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Relationship between *Helicobacter pylori* infection and metabolic syndrome

STOMACH

Emel Işıktaş Sayılar[1], Bülent Çelik[2], Şükrü Dumlu[3]

[1]Department of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Turkey
[2]Department of Statistics, Gazi University Faculty of Science, Ankara, Turkey
[3]Department of Gastroenterology, Department of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Turkey

Original Article

ABSTRACT

Background/Aims: To investigate the prevalence of metabolic syndrome (MS) and its components in patients with Helicobacter pylori that was detected using histopathological diagnostic methods.

Materials and Methods: The study included 200 patients who presented with dyspeptic complaints and had indication for endoscopy. *H. pylori*-positive [HP (+)] and *H. pylori*-negative [HP (–)] patients were compared in terms of MS and its components.

Results: The prevalence of *H. pylori* in general patient population is 49.5%. When patients were examined using a diagnostic criteria of MS, MS was present in 78 patients (78.8%) in the HP (+) (n=99) group and in 22 patients (21.8%) in the HP (–) (n=101) group ($p<0.01$). Logistic regression analysis revealed that *H. pylori* infection enhances the risk of developing MS by approximately 3.6 times (Relative Risk - (RR)=3.617, 95% CI: 2.465–5.307, $p<0.001$). With regard to the MS criteria, mean systolic–diastolic blood pressures and body mass index were significantly higher in HP (+) individuals than in HP (–) individuals. Furthermore, fasting plasma glucose, insulin and homeostatic model assessment–insulin resistance, very low-density lipoproteins, and triglyceride levels were also higher in the HP (+) group, whereas high-density lipoproteins levels were lower.

Conclusion: *H. pylori* infection is a risk factor for MS. *H. pylori* leads to insulin resistance by developing chronic inflammation and accordingly facilitates the development of MS.

Keywords: *Helicobacter pylori*, metabolic syndrome, insulin resistance

INTRODUCTION

Helicobacter pylori infection affects >50% of the world population. Its prevalence and incidence reveal variation among countries depending on the development status and age (1). *H. pylori* infection is diagnosed on the basis of clinical and laboratory findings, microbiological methods, and histopathological examinations. Although endoscopic examination is invasive, expensive, and time consuming, it is of critical importance in determining clinical prognosis on the basis of the localization of a lesion (2). Histological diagnosis is frequently used to determine tissue inflammation and severity of precancerous alterations. With the effect of various factors, the sensitivity and specificity of this test is >95%. It is considered to be the "gold standard" diagnostic method for diagnosing *H. pylori* infection (3).

Metabolic syndrome (MS) is a global epidemic and appears in common genetic and environmental media, and it is characterized together with cardiometabolic risk factors, such as abdominal obesity, atherogenic dyslipidemia, glucose intolerance, and elevated blood pressure (BP). MS is a heterogeneous disease that develops on the basis of insulin resistance (IR), and in 2011, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Table 1) specified the major components of MS as abdominal obesity, IR, elevated BP, and dyslipidemia (4).

Many studies have been conducted to investigate the relationship between MS, the prevalence of which has been rapidly increasing in recent years, and *H. pylori* infection. Although its etiopathogenesis remains unclear, the secretion balance of interleukin (IL)-6 and

Address for Correspondence: Emel Işıktaş Sayılar, E-mail: emelisiktas@yahoo.com
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Table 1. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) 2001, the diagnostic criteria of metabolic syndrome

Any three of the following	
Risk Factor	Defining level
Abdominal Obesity (Waist circumference)	
Men	>102 cm
Women	>88 cm
Triglycerides	≥150 mg/dL
HDL Cholesterol	
Men	<50 mg/dL
Women	<40 mg/dL
Blood Pressure	≥130/≥85
Fasting Glucose	≥110 mg/dL

HDL: High-density lipoproteins

tumor necrosis factor alpha (TNF-α), which are among the proinflammatory cytokines, C-reactive protein (CRP), IL-1β, IL-8, interferon gamma, angiotensinogen, free fatty acids, leptin, and adiponectin is impaired with *H. pylori* infection; moreover, reactive oxygen radicals that are accumulated because of an infection stimulate leukocytes and macrophages. In particular, TNF-α strongly inhibits insulin-mediated glucose uptake in chronic process (5). Adipocytes in the intra-abdominal and visceral adipose tissue secrete signal molecules called adipokine and cytokines and inflammatory markers. Increased lipolytic activity in adipose tissues accelerates the secretion of free fatty acids, whereas increased free fatty acids reduce insulin activity in the muscle, liver, and other tissues (6). Subclinical chronic inflammation occurs because of impaired cytokine balance and increased reactive oxygen radicals. This pathological situation leads to IR and MS (7-9).

This study aimed to determine the prevalence of MS and its components in *H. pylori*-positive [HP (+)] patients in a prospective setting. For this purpose, we compared HP (+) and *H. pylori*-negative [HP (–)] patients on the basis of a histopathological diagnostic method in terms of MS according to the NCEP ATP III criteria.

MATERIALS AND METHODS

Study protocol

Voluntary patients who applied to the Gazi University Gastroenterology polyclinic with distension, postprandial fullness, early satiety, epigastric pain, burning sensation, nausea, gastric flatulence and burp, and dyspepsia and who had an indication for endoscopy on the basis of a clinical evaluation were included in this study. A total of 316 patients were enrolled; however, because of the exclusion criteria, the study was completed with 200 patients after the approval of the Gazi University Faculty of Medicine Research Ethics Committee (Project No: 69) was obtained.

Selection of volunteers

Patients who received proton pump inhibitors, histamine type 2 (H2) receptor antagonists, and/or *H. pylori* eradication therapy in the last month; had received nonsteroidal anti-inflammatory drugs in the last 2 months; have been receiving antidiabetic agent/insulin and lipid-lowering therapy; were at the age <18 and >80 years; had psychiatric disease or were insane; had documented diabetes disease, chronic liver disease, chronic kidney disease, or systemic or local infections; and had been diagnosed with malignancy as well as pregnant women and patients who had undergone gastric surgery were not enrolled. Volunteers were informed in accordance with 2008 Helsinki declaration, and their verbal and written consents were obtained.

Study method

Questionnaire forms that inquired regarding age, gender, presence of symptoms, hypertension, hyperlipidemia, atherosclerotic heart disease, diabetes mellitus, other chronic and concomitant diseases, smoking, alcohol consumption, and therapies were completed for each patient who was selected according to patient inclusion criteria. In addition to physical examination, body weight, height, waist circumference (WC), and BP measurements of all patients were recorded. WC was measured in centimeter by measuring the narrowest diameter between the arcus costarum and spina iliaca anterior superior after a normal expirium while the patient was in ordinary clothes, on empty stomach, and in a standing position. Body mass index (BMI) was calculated according to the kg/m^2 formula, and the normal BMI interval was specified to be 18–24.9 kg/m^2 and obesity was specified to be ≥30 kg/m^2. BP measurements were performed using the Erka (P.M.S Instruments Ltd, Berkshire, United Kingdom) brand sphygmomanometer on the right arm in the sitting position after at least 5 min of resting. Following 12-h fasting, blood samples were obtained at 08:00–10:00 am from the cubital vein, the samples were centrifuged at 3000 rpm for 10 min, and then analyzed for fasting plasma glucose (FPG), insulin, total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), very low-density lipoproteins (VLDL), and triglyceride (TG) by routine techniques in the Gazi University's biochemistry laboratory. Serum insulin concentration was measured by the chemiluminescence immunoassay method using the ADVIA Centaur Assay (Siemens Healthcare Global, Erlangen, Germany) device. IR of patients was calculated by the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR)=fasting insulin (mU/L)×fasting glucose (mg/dL)/405. IR was considered in patients with HOMA-IR ≥2.5. All patients were evaluated in terms of MS according to the NCEP ATP III criteria. All patients underwent esophagogastroduodenoscopy after 8 h of fasting at the Gazi University's Faculty of Medicine, Department of Gastroenterology. For the procedure, the Fujinon EG509WR panendoscope (Endoscopy Division of FUJIFILM Medical Systems, New Jersey, United States) was used following local anesthesia of the pharynx, which was performed with prilocaine (Citanest; Zenica

medical, Paris, France). Using the endoscope, two biopsy specimens were obtained from the anterior and posterior walls of the gastric antrum and corpus mucosa of all patients, and the specimens were transferred to the pathology laboratory and fixed with 10% formalin. *H. pylori* were observed in the biopsy specimens by microscopic examination of the slides that were stained with hematoxylin and eosin. Slides were examined by a single pathologist who was blind for the clinical and endoscopic findings of patients.

Statistical analysis

SPSS (Statistical Package for Social Sciences, proprietary software, IBM Company, New York, USA) version 20 was used to analyze the data obtained and for tabulation. Continuous variables obtained by measurement (quantitative variables) were presented as mean and standard deviation, whereas frequency and percentage were used for the presentation of categorical variables (qualitative variables). Chi-square (χ^2) test was used to evaluate categorical variables. For the comparison of quantitative variables, we investigated whether or not parametric test conditions were met (number of subjects and the investigation of suitability for normal distribution). Comparison of paired groups was performed using Student's *t*-test for the variables that met the parametric test conditions, whereas the Mann–Whitney U test was used when parametric test conditions were not met. Relative risk was used to investigate whether *H. pylori* is a risk for MS. For all statistical analyses, the level of significance was considered to be p<0.05.

RESULTS

Gastric biopsies of 200 patients with dyspeptic complaints due to *H. pylori* infection were examined, and it was determined that 99 patients were HP (+), whereas 101 patients were HP (–). In this study, the prevalence of *H. pylori* positivity was found to be 49.5% (99/200). Comparing HP (+) and HP (–) patients in terms of demographic characteristics, it was observed that the mean age was 48.1±12.4 years and there were 30 (30.3%) males and 69 (69.7%) females in the HP (+) group, whereas the mean age was 46.8±13.9 years and there were 33 (32.7%) males and 68 (67.3%) females in the HP (–) group. Of the patients in the HP (+) group, 29.3% were smokers and 4% were alcohol consumers, whereas in the HP (–) group, these rates were 35.6% and 2%, respectively. No difference was found between the two groups in terms of age, gender, smoking, and alcohol consumption (Chi-square test, p>0.05) (Table 2).

BP and WC of 99 HP (+) patients and 101 HP (–) patients were measured, and their BMIs were calculated. In the HP (+) group, the mean systolic BP was 130.6±17.7 mmHg, and the mean diastolic BP was 83.2±11.7 mmHg; furthermore, the mean BMI value was 30.1±5.2 kg/m^2, and the mean WC was 101.1±10.6 cm. In the HP (–) group, the mean systolic BP was 117.2±15.6 mmHg, and the mean diastolic BP was 74.6±11.9 mmHg; furthermore, the mean BMI was 27.7±4.9 kg/m^2, and the mean WC was 98.2±12.6 cm. There was a significant difference between the HP (+) and HP (–) groups in terms of the mean systolic and diastolic BP (p<0.01); however, no significant correlation was determined between WC and *H. pylori* positivity (p>0.05) (Table 3).

Table 2. Demographic characteristics of patients

Demographic characteristic	HP (+) (n=99)	HP (–) (n=101)	p
Age (year) (±SD)	48.1±12.4	46.8±13.9	0.490
Groups according to ages (n, %)			0.424
<30 (n=22)	9 (40.9)	13 (59.1)	
30-39 (n=34)	15 (44.1)	19 (55.9)	
40-49 (n=54)	25 (46.3)	29 (53.7)	
50-59 (n=51)	31 (60.8)	20 (39.2)	
≥60 (n=39)	19 (48.7)	20 (51.3)	
Sex (n, %)			
Male	30 (30.3)	33 (32.7)	0.718
Female	69 (69.7)	68 (67.3)	
Smoking (n, %)			
Yes	29 (29.3)	36 (35.6)	0.338
No	70 (70.7)	65 (64.4)	
Alcohol (n, %)			
Yes	4 (4.0)	2 (2.0)	0.442
No	95 (96.0)	99 (98.0)	

HP: *Helicobacter pylori*

When HP (+) patients (n=99) and HP (–) patients (n=101) were compared in terms of FPG, insulin level, HOMA-IR value, and lipid panel, FPG (96.2±12.3 vs. 92.9±9.0 mg/dL, p<0.05), insulin (11.3±5.4 vs. 8.6±4.5 µU/mL, p<0.01), HOMA-IR (2.72±1.39 vs. 2.02±1.17, p<0.01), VLDL (31.8±25.1 vs. 25.6±14.3 mg/dL, p<0.05), and TG (159±125 vs. 128±71.4 mg/dL, p<0.05) levels were found to be significantly higher; however, HDL (46.4±12.1 vs. 50.1±12.3 mg/dL, p<0.05) level was found to be lower in the HP(+) group. Moreover, no difference was determined between the two groups in terms of TC (196.2±37.2 vs. 193.9±41.4 mg/dL, p>0.05) and LDL (118±35.8 vs. 120±34.6 mg/dL, p>0.05) levels (Table 4).

When patients were analyzed using a diagnostic criteria of MS, it was observed that MS was present in 78 patients (78.8%) in the HP (+) group and in 22 patients (21.8%) in HP (–) group (p<0.01). In addition, logistic regression analysis demonstrated that *H. pylori* infection enhances the risk of developing MS by approximately 3.6 times (RR=3.617, 95% CI: 2.465–5.307, p<0.001).

DISCUSSION

Many studies have been conducted to demonstrate that *H. pylori* is a risk factor for IR. Eshraghian et al. (10) investigated the relationship between *H. pylori* seropositivity and HOMA-IR, and

Table 3. Anthropometric measurements of patients

	HP (+) (n=99)	HP (–) (n=101)
Systolic blood pressure* (mmHg)	130.6±17.7	117.2±15.6
Diastolic blood pressure* (mmHg)	83.2±11.7	74.6±11.9
Body mass index (kg/m^2)	30.1±5.2	27.7±4.9
Waist circumference (cm)	101.1±10.6	98.2±12.6

HP: *Helicobacter pylori*
*p<0.01

Table 4. Anthropometric measurements of patients

	HP (+) (n=99)	HP (–) (n=101)
FPG* (mg/dL)	96.2±12.3	92.9±9.0
Insulin** (µU/mL)	11.3±5.4	8.6±4.5
HOMA-IR**	2.72±1.39	2.02±1.17
Total cholesterol (mg/dL)	196.2±37.2	193.9±41.4
LDL (mg/dL)	118±35.8	120±34.6
HDL* (mg/dL)	46.4±12.1	50.1±12.3
VLDL* (mg/dL)	31.8±25.1	25.6±14.3
Triglyceride* (mg/dL)	159±125	128±71.4

FPG: fasting plasma glucose; HOMA-IR: The Homeostatic Model assessment-Insulin Resistance; LDL: low-density lipoproteins; HDL: high-density lipoproteins; VLDL: very-low-density lipoproteins; HP: *Helicobacter pylori*
*p<0.05, **p<0.01

they found that serum insulin levels and HOMA-IR values were higher in HP (+) patients than in HP (–) patients. With regard to this subject, in Turkey, Aydemir et al. (11), Aslan et al. (12), and Gen et al. (9) found the HOMA-IR value to be higher in HP (+) patients than in HP (–) patients. Likewise, in this study, HP (+) patients were compared with HP (–) patients, and FPG, insulin, and HOMA-IR values were found to be significantly higher in the HP (+) group than in the HP (–) group (p<0.001).

MS is a heterogeneous disease of unclear etiology caused by genetic, infectious, or environmental factors and that develops on the basis of IR. Although the relationship between MS and *H. pylori*, which is one of the infectious agents that can cause MS, has not been completely explained, *H. pylori* infection impairs secretion balance of proinflammatory cytokines and CRP, angiotensinogen, free fatty acids, and leptin hormone, and thus, reactive oxygen radicals begin to accumulate. Subclinical chronic inflammation occurs via impaired cytokine balance and stimulated macrophages. There are explanations that this leads to unresponsiveness to insulin in the peripheral tissue and subsequently to MS (7-10, 13). Longo-Mbenza et al. (14) determined that HP (+) patients have higher systolic and diastolic BP, larger WC, higher TG and TC but lower HDL concentrations than HP (–) patients and reported a decrease in BP, TC, and FPG concentrations in HP (+) patients after eradication therapy compared with the concentrations before therapy. In this study, HP (+) patients were compared with HP (–) patients, and the systolic and diastolic BP and BMI, which are among the components of MS, were found to be significantly higher in the HP (+) group than in the HP (–) group (p<0.05). In line with these data, FPG and insulin levels and HOMA-IR values were found to be higher in the HP (+) group (p<0.05).

Dyslipidemia, which is a component of MS, is a good indicator of IR. Kucukazman et al. (15) found TC and LDL concentrations to be higher in HP (+) patients than in HP (–) patients. In the same study, no difference was found in terms of TG and HDL concentrations. Sung et al. (16) reported higher TC, LDL, and TG levels but lower HDL levels in HP (+) patients. Similarly, Gen et al. (9) found TC, LDL, and TG levels to be higher but HDL levels to be lower in patients who were detected as HP (+) using a histological method than in those who were detected as HP (-). In recent years, studies have been conducted that have particularly demonstrated that *H. pylori* seropositivity is associated with low HDL level and that HDL level increases with eradication therapy. Hoffmeister et al. (17) and Takashima et al. (18) demonstrated that *H. pylori* causes low HDL level, and Elizalde et al. (19), Ando et al. (20), Kanbay et al. (21), and Gen et al. (9) determined an increase in HDL levels of patients after successful *H. pylori* eradication therapy. In this study, when HP (+) patients were compared with HP (–) patients, TG and VLDL were higher and HDL was lower in HP (+) patients; however, no difference was determined in terms of TC and LDL levels.

Obesity, which is a component of MS, is rapidly becoming a serious health problem worldwide. There are many studies investigating *H. pylori* infection and its prevalence in obese subjects. Perdichizzi et al. (22) determined higher BMI values and WC measurement in HP (+) patients than in HP (–) patients. Kyriazanos et al. (23) conducted a study in 2002 and stated that there is no relationship between *H. pylori* and obesity; however, the accuracy of the study outcome was considered debatable because patients with BMI >25 kg/m^2 were considered as obese in that study. In this study, the mean BMI was 30.1±5.2 kg/m^2 in HP (+) patients and 27.7±4.9 kg/m^2 in HP (–) patients, and the difference was considered statistically significant (p<0.001). While 56.6% (n=56) of HP (+) patients were obese, 33.7% (n=34) of HP (–) patients were obese (p<0.05). In this study, no relationship was determined between WC and *H. pylori* positivity; however, when WC of male and female patients were evaluated according to the NCEP ATP III criteria, it was determined that 81% of HP (+) patients and 63.4% of HP (–) patients had measurements over the criteria (p<0.05). Therefore, no proportional difference was determined between the groups in terms of WC.

There are many studies conducted on diabetes, which is one of the components of MS according to the NCEP ATP III criteria, and *H. pylori* (24). There are studies demonstrating higher *H. pylori* prevalence in diabetics, whereas other studies stating no increase in prevalence. This difference between study results can be attributed to many factors, such as non-homogenous

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patient groups, different diagnostic methods used in the studies, variable disease duration, and different exclusion criteria used in the studies. For example, according to a study conducted in Italy (25), the prevalence of *H. pylori* infection increased as the duration of diabetes was prolonged; however, according to a study conducted in Spain, the prevalence of *H. pylori* infection decreased as the duration of diabetes prolonged (26). It is stated that *H. pylor*i is more prevalent in patients with diabetes because of disease-related decrease in gastric motility, prolonged gastric emptying due to gastroparesis and accordingly bacterial overgrowth, and changes in humoral and cellular immunity due to diabetes (27, 28). However, there are many studies stating that *H. pylori* is less prevalent in patients with diabetes because of impaired gastric mucosal vascularization and gastric supply, achlorhydria, and decreased hydrochloric acid caused by diabetes-related microangiopathy (29).

The most important limitation of our study is the possibility of false negative results in cases, such as small number of bacteria at the diagnosis of *H. pylori*, patch-type gastritis, or wrong-site biopsy, and depending on the experience of the endoscopist or staining techniques. Moreover, independent factors, such as alcohol consumption, smoking, diet, and activity habits, which have effects on the development of IR, were ignored.

In conclusion, the common outcome of this study that was conducted regarding *H. pylori* and MS, which are two important public problems, using invasive and non-invasive diagnostic methods is the higher prevalence of IR and the clinical presence of MS in HP (+) patients. It is also important to evaluate patients who presented with upper gastrointestinal system complaints in terms of MS. Detecting the relationship between upper gastrointestinal system complaints of these patients and *H. pylori* infection and initiating an eradication therapy may result in beneficial outcomes in terms of upper gastrointestinal system diseases and MS (dual).

In the literature, there are numerous studies investigating the relationship between *H. pylori* and IR. These studies used serological tests and histopathological diagnostic methods. However, studies investigating the relationship between *H. pylori* and MS used serological methods alone. This is the first study that investigated the relationship between *H. pylori* and MS and determined *H. pylori* positivity by a histopathological diagnostic method. However, more comprehensive studies are required to investigate the relationship between *H. pylori* and MS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi University Faculty of Medicine Research (Project No:69).

Informed Consent: Written and verbal informed consent was obtained from patients who participated in this study.

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