Effect of *Helicobacter pylori* Infection on Insulin Resistance in non-Obese, non-Diabetic Patients

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Background and study aim: *Helicobacter pylori* is associated with the inflammation of the mucosa-associated lymphoid tissues throughout the digestive tract. Infection by *H. pylori* is related to insulin resistance (IR). The Homeostatic model assessment of IR (HOMA-IR) is a reliable method for assessing IR by basal glucose and insulin levels in humans. The current approach aimed to use the HOMA-IR index to study the relation between *H. pylori* and IR in non-obese and non-diabetic patients.

Patients/Materials and Methods: 62 participants were divided into *H. pylori*-positive and control groups. All participants were non-obese, non-diabetic, and registered in the outpatient virology clinics, Department of Gastroenterology and Hepatology, Sohag University Hospital, Egypt. We performed different laboratory investigations such as liver functions, fasting blood sugar, and fasting blood insulin. HOMA-IR was calculated for each participant of the study population .

Results: *H. pylori* infections were most common among male (73.5%) compared to females (26.5%) patients with a significant P=0.003. *H. pylori* infections were associated with higher levels of C reactive protein (CRP), P=0.039. The levels of serum fasting insulin were higher in *H. pylori*-positive patients (16.95±4.67 µU/ml) than the uninfected individuals (10.49 ±6.5 µU/ml), P=0.001. The values of the HOMA-IR index were significantly higher (3.8 ±1.16) with H. pylori infection, as well, P=0.001.

Conclusion: HOMA-IR index is a reliable indicator of IR in *H. pylori*-infected patients from Sohag, Egypt. Further longitudinal cohort studies are required to investigate the usage of HOMA-IR to predict *H. pylori*-associated diseases in different medical centers from Egypt.

INTRODUCTION

Helicobacter pylori (*H. Pylori*) is one of the Gram-negative bacteria, which was previously known as *Campylobacter pylori*, a spiral macrophile which attacks and lives in the human stomach **[1]**. *H. Pylori* was first identified in 1982 by Barry Marshall and Robin Warren as the cause of active chronic gastritis in the gastric epithelium **[2]**. *H. Pylori* is associated with the inflammation of the mucosa-associated lymphoid tissues through the digestive tract **[3]**, which might participate in the prognosis of other serious diseases such as gastric cancer **[4]**. H. Pylori infection is usually asymptomatic, however in severe infection, it might cause gastritis or ulcers in the stomach or even in the duodenum **[3]**. Sometimes, it can cause an inflammation of the lymphoid tissue surrounding the eye, called ocular adnexal Mucosa-Associated Lymphoid Tissue (MALT) lymphoma **[5]**. Furthermore, the infection by *H. pylori* might cause sharp deficiencies in the levels of some vitamins (A, C, E, and B12) and minerals (Iron and

Copper), which is a dangerous risk factor in some medical situations such as pregnancy and breastfeeding **[6]**. *H. pylori* affect the melatonin secretion and functions, which further disturb the sleep-wake cycles, as well **[5]**.

The infection by *H. pylori* is related negatively to the serum levels of leptin and positively to the tumor necrosis factor α (TNF-α), which commonly induces insulin resistance (IR) and the development of metabolic syndrome (MS) **[7-9]**. IR is a pathologic condition in which the normal insulin levels are not sufficient to function perfectly in the peripheral tissues to allow glycogen storage **[10]**. In humans, IR was found not to be associated with impaired insulin-stimulated glucose disposal **[11]**, but with atherosclerosis and other cardiovascular diseases, as well **[12]**. The prognosis of IR is commonly associated with the excessive production of inflammatory cytokines such as (IL-8, IL-10, IL-12) and acute-phase proteins such as CRP **[13]**. The prevalence of IR increased all over the past years (15.5 to 46.5%, among adults) with associated metabolic disorders, particularly with older ages **[14]**. IR was found to be affected with different variations in the hormones that regulate insulin metabolism, such as gastrointestinal hormone, which deficiency is a common symptom of *H. pylori* infection, as well **[15]**.

The Homeostatic model assessment (HOMA) is a reliable algorithm to evaluate the β-cell function and IR by basal (fasting) glucose and insulin levels in humans **[16]**. It was defined and developed in 1985 by Matthews and colleagues from the Diabetes Research Laboratories, Radcliffe Infirmary, Oxford, UK **[16]**. The combinational term (HOMA-IR) was used to describe a simple and convenient method to evaluate the level of IR and its correlation to the clamp-measured total glucose disposal **[17-18]**.

To our knowledge, there is a limited number of reports related to the usage of the HOMA-IR model to study the relationship between *H. pylori* infection and the abnormal IR, however, there few studies were conducted in Egypt. So, the current study aimed to evaluate the effect of *H. pylori* on insulin resistance in non-obese and non-diabetic patients, registered in the outpatient virology clinics, Department of Gastroenterology and Hepatology, Sohag University Hospital, Egypt, using the HOMA-IR model.

PATIENTS AND METHODS

This study was conducted in outpatient clinic of Sohag University Hospital, Sohag, Egypt, in the period between February 2019 and December 2020. 62 patients were recruited in the study where all of them were complaining of various gastrointestinal manifestations and fulfilling the inclusion and exclusion criteria. Patients older than 30 years with various gastrointestinal symptoms with positive test for *H. pylori* infection (positive *H. pylori* stool Antigen test) were included. On the other hand, patients with liver cirrhosis, chronic renal failure (with or without dialysis), polycystic ovary, obese (BMI ≥ 30 kg/m2), treated with non-steroidal anti-inflammatory drugs (NSAIDS), and smokers were excluded from the current study. Besides, patients with local or systemic infection, diabetic, hypertensive, or those received eradication therapy for *H. pylori* in the last four weeks were excluded, as well. Patients were divided into two groups according to the positivity of *H. pylori* test; control group (1) with *H. pylori* negative and group (2) were *H. pylori* positive by stool antigen test for *H. pylori* infection. HOMA-IR index was used to assess insulin resistance.

All patients and controls were equally tested to the following variables: full medical history report, complete clinical examination, and routine laboratory investigations including complete blood count, serum total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides, liver and kidney functions tests, CRP by latex agglutination, fasting blood glucose, and fasting insulin levels. BMI was calculated as body weight (kg)/height^2 (m).

Laboratory investigations:

To assess the *H. pylori* infection, a fresh stool sample is collected in sterile container and used for assessment of *H. pylori* Antigen. *H. pylori* infection was detected serologically by using the commercially available enzyme-linked immune-sorbent assay (ELISA) kits (*H. pylori* IgG ELISA kit, Padtan Elm Co., Tahran, Iran) and (*H. pylori* Qualitative ELISA kit; Eagle Biosciences Inc., Amherst, NH, USA) following the manufacturer guidelines.

To investigate the above-mentioned laboratory examinations; an amount of 5ml of venous blood was withdrawn from each participant, under aseptic conditions. The blood samples were

allowed to clot at room temperature for 30 minutes and then were centrifuged at 2000-3000 rpm for 15 minutes. The sera supernatants were collected and divided into three aliquots:

a) The portion was used for measurement of fasting blood glucose level (Pars Azmoon commercial kit, Pars Azmoon, Tehran, Iran), ALT (alanine aminotransferase), AST (aspartate aminotransferase), blood urea, and sCr) (serum creatinine) levels. A dedicated spectrophotometer (Cobas C 311 Chemistry Analyser System, Roch Diagnostic GmbH, Indianapolis, IN, USA) was used for OD measurements.

b) The second portion was used to measure the levels of fasting serum insulin level by using by a suitable Immunenzymometric assay (IEMA) (ST AIA-PACK IRI, Tosoh Bioscience Inc., South San Francisco, CA, USA) and a dedicated ELIZA plate reader (ARCHITECT i1000SR immunoassay analyzer, Abbott Laboratories, Chicago, IL, USA).

c) The third portion was used for the assessment of CRP by using Synchron Lx 20 Autoanalyser (Beckman Coulter, Fullertron, CA, USA).

To calculate the HOMA-IR, we used the following equation as described before [18]:

$$\text{HOMA} - \text{IR} = \frac{Fasting\ glycemia\ \left(\frac{mg}{dl}\right) \times Fasting\ insulinemia\ \left(\frac{\mu U}{ml}\right)}{405}$$

Statistical analysis:

The results and data from the above-mentioned observations and tests were analysed by the Statistical Package for Social Science (SPSS) (SPSS version 25, IBM, Armonk, NY, USA). *Pearson Chi-Square* was used to assess the significance of different variables between the two groups. The correlations between homeostasis model assessment of insulin resistance and other variables of the study were assessed by *Pearson* product-moment correlation coefficient (PPMCC) to calculate the *Pearson's* r values and detect the significance of variables at *P value<0.05.*

RESULTS:

In the current study, the participants were divided into two groups according to the results of stool antigen tests for *H. pylori* infection. As shown in Table 1, 35 males versus 27 females were recruited in the study. The results of stool antigen test showed that *H. pylori* infections were most common among male patients (73.5% of positive cases) compared to females (26.5%) with a significant *P=0.003*. All participants had an overall BMI of 26.59±1.48 %, which indicated that most of the participants had normal or little higher weights, but were definitely, not obese. However, the results indicated that patients with *H. pylori* infection had significant increases in BMI values, but were still not obese, *P=0.001*. All participants had an overall mean age of 47.24±5.43 years without any significant variation among patients and control groups.

The laboratory investigations showed significant variation in the results of CRP levels between patients and control groups, *P=0.039. Despite the results of the other blood tests didn't show any significance, the levels of AST, Urea, and sCr were slightly higher in H. pylori-infected patients, compared to the control group. By contrast, the levels of ALT were lower in H. pylori-infected* group, despite insignificancy, as well. Most of the participants (81%) had different types of symptoms, despite none of them were significant to *H. pylori* infection (Table 1).

As shown in Table 2, all participants had normal fasting blood glucose level, as they are non-diabetic, however no significant difference were found between *H. pylori-infected and non-*infected individuals. On the contrary, the serum levels of fasting Insulin were significantly higher in *H. pylori-infected group (16.95±4.67 µU/ml) compared to control group (*10.49 ±6.5 µU/ml), *P=0.001*. The values of HOMA-IR index were significantly higher (3.8 ±1.16) in *H. pylori-*infected as compared to the control group (2.07 ±1.01), *P=0.001 (Table 2).*

To study the factors that might affect the results of the HOMA-IR model, we statically analyzed the correlations between different study variables and HOMA-IR values in both groups. The analysis showed that the level of fasting Insulin is directly proportional to *H. pylori* infection, where the higher levels of fasting Insulin were significantly correlated to positive *H. pylori* results of ELIZA, in contrast to the negative results with lower serum levels of Insulin (Table 3).

Table (1): Demographic and Clinical characteristics of the study population:

Variables		*H. Pylori* Negative (N=28)	*H. Pylori* Positive (N=34)	*P-value*	Total
Gender N. (%)	Male	10 (35.7%)	25 (73.5%)	0.003**	35 (56%)
	Female	18 (64.3%)	9 (26.5%)		27 (44%)
Age (years) Mean ±SD		47.5 ±6.2	47 ±4.82	0.59	
BMI (%) Mean ±SD		25.8 ±1.45	27.24 ±1.17	0.001**	
Laboratory tests					
CRP (mg/L) Mean ±SD		1.63 ±0.48	1.33 ±0.48	0.039*	
AST (U/L) Mean ±SD		30.07 ±8.3	33.68 ±10.41	0.099	
ALT (U/L) Mean ±SD		31.32 ±7.28	27.18 ±12.33	0.51	
Urea (mg/dL) Mean ±SD		25 ±4.6	27.85 ±8.91	0.072	
sCr (mg/dl) Mean ±SD		0.86 ±0.13	0.9 ±0.22	0.366	
Clinical symptoms					
Abdominal pain N (%)		10 (35.7%)	12 (35.3%)	0.623	22(35%)
Constipation N (%)		2 (7.1%)	7 (20.6%)		9(15%)
Diarrhea N (%)		2 (7.1%)	4 (11.8%)		6(10%)
Dyspepsia N (%)		6 (21.4%)	5 (14.7%)		11(18%)
Others N (%)		1 (3.6%)	1 (2.9%)		2(3%)
No symptoms N (%)		7 (25%)	5 (14.7%)		12(19%)

* *P-value* <0.05, ** *P-value* <0.01.

SD: Standard deviation; sCr: serum creatinine; ALT: alanine transferase; AST: aspartate transaminase; CRP: C reactive protein; BMI: Body Mass Index.

Table (2): Correlations between levels of fasting blood glucose, fasting insulin, and homeostasis model assessment of insulin resistance in the studied groups:

Variables	*H. Pylori* Negative (N=28) Mean ±SD	*H. Pylori* Positive (N=34) Mean ±SD	*P-value*
Fasting blood glucose (mg/dl)	90.68 ±11.18	92 ±6.67	0.61
Fasting Insulin (µU/ml)	10.49 ±6.5	16.95 ±4.67	0.001**
HOMA-IR	2.07 ±1.01	3.8 ±1.16	0.001**

** *P-value* <0.01.

SD: Standard deviation; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

Table (3): Correlations between homeostasis model assessment of insulin resistance and other variables in the studied groups:

Variables	*H. Pylori* Negative (N=28)		*H. Pylori* Positive (N=34)	
	r	***P value***	**r**	***P value***
Fasting blood glucose	0.347	0.06	0.027	0.89
Fasting Insulin	0.968	0.001**	0.817	0.001**
Urea	-0.444	0.01*	0.087	0.647
sCr	-0.529	0.003**	0.166	0.318
BMI	0.031	0.872	0.197	0.297
CRP	-0.738	0.001**	-0.179	0.344

* *P-value* <0.05, ** *P-value* <0.01.

sCr: serum creatinine; CRP: C reactive protein; BMI: Body Mass Index.

DISCUSSION

Several studies showed a remarkable association between infection with *H. pylori* and IR **[7, 19]**. IR is associated with metabolic disturbances that cause the elevation of blood sugar in both obese and non-obese patients **[20]**. Several studies reported IR association with different inflammatory and cardiovascular diseases which causes excessive secretions of CRP **[21-22]** and other inflammatory interleukins such as IL-10 **[23]**, IL-12 **[24]**, and IL-29 **[25]**, particularly in

obese and diabetic patients **[26]**. However, the mechanism of IR in non-diabetic, non-obese patients is still unclear. Several studies used the algorithmic model of HOMA-IR to investigate the correlation between IR and different clinical complications **[27]** or other demographic-social features in a specific population **[28]**. In the current study, we tested the correlation between one of the most prevalent gastrointestinal issues, the *H. pylori* infection, and IR in non-diabetic, non-obese individuals in a single medical center (the outpatient virology clinics, Department of Gastroenterology and Hepatology, Sohag University Hospital, Egypt).

The results showed that *H. pylori* infection was more common among male patients. In agreement, a previous study showed that males are more susceptible to H. pylori infection than women (OR: 1.16, 95% CI: 1.11-1.22) which were associated with several inflammatory diseases such as ulcers and gastrointestinal tumors all over the world **[29]**. A previous study showed that most of the *H. pylori* seropositivity was among males (67.94%) in Cameroon **[30]** while another meta-analysis study suggested that the male predominance in *H. pylori* infection might be due to poor hygiene and higher physical activity **[29]**. The hormonal profile of females was suggested to induce more protection against different types of gastric inflammations and infections because of the higher Th2 response and secreted antibodies **[31]**.

The results of the current study showed that *H. pylori* infection had significantly higher CRP levels. Similarly, several studies showed that the serum levels of CRP in infected patients were higher than in healthy individuals **[32-34]** which indicated that H. pylori infection stimulates the production of different inflammatory cytokines such as IL-1β, IL-6, TNF-α **[35]**. Furthermore, the current study reported a slight increase in the blood levels of AST, Urea, and sCr, which is in agreement with the findings of several previous studies **[36-37]**.

The main target of the current study was to evaluate the association between *H. pylori* infection and IR in non-diabetic, non-obese patients from Sohag, Egypt. As shown in the results section, the levels of the fasting insulin in the *H. pylori*-infected group were higher than the control group, despite normal serum glucose level which indicated a higher level of insulin resistance. Furthermore, the results showed higher values for HOMA-IR with *H. pylori* infection compared to the control. In disagreement with our findings, a recent study was conducted on *H. pylori*-infected patients from Cairo, Egypt, showed insignificant difference between infected and healthy individuals in the respect of HOMA-IR, However, the nonalcoholic fatty liver disease (NAFLD) fibrosis scores were significant among H. pylori infection cases **[38]**. Similar to our results, a study from Tanta, Egypt, showed a significant increase in the levels of fasting insulin (17.2±2.74 IU/m) and HOMA-IR scores (3.66±1.26) in the *H. pylori* infection patients who were either non-obese or non-diabetic individuals **[39]**. Another study from Taiwan showed that HOMA-IR score > 2.5 and higher levels of TNFα were associated with *H. pylori* infection in patients with ideal BMI and normal fasting blood sugar levels, but with higher leptin values which indicated an insulin resistance and metabolic syndrome **[7]**. Another study from Iran compared the levels of insulin resistance and HOMA-IR in both diabetic and non-diabetic patients and reported that in both categories the infection with *H. pylori* had a higher value of IR and HOMA-IR scores >3 **[40]**. All of these studies demonstrated the robust direct relationship between H. pylori infection and IR which might explain all the observed inflammatory activities reported in the non-obese non-diabetic patients.

CONCLUSIONS:

The current study demonstrated the positive relationship of *H. pylori* infection with the abnormal levels of serum insulin in non-diabetic, non-obese patients from Sohag, Egypt. HOMA-IR index is a reliable indicator of IR accompanied with *H. pylori* infection which might a significant indicator for other more complications and severe medical issues. Further longitudinal cohort studies are required to investigate the usage of HOMA-IR in the prediction of different IR and *H. pylori*-associated diseases in different medical centers from Egypt.

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Conflict of interest: None.

Ethical Consideration:

The current study had an approval from the Ethics Committee of the Faculty of Medicine,

Sohag University, Egypt, according to the World Medical Association (WMA) Declaration of Helsinki https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ . All informed consents were approved and signed by all participants.

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