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Association between type 2 diabetes mellitus and *Helicobacter pylori* infection among Saudi patients attending National Guard Primary Health Care Centers in the Western Region, 2018

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Abstract:

BACKGROUND: Reports on *Helicobacter pylori* infection in diabetics are inconsistent and contradictory. This study attempted to identify the possible association between type 2 diabetes and *H. pylori* infection.

MATERIALS AND METHODS: Following a cross-sectional design, participants were recruited from four National Guard Primary Health Care Centers in Jeddah City, Saudi Arabia. The study was conducted from December 2017 to November 2018. All participants underwent hemoglobin A1C (HbA1c) assessment and stool antigen test for *H. pylori.*

RESULTS: A total of 212 type 2 diabetic patients aged 40 years or more, and 209 age-matched nondiabetic subjects were included in the study. About one-quarter of the diabetics and nondiabetics were positive for *H. pylori* (26.9% and 26.3%, respectively). There was no significant difference. The prevalence of *H. pylori* did not differ significantly in the type 2 diabetics, with regard to their age groups, gender, smoking status, body mass index, chronic diseases, their HbA1c level, duration of diabetes, or received type of therapy. The prevalence of *H. pylori* was significantly higher in overweight and obese nondiabetic subjects ($P = 0.013$). Obese participants in both groups had the highest prevalence of infection (57.9% and 54.5%, respectively, $P = 0.038$).

CONCLUSION: About one-quarter of type 2 diabetics and nondiabetics in Jeddah City have *H. pylori* infection. There is no association between diabetes and *H. pylori* infection. *H. pylori* was significantly higher in patients with a high body mass index.

Keywords:

Diabetes mellitus type 2, *Helicobacter pylori*, risk factors, stool antigen test

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Introduction

As a microaerophilic bacterium (Gram-negative), *Helicobacter* is known to cause infection in gastric mucous layer's epithelial lining. As a matter of the fact, it is the primary reason for chronic gastritis, and those infected with this bacterium are faced with a significantly heightened risk of being diagnosed with gastric cancer. It is also responsible for nearly 90% of all peptic ulcer cases. A systematic worldwide study conducted in 2015 showed that

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nearly 4.4 billion individuals were reported to be positive for *Helicobacter pylori*, which is more common in low socioeconomic populations, Hispanics, Asian Americans, as well as older adults.[1] For this reason, the prevalence of *H. pylori* is greater in developing countries.[2] This high prevalence has also been observed in Saudi Arabia although studies conducted recently suggest that the prevalence of infection has dropped considerably.

Infection with *H. pylori* is commonly associated with several gastric diseases (e.g. chronic gastritis, peptic ulceration, and gastric cancer),[3] as well as extra-gastrointestinal disorders such as metabolic syndrome and cardiovascular diseases, and some have been characterized by persistent and low-grade systemic inflammation.[4]

Although *H. pylori* infection and diabetes mellitus are two separate diseases, it has been observed that poor glycemic control in type 2 diabetics is related to higher rates of *H. pylori* infection. *H. pylori* infection has been described as one of the most common complications in diabetics with gastric symptoms.[5]

Chung *et al*.[6] observed that the eradication of *H. pylori* improves insulin resistance. Talley *et al*.[7] added that neuropathy and hyperglycemia play an important role in *H. pylori* colonization in the gastric epithelium. Furthermore, a significant correlation has been observed between *H. pylori* infection and microvascular complications.[8]

Reports on *H. pylori* infection in diabetic patients have been found to be conflicting and inconsistent,[9] the prevalence of *H. pylori* in type 2 diabetic patients having been reported as high,[10,11] low,[12] or even normal.[13] Therefore, the association of diabetes mellitus and infection with *H. pylori* has to be explored.

The aim of the present study was to identify the possible association between type 2 diabetes and *H. pylori* infection.

Materials and Methods

This study using a cross-sectional design was conducted from December 2017 to November 2018. Participants were recruited from four Primary Health Care of National Guard (NG) Centers in Jeddah City, Saudi Arabia (Alwaha, Iskan, Family Medicine Clinic NG Hospital, and Bahra Centers).

The sample size was determined according to the association of *H. pylori* with type 2 diabetes, assuming a 13% frequency difference between diabetic and nondiabetic patients provided in the published reports.[14,15] Under these parameters, we estimated that approximately 210 diabetic patients and 210 nondiabetic patients (control subjects) would provide 80% of the power to reject the null hypothesis at $P < 0.05$. We included individuals aged 40 years and above. Exclusion criteria were patients known to have *H. pylori* and who have received eradication treatment or were on proton pump inhibitor, those with hemoglobinopathies and with a previous history of renal failure, chronic liver disease, or malignant disease, or those on immunosuppressant agents.

The diabetics (cases) were selected randomly from the chronic disease clinic of the primary health care centers, and the nondiabetics were randomly selected from the day-to-day appointment list of those who presented at the primary health care centers with ailments other than diabetes mellitus. The study utilized a questionnaire to gather information on their sociodemographic characteristics. All participants underwent hemoglobin A1c (HbA1c) assessment and stool antigen test for *H. pylori.*

The control subjects were proven as nondiabetics by HbA1c performed according to the American Diabetes Association's Criteria of Medical Care in Diabetes.[16]

The 13C-urea breath test is accepted as a reliable noninvasive test for detecting *H. pylori* infection, but this 13C-urea breath test was not available in most clinical care centers, particularly in primary health care centers. The stool antigen test of *H. pylori*, the validity of which, has been well studied and approved as an alternative test for the 13C-urea breath test was, however, available in the primary care centers. Tanaka and Takahashi[17] found that the specificity and sensitivity of the *H. pylori* stool antigen test were 95% and 98.3%, respectively, for primary diagnosis.

Ethical approval from the institutional review board/ethics committee was obtained, and informed written consent was taken from all participants. The researchers obtained an official approval from the directors of the primary health care centers for the study. Symptomatic participants who were positive for the stool antigen test were given the necessary treatment.

IBM SPSS Statistics program software version 24 (2015) was used to analyze the data. Frequency and percentages were calculated. The data were expressed by mean ± standard deviation of age among the numerical parameters. The *t*-test was used to compare the means of two independent groups. The Chi-square test was applied to compare categorical variables, with two or

more categories (e.g., *H. pylori* positive and negative with gender and other categorical risk factors). Multivariate regression analysis was performed to identify the risk factors associated with the presence of *H. pylori* infection. Odds ratios and their 95% confidence intervals were calculated. $P < 0.05$ was considered statistically significant.

Results

A total of 212 diabetic patients aged 40 years or more and 209 age-matched nondiabetic subjects were included.

Figure 1 shows that 26.9% of the diabetics and 26.3% of the nondiabetics were positive with *H. pylori*. There was no significant difference between the two groups of participants regarding the prevalence of *H. pylori.*

Table 1 shows that, of the type 2 diabetics, the prevalence of *H. pylori* did not differ significantly according to their age groups, gender, smoking status, body mass index, or chronic diseases. Moreover, it shows that, of the nondiabetics, the prevalence of *H. pylori* was significantly higher in overweight and obese subjects ($P = 0.013$). However, it did not differ significantly with regard to their age groups, gender, smoking status, chronic diseases, or their health care center.

Table 2 shows that the prevalence of *H. pylori* in the diabetics did not differ significantly by their HbA1c level, duration of diabetes, or type of therapy received.

Table 3 shows the results of multivariate regression analysis of factors that predict diabetes mellitus in the studied population. Male patients and those with hypertension or dyslipidemia were significantly associated with diabetes mellitus ($P < 0.05$). Although older patients (≥60 years old), smokers, and those with positive *H. pylori* were more likely to have diabetes mellitus, none of the differences were statistically significant ($P > 0.05$).

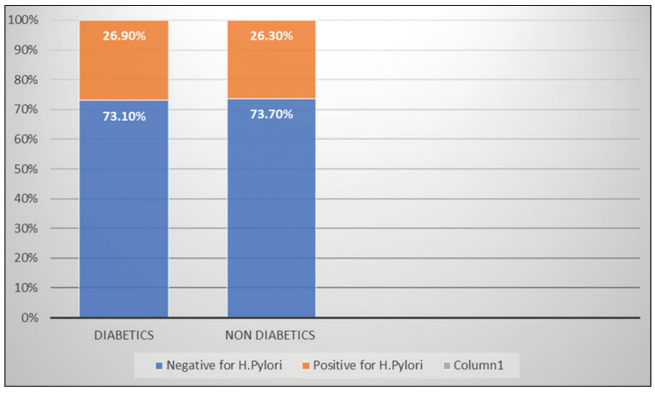

Figure 1: Prevalence of *Helicobacter pylori* in diabetic and nondiabetic participants*. *$P = 0.09$

Discussion

The results of this study revealed that the prevalence of *H. pylori* infection was slightly higher in diabetics than in nondiabetics (26.9% and 26.3%, respectively). This finding accords with those of several studies.

The prevalence of *H. pylori* infection in type 2 diabetics ranges from 30% to 78%.[9] Bener *et al*.[18] stated that the variability in prevalence of *H. pylori* infection might be attributed to epidemiological distribution of *H. pylori.*

Regarding risk factors of *H. pylori* infection, the current study showed that of the diabetics, there was no significant difference as regards their HbA1c level, duration of diabetes, or type of therapy received. Moreover, *H. pylori* infection was highest in obese participants of both groups. However, the prevalence of *H. pylori* infection did not differ significantly according to gender or smoking status.

Chen and Blaser[19] described a synergistic effect of body mass index and *H. pylori* infection on increased levels of HbA1c, indicating a possible role of *H. pylori infection* in adults with impaired glucose tolerance possibly potentiated by a higher body mass index.

Malecki *et al*.[12] reported no association between *H. pylori* infection, levels of HbA1c, and duration of diabetes with upper gastrointestinal symptoms in diabetics. Moreover, Oluyemi *et al*.[20] noted that the prevalence of *H. pylori* was neither associated with duration of diabetes nor associated with gender, body mass index, smoking status, or age.

The present study showed no significant difference in the prevalence of *H. pylori* infection between diabetics and nondiabetics. This finding is in accordance with those of other studies which reported no significant difference in the prevalence of *H. pylori* infection between diabetics and nondiabetics.

In Hong Kong, Malecki *et al*.[12] reported the prevalence of *H. pylori* infection in Chinese subjects with type 2 diabetes at around 50%, similar to that of the control subjects. In Athens, Greece, Anastasios *et al*.[9] stated that the *H. pylori* infection was slightly higher in diabetics than in nondiabetics (37.3% and 35.2%, respectively), but the difference was not statistically significant.

Cohen and Muhsen[21] demonstrated a higher body mass index in patients with *H. pylori* infection. Bener *et al*.[18] noted that the prevalence of *H. pylori* infection was higher in obese type 2 diabetic patients as opposed to the normal population. Takashima *et al*.[22] added that *H. pylori* infection has been shown to interfere with serum lipid profile of patients and can, therefore, be a risk factor for diabetes.

Table 1: *Helicobacter pylori* infection occurrence according to demographic characteristics of studied patients

Demographic characteristics	Type 2 diabetics (*n*=212)		*P*-Value	Nondiabetics (*n*=209)		*P*-Value
	Negative for *H. pylori* *N* (%)	Positive for *H. pylori* *N* (%)		Negative for *H. pylori* *N* (%)	Positive for *H. pylori* *N* (%)	
Age groups (years)						
<50	31 (70.5)	13 (29.5)	0.491	60 (65.9)	31 (34.1)	0.080
50-60	64 (70.3)	27 (29.7)		60 (78.9)	16 (21.1)	
≥60	60 (77.9)	17 (22.1)		34 (81.0)	8 (19.0)	
Gender						
Male	71 (76.3)	22 (23.7)	0.348	42 (70.0)	18 (30.0)	0.443
Female	84 (70.6)	35 (29.4)		112 (75.2)	37 (24.8)	
Smoking status						
Smoker	36 (75.0)	12 (25.0)	0.737	24 (68.6)	11 (31.4)	0.452
Nonsmoker	119 (72.6)	45 (27.4)		130 (74.7)	44 (25.3%)	
BMI (kg/m^2)						
<25	16 (57.1)	12 (42.9)	0.061	25 (82.2)	4 (13.8)	0.013
25-29.9	51 (81.0)	12 (19.0)		47 (69.1)	21 (30.9)	
≥30	88 (72.7)	33 (27.3)		82 (73.2)	30 (26.8)	
Chronic diseases						
Hypertension	88 (76.5)	27 (23.5)	0.223	32 (76.2)	10 (23.8)	0.680
Dyslipidemia	73 (76.8)	22 (23.2)	0.270	26 (74.3)	9 (25.7)	0.929
Primary health care center						
Family medicine clinic NG hospital	38 (71.7)	15 (28.3)	0.615	38 (73.1)	14 (26.9)	0.812
Waha	39 (73.6)	14 (26.4)		39 (75.0)	13 (25.0)	
Iskan	36 (67.9)	17 (32.1)		36 (69.2)	16 (30.8)	
Bahra	42 (79.2)	11 (20.8)		41 (77.4)	12 (22.6)	

BMI=Body mass index, *H. pylori=Helicobacter pylori*

Table 2: Prevalence of *Helicobacter pylori* infection in diabetics according to their glycated hemoglobin level, duration of disease and type of therapy

Characteristics	Negative for *H. pylori* (*n*=155) *N* (%)	Positive for *H. pylori* (*n*=155) *N* (%)	*P*-Value
HbA1c (%)			
<7	56 (69.1)	25 (30.9)	0.194
7-10	88 (77.9)	25 (22.1)	
≥10	11 (61.1)	7 (38.9)	
Duration of disease (years)			
<5	53 (74.6)	18 (25.4)	0.375
5-10	58 (68.2)	27 (31.8)	
≥10	44 (78.6)	12 (21.4)	
Type of therapy			
Oral hypoglycemic agents	138 (73.4)	50 (26.6)	0.789
Insulin	54 (71.1)	22 (28.9)	0.613

HbA1c=Glycated hemoglobin, *H. pylori=Helicobacter pylori*

Salih[23] stated that, in adults, *H. pylori* infection increased with age, but no association was found between *H. pylori* infection and age in our study. Zaterka *et al*.[24] noted that smoking was considered as a risk factor for *H. pylori* infection. However, the association between *H. pylori* infection and smoking has been attributed mainly to the socioeconomic conditions of patients.[25]

Other studies have also reported no association between *H. pylori* infection and diabetes. Xia *et al*.,[26] in China, noted that seroprevalence of *H. pylori* infection was not significantly different in diabetics compared to nondiabetic controls. Oluyemi *et al*.[20] also found no significant difference in the prevalence of *H. pylori* infection between type 2 diabetics and controls in Nigeria. Similar findings have been reported in other countries, including Italy,[27] China,[28] Turkey,[29] and Romania.[30]

He *et al*.[31] noted that the discrepancies concerning the reported association between *H. pylori* infection and diabetes might be the result of the differences in the methods used to define *H. pylori* positivity and diabetic status, limited sample sizes, and adjustments for potential confounders, such as age and socioeconomic status. Moreover, the sources of bias may include inaccuracies of self-reported data, which mainly depends on participants' knowledge and understanding of the relevant information, their ability to recall, and their willingness to report.

It is to be noted that the lack of significant differences regarding *H. pylori* infection in diabetics in the present study regarding their HbA1c level, duration of diabetes, or type of therapy received supports the lack of association between *H. pylori* infection and type 2 diabetes mellitus.

Table 3: Multivariate logistic regression analysis of variables associated with occurrence of *Helicobacter pylori* infection in the studied patients

Characteristics	Diabetics (*n*=209) *N* (%)	Nondiabetics (*n*=208) *N* (%)	OR	95% CI	*P*-Value
Age groups (years)					
<60	129 (44.2)	163 (55.8)	-	-	-
≥60	83 (64.3)	46 (35.7)	1.56	0.96-2.53	0.07
Gender					
Male	93 (60.8)	60 (39.2)	1.85	1.18-2.89	0.01
Female	119 (44.4)	149 (55.6)	-	-	-
Smoking status					
Smoker	48 (57.8)	35 (42.2)	1.53	0.87-2.69	0.14
Nonsmoker	164 (48.5)	174 (51.5)	-	-	-
BMI (kg/m^2)					
<25	71 (49.7)	72 (50.3)	-	-	-
25-29.9	22 (46.8)	25 (53.2)	1.02	0.48-2.17	0.96
≥30	117 (51.1)	112 (48.9)	1.33	0.82-2.15	0.25
Chronic diseases					
Hypertension					
Yes	115 (73.2)	42 (26.8)	3.39	2.11-5.45	0.001
No	97 (36.7)	167 (63.3)	-	-	-
Dyslipidemia					
Yes	95 (73.1)	35 (26.9)	2.85	1.75-4.64	0.001
No	117 (40.2)	174 (59.8)	-	-	-
H. pylori					
Positive	57 (51.4)	54 (48.6)	1.23	0.75-2.00	0.41
Negative	152 (49.7)	154 (50.3)	-	-	-

OR=Odds ratio, CI=Confidence interval, BMI=Body mass index, *H. pylori*=*Helicobacter pylori*

Therefore, the results of the present study indicate that diabetes mellitus might not be a risk factor for *H. pylori* infection and vice versa, in the population in Jeddah, Saudi Arabia. This is also in agreement with Tamura *et al*.[32] in Japan, who reported negative or neutral results for such an association.

Vafaeimanesh *et al*.[33] stated that, regardless of the debate about which causes the other, the association between diabetes and *H. pylori* needs to be reviewed in different studies.

On the other hand, some case–control studies have reported that *H. pylori* infection was significantly associated with diabetes.[5,18] Bener *et al*.[18] explained that *H. pylori* gastric infection increased the secretion of pro-inflammatory cytokines, resulting in changes in the structure of insulin receptor, thus interfering with the interaction between its receptor and insulin. Nevertheless, Anastasios *et al*.[9] stressed that there is no satisfactory explanation for the differences in *H. pylori* infection between diabetics and nondiabetics.

Hsieh *et al*.[34] reported that long-term *H. pylori* infection was significantly associated with high levels of HbA1c, decreased insulin secretion, and a higher prevalence of type 2 diabetes mellitus. These results seem to support the validity of the proper screening of *H. pylori* infection together with regular monitoring of blood glucose and HbA1c levels for the early detection of glucose dysregulation and the prevention of type 2 diabetes mellitus.

Moreover, Tamura *et al*.,[32] who also found a significantly higher prevalence of diabetes in relation to *H. pylori* infection, reported that after age adjustment, there was no significant difference. They stated that the significant difference could be explained by the older age of those infected and the higher prevalence of diabetes in the elderly.

In addition, Azuma[35] stated that there are two major subtypes of CagA strain of *H. pylori*, i.e., the East Asian and the Western types. Only one-half to two-thirds of Western infections carry Western CagA, while nearly all East Asian strains have East Asian CagA. The association between *H. pylori* and diabetes has been hypothesized to be limited to Western CagA.[36,37]

Chen and Blaser[19] added that *H. pylori* seropositivity, but CagA positivity in particular, was associated with higher mean HbA1c levels. This association persisted even after excluding individuals with a history of diabetes and controlling for potential confounders.

The limitations of our current study are that we had limited data on systemic complications of diabetes

mellitus in our study and we did not stress the complications of diabetes mellitus.

As part of this study, we did the stool antigen test (*H. pylori)*, but the 13C-urea breath test and/or endoscopy were not done because of the limited access to these tests in the primary health care centers.

Further studies should be undertaken to evaluate the association between the complications of diabetes and *H. pylori* infection in relation to gastrointestinal disease in diabetics.

Conclusion

About one-quarter of type 2 diabetics and nondiabetics in Jeddah City had *H. pylori* infection. The lack of a significant difference between type 2 diabetic patients and controls regarding *H. pylori* infection suggests that there is no association between diabetes and *H. pylori* infection, although *H. pylori* infection is significantly higher patients with a high body mass index.

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Conflicts of interest
There are no conflicts of interest.

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