Helicobacter pylori Infection Associated with Type 2 Diabetes: A Case–Control Study

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***Abstract*—*Helicobacter pylori* (Hp) is a spiral Gram-negative bacterium that causes gastritis and peptic ulcers. It has been identified as a risk factor for gastric cancer and has become a significant global health burden. This is further complicated by being associated with increasing the prevalence of Type 2 diabetes (T2D). The study aimed to evaluate the possible associations between Hp infection and T2D, as well as its impact on glycated hemoglobin. A 1:1 matching case–control study is conducted on 548 individuals with T2D as cases and 548 controls, and a ^{14}C-urea breath test is used to determine the presence of Hp infection. All diabetic subjects are tested for glycated hemoglobin, and binary logistic regression analysis is used to evaluate the associations between Hp infection and T2D. The prevalence of Hp infection is higher among cases (58.94%) than control subjects (38.69%) ($p < 0.001$). A significant association is observed between Hp infection and T2D according to logistic regression analysis (OR = 2.275; 95% CI: 1.786-2.898; $p < 0.001$), and there is a significant association ($p = 0.022$) between glycated hemoglobin levels and Hp infection. Individuals infected with Hp had a higher-level glycated hemoglobin (7.84 ± 1.797) than Hp-negative individuals ($p < 0.001$). Hp infection is associated with elevated glycated hemoglobin levels. Type 2 diabetes is considered a risk factor for developing Hp infection.**

IIndex Terms*—^{14}C-urea breath test, Case–control study, Diabetes mellitus, HbA1C, *Helicobacter pylori

I. Introduction

Helicobacter pylori (Hp) is a gram-negative microaerophilic pathogen that causes gastrointestinal disorders such as chronic inflammation, gastric ulcers, and gastric cancer (Malfertheiner, et al., 2023). It was noted that chronic Hp infection is a significant contributor to cancer-related mortality on a global scale (Thrift and El-Serag, 2020). Up to 3% of individuals with Hp-infection develop gastric cancer (Uemura, et al., 2001). However, early detection of Hp-infection with accurate testing can help prevent this progression (Dore and Graham, 2022). In which the ^{14}C-urea breath test was a reliable diagnostic tool for identifying active Hp-infections (Sabbagh, et al., 2019).

The Hp-infections affect more than half of the population worldwide, and their prevalence varies depending on geographical location, which recorded a higher rate of infections in developing regions than in developed countries (Li, et al., 2023; Shah, et al., 2024). However, the chronic metabolic disorder Type 2 diabetes (T2D) has been increasing and linked to various complications (Andrew and Adrian, 2022), and the incidence has rapidly increased globally in the past three decades, particularly in developing countries (Lovic, et al., 2020; Liu, et al., 2022). In which individuals with T2D have increasing susceptibility to infections (Cooke, 2022) and become a significant risk factor for all types of infections when blood glucose levels are uncontrolled (Chávez-Reyes, et al., 2021). Moreover, individuals with T2D are more likely to have Hp infections compared to those without T2D (Kouitcheu Mabeku, Noundjeu Ngamga, and Leundji, 2020).

The exact mechanism by which Hp-infection might contribute to the development of diabetes is incompletely understood. One hypothesis states that Hp-induced chronic inflammation and release of inflammatory cytokines may increase insulin resistance and affect the pancreatic B cells, then reduce insulin secretion (Hosseininasab Nodoushan and Nabavi, 2019). Besides, Hp-infection can disrupt the composition and diversity of the gut microbiota, possibly affecting the host's serum metabolism (Zang, et al., 2023). However, the findings on the association between Hp-infection and T2D have yielded conflicting results. Several studies have revealed no significant link between Hp-infection and T2D (Xia, et al., 2001; Tamura, et al., 2015; Man, et al., 2020). Others found a significant positive correlation between Hp-infection and T2D (Bajaj, et al., 2014; Mansori, et al., 2020).

The correlation between T2D and Hp infection is still unclear and poorly understood. Thus, the relationship remains unclear and warrants further exploration. The impact of this research may result in the development of new prevention and intervention strategies for T2D and Hp infections. These strategies will improve patient outcomes, particularly in populations where these conditions are common. Therefore, the present study has been conducted to evaluate the link between T2D and Hp infection and the impact of glycemic control on this relationship.

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II. Materials and Methods

A. Study design and participants

A 1:1 matching case–control study in Erbil, Iraq, was undertaken from January 2020 to July 2022. The study was conducted on 548 cases and an equal number of controls attending private clinics in the same residential area by a convenience sampling technique. The case group was defined as individuals with T2D who were diagnosed by official documents indicating they have been having T2D for two years and excluded individuals who had Type 1 diabetes. The control group was composed of 548 healthy non-diabetic individuals matching cases based on gender, age, and body mass index (BMI). Furthermore, the study excluded individuals who had a history of gastric surgery, used antibiotics or proton pump inhibitors in the past two months, smoked, were pregnant or lactating, or had any other chronic diseases that could potentially impact the results. As well, case–control pairs that were not matched were excluded from the data analysis.

Data were collected from both groups using a questionnaire that collected information on demographics. Height and weight measurements were taken for each participant, and their BMI was calculated by dividing their weight in kilograms by the square of their height in meters. To estimate glycated hemoglobin (HbA1c) levels, blood venous samples were withdrawn from participants with T2D into EDTA tubes and subsequently analyzed using the Roche Diagnostics Cobas analyzer.

B. Detection of Hp infection status

The ^{14}C-urea breath test was used to detect Hp-infection status under the instructions provided by the manufacturer (Headway, China). Briefly, each participant swallowed a capsule containing ^{14}C-labeled urea with 200 mL of water. After 15 min, a breath sample was obtained by blowing it into a collection card for 3-5 min. The presence of Hp was then determined by measuring the quantity of ^{14}C-labeled urea within the breath sample using the Hp-detector (Headway, China).

C. Ethical approval

The study strictly adheres to ethical guidelines and obtains ethical approval from the Ethical Committee at Hawler Medical University. Before inclusion in the study, the participants provided their informed consent. Throughout the study process, data were consistently maintained, and participants were informed of their right to withdraw without facing any negative consequences. The use of a ^{14}C-urea breath test is safe and involves minimal radiation exposure.

D. Statistical analysis

The statistical data analysis was conducted using SPSS software version 25.0 for Microsoft Windows. Descriptive statistics were used to summarize the characteristics of both case and control subjects. Logistic regression was applied to determine the odds ratio (OR) and 95% confidence interval (CI) to express the association between Hp-infection and T2D. Categorical data are provided as frequencies (percentages), while continuous variables are reported as means ± standard deviation (SD). The Pearson chi-square test was applied to analyze associations between categorical variables, and the t-test was applied to compare the mean values of continuous variables between groups. The p-value < 0.05 was considered statistically significant.

III. Results and Discussion

A. Results

Table I presents the baseline characteristics of the 1096 subjects, comprising 548 individuals with T2D as the case group and 548 non-diabetic individuals as the control group. Of all participants, 509 (46.44%) were male, and 587 (53.56%) were female. The participants had an average age of 60.48 years, with 39.60% between 55 and 64 years old, and 35.13% aged 65 or older. Approximately 69% of participants were obese, with a mean BMI of 32.77±4.01 for cases and 31.55±3.63 for controls.

Among all participants, 48.81% (535 out of 1,096) were identified as having Hp-infection based on the urea breath test. This prevalence was significantly higher ($p < 0.001$) in participants with T2D (58.94%, 323 out of 548) compared to non-diabetic control subjects (38.69%, 212 out of 548). A logistic regression analysis further confirmed the association between Hp infection and T2D (OR = 2.275; 95% CI: 1.786–2.898; $p < 0.001$) (Table II).

A total of 535 individuals were infected with Hp, with 323 in the case group (T2D individuals) and 212 in the control group. The prevalence of males was 45.82% (148 out of 323) in the case group and 47.64% (101 out of 212) in the control group. Among the cases, 40.87% were aged 65 years or older, and 40.56% were aged 55 to 64 years, with a mean age of 61.76 ± 7.816 years. In the control group, the mean age was 60.60 ± 8.333 years. The majority (70.84%) of all Hp-infected individuals were classified as obese, with a mean BMI of 33.08 ± 3.936 in the cases and 31.40 ± 3.30 in the

TABLE I
Baseline Characteristics of Individuals with T2D as the Case Group and Non-diabetic Control Groups

Characteristics	Case group (*n*=548)	Control group (*n*=548)	All subjects (*n*=1,096)
Gender			
Male	255 (46.53%)	254 (46.35%)	509 (46.44%)
Female	293 (53.47%)	294 (53.65%)	587 (53.56%)
Age groups (years)			
35-44	9 (1.64%)	10 (1.82%)	19 (1.73%)
45-54	130 (23.72%)	128 (23.36%)	258 (23.54%)
55-64	214 (39.05%)	220 (40.15%)	434 (39.6%)
≥ 65	195 (35.58%)	190 (34.67%)	385 (35.13%)
Age (mean±SD)	60.57±8.313	60.39±8.471	60.48±8.389
BMI (kg/m^2)			
Normal (18.5–<25)	20 (3.65%)	19 (3.47%)	39 (3.56%)
Overweight (25.0–<30)	148 (27.01%)	154 (28.1%)	302 (27.55%)
Obese (30.0 or higher)	380 (69.34%)	375 (68.43%)	755 (68.89%)
BMI (Mean±SD)	32.77±4.012	31.55±3.629	32.16±3.872

BMI: Body mass index, HbA1c: Glycosylated hemoglobin

controls. There were no statistically significant differences in the prevalence of Hp-infection based on gender, age, or BMI between the case and control groups (Table III).

Among the individuals with T2D who were positive for Hp, 55.72% (180 out of 323) had an HbA1c level of 7% or higher. In contrast, the rate was 45.33% (102 out of 225) in individuals with Hp-negative (Table IV). Statistical analysis using the Pearson Chi-Square test revealed a significant association between Hp-infection and HbA1c levels ($p = 0.022$). Moreover, the individuals with Hp-infection had slightly higher mean HbA1c levels (7.84 ± 1.797) compared to those without Hp-infection, and this difference is statistically significant ($p < 0.001$).

B. Discussion

An important issue is the growing coexistence of Hp infection and T2D, which poses a significant public health burden, particularly in developing countries (Hooi, et al., 2017; Ren, et al., 2022; Ye, et al., 2023). The present study demonstrated an association between Hp-infection and T2D. The individuals with T2D and simultaneous Hp-infection showed a high value of HbA1c in comparison to those without Hp infection. The logistic regression analysis further confirmed this relationship and demonstrated that the individuals with T2D were 2.275 times more likely to be infected with Hp. Hence, this suggests a potential role of T2D in Hp acquisition, and this was in line with previous studies (Shi, et al., 2018; Chen, et al., 2019a; Bener, et al., 2020).

It has been reported that Hp infection can increase the risk of T2D in the Chinese elderly and middle-aged population (Zhou, et al., 2022). On the contrary, three previous studies reported no association between T2D and Hp-infection (Alzahrani, et al., 2017; Pyo, et al., 2019; Alias and Elkarsany, 2022). In my opinion, there are several reasons why different studies have reported varied results. Some of the critical contributors to these differences are due to different study designs and the inclusion of studied different populations. In addition, the diverse methods applied for the diagnosis of Hp infection may be a potential source for different results. In the current study, Hp infection was confirmed by a ^{14}C-urea breath test that gave high sensitivity

TABLE II
Binary Logistic Regression Analysis of the Association between Hp Infection and Type 2 Diabetes (T2D)

Hp status	Case group (*n*=548) (%)	Control group (*n*=548) (%)	All subjects (*n*=1,096) (%)	p-value*	Logistic regression	
					OR (95 CI)	p-value
Hp-positive	323 (58.94)	212 (38.69)	535 (48.81)	<0.001	2.275 (1.786–2.898)	<0.001
Hp-negative	225 (41.06)	336 (61.31)	561 (51.19)			

*Pearson Chi-square. Hp: *Helicobacter pylori*, OR: Odds ratio, CI: Confidence interval

TABLE III
Characteristics of Individuals with *Helicobacter pylori* Infections in the Case (Type 2 Diabetes) and Control Groups

Characteristics	Case group (*n*=323)	Control group (*n*=212)	All subjects (*n*=535)	p-value*
Gender				0.68
Male	148 (45.82%)	101 (47.64%)	249 (46.54%)	
Female	175 (54.18%)	111 (52.36%)	286 (53.46%)	
Age groups (years)				0.272
35–44	2 (0.62%)	3 (1.42%)	5 (0.93%)	
45–54	58 (17.96%)	50 (23.58%)	108 (20.19%)	
55–64	131 (40.56%)	84 (39.62%)	215 (40.19%)	
≥65	132 (40.87%)	75 (35.38%)	207 (38.69%)	
Age (mean±SD)	61.76±7.816	60.60±8.333	61.30±8.038	
BMI (kg/m^2)				0.508
Normal (18.5–<25)	9 (2.79%)	5 (2.36%)	14 (2.62%)	
Overweight (25.0–<30)	80 (24.77%)	62 (29.25%)	142 (26.54%)	
Obese (30.0 or higher)	234 (72.45%)	145 (68.4%)	379 (70.84%)	
BMI (mean±SD)	33.08±3.936	31.40±3.301	32.42±3.784	

BMI: Body mass index, HbA1c: Glycosylated hemoglobin.
*Pearson Chi-square

TABLE IV
Association between Hp Infection and Glycated Hemoglobin (HbA1c) Levels in the Case Group (Type 2 Diabetes)

HbA1c levels	Hp-positive		Hp-negative		Total	
	n (%)	Mean±SD	n (%)	Mean±SD	n (%)	Mean±SD
Below 7%	143 (44.27%)	6.30±0.455	123 (54.67%)	6.06±0.534	266 (48.54%)	6.19±0.506
7–10%	139 (43.03%)	8.38±0.879	86 (38.22%)	7.90±0.738	225 (41.06%)	8.19±0.859
Above 10%	41 (12.69%)	11.36±0.682	16 (7.11%)	10.20±1.396	57 (10.4%)	11.03±1.063
Total	323	7.84±1.797	225	7.06±1.418	548	7.52±1.694

Hp: *Helicobacter pylori*, SD: Standard deviation. The Chi-square test demonstrated a statistically significant association between Hp infection and HbA1c levels (p=0.022). The t-test indicated significantly elevated mean HbA1c levels in Hp-positive individuals compared to those who were Hp-negative ($p < 0.001$)

and specificity results (Chey, 2000). This test is considered more accurate and reliable than serological or stool tests as it directly identifies active Hp infection by detecting ^{14}C-labeled carbon dioxide produced when bacterial urease breaks down labeled urea. In contrast to stool tests, which may yield false positives due to residual antigens after infection resolution, or serological tests, which detect long-lasting antibodies even after the infection has been eradicated (Talebi Bezmin Abadi, 2018; Costa, et al., 2024).

The relationship between Hp infection and T2D cannot be confirmed due to the lack of enough evidence. Still, there are a few reasons that can be suggested to support this association. First, it has been shown that the immune system response in individuals with T2D is suppressed and they are more prone to Hp-infection (Daryabor, et al., 2020). Second, changes in glucose metabolism can result in alterations in the production of chemicals in the gastric mucosa and increase the colonization by bacteria (Martin-Nuñez, et al., 2021). Third, diabetic patients are more exposed to pathogens than healthy patients, possibly due to the great number of interactions with the healthcare environment (Toniolo, et al., 2019). Fourth, diabetes reduces gastrointestinal movements and gastric acid secretion and increases colonization, overgrowth, and subsequent infections (Singh, et al., 2021). Diabetes also causes damage to the stomach lining, making it more susceptible to Hp colonization (Sharndama and Mba, 2022).

The present study demonstrates a significant correlation between Hp-infection and elevated HbA1c levels. In addition, the T2D subjects with Hp infection had significantly higher median HbA1c levels compared to Hp-negative subjects. These results are consistent with the preceding studies (Wan, et al., 2020; Chen, et al., 2023). They support the hypothesis that Hp-infections are associated with T2D and raised HbA1c levels. Furthermore, a meta-analysis and systematic review that included 36 studies provided evidence that Hp-eradication could improve HbA1c control (Song, et al., 2021). On the other hand, HbA1c levels remained unchanged after Hp-eradication in T2D patients based on another study (Wada, et al., 2013). Moreover, a study observing high HbA1c levels could contribute to the susceptibility of Hp infection (Maluf, et al., 2020). A meta-analysis report indicated a potential relationship between Hp infection and HbA1c level in diabetic patients (Chen, et al., 2019b). Those with both T2D and an existing Hp infection may require improved glycemic control. A cross-sectional study in Taiwan showed that eradication of Hp can decrease HbA1c levels and improve glycemic control (Cheng, et al., 2019).

The author concludes that Hp status may represent an aggravating factor of glycemic control in individuals with T2D and argues that individuals with diabetes should undergo screening for a status of Hp infection. Gender, age, and BMI have not been a factor in the relationship between Hp infection and T2D in the present study. However, further investigations need to investigate the role of BMI on the association between Hp infection and T2D, and the research should consider a broader range of factors and employ more robust study designs. In addition, more well-designed studies such as longitudinal and cohort studies need verification of the causal relations between Hp and T2D as well as to explore the biological pathways.

IV. Conclusion

The study revealed a definite association of T2D with Hp infection. Individuals diagnosed with T2D are at more risk for Hp infection than the control population, and the logistic regression analysis further proves this association. Furthermore, HbA1c was significantly increased in T2D individuals with positive Hp infection when compared with uninfected counterparts. This suggests that T2D and worse glycemic control might be important risk factors for Hp-infection.

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