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ORIGINAL ARTICLE

Impact of *Helicobacter pylori* Infection on the Onset of Microalbuminuria in Individuals with Type 2 Diabetes Mellitus

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ABSTRACT

Background: *Despite the correlation between H. pylori infection and gastrointestinal disorders being extensively established, the primary issue with H. pylori comes from the capacity to induce extra-gastric conditions and its tendency to modify disease phenotypes. Microalbuminuria serves as an early indicator of diabetic nephropathy, a prevalent consequence of diabetes possibly associated with H. pylori infection.* ***Objectives:*** *This study evaluates the correlation between H. pylori infection and microalbuminuria in patients with type 2 diabetes mellitus.* ***Methodology:*** *The case-control study was conducted from August 2024 to December 2024 at the Specialized Hospital for GIT and Liver Surgery Center in (Najaf, Iraq). A total of 180 participants, aged 20 to 75 years, ninety patients with type 2 diabetes mellitus, either with or without H.pylori infection were incorporated alongside 45 individuals exhibiting dyspeptic symptoms without type 2 diabetes, and 45 healthy control volunteers matched for sex and age. All participants have undergone a comprehensive assessment, including a full history and plasma glucose levels, glycated hemoglobin(HbA1c), albumin creatinine ratio (ACR), and H.pylori stool antigen and serum antibodies.* ***Results:*** *There were no significant differences among the study groups T2DM, dyspeptic without type 2 diabetes, and control group in age, weight, height, BMI, Sex, SBP, and DBP (all p>0.05). The comparative results across T2DM subgroups indicate a significant elevation in SBP (p=0.027) and ACR (p=0.001) in the DM-positive H.pylori group relative to the DM-negative H.pylori group. A substantial reduction in body weight (p=0.037) is observed in the DM-positive H.pylori group compared to the DM-negative H.pylori group although there was no significant difference in fasting blood glucose or HbA1c% between the two DM groups.* ***Conclusion:*** *H. pylori infection may significantly facilitate the development of microalbuminuria in individuals with type 2 diabetes.*

INTRODUCTION

Diabetes mellitus is a complex chronic metabolic disorder defined by a high concentration of glucose levels in the blood secondary to insufficient insulin biosynthesis or end-organ resistance to the action of endogenous insulin. Inadequate management of diabetes mellitus is linked to long-term metabolic disturbances, as well as microvascular and macrovascular consequences that influence morbidity and mortality rates across many ethnic groups worldwide[1]. Diabetic nephropathy (DN) is a prevalent complication of chronic diabetes mellitus[2], manifesting in over 40% of individuals diagnosed with type 2 diabetes mellitus after a decade. This condition is defined by chronic albuminuria (albuminuria excretion rate above 300 mg/d or 200 µg/min) confirmed on a minimum of two occasions within three to six months, a progressive decline in GFR, frequently exacerbated by hypertension, ultimately resulting in end-stage renal failure[3]. The albumin creatinine ratio (ACR) is the gold standard for nephropathy diagnosis, indicating that ACR lab values from spot urine samples are indeed an accurate method for assessing albuminuria in chronic kidney disease[4].

Helicobacter pylori (*H. pylori*) is a gram-negative spiral bacterium prevalent in the stomach, *Helicobacter pylori* infection is among the most pervasive chronic infections globally, impacting over fifty percent of the global population[5]. Diagnosing *H. pylori* infection can be achieved using non-invasive diagnostics, including serum IgG antibodies, which remain unaffected by medication, are widely accessible, and are the most cost-effective; however, they do not reliably differentiate between active and past infections. The stool antigen test identifies *H. pylori* antigen in fecal matter. Invasive methods, such as endoscopy with biopsy, enhance visibility and enable histological examination [6]. The primary issue with *H. pylori* comes from its capacity to induce extra-gastric conditions and its tendency to modify disease phenotypes Albuminuria is consistently associated with endothelial low-grade

inflammation[7]. Many studies investigate *H. pylori* infection and its relation with the development of microalbuminuria. Wang et al.[8] found that early eradication of *H. pylori* is advantageous in the prevention of chronic renal disorders in patients. Other studies indicated a decrease in proteinuria in patients with type 2 diabetes who presented with membranous nephropathy and dyspeptic symptoms after the eradication of *H. pylori* infection[9]. However, a disagreement remains regarding the association between *H. pylori* infection and the occurrence of proteinuria in individuals with type 2 diabetes mellitus; numerous studies have identified no significant correlation between the presence of *Helicobacter pylori* infection and microalbuminuria.

The study question is *H.pylori* infection correlated with elevated microalbuminuria levels in individuals with type 2 diabetes?

The study aims To investigate the correlation between H. pylori infection and the onset of microalbuminuria in individuals with type 2 diabetes mellitus.

METHODOLOGY

Study design:

The present case-control study was done from August 2024 to December 2024 at the Specialised Hospital for Gastrointestinal and Liver Surgery Centre in (Najaf, Iraq).

A total of 180 participants, ages 20 to 75 years included 90 individuals with type 2 diabetes mellitus, with or without *H. pylori* infection, 45 patients exhibiting dyspeptic symptoms without type 2 diabetes, and 45 age- and sex-matched healthy control participants enrolled in this study. The participants in this study provided informed consent prior to the administration of screening tests.

Inclusion criteria for case group:

Patients with type II diabetes mellitus, with and without *H.pylori* infection and Patients with dyspeptic symptoms diagnosed as *H.pylori* infected without type 2 diabetes mellitus.

Exclusion criteria for case group:

Patients with chronic renal failure, Nephrotic and nephritic syndrome, Hypertension**,** Pregnancy**,** Chronic Urinary tract infection (UTI), and Malignancy (mostly lung cancer, renal cell carcinoma) all these conditions are accompanied by proteinuria. Dyspeptic patients with NSAIDs in the dyspeptic group.

Ethical considerations:

Ethical approval was obtained from the scientific committee at the Faculty of Medicine/University of Kufa (Ref#: MEC-64), and the Specialized Hospital for GIT and Liver Surgery Center in Al Najaf province in Iraq (Ref#Augast-2024-28122). According to the Declaration of Helsinki written consent was obtained from all participants before the commencement of the study.

History and data collection

All participants have undergone a thorough examination encompassing a complete history based on a meticulously designed questionnaire, which included name, age, sex, duration of diabetes mellitus, oral antidiabetic medications, chronic renal disease, prescribed medications, history of hypertension, familial diabetes history, chronic use of NSAIDs, and smoking status. All patients with type 2 diabetes mellitus received treatment with oral hypoglycemic agents. All participants are tested for *H. pylori* both antibodies (serum) and antigens (stool) because the serum antibodies test can't distinguish between past or active infection. Height, weight, and body mass index (BMI) were measured with a digital scale. Systolic and diastolic blood pressures were measured in a seated position after a 5-minute rest period.

Biochemical and laboratory tests:

From all study participants, five milliliters (ml) of blood were collected after 12 hours of fasting and divided into 2 tubes; one gel tube and the other EDTA tube. The blood in the gel tube was centrifuged at 3000 rpm for 10 minutes to yield serum. This serum was used to measure *H.pylori* antibodies, The blood in EDTA tubes was used for fresh determination of HbA1c. HbA1c was assessed using the D-10 Hemoglobin A1c Testing System using a Nycocard immunoassay kit (USA). IgG antibodies for Helicobacter pylori are detected by using the Helicobacter pylori IgG ELISA kit from I B L International, Germany. A single void urine sample was obtained via clean-catch technique following a minimum of 12 hours of fasting for assessment of the albumin/Creatinine Ratio which was analyzed by an auto-analyzer (BS-120 Chemistry Analyzer), which had an operation system: Windows® 7. The *H.pylori* antigen was detected by using a stool *H.pylori* antigens Rapid Test Cassette from Lungene company, China.

Statistical analysis

All statistical analyses were conducted via IBM SPSS for Windows 27, 2019. Tables were plotted using the Excel software of Windows Office 2021. The Lilliefors-corrected Kolmogorov-Smirnov test was employed to analyze the distribution types of the result groups. A statistical distribution categorizes variable outcomes into two types: non-normally distributed variables and normally distributed variables. The data were presented as mean ± standard deviation for the normally distributed variable. The control and subdivided groups were compared using analysis of variance (ANOVA) in the measured parameters. Bonferroni's post-hoc analysis was done following the analysis to calculate the pairwise comparison between each pair of groups— Examination of contingency tables ($\chi 2$ test) to assess relationships among categorical

variables. The results were expressed as median (25-75% percentile) for the non-normal variables. The subdivided groups among patients and between control groups in the non-normally distributed parameters were compared using the Mann-Whitney U test for two groups and the Kruskal-Wallis test for comparison of more than two groups. We conducted a binary logistic regression analysis to investigate the predictors of microalbuminuria (dependent variable) compared to controls, showing odds ratios with 95% confidence intervals.

RESULTS

Table 1 represents the results of the sociodemographic and clinical parameters of patients with type II diabetes mellitus with and without *H.pylori* infection, patients with dyspeptic symptoms, and the control group. The results revealed no statistically significant differences among the study groups concerning age, weight, height, BMI, sex, SBP, and DBP (all p>0.05). The duration of T2DM is a median of 6 years and the range is (5-10) years.

Table 2 illustrates the comparative analysis of parameters between subgroups of type two diabetic patients with positive *H. pylori* and those with negative *H. pylori* regarding both blood *H. pylori* antibodies and stool *H. pylori* antigens. The findings indicate a significant elevation in SBP(p=0.027) and ACR (p=0.001) in the (DM+*H.pylori*) cohort vs to the (DM-*H.pylori*) cohort. A significant reduction in body weight (p=0.037) is observed in the (DM+*H.pylori*) group compared to the (DM-*H.pylori*) group. Other parameters exhibit no significant differences between the groups.

Table 1: Socio-demographic and clinical characteristics of type 2 diabetes mellitus (T2DM), dyspeptic, and control.

Parameter	Control	Dyspepsia	T2DM	F or χ2	P
Age years	49.622±9.787	49.467±10.047	51.033±11.297	0.444	0.642
Weight kg	75.733±9.569	74.600±9.875	76.767±11.628	0.627	0.536
Height cm	166.667±8.413	167.044±8.196	166.900±8.317	0.024	0.976
BMI kg/m2	27.241±2.562	26.762±3.137	27.587±3.914	0.874	0.419
Female/Male	21/24	22/23	43/47	0.045	0.978
GITdiseaseNo/Yes	45/0B,C	0/45A,C	45/45A,B	90.000	<0.001
H.pylori IgG & Ag	45/0B,C	0/45A,C	45/45 A,B	90.000	<0.001
SBP mmHg	117.700±3.188	117.800±4.484	118.167±6.068	0.941	0.097
DBP mmHg	66.378±2.724	68.444±3.307	68.278±3.013	0.712	0.102
Duration of DM years	-	-	6(5-10)		-
Oral hypoglycemic drugs No/ Yes	-	-	0/90		-
ACR mg/g	2.2(1.61-6)C	3(2-10)C	48(27.75-90.75)A,B	KWT	<0.001
FBG mg/dl	89.482±7.89[C]	91.8±8.575[C]	218.322±89.458[A,B]	MWUT	<0.001
HbA1c%	5.796±0.477[C]	5.801±0.477[C]	9.382±1.863[A,B]	MWUT	<0.001

A, B, C: pair-wise comparisons. Results are expressed as mean ± standard deviation for normally distributed data and analyzed by ANOVA, Non-normally distributed data are expressed as median(interquartiles). Binomial data were expressed as ratios and analyzed by Chi-squared test (χ2), KWT: Kruskal-Wallis test for ACR, and MWUT: Mann-Whitney U test for FBG and HbA1c%,p. probability value, GIT: gastrointestinal tract, BMI: Body mass index, SBP: systolic blood pressure, and DBP: Diastolic blood pressure, FBG:Fasting glucose and HbA1c:glycated hemoglobin , ACR: Albumin creatinine ratio.

Table 2: Comparison of Diabetic Patients with Positive and Negative *Helicobacter pylori* infection for different parameters

Parameters	DM-*H.pylori*	DM+*H.pylori*	F	Sig.
Age years	50.156±11.277	51.911±11.375	0.541	0.464
Weight kg	74.189±11.646	70.167±5.225	4.468	**0.037**
Height m	167.960±8.257	166.69±7.115	0.608	0.438
BMI kg/m2	26.283±3.574	25.286±1.721	2.843	0.095
FBG mg/dl	212.111±87.995	224.533±91.462	0.431	0.513
HbA1c%	9.298±2.195	9.466±1.479	0.182	0.670
Duration of DM Yrs.	7.587±3.012	7±2.772	0.925	0.444
SBP mmHg	119.356±6.623	122.578±7.002	5.030	**0.027**
DBP mmHg	68.111±2.648	68.444±3.361	0.273	0.603
ACR mg/g	39.6(25.5-75.5)	53(29.15-162.7)	MWUT	**0.001**

MWUT: Mann-Whitney U test.

Table 3 represents the results of binary logistic regression analysis. The methodology utilized an automated stepwise approach, employing *H. pylori* results as an explanatory variable while accounting for the influences of age, sex, and BMI. The regression analysis indicates that microalbuminuria was most well predicted by positive *H. pylori* results ($\chi 2=4.799$, df=1, $p<0.041$), with a Nagelkerke effect size of 0.196 and an overall accuracy of 68.2%. This means the *H.pylori* results can explain 19.6% of the variance in microalbuminuria.

Table 4 calculates the diagnostic characteristics of the *H.pylori* test for microalbuminuria, the crosstab was made in Table 4. The results of *H.pylori* can predict macroalbuminuria in T2DM patients with a sensitivity of 61.11%, specificity of 50%, and an odd ratio of 1.57 means Infection with *H. pylori* elevates the likelihood of microalbuminuria, exhibiting moderate sensitivity and specificity.

Table 3: Binary logistic regression analysis results for patients with microalbuminuria (ACR>30mg/g) as the dependent variable, patients with normoalbuminuria (ACR<30mg/g) as the reference group, and the positive *H.pylori* antibodies and stool antigen as the explanatory variable.

Dependent variables	Explanatory variables	B	SE	Wald	P	OR	95% CI
#1. Microalbuminuria versus Normoalbuminuria	Positive *H.pylori* tests	0.223	0.300	0.553	**0.041**	1.27	0.694-2.250

Table 4: Diagnostic features of *H. pylori* antibody and stool antigen results in patients with microalbuminuria (ACR > 30 mg/g) and normoalbuminuria (ACR < 30 mg/g).

	ACR>30mg/g	ACR<30mg/g
Positive H.pylori tests	55	35
Negative H.pylori tests	45	45
Sensitivity	61.11	
Specificity	50	
Positive Predictive Value (PPV)	55	
Negative Predictive Value (NPV)	56.25	
Accuracy	55.56	
Relative risk (RR)	1.22	
Attributable risk	0.11	
Odd Ratio (OR)	1.57	
CI 95%	0.98-2.16	

DISCUSSION

H.pylori is a common infection in diabetic patients and has been investigated for its potential role in developing microalbuminuria in type 2 diabetic patients. Numerous studies have investigated the relationship between type 2 diabetes and *H. pylori* infection. Some have validated this association, whilst others have failed to establish any correlation between the two illnesses. The current investigation revealed a positive connection between *H. pylori* infection and the emergence of microalbuminuria in individuals with type 2 diabetes, based on comparisons between two subgroups those with and without *H. pylori* infection. It was determined that *H. pylori* infection serves as an independent risk factor for microalbuminuria, despite governing for other variables such as age, gender, HbA1c%, fasting blood glucose, and duration of diabetes mellitus.

The sociodemographic and clinical data are presented in table (1) and reveal no significant differences among the study groups concerning age, weight, height, BMI, sex, SBP, and DBP (all $p>0.05$).

The present study demonstrated a significant disparity in albuminuria, measured by the Albumin Creatinine Ratio (ACR), with ACR ($p=0.001$) in type 2 diabetes patients with *H. pylori* infection versus those without *H. pylori* infection. This is consistent with Ahmad et al,[11] who demonstrated a notable disparity in albuminuria levels between diabetic individuals with active *H. pylori* infection and those without infection. Furthermore, Multiple studies reported that *H. pylori* infection is significantly associated as a separate risk indicator for the development of microalbuminuria in individuals with type 2 diabetes, they explain that *H.pylori* infection affects the level of the inflammation markers such as C-reactive protein, Erythrocyte

sedimentation rate (ESR), and Fibrinogen levels[13-12]. A meta-analysis indicated that T2DM patients with *H. Pylori* infection had a 2.00-fold increased risk of developing proteinuria compared to those without H. Pylori infection (OR: 2.00, 95% CI: 1.48–2.69) [14].

Zhou et al,[15] reported that patients with Type 2 Diabetes Mellitus (T2DM) exhibited a higher prevalence of *Helicobacter pylori* infection compared to individuals without T2DM, which contributes to heightened T2DM complications, such as diabetic nephropathy, through the following mechanism: the immune systems may be activated post *H. pylori* infection, resulting in a significant elevation of interleukin IL-8 and tumor necrosis factor α (TNF‑α)[16].

A significant amount of immunological complexes will eventually accumulate during prolonged inflammation, potentially impacting various organs and tissues, including the kidneys, in addition to cytokines that promote inflammatory cells, and immune complexes in patients with Type 2 Diabetes Mellitus (T2DM)[17]. The colonization and infection rates of pathogens in the gut may be exacerbated by diabetes-related decreases in gastrointestinal motility and acid secretion[18].

Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), inflammatory cytokines that induce insulin resistance, play a significant role in diabetes consequences[19].

A contrast to our results study done in China involved 22,044 adult participants. This study found no relationship between *H. pylori* infection and chronic kidney disease (CKD), with no significant differences in albuminuria or glomerular filtration rate (GFR) between the *H. pylori*-positive and *H. pylori*-negative groups after adjusting other risk factors[20].

Oruc & Koroglu,[7] contrasted our results, studies demonstrate no substantial association between H. pylori infection and chronic renal disease and/or albuminuria; however, it suggests a potential link between albuminuria and moderate to severe *H. pylori* colonization. The difference in result may be due to the use of random urine samples to determine albuminuria, whereas we used ACR which is more accurate additionally geographic and genetic factors may influence on results of diseases.

The present study revealed a significant increase in SBP (p=0.027) in diabetic patients with *H.pylori* group than in diabetic patients without *H.pylori* infection; this result agrees with the meta-analysis included a total of 55 studies with 198,750 individuals; It demonstrated that *H. pylori* infection elevated the risk of hypertension[21]. A separate experiment assessed the relationship between *H. pylori* infection and the prevalence of hypertension in the middle-aged and elderly Chinese demographic. This cross-sectional study included 17,100 participants, demonstrating that persons with *H. pylori* infection had a greater incidence of hypertension (57.5% versus 55.1%, P = .002). Moreover, the infection rate of *H. pylori* in hypertension patients exceeded that in non-hypertensive persons (48.8% vs 46.4%, P = 0.002) after adjusting for potential variables[22].

Although there is no consensus about the correlation between *H. pylori* infection and hypertension, the underlying process remains unclear and may involve various factors. First, the antibody targeting the virulence factor of *H. pylori* CagA can directly cross-react with the vascular wall's membrane antigen[23]. Secondly, *H. pylori* induce lymphocyte proliferation and triggers the release of various pro-inflammatory mediators, including interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and fibrinogen, resulting in localized inflammation of the arterial wall, ultimately causing damage and dysfunction of vascular endothelial cells, proliferation of smooth muscle cells, and the development of atherosclerosis[24].

Third, inflammation may aggravate hypertension by generating endothelial dysfunction and oxidative stress, alongside the activation of inflammatory cytokine cascades and the release of vasoactive chemicals from the site of infection[25], The levels of IL-1beta, IL-2, IL-6, and TNF-alpha are markedly increased in patients infected with *H. pylori*. These inflammatory cytokines may exacerbate insulin resistance, perhaps increasing overall peripheral vascular tension.

Finally, Individuals infected with *H. pylori* may elevate fibrinogen levels, a biomarker signifying vascular inflammation, potentially obstructing the decrease of nitric oxide (NO), so provoking vasoconstriction and increasing peripheral vascular stress[26]. This difference in results may be because elevated blood pressure is multifactorial and *H.pylori* infection may be a chronic effect which we have not specified in the study.

At the same time, the present study demonstrates a significant reduction in body weight (p=0.037) in the type 2 diabetes mellitus cohort with *H. pylori* positivity compared to the cohort with *H. pylori* negativity; this corresponds to the findings of Reza et al,[27] who discovered that *H. pylori* infection was correlated with a significantly lower body mass index (BMI) in *H.Pylori* positive women compared to *H.Pylori* negative women, suggesting a possible impact on body weight in individuals with type 2 diabetes. A further study revealed that *H. pylori* eradication markedly elevated BMI without affecting HbA1c levels in subjects with type 2 diabetes, notwithstanding diabetic treatment[28], *H. pylori* may influence the release of gastric hormones and therefore plays a role in the regulation of body weight, hunger, and satiety[29]. A further study indicated that *H. pylori* infection increased the likelihood of obesity (BMI ≥30) (odds ratio, OR = 1.836, 95% CI = 1.079–3.125, P = 0.025) after controlling for

demographic variables in individuals under 50 years old. Moreover, individuals under 50 years of age with *H. pylori* infection may have an increased risk of obesity relative to those without the infection[30].

Another study[31] found no statistically significant association ($p > 0.05$) between the body mass index (BMI) of participants and *H. pylori* infection suggesting that *H. pylori*-positive individuals with type 2 diabetes do not demonstrate a substantial variation in body weight.

Contradictory to our findings meta-analysis, including 25,519 participants, identified a substantial positive association between the risk of *H. pylori* infection and the incidence of obesity development [32].

While *H. pylori* infection is associated with increased BMI and body weight following eradication, its role in directly influencing body weight in diabetic patients remains unclear. *H.pylori* infection is linked to worsened metabolic parameters, including insulin resistance and poor glycemic control, which could indirectly affect body weight management in diabetic individuals. Further research is needed to clarify these relationships and the potential benefits of *H. pylori* eradication in managing diabetes-related metabolic issues and complications.

The present study revealed No significant difference was observed in HbA1c levels and FBG between type 2 diabetics groups with and without *H. pylori* infection means there is no association between *H. pylori* infection and glycemic control. An additional investigation revealed no substantial difference in random blood glucose levels between *H. pylori*-infected and non-infected groups[33]. Supporting these findings, several investigations have also determined The *H. pylori* infection is not correlated with fasting glucose or glycosylated hemoglobin levels[34]. In contrast to our results Suman et al, [35] found that microalbuminuria showed a significant connection with HbA1c levels. An elevation in HbA1c correlated with a rise in microalbuminuria above the optimum threshold of 7% HbA1c, following the exclusion of other aetiologies for microalbuminuria[35].

The study used multiple different tests for comparison, Binary logistic regression analysis, and diagnostic test to study the sensitivity and specificity of the effect of *H.pylori* infection on microalbuminuria, all subjects were apparently healthy and only had dyspeptic symptoms and did not have kidney complications so screening for *H.pylori* in patients with early onset of microalbuminuria is important.

CONCLISION

The current study demonstrated a positive association between *H. pylori* infection and the start of microalbuminuria in patients with type 2 diabetes, as proven by a comparison of infected and uninfected individuals. Furthermore, *H. pylori* infection is recognized as an independent risk factor for microalbuminuria, regardless of the matching or insignificance of other risk factors such as age, gender, HbA1c%, fasting blood glucose, and duration of diabetes mellitus.

Recommendations

The diagnosis of *H.pylori* infection is done by using noninvasive methods mainly serum antibodies and stool antigens while the standard H.pylori diagnosis is upper gastrointestinal endoscopy but some patients refused it so we were satisfied with noninvasive methods and recommended in future studies.

Ethical of Specimen

All the participants provided informed consent for inclusion in the study and were assured that all the information provided would be used solely for the purposes of this study and treated confidentially.

Conflicts of interest

there are no conflicts of interest.

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