-2 and 9.8% (n=20) were observed to be Hp density-3 (Table 1). The mean HbA1c level of Hp-negative patients was  $7.59 \pm 1.66$  while that of Hp-positive patients was found to be  $7.57 \pm 1.77$ , and there was no statistically significant difference between them ( $p > 0.05$ ). Considering the classification of Hp density, no statistical significance was detected in terms of HbA1c ( $p > 0.05$ ).

Also, there was no statistically significant difference among Hp-positive patients ( $p > 0.05$ ) (Table 2). In female patients, the mean HbA1c level of Hp-negative patients was  $7.33 \pm 1.42$  while that of Hp-positive patients was found to be  $7.53 \pm 1.67$ , and there was no statistically significant difference between them ( $p > 0.05$ ). Also, no statistically significant difference was detected in terms of HbA1c regarding the classification according to Hp density ( $p > 0.05$ ). In male, the mean HbA1c level of Hp-negative patients was  $7.95 \pm 1.91$  while that of the Hp-positive cases was found to be  $7.64 \pm 1.97$ , and there was no statistically significant difference between them ( $p > 0.05$ ). No statistically significant difference was detected in terms of HbA1c regarding the classification of Hp density ( $p > 0.05$ ) (Table 3).

Type 2 DM		Mean $\pm$ SD (n/%)
Age		58.33 $\pm$ 11.21
Gender	Female patients	130 (63.4%)
	Male patients	75 (36.6%)
HbA1c		7.58 $\pm$ 1.72
Hp	Negative	88 (49%)
	Density 1	59 (28.7%)
	Density 2	38 (18.5%)
	Density 3	20 (9.8%)

**Table 1:** Evaluation of demographic characteristics of the patients [Hp: *Helicobacter pylori*].

Hp	n	HbA1C (Mean $\pm$ SD)	p
Negative	88	7.59 $\pm$ 1.66	a0.935
Positive	109	7.57 $\pm$ 1.77	
Negative	88	7.59 $\pm$ 1.66	b0.500
Density 1	54	7.46 $\pm$ 1.67	
Density 2	35	7.44 $\pm$ 1.76	
Density 3	20	8.10 $\pm$ 2.00	b0.330
Density 1	54	7.46 $\pm$ 1.67	
Density 2	35	7.44 $\pm$ 1.76	
Density 3	20	8.10 $\pm$ 2.00	

**Table 2:** Evaluation of HbA1c according to Hp status [a: Student t test, b: Oneway ANOVA test].

Hp	n	Female patients		Male patients		
		HbA1C (Mean $\pm$ SD)	p	n	HbA1C (Mean $\pm$ SD)	p
Negative	52	7.33 $\pm$ 1.42	a0.487	36	7.95 $\pm$ 1.91	a0.498
Positive	72	7.53 $\pm$ 1.67		37	7.64 $\pm$ 1.97	
Negative	52	7.34 $\pm$ 1.42	c0.321	36	7.96 $\pm$ 1.91	c0.441
Density 1	38	7.56 $\pm$ 1.69		16	7.21 $\pm$ 1.66	
Density 2	22	7.18 $\pm$ 1.47		13	7.87 $\pm$ 2.17	
Density 3	12	8.06 $\pm$ 1.91		8	8.17 $\pm$ 2.27	

**Table 3:** Evaluation of HbA1c according to Hp status in female and male patients; [a: Student t test, c: Kruskal Wallis test].

### Discussion

The association of Hp, one of the most common chronic infections, with DM, the chronic disease with increasing frequency has been the subject of many studies for years. One of the meta-analysis including

41 studies and 14,080 diabetic patients revealed that the rate of having Hp in diabetic patients is significantly higher than non-diabetic patients [5].

In our study, 42.9% (n=88) of the patients were Hp-negative and 57.1% (n=117) of them were observed to be Hp-positive which is consistent with the literature. Examining the study participants who were divided into two main groups, namely, Hp-negative and Hp-positive groups from statistical point of view, the mean HbA1c level of Hp-negative patients was found to be  $7.59 \pm 1.66$  while that of Hp-positive patients was  $7.57 \pm 1.7$  without a significant difference between them ( $p>0.05$ ). Considering the Hp density, there was also no statistically significant difference in terms of HbA1c levels among them ( $p>0.05$ ).

Our study was conducted on diabetic patients. Considering the studies conducted with non-diabetic patient groups in order to provide insight about the relation between Hp and blood glucose regulation, Yu Chen and Blazer found that the mean HbA1c level was significantly higher in Hp-positive patients in the non-diabetic general population in their studies including two national studies and approximately 14,000 patients (National Health and Nutrition Examination Survey (NHANES) III and the NHANES 1999-2000) [7]. Hsieh et al. found that the HbA1c levels of Hp positive patients were significantly higher than those of Hp negative in their study including 2060 patients in China. Also, in that study, type 2 diabetes frequency was significantly higher in the Hp-positive group [8].

There was no significant difference in terms of HbA1c levels among Hp-positive and Hp-negative diabetic patients in the meta-analysis including 14 studies and 1781 diabetic patients [9], supporting the results of our study. In that meta-analysis, various studies including type 1 and type 2 diabetic patients with the age range of 11 to 66 years and with the duration of diabetes ranging from 2.9 to 16.1 years were reviewed. The presence of Hp was determined by biopsy in five studies while other nine studies used serology and urea breath test (UBT) for diagnosis. When all groups and subgroups were examined including type 1 and type 2 diabetic patients and the group including both of them, the mean HbA1c level of diabetic patients with Hp was determined not be significantly different from Hp-negative diabetic patients.

The HbA1c values between the Hp-positive diabetic group and Hp-negative diabetic group did not differ significantly in the study by Demir which included 141 diabetic and 142 non-diabetic patients [10]. Again, the HbA1c values did not differ between Hp-negative and Hp-positive patients in the study conducted by Gulcelik et al. on 75 diabetic patients [11]. The study conducted on 63 Chinese diabetic patients by Gray et al. also supported these two studies [12]. In another study from Turkey on diabetic patients in 2011, the impact of Hp positivity on HbA1c level could not be confirmed [13].

In a study, which was conducted on 333 diabetic patients in Japan, the HbA1c level was not found to be higher in Hp-positive group [14]. According to the result of the research in which 127 diabetic patient was screened in Spain, the HbA1c value did not differ between the diabetics with and without Hp infection [15].

The studies which include type 1 diabetic patients have similar results with the studies on type 2 diabetic patients. For example, in a study conducted by Candelli et al. on 121 type 1 diabetic children in 2002, glycemic control and HbA1c levels did not change in both groups (those with and without Hp infection) [16]. Also, no difference was noted between both groups in the study conducted on 138 type 1

diabetic patients in Italy [17]. Similarly Vafaeimanesh et al. observed 211 patients with type 1 and type 2 diabetes in 2014, no difference was revealed between the diabetic groups with and without Hp [18].

Findings of our study contradicts the idea that Hp increases insulin resistance through inflammatory cytokines such as CRP and IL-6 and leads to permanent hyperglycemia [19,20]. This contradictory result can be explained in such a way that glycemic control does not become significant due to increasing the anti-hyperglycemic treatment in response to hyperglycemia in Hp-positive patients [21]. Or it can be considered that weight loss occurring as a result of chronic gastritis and reduced appetite caused by Hp may prevent worsening of glycemic control to some extent. Further analysis of the anti-hyperglycemic treatments, other medications and dietary habits engaged in by the patients is required in order to elucidate these speculations and to determine their impact on the study.

Bajaj et al. found high HbA1c levels in Hp-positive group on 80 diabetic patients in Iran [22]. The HbA1c levels was also found to be significantly higher in the Hp-positive diabetic group in the study by Fernandini et al. conducted on 75 diabetic patients [23]. The fact that detecting HbA1c higher in Hp-positive patients were interpreted by various investigators as a detrimental effect of Hp inflammation at gastric and duodenal level by impairing the balance of blood glucose and lipid absorption.

Another mechanism might be that Hp reduces ghrelin secretion and increase leptin secretion through ghrelin-producing cells in the gastric mucosa. As is known, ghrelin and leptin are two hormones which are effective on energy consumption and appetite. While Ghrelin supports weight gain by reducing energy consumption, leptin reduces weight gain by increasing energy consumption and decreasing appetite. In the presence of Hp, the change in the levels of these two hormones is considered to have a negative effect on blood glucose regulation through various means, the exact mechanism of which cannot be elucidated [7].

There are some limitations in this study. First this is a cross-sectional study of a relatively small number of patients. Second, one of the exclusion criteria is the Hp eradication history that depends on patients' declaration which decreases the reliability of the data.

## Conclusion

The impact of Hp positivity on diabetic patients is still being intensively explored in the research. Further studies are needed to clarify the effect of Hp on these patients, especially on blood glucose regulation.

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