Original Article

DOI: 10.7860/JCDR/2023/61631.17487

Is *Helicobacter Pylori* Infection Associated with Insulin Resistance? A Tertiary Care Centre Experience at Kattankulathur, Tamil Nadu, India

Pathology Section

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ABSTRACT

Introduction: *H.pylori* is the most common infection leading to gastrointestinal and extra-gastrointestinal lesions. Few studies had studied about *H.pylori*'s effect on glucose metabolism and insulin resistance and found that *H.pylori* is associated with increase in mean Glycated Haemoglobin (HbA1c) levels and insulin resistance. But few studies have found no association between *H.pylori* and glucose metabolism.

Aim: To determine the relationship between *H.pylori* infection and glucose metabolism profiles in dyspeptic patients, based on the histopathological examination.

Materials and Methods: This prospective case-control study was carried out in the Department of Pathology at SRM Medical College Hospital and Research Centre from April 2021 to September 2021 on 70 dyspeptic patients. They were split into two groups: *H.pylori* positive (Group I, n=35) and *H.pylori* negative (Group II, n=35) groups. The age and gender of Group I were matched with Group II. Endoscopic gastric biopsy was taken and tissue sections were stained with Haematoxylin and Eosin (H&E), and Immunohistochemical (IHC) stain using *H.pylori* (Clone: EP279) rabbit monoclonal antibody. Blood samples were collected to test Fasting Blood Glucose (FBG) and insulin. Insulin resistance was calculated using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Histomorphological changes and *H.pylori* colonisation were graded according to Updated Sydney System and correlated with HOMA-IR levels. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 22.0.

Results: There was no significant variation between *H.pylori* positive and negative groups in demographic variables such as age (p-value=0.45) and gender (p-value=0.23). Body Mass Index (BMI) and *H.pylori* infection showed statistically significant association (p-value=0.04). Increase in mean values of FBG, insulin and HOMA-IR were statistically associated with *H.pylori* positive (p-value <0.05). Degree of *H.pylori* bacterial density (r_s=0.2992), chronic inflammation (r_s=0.3193), activity (r_s=0.4576) and atrophy (r_s=0.2542) were positively correlated with HOMA-IR.

Conclusion: This study showed that chronic active gastritis with atrophic related changes and *H.pylori* colonisation were significantly correlated with HOMA-IR. Patients with *H.pylori* induced gastritis should be followed with regular monitoring of HOMA-IR; as early diagnosis and eradication of *H.pylori* might reduce the risk of insulin resistance and glucose metabolism dysregulation.

Keywords: Dyspepsia, Gastritis, Glucose metabolism, Homeostatic model assessment of insulin resistance

INTRODUCTION

Helicobacter pylori (H.pylori) is a non invasive, gram negative, microaerophilic and spiral shaped bacteria [1]. It is one of the most common prevailing infections worldwide affecting approximately 4.4 billion people and in India, the prevalence ranges between 53.4% and 73.5% [2]. The majority of *H.pylori* infections are acquired during childhood and last lifelong.

The gastrointestinal lesions caused by *H.pylori* include gastritis, peptic ulcers, gastric cancer and Mucosa Associated Lymphoid Tissue lymphoma (MALToma) [3]. According to recent research studies, *H.pylori* has been associated with extra-gastrointestinal illnesses such as metabolic syndrome, diabetes mellitus, coronary artery disease, stroke, non alcoholic fatty liver disease, iron deficiency anaemia and thrombocytopenia [4-7].

Maluf S et al., and Hsieh MC et al., reported that *H.pylori* infection was linked to higher mean Glycated Haemoglobin (HbA1c) levels [8,9]. However, some studies found no association between *H.pylori* infection and diabetes mellitus [10,11]. The proposed pathogenesis includes the proinflammatory cytokines, Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-6,, and IL-1β, and also acute phase reactants, such as C-reactive Protein (CRP), which will inhibit Glucose Transporter Protein Type-4 (GLUT4) and phosphorylate serine residues in insulin receptor substrate proteins, impairing insulin sensitivity and causing a condition known as insulin resistance [12]. Insulin resistance is a strong predictor and plays a key role in the development of type 2 diabetes mellitus. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is used to calculate insulin resistance.

The association between *H.pylori* infection and IR was first proved with evidence by Aydemir S et al., using HOMA-IR scores [13]. Studies have shown variations regarding the outcome of glucose metabolism and insulin sensitivity following *H.pylori* eradication [5]. Successful treatment of *H.pylori* has been shown to reduce mean HbA1c levels, fasting insulin levels, and HOMA-IR levels, according to studies by Zojaji H et al., and Gen R et al., [14,15]. However, Vafaeimanesh J et al., reported no discernible impact on the elimination of *H.pylori* [16].

Understanding how *H.pylori* affects the profiles of glucose metabolism is essential for comprehension. Most of the literatures report the link between *H.pylori* and glucose metabolism profiles using antibody titres and stool antigen assays. But these investigations for diagnosing *H.pylori*, are likely to produce false positive and false negative results. Additionally, the correlation of the *H.pylori*-induced gastric changes is crucial for the precise correlation of concurrent activity, which has not been considered in these studies [5,9]. The relationship between *H.pylori*-induced histomorphological changes in gastric mucosa and glucose metabolism profiles has only been investigated in a small number

of studies [8]. Therefore, this study was done to determine the relationship between *H.pylori* infection and glucose metabolism profiles, using the histomorphological changes according to the updated Sydney system [17].

MATERIALS AND METHODS

This prospective case-control study was done in the Department of Pathology at SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu from April 2021 to September 2021 after getting approval from IRB (2419/IEC/2021). Informed consent was obtained from all individual participants included in the study. This study included patients who presented with complaints of dyspeptic symptoms.

Inclusion criteria: Patients with dyspeptic symptoms like epigastric pain, heart burns, regurgitation and nausea who were ≥18 years of age, without any co-morbidities and were willing to participate in the study providing their informed written consent were included in the study.

Exclusion criteria: Patients under the age of 18 years, women who were expecting pregnancy, those who had already undergone treatment for *H.pylori* infection, those who had recently taken proton pump inhibitors within four weeks, and those who declined to take part in the trial were excluded from this study.

The present study had 70 patients and these patients underwent endoscopic gastric biopsy. Based on the *H.pylori* status all participants were split into two groups as:

- **Group I:** These are cases (n=35) with positive biopsy report for *H.pylori* and
- **Group II:** These are controls (n=35) with negative biopsy report for *H.pylori*.

Study Procedure

The patient's age and gender were recorded along with the anthropometric measurements for Body Mass Index (BMI) calculation. The patients were subjected to endoscopic examination and gastric biopsy. Blood samples were collected for testing Fasting Blood Glucose (FBG), and insulin levels to determine the status of glucose metabolism.

Diagnosis of *H.pylori* was done based on gastric endoscopic biopsy taken from body and antral region by histopathological examination. The gastric biopsy specimens were immediately fixed in 10% formalin and processed routinely. Minimum 2-3 sections of 3-5 μ thickness were cut using microtome (Leica-HistoCore AUTOCUT). Routine Haematoxylin and Eosin (H&E) staining to assess the histomorphological features of chronic gastritis, and Immunohistochemical (IHC) stain using *H.pylori* (Clone: EP279) rabbit monoclonal antibody to assess the *H.pylori* colonisation were done on the sections. Updated Sydney system was used to evaluate the histomorphological variables like chronic inflammation, activity, atrophy and bacterial density [17].

Chronic inflammation was graded as mild when only scattered mononuclear inflammatory cells were seen per high power field; as moderate degree when diffuse infiltration of dense mononuclear inflammatory cells was seen and as severe when nearly entire mucosa showed mononuclear inflammatory cells which separates the gastric glands [17].

Activity was graded as mild when 1-2 crypts were involved by neutrophils per biopsy; as moderate when upto 50% of the crypts were involved by neutrophils; and as severe when >50% of the crypts were involved by neutrophils [17].

Atrophy was graded as mild when gastric glands were lost in only a small area; as moderate when upto 50% of the glands were lost; and as severe when >50% of glands were lost [17].

Bacterial density was grades as mild when only a few *H.pylori* were found; as moderate when multiple foci showed *H.pylori*; and as severe when nearly entire surface was covered by *H.pylori* [17].

A 2 mL of venous blood sample was collected in grey colour (sodium fluoride coated) vacutainer for biochemical analysis of FBG by Hexokinase (enzymatic) method using Beckman AU480 and AU680 automated clinical chemistry analyser and 2 mL of venous blood sample in red coloured (No anticoagulant) vacutainer for fasting insulin level by immunoassay using commercial kits from Vitrous ECi Immunodiagnostic system. The insulin resistance index was calculated using HOMA-IR formula on the basis of FBG and fasting plasma insulin. HOMA-IR=FBG (mg/dL)×Fasting plasma insulin (mIU/mL)/405 [18]. HOMA-IR ≥2 is considered as insulin resistance [18].

STATISTICAL ANALYSIS

Statistical analysis was carried out through Statistical Package for the Social Sciences (SPSS) software version 22.0. Categorical variables were represented by frequency and percentage whereas continued variables were represented by mean and standard deviation. Independent sample t-test was used to find the difference between two groups based on mean and standard deviation. Spearman's rank correlation coefficient was used to find correlation between two variables. A p-value <0.05 was considered statistically significant.

RESULTS

In the present study, 70 patients studied were divided into two groups based on *H.pylori* status as Group I, *H.pylori* positive (n=35) and Group II, *H.pylori* negative (n=35). No significant difference was found between *H.pylori* positive and negative groups based on age and gender [Table/Fig-1]. There was a significant increase in BMI in *H.pylori* positive group compared to *H.pylori* negative group (p-value=0.04) [Table/Fig-1]. Significant increase in FBG, insulin and HOMA-IR levels were seen in *H.pylori* positive group (Group I) compared to Group II with p-value of <0.05 [Table/Fig-1].

Variables	Group I (n=35) (Mean±SD)	Group II (n=35) (Mean±SD)	p-value
Age (years)	40.34±14.38	40.69±12.39	0.45
Gender (Male/Female) (n)	22/13	19/16	0.23
BMI (Kg/m^2)	26.27±4.95	24.47±4.04	0.04*
Fasting blood glucose (mg/dL)	106.89±14.66	98.49±13.28	<0.001*
Insulin (IU/mL)	10.08±9.41	6.86±2.08	0.02*
HOMA-IR	2.76±2.46	1.69±0.60	<0.001*

[Table/Fig-1]: Demographic and laboratory findings of *H.pylori* positive and negative group.
SD: Standard deviation; HOMA-IR: Homeostatic model assessment of insulin resistance; *p-value <0.05 was considered statistically significant

Mean HOMA-IR levels were higher in *H.pylori* positive patients (Group I) with severe bacterial density compared to *H.pylori* negative group (Group II) [Table/Fig-2]. Significant positive correlation was found between *H.pylori* colonisation and HOMA-IR with a r_s-value of 0.2992 and p-value of 0.01 [Table/Fig-2]. Higher mean HOMA-IR levels were noted in *H.pylori*-infected group with moderate/severe chronic inflammation [Table/Fig-3], moderate/severe activity [Table/Fig-4], and moderate/severe atrophy [Table/Fig-5] compared to Group II (*H.pylori* negative). There was significant positive correlation noted between chronic inflammation and HOMA-IR (r_s=0.3193, p-value <0.001), activity and HOMA-IR (r_s=0.4576, p-value<0.001), and atrophy and HOMA-IR (r_s=0.2542, p-value=0.03) [Table/Fig-3-5]. Microscopic images of *H.pylori* positive case with severe degree of chronic inflammation, activity, atrophy and bacterial density were shown in

[Table/Fig-6a-d] along with microscopic image of *H.pylori* negative case in [Table/Fig-6e,f].

Bacterial density grading	HOMA-IR (Mean)	r_s-value	p-value
Group I with mild density	2.49	0.2992	0.01*
Group I with moderate density	2.54		
Group I with severe density	3.19		
Group II	1.69		

[Table/Fig-2]: Correlation of bacterial density grading with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).
*p-value <0.05 was considered statistically significant

Chronic inflammation grading	HOMA-IR (Mean)	r_s-value	p-value
Group I with mild inflammation	1.66	0.3193	<0.001*
Group I with moderate/severe inflammation	2.88		
Group II	1.69		

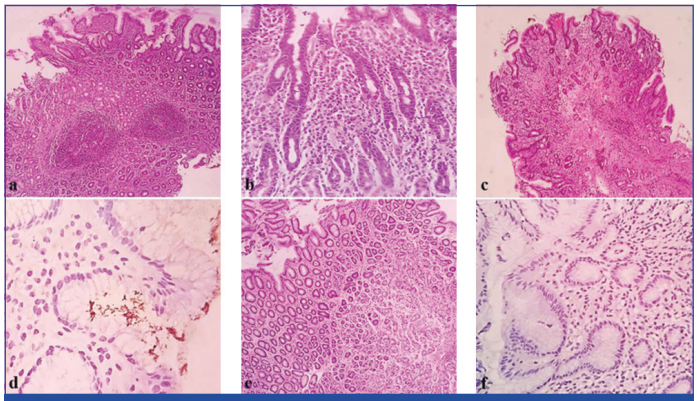
[Table/Fig-3]: Correlation of chronic inflammation of gastric mucosa with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).
*p-value <0.05 was considered statistically significant

Activity grading	HOMA-IR (Mean)	r_s-value	p-value
Group I with absent activity	1.81	0.4576	<0.001*
Group I with mild activity	2.58		
Group I with moderate/severe activity	3.86		
Group II	1.69		

[Table/Fig-4]: Correlation of activity of gastric mucosa with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).
*p-value <0.05 was considered statistically significant

Atrophy grading	HOMA-IR (Mean)	r_s-value	p-value
Group I with absent atrophy	2.09	0.2542	0.03*
Group I with mild atrophy	2.67		
Group I with moderate/severe atrophy	3.66		
Group II	1.69		

[Table/Fig-5]: Correlation of atrophy of gastric mucosa with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).
*p-value <0.05 was considered statistically significant



[Table/Fig-6]: Histomorphological features of *H.pylori* positive case: a) Chronic inflammation-severe grade with diffuse mononuclear infiltration (H&E,10X); b) Activity-severe grade with >50% of the crypts showing neutrophilic infiltration (H&E, 40X); c) Atrophy-severe grade with loss of >50% of the glands (H&E,10X); d) *H.pylori* bacterial density-severe grade with dense bacterial colonies on the surface epithelium (H&E,100X); e) Histomorphological features of *H.pylori* negative case showing no chronic inflammation, no activity and atrophy seen (H&E,10X); f) Histomorphological features of *H.pylori* negative case with absence of bacterial colonies (IHC,40X).

DISCUSSION

Helicobacter pylori is a chronic inflammation which causes various gastrointestinal and extra-gastrointestinal disorders. In the past decade, studies have been done to explore the *H.pylori*'s effect on glucose metabolism profiles. In the majority of earlier studies, the link between *H.pylori* and glucose metabolism profiles were discovered using stool antigen assays and antibody titres [5]. The stool antigen assay might show false negative results in case of use of antibiotics and proton pump inhibitors [19]. The serology test may also show false positive results [19]. In the current study, authors correlated the histopathological characteristics of gastric biopsies according to Updated Sydney System with HOMA-IR levels between *H.pylori* positive and negative groups.

The present study showed no significant difference in age between two groups which was similar to study done by Esheba N and Nagy H and, Allam AS et al., [20,21]. Esheba N and Nagy H and, Askar A et al., found that most of the *H.pylori* positive individuals were males with 65% and 73.5%, respectively [20,22]. However, among *H.pylori* positive cases, female dominance with 63.6% and 57.5% was noted by Maluf S et al., and Allam AS et al., respectively [8,21]. Though there was male preponderance (62.8%) in *H.pylori*-infected group in the present study, it was not statistically significant [Table/Fig-1]. Smoking, alcohol use, poor personal cleanliness, and increased physical activity might indeed contribute to this male predominance [22]. No significant difference in gender between two groups observed in the studies done by Esheba N and Nagy H and, Allam AS et al., [20,21].

Helicobacter pylori lowers ghrelin and leptin levels, which delays the sensation of fullness while eating and leads to obesity. Insulin resistance and the hormonal impact of *H.pylori* may be responsible for the rise in BMI. Maluf S et al., and Hsieh MC et al., noted that the mean BMI for those with *H.pylori* infection was 24.4 and 23.53, respectively [8,9]. In the present study, participants who tested positive for *H.pylori* had a mean BMI of 26.27 and was statistically significant (p-value=0.04) [Table/Fig-1].

Fasting blood glucose testing is a common biochemical test performed to assess the glycaemic status [9]. *H.pylori* infection and FBG levels had reported to have a significant correlation by Esheba N and Nagy H, Allam AS et al., Han X et al., and Sayilar EI et al., [20,21,23,24]. In this study also, it was noted that a significant correlation was existing between *H.pylori* and FBG levels (p-value <0.001) [Table/Fig-1]. However, no association was found between *H.pylori* and FBG by Hsieh MC et al., Askar A et al., and Gabra HM et al., [9,22,25]. It was mentioned that FBG testing could be influenced by the diet and exercise [9]. In the present study, the patients were advised to strictly adhere to the instructions of overnight fasting and to refrain from engaging in any strenuous exercise before collecting blood samples for the test.

Insulin is an important regulatory hormone of glucose metabolism [5]. Esheba N and Nagy H, Askar A et al., Sayilar EI et al., and Gabra HM et al., showed a notable rise in the mean value of insulin levels in the *H.pylori*-infected group as compared to the *H.pylori* negative group [20,22,24,25]. In this study, strong correlation between *H.pylori* infection and mean insulin level was observed with a p-value of 0.02 [Table/Fig-1]. In contrast to the above results, Allam AS et al., did not find any correlation between *H.pylori* and insulin levels [21].

Insulin resistance is characterised by decreased sensitivity to insulin mediated utilisation of glucose, inspite of normal or elevated insulin levels [5]. Insulin resistance, immune system activation, and chronic inflammation all play an important role in the pathogenesis of diabetes mellitus [5]. Infection with *H.pylori* occurring in the early decades of life, results in chronic low-grade inflammation. Pro-inflammatory cytokines and mediators like TNF-α, IL-6, and CRP will be activated. As a result of these pro-inflammatory cytokines' inhibition of the glucose transporter protein and phosphorylation of the insulin receptor substrate protein's serine residues, insulin resistance and diabetes mellitus are developed [5,8]. *H.pylori* infection will increase the secretion of lipopolysaccharides, which will further exacerbate the inflammation [26]. The gut hormones ghrelin and leptin are known to be affected by *H.pylori* infection and

have less of their release [27]. These hormones play a crucial role in the development of diabetes mellitus and obesity-related impaired glucose metabolism [5]. Insulin resistance is also brought on by the *H.pylori* infection's effects on somatostatin levels and gastrin levels [28]. The regulation of insulin release is carried out by these two gastrointestinal hormones.

Mathews DR et al., was the first to calculate HOMA-IR to measure insulin resistance [18]. Aydemir S et al., noted that it was useful in detecting relationship between *H.pylori* infection and insulin resistance [13]. According to studies by Gen R et al., Esheba N and Nagy H, Askar A et al., Sayilar EI et al., and Gabra HM et al., patients with *H.pylori* infections had statistically significantly higher mean HOMA-IR levels [15,20,22,24,25]. In this study, a significant rise in mean HOMA-IR values among *H.pylori*-infected group compared to *H.pylori* negative group using gold standard IHC method on gastric biopsies to detect *H.pylori* was noted (p-value <0.001) [Table/Fig-1]. Whereas, in the studies by Hsieh MC et al., and Allam AS et al., the levels of HOMA-IR and *H.pylori* infection were not significantly correlated [9,21]. Non uniformity in the use of methodologies to diagnose *H.pylori* positivity would have led to the disparity between studies [5].

In the present study, all the histomorphological features and bacterial density grading of chronic gastritis (using the Updated Sydney system classification) were correlated with HOMA-IR levels. To the best of our knowledge, till date, no studies have been conducted so far to assess their correlation. In comparison between the two groups, the *H.pylori* infected group (Group I) with severe degree of bacterial colonisation had significantly higher mean HOMA-IR levels than the *H.pylori* negative group (Group II) [Table/Fig-2].

It was also noted that the mean HOMA-IR values were higher in the *H.pylori*-infected group (Group I) with moderate/severe chronic inflammation, activity and atrophy than in the *H.pylori*-negative group (Group II) [Table/Fig-3-5]. There was significant positive correlation noted between chronic inflammation and HOMA-IR (p-value <0.001), activity and HOMA-IR (p-value <0.001) and atrophy and HOMA-IR (p-value=0.03) [Table/Fig-3-5].

Higher levels of *H.pylori* bacterial colonisation will be evident in long-term chronic *H.pylori* infections [29]. A higher level of colonisation will lead to more activity and inflammation as well as atrophy-related alterations that are more pronounced [30]. These findings support two hypotheses. First, severe bacterial density of *H.pylori* has significant effect on HOMA-IR levels. Second, severe chronic active inflammation with atrophic changes in gastric mucosa has significant effect on HOMA-IR levels.

Limitation(s)

Small sample size and single-centre study could be limitations of the current study. The potential impact of eradicating the *H.pylori* infection on HOMA-IR values is not evaluated in this study. Further many multicentric studies are required to determine the association of HOMA-IR with histomorphological features of *H.pylori* induced gastritis. The association of TNF-α, IL-6, and CRP levels with HOMA-IR levels in *H.pylori* induced gastritis patients need to be evaluated.

CONCLUSION(S)

The present study recommends to scrupulously adheres to the updated Sydney system for routine histopathological evaluation of the endoscopic gastric biopsies. The severity of tissue inflammatory response to be correlated with *H.pylori* infection using the gold standard method. Patients with chronic gastritis who have severe bacterial density, inflammation, activity and atrophy require special attention. The patients who are diagnosed with *H.pylori* induced gastritis should be preferably, followed with HOMA-IR values, to predict the risk of insulin resistance; as early detection and eradication of *H.pylori* would decrease the risk of development of insulin resistance, diabetes mellitus and its complications.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 26, 2023
- Manual Googling: Dec 28, 2022
- iThenticate Software: Jan 01, 2023 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Nov 20, 2022**
Date of Peer Review: **Dec 07, 2022**
Date of Acceptance: **Jan 04, 2023**
Date of Publishing: **Feb 01, 2023**