

Prevalence and association of *Helicobacter pylori* infection in patients with metabolic syndrome: A case-control study

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Abstract

Background and objective: *Helicobacter pylori* infection and metabolic syndrome are two progressive factors noticed in developing countries, but their association is still controversial. This study aimed to determine the prevalence and association of *Helicobacter pylori* infection in both subjects with and without metabolic syndrome.

Methods: A case-control study was conducted at the Ble General Hospital, 658 subjects taken and divided into two groups first those who were diagnosed as metabolic syndrome (328 subjects) and second control group (330 subjects). *Helicobacter pylori*-specific IgG antibody and some biochemical tests were performed for both groups besides other parameters like blood pressure and BMI.

Results: Having metabolic syndrome is associated with a higher probability of having *Helicobacter pylori* Abs (OR = 1.6; 95% CI = 1.096-2.341). Age group 40-49 years had more probability to have *Helicobacter pylori* Abs (OR = 2.054; 95% CI = 1.086-3.883). The prevalence of metabolic syndrome reported higher in females (77.4 %). No significant differences were detected between the rapid method and the ELIZA method for the detection of stool Ag ($P = 0.921$) but differences were significant in the detection of *Helicobacter pylori* Abs ($P < 0.001$).

Conclusion: The study demonstrates that having metabolic syndrome is associated with a higher probability of having *Helicobacter pylori* Abs compared with the controls. This study also showed immunochromatography is reliable for the detection of *Helicobacter pylori* stool Ag but not Ab.

Keywords: *Helicobacter pylori*; Metabolic syndrome.

Introduction

The elevated curve of *Helicobacter pylori* (*H. pylori*) infection rate parallel to subjects diagnosed with metabolic syndrome (MetS) in developing countries indicates the possibility of an association between these two factors. Although this bacterium has been linked to duodenal, gastric, and cancer ulcers, there is evidence of a link between *H. pylori* colonization and clinical aspects such as obesity, diabetes, hypertension, and dyslipidemia, all of which are components of metabolic syndrome disease.⁽¹⁾ According to the American Heart Association and National Heart Lung and Blood Institute the metabolic syndrome

can be defined as "a clustering of at least three of the following five medical conditions: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL)" which are known to be interrelated.⁽²⁾

In general, the presence of *H. pylori*-specific immunoglobulin G in suspected serum samples could be used to assess the association between *H. pylori* infection and MetS, but this association is theoretically related to cytokines implicated in the pathogenesis of *H. pylori*, which is considered a source of developing the metabolic syndrome's components as

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follows: First, urease activity and flagellar motility of *H. pylori* help the bacterium neutralize gastric acid and consequently tend toward colonization, inflammation, and tissue destruction of the deep layers of gastric mucosa.⁽³⁾

H. pylori-induced inflammatory response to damaged gastric cells causes the release of CRP, IL-1, IL-6, IL-8, IL-10, and TNF- α cytokines the results of Cag A & Vac A virulence factors activity which mediate neutrophil attraction and induce acute inflammation,⁽⁴⁾ increase the level of TNF- α and IL-8 together with the decrease of serum leptin (regulatory feeding behavior) as results of *H. pylori* infection play a key role in developing insulin resistance condition.⁽⁵⁾

Second, colonization and eradication of *H. pylori* induce changes in gut microbiome flora (due to utilization of excessive antibiotics) and interfere with gastric hormone regulation such as ghrelin and leptin, eventually affecting energy balance and interfering with obesity and waist circumstance.⁽⁶⁾

And third, one characteristic feature of subjects with MetS is an alteration in their lipid panel. TNF- α has been shown to inactivate the lipoprotein lipase (LPL) enzyme, which is responsible for circulating triglyceride (TG) degradation. eventually results in hypertriglyceridemia and HDL reduction.⁽⁷⁾

High prevalence of *H. pylori* and MetS has been reported in developing countries including our country⁽⁸⁻¹⁰⁾ due to several factors such as lower socioeconomic status, but no study shows the association between these two factors in our region. As previously reported, the association between *H. pylori* and MetS remains controversial, and the purpose of this case-control study was to determine the likelihood of association between these two factors in the Kurdistan region. The main objectives include determining the prevalence of *H. pylori* infection in both subjects with MetS and control groups with the association of different

sociodemographic variables like age group, gender, and education. Also comparing two methods of detection (ELISA and immunochromatography) for both *H. pylori* serum IgG antibodies and stool antigens

Methods

A case-control study was conducted at the Ble General Hospital (in Erbil province) between June 2022 and November 2022 that included 658 (control 330, case 328) outpatient subjects that underwent several clinical and laboratory check-ups according to standardized questionnaire forms by the trained nurse and internal specialist interviewers. The questionnaire contained points on socio-demographic characteristics as well as information regarding the diagnostic criteria for MetS. Subjects with MetS selected according to the NCEP ATP III definition and guidelines. The diagnostic criteria include three of the following five standards;⁽²⁾

- Visceral obesity which is determined by increased waist circumference, at least 102 cm in men or 85 cm in women, measured at the top of the iliac crest at the end of a normal expiration.
- Elevated triglycerides (TG), at least 150 mg/dL, or undertreatment with lipid-lowering agents.
- Decreased HDL cholesterol level of fewer than 40 mg/dL in men or less than 50 mg/dL in women, or undertreatment with lipid-lowering agents.
- High blood pressure, systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg, or undertreatment with hypertensive-lowering agents.
- High serum glucose, fasting glucose level of at least 100 mg/dL, or undertreatment with glucose-lowering agents.

Subjects with previous gastric surgery, anti-*H. pylori* therapy, use of antibiotics, proton pump inhibitors, H₂ blockers, or bismuth within the previous 4 weeks, however history of cancer, severe liver or renal dysfunction, or neoplasm were excluded

from the study.

Non-invasive techniques are used to diagnose the *H. pylori* infection through serum IgG Ab and stool Ag in the hospital pathology department, as well as biochemical investigations like TG, HDL, and glucose. A commercially available enzyme-linked immunosorbent assay kit (ELISA method) was used to detect serum *H. pylori*-specific immunoglobulin G (AccuBind test system, USA) with a specificity of 90% and sensitivity of 0.1424 U/ml. Samples with an antibody titer higher than 20 U/mL were considered seropositive for *H. pylori* infection. However, an ELIZA kit used for the detection of stool *H. pylori*-specific antigen (AccuDiag test system, USA) with a specificity of 100% and sensitivity of 0.5 ng/ml, stool samples with an antigen titer higher than 20 U/mL represent an active infection (Biotech washer and reader instruments, USA). In addition, immunochromatography or the rapid method (AVONCHEM rapid test cassette kit, UK) was utilized to detect *H. pylori* antibodies and antigens (sensitivity: 96.7%, specificity: 93.8%) to compare the accuracy of the rapid method against the ELISA method. Biochemical investigations such as serum glucose and lipid profile were carried out using an autoanalyzer machine (KENZA 480 autoanalyzer, Franca e) the

rough common enzymatic method.

The factors found to be significantly associated (according to the Chi-square test) with the *H. pylori* positivity, were entered into a binary logistic regression model, where the dependent variable was Ab positivity by ELIZA. A *P*-value of ≤ 0.05 was considered statistically significant.

Ethical Consideration

The ethical committee of the college of health sciences at Hawler Medical University approved the study proposal, and formal permission was obtained from the administrator of Ble General Hospital. The purpose of the study was explained, and personal consent was obtained from all study participants; they had the option to withdraw from the study at any time.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 26. The chi-square test of association was used to compare proportions between cases and controls. A student's t-test of two independent samples was used to compare means. The McNemar test was used when the results of the rapid method were compared with the ELISA method results of the same patients. The following table shows how the validity indicators of the rapid method were calculated (Table 1).

Table 1 Calculation of validity indicators with the rapid method

		ELIZA		
		Positive	Negative	
Rapid test	Positive	TP	FP	TP+FP
	Negative	FN	TN	FN+TN
Total		TP+FN	FP+TN	Total

TP=True positive; TN=True negative; FP=False positive; FN=False negative.

Sensitivity = $TP / (TP+FN) * 100$; *Specificity* = $TN / (FP+TN) * 100$; *Predictive value positive* (PV⁺): $TP / (TP+FP) * 100$; *Predictive value negative* (PV⁻): $TN / (FN+TN) * 100$; *Total agreement* = $(TP + TN) / \text{total}$.

Results

A group of 328 out of a total of 658 subjects met the diagnostic criteria for metabolic syndrome (cases), and the remaining 330 were identified based on baseline characteristics and compared with a control group without metabolic syndrome. The age range of the whole sample was 20–80 years, and the median was 47 years. The mean age of the cases (50.9 years) was significantly ($P < 0.001$) higher than that of the control group (41.9 years). More than three-quarters (77.4%) of the cases were female, compared with 65.8% of the control group ($P = 0.001$).

The educational level of the cases was lower than that of the controls, where it is evident that the majority of the cases (87.5%) were either illiterate or of primary education, compared with 76.7% of the control group ($P = 0.002$). The prevalence of smoking was (7%) and (11.5%) in the case and control respectively ($P = 0.046$). about half (45.1%) of the cases had a BMI of ≥ 35 kg/m², compared with 16.7% among the controls ($P < 0.001$).

No significant differences were detected between the two groups regarding the fasting status ($P = 0.709$) and the presence of symptoms ($P = 0.438$) (Table 2).

Table 2 Basic characteristics

	Control No. (%)	Case No. (%)	Total No. (%)	<i>P</i> *
Age (years)				
< 30	53 (16.1)	3 (0.9)	56 (8.5)	
30-39	74 (22.4)	28 (8.5)	102 (15.5)	
40-49	113 (34.2)	117 (35.7)	230 (35.0)	
50-59	64 (19.4)	99 (30.2)	163 (24.8)	
≥ 60	26 (7.9)	81 (24.7)	107 (16.3)	< 0.001*
Mean (SD)	41.9 (11.6)	50.9 (9.9)	46.4 (11.7)	< 0.001†
Gender				
Male	113 (34.2)	74 (22.6)	187 (28.4)	
Female	217 (65.8)	254 (77.4)	471 (71.6)	0.001*
Education				
Illiterate	197 (59.7)	214 (65.2)	411 (62.5)	
Basic education	56 (17.0)	73 (22.3)	129 (19.6)	
High school	63 (19.1)	30 (9.1)	93 (14.1)	
Graduated	14 (4.2)	11 (3.4)	25 (3.8)	0.002*
Smoking				
Yes	38 (11.5)	23 (7.0)	61 (9.3)	
No	292 (88.5)	305 (93.0)	597 (90.7)	0.046*
BMI (Kg/m²)				
< 25	64 (19.4)	10 (3.0)	74 (11.2)	
25-29	105 (31.8)	76 (23.2)	181 (27.5)	
30-34	106 (32.1)	94 (28.7)	200 (30.4)	
≥ 35	55 (16.7)	148 (45.1)	203 (30.9)	< 0.001*
Fasting status				
Yes	228 (69.1)	231 (70.4)	459 (69.8)	
No	102 (30.9)	97 (29.6)	199 (30.2)	0.709*
Symptoms				
Asymptomatic	146 (44.2)	155 (47.3)	301 (45.7)	
Symptomatic	184 (55.8)	173 (52.7)	357 (54.3)	0.438*
Total	330 (100.0)	328 (100.0)	658 (100.0)	

*By Chi-square test. †By t-test for two independent samples.

The prevalence of *H. pylori*-specific Abs (detected by ELIZA) increases with increasing age, reaching a maximum in the age group 40-49 years, and then it starts to decrease, as presented in Table 2 ($P = 0.001$). No significant association was detected between the Abs positivity by ELIZA with gender ($P = 0.150$), educational level ($P = 0.760$), and BMI ($P = 0.177$).

It is worth mentioning that the higher the BMI, the higher the rate of Abs positivity, but the differences were not significant (Table 3).

The prevalence of *H. pylori* antibody (as detected by ELIZA) among cases was 75.3%, compared with 66.4% among the controls ($P = 0.012$) (Figure 1).

Table 3 ELIZA antibody positivity by the studied factors

	No.	ELIZA Ab		P^*
		Positive No. (%)	Negative No. (%)	
Age				
< 30	56	33 (58.9)	23 (41.1)	0.001
30-39	102	67 (65.7)	35 (34.3)	
40-49	230	180 (78.3)	50 (21.7)	
50-59	163	122 (74.8)	41 (25.2)	
≥ 60	107	64 (59.8)	43 (40.2)	
Gender				
Male	187	140 (74.9)	47 (25.1)	0.150
Female	471	326 (69.2)	145 (30.8)	
Education				
Illiterate	411	286 (69.6)	125 (30.4)	0.760
Basic	129	94 (72.9)	35 (27.1)	
High school	93	69 (74.2)	24 (25.8)	
Graduated	25	17 (68.0)	8 (32.0)	
BMI				
< 25	74	48 (64.9)	26 (35.1)	0.177
25-29	181	126 (69.6)	55 (30.4)	
30-34	200	137 (68.5)	63 (31.5)	
≥ 35	203	155 (76.4)	48 (23.6)	
Total	658	466 (70.8)	192 (29.2)	

*By Chi-square test.

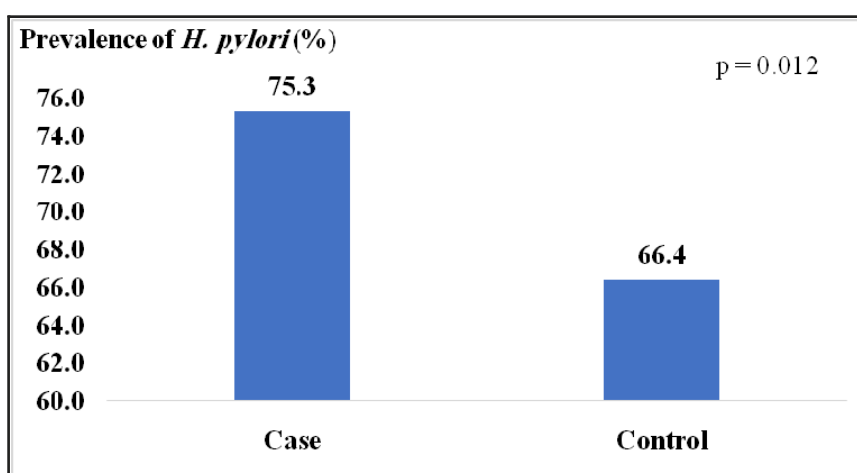


Figure 1 Seropositive antibody among cases and controls detected by ELISA method

Having metabolic syndrome is associated with a higher probability of having *H. pylori* Abs compared with the controls, irrespective of age (OR = 1.6; 95% CI = 1.096-2.341). Those in the age group 40-49 years had more probability to have *H. pylori* Abs compared with those aged less than 30 years (OR = 2.054; 95% CI = 1.086-3.883), as presented in Table 4. The agreement rate between the rapid method and ELIZA method to detect *H. pylori* Abs was 63.4%, and the difference was significant between the two test results ($P < 0.001$). The sensitivity of the rapid

method was low (53.9%) compared with the ELIZA method in the detection of serum *H. pylori* Abs (Table 5).

No significant differences were detected between the immunochromatography method (rapid) and ELIZA method for the detection of stool Ag ($P = 0.921$), and the rate of agreement was 84.5%. The measures of accuracy of *H. pylori* stool Ag with rapid method were relatively high (sensitivity = 78.8%, specificity = 87.7%, PV+ = 78.2%, and PV- = 88.1%) as presented in Table 6.

Table 4 SPSS output of binary logistic regression analysis where the dependent variable is seropositive IgG antibody (by ELIZA)

	B	P	OR	95% C.I. for OR	
				Lower	Upper
Group					
Control (reference)					
Case (metabolic syndrome)	0.471	0.015	1.602	1.096	2.341
Age		0.001			
< 30 (reference)					
30-39	0.190	0.582	1.210	0.615	2.380
40-49	0.720	0.027	2.054	1.086	3.883
50-59	0.480	0.159	1.616	0.828	3.155
≥ 60	-0.293	0.419	0.746	0.367	1.519
Constant	0.337	0.215	1.401		

Table 5 Comparing IgG antibody detected by 'Rapid method' with 'ELIZA method'

Rapid method Abs	ELIZA method Abs		Total	P*
	Positive	Negative		
Positive	251	26	277	< 0.001
Negative	215	166	381	
Sensitivity	Specificity	PV+	PV-	Agreement
53.9%	86.5%	90.6%	43.6%	63.4%

*By McNemar test.

Table 6 Comparing stool Ag detected by 'rapid method' with 'ELIZA stool Ag test'

Ag stool rapid test	ELIZA stool Ag		Total	P*
	Positive	Negative		
Positive	186	52	238	0.921
Negative	50	370	420	
Sensitivity	Specificity	PV+	PV-	Agreement
78.8%	87.7%	78.2%	88.1%	84.5%

*By McNemar test.

Discussion

The frequency of *H. pylori* infection and MetS show a high rate in our community, and performing surveys in this context could have great importance. This study aimed to investigate the association between *H. pylori* infection, as a latent risk, and the progression of MetS and its relation to other sociodemographic variables. The study demonstrates an association between *H. pylori* and MetS. The prevalence of *H. pylori* is higher in the case than in the control subjects. Metabolic syndrome is associated with a higher risk of *H. pylori* infection when compared to control, regardless of age. These findings support the previous. Sayilar *et al.* (2015) concluded that *H. pylori* infection is a risk factor for MetS. So that *H. pylori* leads to insulin resistance by developing chronic inflammation and accordingly facilitates the development of MetS.⁽¹¹⁾

In two large cross-sectional studies in the Japanese population and a study in Israel, *H. pylori* infection was significantly associated with metabolic syndrome⁽¹²⁻¹⁴⁾ however *H. pylori* infection plays an independent role in the pathogenesis of metabolic syndrome in Koreans under 65 years old⁽¹⁵⁾ but the inverse relationship was found in previous findings. The mechanism behind this association is still unknown but the chronic expression of inflammatory proteins and cytokines like CRP, IL-1, IL-6, IL-8, IL-10, and TNF- α assumed a key role in the pathogenesis of MetS.⁽¹⁶⁾

Females have a higher prevalence of MetS than males because, among the components of MetS, females have a higher BMI, lower HDL cholesterol, a larger waist circumference, and higher levels of hyperglycemia, whereas men have hypertension and elevated TG.⁽¹⁰⁻¹⁷⁾

In this study, more than three quarters (77.3%) of the subjects with MetS were female, which means the risk of MetS in females is high. This result agreed with a study on the aged female population in China that believes the presence of

H. pylori-specific antibodies is a predictor for progression of MetS.⁽¹⁸⁾

The prevalence of *H. pylori*-specific Abs increases with increasing age, reaching a maximum in the age group 40–49 years. This finding backs up two studies from Taiwan and one from Turkey, with the exception that *H. pylori* prevalence is higher in subjects aged 50 to 59.^(14,19,20)

Despite non-significant differences, the frequency of seropositive IgG Abs was higher in subjects with a high BMI (35 kg/m²) than in the control group. The result can be interpreted as the possibility of an association between *H. pylori* infection and obesity, which was reported significantly in some studies⁽²⁰⁻²⁴⁾ while non-significant in an ecological⁽²⁵⁾ and a retrospective study.⁽²⁶⁾ This association may be due to the change in gut microbiota, leading to a change in energy homeostasis and eventually cause develop obesity.^(6,27)

The prevalence of smoking among cases was significantly lower than that of the control group. The reason may refer to the efforts of people who suspected MetS to change their lifestyle and reduce the effects of multiple chronic diseases. But smoking is significantly associated with MetS^(28,29) especially in long-life smokers aged < 70.⁽³⁰⁾ Similar frequency of smoker and non-smoker in both groups (case and control) were found in other study⁽¹³⁾ or maybe play the role as an independent risk factor in the development of MetS.⁽³¹⁾

Nowadays, diagnosis of *H. pylori* infection supported by conventional and advanced techniques that focused on the rapidity, sensitivity, and selectivity of the detection method. There are different diagnostic tests today, but each has its advantages and disadvantages, followed by limitations. The selection of test depends on the availability of test kits and laboratory equipment, as well as the clinical conditions of patients. The detection of *H. pylori* is achieved by invasive and non-invasive methods, depending on the purpose of the detection. In this study, two methods of detection were used to assume

the presence of *H. pylori* infection: first ELISA method as a long procedure and second immunochromatography method as a rapid procedure. The results of serum IgG Abs and stool Ag that were evaluated using the ELISA method were utilized to investigate the association between *H. pylori* infection and MetS. On the other hand, the same samples were used for *H. pylori* detection with a different method, immunochromatography or rapid testing, to compare sensitivity and specificity among both methods.

In this study, the McNemar test showed no significant differences between the immunochromatography method (rapid) and the ELISA method for the detection of stool Ag, and the rate of agreement was 84.5%. The measures of accuracy of the *H. pylori* stool Ag with the rapid method were relatively high in sensitivity and specificity, as presented in table five. It means we can trust the results that are given from the rapid method for the detection of *H. pylori* in stool Ag. It's a cheap, fast, and easy-to-carry-out method among non-invasive tests and a good alternative for the ELISA method in clinical decisions about active *H. pylori* infection. This finding agreed with a previous study in 2019⁽³²⁾ but also may provide less reliable results and low agreement with laboratory standards criteria⁽³³⁾ however the diagnostic performance does not recommend its use in the primary diagnosis, when the patient may have an active infection.⁽³⁴⁾

Significant differences were statistically found in the detection of serum Abs between the rapid and ELISA methods by use of the McNemar test; the rapid test for the detection of Ab is not reliable, and the ELISA method is the most trustworthy, which agrees with other studies for the diagnosis of *H. pylori* infection⁽³⁵⁾ but some studies show similarities in the immunochromatographic results with the other serologic tests, nonetheless the specificity was relatively low.⁽³⁶⁾

Conclusion

The frequency of *H. pylori* infection and MetS show a high rate in our community and performing surveys in this context could have great importance. The study demonstrates that there is an association between *H. pylori* and MetS and having metabolic syndrome is associated with a higher probability of having *H. pylori* Abs compared with the controls. Other parts of the study demonstrate immunochromatography is reliable in the detection of *H. pylori* stool Ag but not Ab.

Competing interests

The authors declare that they have no competing interests.

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