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Research Article

Effect of Proton Pump Inhibitors on Some Immunologic Parameters in Patients with *Helicobacter pylori* Infection and Diabetes

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I N F O

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A B S T R A C T

Introduction: Infection by the gram-negative Helicobacter pylori bacteria affects about 4.4 billion people worldwide. It has numerous mechanisms that help with adhesion, movement, and gastrointestinal environment regulation. It can spread through the faeco-oral route.

Objective: To determine the levels of tumour necrosis factor (TNF-α) and interleukin-8 (IL-8) in Type 2 diabetic patients with H. pylori infection compared to control

Materials and Methods: The bacterium is more harmful due to its virulence. This study was conducted on 90 participants admitted to the Gastrointestinal Tract (GIT) Department of the Mihrabani Surgical Hospital in Erbil City. H. pylori was detected using both endoscopic and non-endoscopic methods and antibody response. The 13C urea breath test (13C-UBT) was used to detect H. pylori in the stomach by looking for bacterial urease. The study also examined blood samples and stomach biopsies to assess the infection's severity.

Results: The presence of H. pylori urease is indicated by an increase in pH and the appearance of a new colour on the test strip. TNF-α, RBS and IL-8 levels over a threshold were related to moderate to severe chronic inflammation in 90% of the patients. The data suggest that H. pylori may pose a significant risk to diabetics.

Conclusion: The study indicates a complex relationship between TNF-α, interleukin-8, diabetes, proton pump inhibitors (PPIs), and Helicobacter pylori. H. pylori infections increase consumption of PPIs and acid reflux symptoms. Diabetes raises RBS and HbA1C. PPIs suppress cytokine levels, affecting the inflammatory response in H. pylori diabetic patients. However, diabetes therapy may lessen these elevated levels.

Keywords: *Helicobacter pylori.* T2DM, IL-8, TNF-α, PPI

Introduction

Helicobacter pylori is a gram-negative ubiquitous pathogen that poses a consequential health threat. The gastrointestinal tract infection caused by *H. pylori* is acquired in childhood by the faecal-oral pathway, and in around 2–10% of cases, the infection results in chronic gastric inflammatory complications.[1] *H. pylori* can be diagnosed using endoscopic or non-endoscopic methods. Direct techniques include the breath urease test and antibody response, whereas indirect methods include identifying bacterial antigens in culture, histology, biopsy tissue, or faeces. Antibody serology can detect prior pathogen exposure but cannot diagnose ongoing illness. It is critical to take into account the pre-test infection risk, clinical context, cost, availability, and family history when choosing which test to perform. Bismuth-containing medications, antibiotics, and proton pump inhibitors may interfere with several tests.[2] According to reports, *H. pylori* is associated with a potentially high frequency in patients with diabetes.[3] Moderate to severe gastritis inflammation has been associated with serum tumour necrosis factor (TNF-α) and interleukin-8 (IL-8) levels over a specific threshold.[4] The phosphorylation of serine residues by inflammatory cytokines disrupts insulin function and the substrate's interaction with insulin receptors. The 13C urea breath test (13C-UBT) detects *H. pylori* by looking for bacterial urease in the stomach. The notion is demonstrated by the hydrolysis of orally administered 13C- or 14C-labeled urea, which creates ammonia and carbon dioxide, which diffuse into the blood and are evacuated via the lungs. A spike in 13C-labeled CO_2 in breath samples collected before and 30 minutes after urea ingestion indicates the presence of urease which could be measured using mass spectrometry, infrared spectroscopy, or laser-assisted ratio analysis.[5] Patients on antibiotics or a proton pump inhibitor (PPI) within two weeks of a test may experience a false-negative result. Similarly, the accuracy of the test could be influenced if the patient is suffering from stomach bleeding or having corpus-predominant gastritis.[5,6] Hence, this study aimed to find out the levels of IL-8 and TNF-α in infected type 2 diabetic patients with *Helicobacter pylori* infection and compared to control, those who do not suffer from any chronic diseases, diabetes, *Helicobacter pylori* infection, and do not take PPI drugs.

Materials and Methods

Samples

Eighty-five samples were collected between November 2022 and July 2023 from patients of all ages and genders who were admitted to the Gastrointestinal Tract (GIT) Department of the Mihrabani Surgical Hospital in Erbil City. The study sample included 48 (56.47%) patients and 37 (43.53%) healthy persons as control. Endoscopic examination was performed on all patients and gastric tissue samples (48) were collected for biopsy and culture. Blood samples were collected from all patients and each sample tested for HbA1c, TNF-α, RBS, and IL-8.

Helicobacter pylori Detection

Diagnosis of *H. pylori* infection was done using the rapid urease test,[7,8] wherein the presence of *H. pylori* urease is determined by a rise in pH and a colour change (yellow to red) on a test strip[9]. The urea breath test was performed in the Mehrabani Lab (FR-9201). *H. pylori* was also identified using the Pylokit (C.R. Kennedy, Australia), which is a non-invasive method for identifying the bacterium.

Serological Test

RBS and HbA1c were measured in the Mehrabani Laboratory using the automated Cobas version C311 instrument (ROCHE Company, Germany). The Enzyme-linked immunosorbent assay kit (cat. no. E0082Hu, BT-Lab, China) was used to analyse serum levels of TNF-α and IL-8.

Results

An evaluation of the medical history of patients and control group individuals showed a significant difference (p value < 0.001) in the frequency of acid reflux among the two (Table 1). A substantial percentage of patients (89.58%) reported having symptoms of acid reflux, as compared to only 43.24% in the control group.

The information collected also indicated that patients use PPI medications at a significantly higher rate (66.67%) than the control group (37.83%). PPI medications are distributed across the patient group as follows: rabeprazole (4.17%), lansoprazole (20.83%), omeprazole (18.75%), esomeprazole (8.33%), and pantoprazole (14.58%) (Table 1).

Table 1.Medical History of Patients and Control Group

Parameters	Presence	Patients			Control		p Value
		No.		%	No.	%	
Acid reflux	Yes	43		89.58	16	43.24	< 0.001
	No	5		10.42	21	56.76	
PPI drugs	Yes	32		66.67	14	37.83	0.007
		Pantoprazole	7	14.58	2	14.28	
		Esomeprazole	4	8.33	1	7.15	
		Omeprazole	20	18.75	8	57.14	
		Lansoprazole	10	20.83	3	21.43	
		Raberprazole	2	4.17	0	0.00	
	No	16		33.33	23	62.17	

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Medication for bowel problem	Yes	36	75.00	18	48.64	0 .014
	No	12	25.00	19	51.36	
Diabetes	Yes	7	14.58	0	0.00	0.001
	No	41	85.42	37	100.00	

Among patients, the use of medication for bowel movement was significantly (p value = 0.014) higher (75%) than among controls (48.64%). The prevalence rate of diabetes among patients was 25%, indicating a significant difference in incidence compared to the control group, which has no diabetes at all. This difference in proportions was significant (p value of 0.001) (Table 1).

Table 2 shows that diabetic patients had significantly higher RBS levels (146.30 mg/dL) than non-diabetics (91.02 mg/dL), although non-diabetic controls (90.76 mg/dL) had similar RBS levels to non-diabetic *H. pylori*-infected patients. Diabetes RBS levels were observed to be significantly related to infection (p value = 0.0007).

Diabetes patients were observed to have significantly higher HbA1C values (7.8360) than non-diabetic infected patients (5.3463), although non-diabetic controls (5.3000) have HbA1C levels similar to non-diabetic infected patients. The significance of the p value (0.0009) reflects the link between diabetes and HbA1C (Table 2).

There is no significant relationship between IL-8 levels, *H. pylori* infection, and diabetes in the patient or control groups (p value = 0.830). It shows high levels in non-diabetic patients and controls, indicating that the association is due to diabetes rather than *H. pylori*. Similarly, TNF-α levels were found not to be associated with diabetes in the patient or control groups (p value = 0.673). Only non-diabetic patients were seen to have increased TNF-α levels (Table 2).

The average levels of IL-8 in different groups based on their diabetes status and use of PPIs are indicated in Table 3. The mean IL-8 levels varied among groups. The control group's IL-8 concentration was 0.78 ng/L. There were no statistically significant differences in IL-8 levels across the groups type 2 diabetes mellitus (T2DM) without PPI, No T2DM without PPI, and T2DM with PPI. The lack of robust statistically significant differences among these categories suggests a lack of significant linkages in IL-8 levels within these groups.

This table is similar to correlation tables and is used to compare the groups with each other and to avoid errors. The value in the empty boxes has been crossed out to avoid error and confusion.

The TNF-α concentrations among the categories are given in Table 4. The control group, which included people who did not have T2DM and were not on PPIs, had an average TNF-α level of 0.68 ng/L. The statistical analysis indicated significant differences between this control group and the No T2DM, No PPI group (p = 0.02) and the No T2DM, PPI group (p < 0.001).

Table 2.Correlation of Diabetes with HbA1C, RBS, IL8 and TNF-α Level in Patients

Participants	Mean ± SD RBS (mg/dL)	Mean ± SD HbA1C (%)	Mean ± SD IL-8 (ng/L)	Mean ± SD TNF-α (ng/L)
Non-diabetic patients	91.02 ± 13.00^{b}	5.3463 ± 0.4388^{b}	0.9583 ± 0.5637^{a}	0.9237 ± 0.4508^{a}
Diabetic patients	146.30 ± 20.20^{a}	7.8360 ± 2.2550^{a}	0.8712 ± 0.2896^{a}	0.8601 ± 0.1933^{a}
Non-diabetic control	90.76 ± 13.64^{b}	5.3000 ± 0.3993^{b}	0.9555 ± 0.4323^{a}	0.8486 ± 0.3329^{a}
p value	0.0007**	0.0009**	0.830^{ns}	0.673^{ns}

Mean ± SD: Mean ± standard deviation
a and b: Differences between the averages are significant in the same column with a different letter.
**Highly significant, ns: Not significant

Table 3.IL-8 Levels Among Different Groups of *H. pylori* Patients

IL-8 (ng/L)		p Value (Sig ≤ 0.05)			
Group	Mean ± SD	T2DM, No PPI	No T2DM, No PPI	T2DM, PPI	No T2DM, PPI
Control	0.78 ± 0.12	0.65	0.21	0.93	0.05
T2DM, No PPI	0.87 ± 0.06	-	0.74	0.66	0.46
No T2DM, No PPI	0.93 ± 0.24	-	-	0.37	0.44
T2DM, PPI	0.76 ± 0.17	-	-	-	0.19
No T2DM, PPI	1.0 ± 0.36	-	-	-	-

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Table 4.Levels of TNF-α Among Different Groups of H. pylori Patients

TNF-α (ng/L)		p Value (Sig ≤ 0.05)			
Group	**Mean ± SD**	**T2DM, No PPI**	**No T2DM, No PPI**	**T2DM, PPI**	**No T2DM, PPI**
Control	0.68 ± 0.15	0.12	0.02	0.21	< 0.001
T2DM, No PPI	0.89 ± 0.12	-	0.96	0.8	0.68
No T2DM, No PPI	0.88 ± 0.25	-	-	0.78	0.37
T2DM, PPI	0.85 ± 0.14	-	-	-	0.45
No T2DM, PPI	0.94 ± 0.05	-	-	-	-

Individuals with T2DM who did not undergo PPI medication, on the other hand, had a slightly higher average level of TNF-α at 0.89 ng/L. However, this difference did not reach statistical significance compared to the other groups. Individuals without T2DM but not using PPIs had an average level of TNF-α of 0.88 ng/L, which was not statistically significant when compared to the group without (T2DM) but using a PPI (p = 0.37). However, the available data did not allow for precise comparisons between the group with T2DM and PPI use and those without T2DM but PPI use.

Discussion

Numerous studies have examined the link between the prevalence of *H. pylori* infection and acid reflux; the results of some being consistent with and of others being different from our investigation. Consistent with our results, Niknam et al. reported a link between *Helicobacter pylori* infection and erosive gastroesophageal reflux disease (GERD).[10] On the other hand, Bazarah et al. found that a sizable fraction of patients with GERD in their study did not have an infection with *H. pylori*.[11]

Several empirical studies have demonstrated that PPI drugs are commonly used for treating *H. pylori* infection. PPIs were prescribed to a considerable percentage of patients (36.2%) who had been diagnosed with *H. pylori* infection, according to a recent study.[11] In addition, these individuals used PPIs more frequently than those on other treatments. Similarly, Li et al. reported that 50% of patients diagnosed with *H. pylori* infection received a PPI treatment regimen.[12] The facts above demonstrate how widely PPIs are used in treating *H. pylori* infections.

Regarding the prevalence of *H. pylori* in people with and without diabetes, our investigation supports the findings published by Kouitcheu-Mabeku et al. which indicated that *H. pylori* was present in 58.05% of participants without diabetes.[13]

Regarding bowel treatment, there appears to be a negative correlation between *H. pylori* prevalence and the incidence of inflammatory bowel disease (IBD). It has been proposed that Helicobacter pylori, often known as *H. pylori*; may have a prophylactic effect on IBD. Furthermore, a study by Zhong et al. suggests that eradicating *Helicobacter pylori* is linked to the recurrence of IBD.[14] The previously reported results highlight the intricate relationship between the beginning of IBD, gastrointestinal medications, and *H. pylori* infection.

Extensive research has investigated the relationship between diabetes and markers such as HbA1c, RBS, IL-8, and TNF-α in individuals with *H. pylori* infection versus control groups. This finding is congruent with the findings of Maluf et al. who discovered a strong link between chronic *H. pylori* infection, elevated HbA1c levels, and the prevalence of type 2 diabetes.[15]

Furthermore, Uttam et al. discovered a substantial increase in blood glucose levels in diabetes patients who were also infected with *H. pylori* compared to non-diabetic individuals with the same infection.[16]

Numerous research investigations have proven the complex and diverse nature of the interplay between *H. pylori* infection, diabetes, PPI medication, and the control of IL-8 and TNF-α. This study indicated *H. pylori* infection to be associated with increased levels of the pro-inflammatory cytokines IL-8 and TNF-α, which is in agreement with the other studies[17,18] that reported higher levels of IL-8 and TNF-α in diabetic rats, suggesting a potential relationship between diabetes and heightened inflammatory biomarkers. This finding indicates that *H. pylori* and diabetes may interact to promote inflammatory responses.

According to Abdel-Moneim et al., diabetes treatment has been postulated to potentially impact TNF-α levels, which in turn, may affect IL-8 concentrations.[19] Furthermore, as indicated by other studies,[20,21] the use of PPIs has consistently shown a reduction in the concentrations of many pro-inflammatory cytokines, such as IL-8 and TNF-α. This study suggests that PPIs may regulate these cytokines in patients with *H. pylori* infection and diabetes. This could be further complicated as the diversity of *H. pylori* strains may alter their interaction with PPIs, potentially leading to a range of cytokine effects.[22] Furthermore, Sorkhabi et al. reported higher TNF-α and IL-8 levels in diabetic

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patients, particularly those in advanced stages of the disease.[23] The examination of the various groups in this study, namely the control group, T2DM without PPI group, No T2DM without PPI group, T2DM with PPI group, and No T2DM with PPI group, reveals that the presence of *H. pylori* infection and diabetes may have an impact on the levels of IL-8 and TNF-α, either alone or in combination. The use of PPIs is associated with reducing the levels of these pro-inflammatory cytokines. This suggests a possible therapeutic effect on cytokine management, notably IL-8 and TNF-α, in the context of *H. pylori* infection and diabetes.

Conclusion

This study emphasised the complex link between Helicobacter pylori, diabetes, PPI medication, and IL-8 and TNF-α expression. *H. pylori* infection has been shown to cause an increase in the levels of these cytokines, and the presence of diabetes exacerbates this tendency. PPI medications decrease the cytokine levels, affecting the inflammatory response in patients with *H. pylori* infection and diabetes.

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