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ORIGINAL ARTICLE

The potential relationship between *Helicobacter pylori*-induced gastritis and diabetic retinopathy in Iraqi patients with type 1 and type 2 diabetes mellitus

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ABSTRACT

BACKGROUND: It was claimed that *Helicobacter pylori* infection affects diabetic control. Few studies explore the relationship between *Helicobacter pylori* infection, diabetic control, and diabetic complications, especially diabetic retinopathy. Our research aims to explore the potential linkage between *Helicobacter pylori* (HP) infection, diabetes, and diabetic retinopathy (DR) in Iraqi individuals with type 1 diabetes (DM) or type 2 DM.
METHODS: This prospective study included data from four hundred patients regarding age, sex, fasting blood sugar (FBS), and glycated hemoglobin (HbA_{1c}). An ophthalmoscopic examination was done at baseline and after one year of follow-up. The HP infection status was checked only at baseline. The degree of DR lesions and HP infection was assessed by recording and analyzing the data for comparison.
RESULTS: HP infection is significantly related to glycated hemoglobin levels. There was a significant relationship between HP infection and the development of DR ($P<0.001$).
CONCLUSIONS: Infection by *H. pylori* could be a significant factor in the poor control of diabetes. Furthermore, a strong correlation has been noted between the development of DR and HP infections.

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KEY WORDS: Diabetes mellitus; Diabetic retinopathy; *Helicobacter pylori*.

It is estimated that 10.5% of the population all over the world between the ages of 20 and 80 has diabetes mellitus (DM). In addition, it is anticipated to increase globally by the year 2045.[1] Based on a prior investigation, the global occurrence of DR was 22.27%.[2]

Helicobacter pylori (HP) is a Gram-negative bacterium that colonizes the gastric mucosa, increasing susceptibility to acute and chronic gastritis, gastric ulcers, duodenal ulcers, and malignancies. In less affluent countries, there is a higher incidence of *Helicobacter pylori* infec-

tion. Estimations indicate that approximately 4.4 billion individuals worldwide were infected with *Helicobacter pylori* in 2015. In addition to gastritis, gastric cancer, and gastroduodenal ulcers, *H. pylori* is believed to have connections with extra-digestive illnesses such as diabetes.[3]

If a causal relationship is proven between HP infection and diabetes or diabetic retinopathy, it will result in a new era for better control of diabetes and prevention of eye complications.[4]

Many research studies have investigated the relationship between DM and HP infection; however, the findings were contradictory.[3]

Materials and methods

This is a prospective study performed on four hundred patients of both sexes, either male or female, in the age range of 18 to 60 years old, who visit the diabetes clinic at the Alfayha Hospital in Iraq.

In the clinic, a full history and exam were obtained.

The patient is diagnosed with type 1 DM or type 2 DM based on their history, level of fasting blood sugar (FBS), and glycated hemoglobin (HbA_{1c}).

Helicobacter pylori infection is checked either positive or negative by the *Helicobacter pylori* stool antigen test.

Then the patient was referred for an ophthalmoscopic evaluation.

Ophthalmic examination for diabetic retinopathy severity using a standardized grading system (Early Treatment Diabetic Retinopathy Study Scale). Fundus examined by slit-lamp and +90D lens after pupil dilation Supported by OCT and Fundus Camera Pictures. Plus, basic eye exams like the BCVA +IOP anterior segment exam.

The patient is classified as having "PDR (proliferative diabetic retinopathy), NPDR (non-proliferative diabetic retinopathy), or NDR (non-diabetic retinopathy)."

The patient is classified into HP-positive and HP-negative (as the control group) based on the results of the *Helicobacter pylori* stool antigen test.

Women who are pregnant or breastfeeding, individuals with gastrointestinal bleeding, individuals with other comorbidities, or other eye diseases, such as diabetic retinopathy were excluded.

At baseline: FBS, HbA_{1c}, HP stool antigen, and fundus exam were done.

After one-year scheduled follow-up visits for the patients that were included in the study are evaluated for HbA1c and fundus exams.

For this study, participants were categorized as having diabetes if they reported being under treatment for diabetes or possessed a fasting plasma glucose level of ≥7 mmol/L (126 mg/dL) and a hemoglobin A1c (HbA_{1c}) level of ≥6.5%.

Statistical analysis

A statistical analysis was performed to determine whether or not there is a connection between the existence of *H. pylori* infection at the beginning of the trial and the development of diabetic retinopathy throughout the investigation.

Results

A look at Table I reveals that the age averaged around 42.22 years, with a standard deviation of

TABLE I.—*Baseline data.*

Characteristics	Value
Age	42.22±9.37
Gender, male	230
FBS	142.49±34.74
HbA_{1c} at baseline	7.98±1
HbA_{1c} one year later	8.58±2
HP infection: positive test	280
Fundus exam at baseline	
NDR	50
NPDR	280
PDR	70
Fundus exam one year later	
NDR	50
NPDR	276
PDR	74

Data presented as mean±SD or number.

TABLE II.—*Compare HP-positive and HP-negative individuals.*

Parameter	HP (positive) (N.=280)	HP (negative) (N.=120)	P value
Age	48.37±10.96	39.82±8.21	>0.05
Sex, male	250	20	<0.001
FBS	168.63±46.9	138.42±25.05	<0.001
Baseline HbA_{1c}	7.9±1.2	6.9±0.4	<0.001
After 1-year HbA_{1c}	8.45±1.3	8.41±2.73	<0.001

t-test, data expressed as mean±SD or number.

TABLE III.—*Compare between NDR, NPDR, and PDT.*

Parameter	NDR (N.=80)	NPDR (N.=280)	PDR (N.=40)	P value
Age	38.5±3.11	46.71±10.42	48.67±13.92	<0.001
Sex male	80	280	40	<0.001
FBS	164.63±45.48	184.35±45.75	134.29±20.3	<0.001
HbA_{1c} at baseline	7.1±1.2	7.2±1.35	7.5±1.9	>0.05
HbA_{1c} one year later	8.71±3.25	8.37±1.4	9.13±1.59	<0.001
HP positive	20	260	20	<0.001

ANOVA test. Data expressed as mean±SD or number.

TABLE IV.—*Univariate and multivariate logistic analysis of DR.*

Parameter	P value	OR	P value	OR
Age	<0.001	1.076	<0.001	1.087
Female sex	<0.001	0.30	<0.001	0.46
HP (positive/negative)	<0.001	1.2	<0.001	1.1

OR (95% CI).

9.37 years. There were 230 males. 142.49±34.74 was the FBS value. Initially, the HbA1C level was 7.9±1, and after a year, it had increased to 8.5±2. Positive HP was found in 280. Concerning the ophthalmoscopic examination (baseline), there were 280 cases of NPDR, 50 cases of NDR, and 70 cases of PDR. When it came to the ophthalmoscopic examination (after one year), there were 276 cases of NPDR, 50 cases of NDR, and 74 cases of PDR.

Table II demonstrates a substantial disparity between individuals with positive and negative for HP tests regarding sex, FBS (fasting blood sugar), and HbA_{1c} (glycated hemoglobin) levels at baseline and after one year. FBS and HbA_{1c} were significant in HP-positive cases.

Table III demonstrates a substantial disparity in NDR, NPDR, and PDR concerning age, sex, FBS, HbA1C after 1 year, and HP infection.

Table IV shows a highly significant association between DR and age, gender, and HP infection.

Discussion

There is a suggestion that HP infection can impact insulin resistance and diabetic control, although the precise mechanism behind this is not well known. The inflammatory theory hypothesizes that HP infection initiates an inflammatory response with the release of many cytokines that affect insulin sensitivity and induce the emergence of diabetes and poor glycemic control in already established diabetes. Another theory hypothesizes that HP infection affects ghrelin and leptin hormones (produced and released by the human stomach); such hormone dysregulation affects energy balance and obesity.[2]

The study design was to assess the relationship between HP infection and glycemic control, investigating its involvement in the onset and advancement of diabetic retinopathy (DR).

Multiple research studies suggest that HP eradication helps patients with type 2 diabetes reduce their FBS levels and HbA_{1c}. There is still an ongoing argument over whether HP eradication leads to better glycemic control. Research has demonstrated that the eradication of HP leads to enhanced insulin sensitivity in type 2 DM and lowers inflammatory cytokines.[5]

Our analysis indicated substantial differences between individuals who tested positive and negative for HP in terms of sex, fasting blood sugar (FBS), HbA1C levels at the beginning of the study, and HbA1C levels after one year. In contrast to the HP-negative cases, HP-positive cases exhibited significantly higher levels of FBS and HbA1c.

Sarita *et al.* reported an increased incidence of HP infection among type 2 DM patients than in non-diabetics.[6] A study was conducted by Kato *et al.* to determine the DM prevalence among HP-infected individuals. The classification of HP infection was split into 3 groups: "never," "current," and "past." The prevalence of DM was statistically significant in the "current" group compared to the "past" group.[7]

Two big studies were done by Wang *et al.* and Mansori between 1990 and 2020. The first study concluded that HP infection increases the risk of

type 1 DM,[8] and the other study showed the same results.[9]

The result of previous studies was opposed; in some studies, there were no significant results between HP negative and HP positive cases (56% *versus* 50% and 35% *versus* 37%, (HP seronegative *versus* HP seropositive); respectively).[10, 11]

However, this is in contrast to Jeon *et al.*, who specified that diabetes is more prevalent in HP-positive groups than HP-negative groups.[12]

In contrast, Candelli *et al.*, Gillum *et al.*, and Sarita *et al.* discovered a significant increase in HbA1c levels among individuals with HP infection compared to those without HP infection.[13, 14]

It is hypothesized that HP infection initiates a cascade of inflammatory reactions that affect insulin sensitivity. Another theory by Butler *et al.* is that HP infection impairs gastroduodenal emptying and creates bacterial colonization.[15]

According to the present findings, statistically significant differences occurred between diabetic retinopathy (DR) and many factors such as age, sex, and diabetic profile (FBS, HbA_{1c}).

Early research studies included variables like hypertension, hyperlipidemia, duration of diabetes, and BMI (Basal Metabolic Index), along with age, sex, diabetic control, and HP infection. Unfortunately, this was not tested in our studies.

Sarita *et al.* reported an insignificant connotation between diabetic retinopathy and HP infections.[6] Hadidy *et al.* also observed no statistically significant difference in diabetic retinopathy between seropositive and seronegative cases.[16]

Our findings revealed that there is a variation in NDR, NPDR, and PDT that is statistically significant in connection to age, gender, fasting blood sugar, HbA1C after one year, and *Helicobacter pylori* infection.

An investigation was carried out by Zhen *et al.* to determine the connection between DR and HP infection (based on a urea breath test). It was Significant disparities were noticed between the HP positive and HP negative groups as regards age, sex, and levels of FBS and HbA_{1c}. It has been discovered that there is a significant association between HP infection and DR; however, HP infection does not appear to be associated with the severity of DR (only a single patient with PDR was HP-positive).[17]

Conclusions

Helicobacter pylori infection could be a contributing factor in poor glycemic control and the development of diabetic retinopathy in type 1 DM and type 2 DM patients.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Heba Albayati selected and collected the diabetic patients according to the selection criteria; diagnosed *H. pylori* infected persons; ordered the required investigation tests; referral to an ophthalmic specialist. Firas Alfuraiji diagnosed and grading the retinopathy according to (early treatment diabetic retinopathy study scale); excluding patients who have other eye disease which should be excluded according to the criteria of selection; made and ordered the mandatory tests that should be done for the patients selected in the study; referral to internal medicine specialist. Both authors contribute to the writing, interpretation, analysis of the data, and completing the study manuscript file. Both authors read and approved the final version of the manuscript.

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