

Research Article

# Association of *Helicobacter Pylori* Infection with Endothelial Dysfunction in Metabolic Syndrome

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## Abstract

**Background:** Metabolic risk factors play a critical role in metabolic syndrome (MetS), and endothelial dysfunction is important in its development. On the other hand, *Helicobacter pylori* (*H. pylori*) infection has an essential role in MetS. The goal of present study was to evaluate the effect of *H. pylori* infection on endothelial dysfunction in MetS patients.

**Methods:** Based on the International Diabetes Federation (IDF) criteria, 80 MetS patients (59 females and 21 males, mean age:  $48.94 \pm 10.00$  years) were selected. Plasma samples were assayed for *H. pylori* IgG using the ELISA method. Endothelial function was also evaluated by measuring plasma concentrations of endothelin-1 (ET-1), E-selectin, and intracellular adhesion molecule-1 (ICAM-1) using ELISA method. Also,  $\text{NO}_2^-$  and  $\text{NO}_3^-$  concentrations were measured by Griess method.

**Results:** Fifty patients (62.5%) had *H. pylori* infection. Plasma concentrations of ET-1,  $\text{NO}_2^-$ , and  $\text{NO}_3^-$  were significantly higher in MetS patients with positive *H. pylori* infection than in MetS patients with negative *H. pylori* infection (ET-1:  $2.92 \pm 2.33$  vs  $1.9 \pm 1.4$  pg/ml;  $P = 0.037$ ;  $\text{NO}_2^-$ :  $19.46 \pm 7.11$  vs  $15.46 \pm 4.56$   $\mu\text{M}$ ;  $P = 0.003$ ;  $\text{NO}_3^-$ :  $20.8 \pm 10.53$  vs  $16.85 \pm 6.03$   $\mu\text{M}$ ,  $P = 0.036$ ). However, plasma concentrations of ICAM-1 and E-selectin did not show any significant difference in the two groups.

**Conclusion:** The results showed a relationship between *H. pylori* infection and endothelial dysfunction. *H. pylori* infection can lead to atherosclerosis by causing chronic inflammation and affecting the factors contributing to the MetS.

**Keywords:** metabolic syndrome, *H. pylori*, endothelial dysfunction

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## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is a gram-negative and urease-positive bacterium that is found in gastritis epithelium. It is one of the most common infections with a prevalence of over 50% worldwide [1]. Although developing countries have a high prevalence (50.8%) of *H. pylori*, but 34.7% of developed countries are infected [2]. Chronic infection in individuals with *H. pylori* infection results in the release of inflammatory cytokines such as tumor necrosis (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) [3], and increased c-reactive protein (CRP) and intracellular adhesion molecule-1 (ICAM-1) [4], which affects vasomotor microvascular function and cause vasoconstriction and endothelial dysfunction. This evidence shows that *H. pylori* infection participates in the atherosclerosis pathogenesis through the development of chronic inflammation along with other mechanisms such as hyperhomocysteinemia, dyslipidemia, impaired glucose metabolism, and endothelial dysfunction [4]. The same pathogenesis is also found in metabolic syndrome (MetS), which increases the risk of cardiovascular disease or atherosclerosis through proinflammatory factors [5]. MetS is a multiplex risk factor for atherosclerotic cardiovascular disease and type 2 diabetes [6]. Endothelial dysfunction is one of the early stages of atherosclerosis [7] and numerous markers have been utilized to evaluate endothelial dysfunction and inflammatory activation of endothelium, including cell adhesion molecule (CAM) [8]. Endothelial E-selectin, which is absent in inactive cells, is caused by inflammatory damage. ICAM-1 is also expressed by endothelial cells in response to inflammatory cytokines [9]. Also, the factors involved in the regulation of vasoconstriction and vasodilation, and evaluation of endothelial dysfunction include decreased nitric oxide (NO) as a vasodilator and increased endothelin-1 (ET-1) as a vasoconstrictor [10]. On the other hand, some studies have reported that clinical markers of MetS and systemic inflammation improve after treatment and destruction of *H. pylori* infection, indicating the role of *H. pylori* infection in MetS [11, 12]. In this study, we studied endothelial function and *H. pylori* infection in patients with MetS and their possible association.

## 2. Methods

In this cross-sectional study (from 2011 to 2012), following the International Diabetes Federation (IDF) criteria [35], 80 patients with MetS (59 females and 21 males, mean age:  $48.94 \pm 10.00$  years) were selected. IDF defines a MetS patient as a person with central obesity (waist circumference:  $\geq 80$  cm for women and  $\geq 94$  cm for men), plus

two of the following four factors: (1) raised blood pressure (BP): systolic BP  $\geq 130$  mmHg or diastolic BP  $\geq 85$  mmHg, or treatment of previously diagnosed hypertension; (2) reduced high density lipoprotein-cholesterol (HDL-C):  $< 50$  mg/dL in women,  $< 40$  mg/dL in men, or specific treatment for this lipid abnormality; (3) raised triglyceride (TG):  $\geq 150$  mg/dL, or specific treatment for this lipid abnormality; and (4) raised fasting blood sugar (FBS)  $\geq 100$  mg/dL, or previously diagnosed type 2 diabetes. In this study, central obesity and high BP were present in all patients. Patients were studied as two groups: MetS patients with positive and negative *H. pylori* infection. Research exclusion criteria included: pregnancy, smoking, taking any drug that affects glucose or fat metabolism, hypoglycemic or hypolipemic drug use, renal dysfunction, advanced heart failure, history of untreated thyroid disease, acute and chronic inflammatory disease, surgery in the last three months, and malignancies. Diastolic and systolic BP values of all patients in mmHg, abdominal circumference in cm, weight in kg, and height in meters were measured. After at least 12 hr of fasting, 8 ml of intravenous blood was collected from all subjects using sterile Venugect syringes including ethylenediamine tetraacetic acid (EDTA) anticoagulants and blood samples were centrifuged at 3000 g for 7 min to obtain plasma. The plasma samples were stored at  $-80^{\circ}\text{C}$  until analysis. TG, total cholesterol (TC), glucose, HDL-C, low density lipoprotein-cholesterol (LDL-C) were detected by the photometric method using an automated analyzer by kits (Pars azmoon, Iran); ET-1, ICAM-1, E-selectin were detected by ELISA method using kit (IBL, Hamburg, Germany); and  $\text{NO}_2^-$  and  $\text{NO}_3^-$  were measured by Griess method using kit (Cayman, USA). *H. pylori* exposure was distinguished via plasma IgG test by kit (Globe diagnostics, Italy) using ELISA method. The SPSS (v. 16) software was used for data analysis and significance was considered as  $P < 0.05$ . Results were presented as mean  $\pm$  SD.

### 3. Results

Patients were evaluated in two groups: 50 MetS patients with positive *H. pylori* infection and 30 MetS patients with negative *H. pylori* infection. The clinical and demographic characteristics of patients are shown in Table 1. The systolic BP in MetS patients with positive *H. pylori* infection was significantly higher than in those with negative *H. pylori* infection ( $P = 0.033$ ). However, no significant difference was seen in age, waist circumference, body mass index (BMI), TG, FBS, TC, LDL-C, HDL-C, and diastolic BP between the two groups. Plasma concentrations of ET-1, ICAM-1, E-selectin,  $\text{NO}_2^-$ , and  $\text{NO}_3^-$  in MetS patients with positive and negative *H. pylori* infection are shown in Table 2. Plasma concentration of ET-1 showed a significant increase ( $P = 0.037$ ) in

MetS patients with positive *H. pylori* infection ( $2.92 \pm 2.33$  pg/ml) compared with MetS patients with negative *H. pylori* infection ( $1.9 \pm 1.4$  pg/ml). On the other hand, significant differences existed in plasma concentrations of  $\text{NO}_2^-$  and  $\text{NO}_3^-$  between MetS patients with positive *H. pylori* infection ( $19.46 \pm 7.11$  and  $20.8 \pm 10.53$  mM, respectively) and MetS patients with negative *H. pylori* infection ( $15.46 \pm 4.56$  and  $16.85 \pm 6.03$   $\mu\text{M}$ , respectively). Plasma concentrations of ICAM-1 and E-selectin were not different in both groups of MetS patients with positive and negative *H. pylori* infection.

TABLE 1: Clinical and demographic characteristics of MetS patients with positive and negative *H. pylori* infection.

Variable	MetS patients with <i>H. pylori</i> (+)	MetS patients with <i>H. pylori</i> (-)	P-value
Gender (man/woman)	50 (11/39)	30 (7/22)	0.492
Age (yr)	$50.18 \pm 8.76$	$46.76 \pm 11.64$	0.184
BMI ( $\text{kg}/\text{m}^2$ )	$33.92 \pm 5.30$	$32.26 \pm 4.45$	0.138
Waist circumference (cm)	$109.72 \pm 10.1$	$107.166 \pm 9.18$	0.250
Systolic blood pressure (mmHg)	$149.6 \pm 21.1$	$140.6 \pm 15.50$	0.033
Diastolic blood pressure (mmHg)	$94.50 \pm 7.30$	$92.80 \pm 8.60$	0.089
FBS (mg/dl)	$98.52 \pm 13.01$	$105.53 \pm 16.18$	0.049
TG (mg/dl)	$275.54 \pm 153.22$	$225.83 \pm 176.55$	0.206
TC (mg/dl)	$241.50 \pm 37.2$	$248.33 \pm 79.05$	0.659
LDL-C (mg/dl)	$146.08 \pm 33.85$	$141.53 \pm 35.32$	0.573
HDL-C (mg/dl)	$59.26 \pm 9.62$	$59.23 \pm 14.05$	0.993

BMI: body mass index; FBS: fasting blood sugar; TG: triglyceride; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol

TABLE 2: Plasma concentration of endothelial function markers-C in MetS patients with positive and negative *H. pylori* infection.

Variable	MetS patients with <i>H. pylori</i> (+)	MetS patients with <i>H. pylori</i> (-)	P-value
ET-1 (pg/ml)	$2.92 \pm 2.33$	$1.90 \pm 1.40$	0.037
E-selectin (ng/ml)	$10.66 \pm 4.37$	$10.33 \pm 5.24$	0.770
ICAM-1 (ng/ml)	$39.21 \pm 14.55$	$37.74 \pm 18.57$	0.695
$\text{NO}_2^-$ ( $\mu\text{M}$ )	$19.46 \pm 7.11$	$15.46 \pm 4.56$	0.003
$\text{NO}_3^-$ ( $\mu\text{M}$ )	$20.80 \pm 10.53$	$16.85 \pm 6.03$	0.036

ET-1: Endothelin-1; ICAM-1: intercellular adhesion molecule-1;  $\text{NO}_2^-$ : nitrite;  $\text{NO}_3^-$ : nitrate.

## 4. Discussion

MetS patients have a two-fold increased risk of developing cardiovascular disease [13]. MetS occurs worldwide with a prevalence of 10–40% [14]. Mozumdar's study reports that the prevalence of this syndrome was higher in women than the men [15]. This study showed that MetS patients had a higher incidence of *H. pylori* infection (62.5%) indicating a relationship between MetS and *H. pylori* infection. This incidence is also higher in women than the men. As shown in the Tsung-po Chen study, *H. pylori* infection is positively related to MetS in women [16]. *H. pylori* infection is associated with a decrease in HDL-C, an increase in TC, LDL-C, and TG [17], which increased TG and decreased HDL-C as lipid markers are criteria for MetS, but no significant increase in TG and decrease in HDL-C were seen among patients with positive and negative *H. pylori* infection. Obesity is another feature of patients with MetS [18]. Insulin resistance is associated with obesity [19]. The previous studies have demonstrated that MetS and *H. pylori* infection are associated with insulin resistance [20, 21]. On the other hand, insulin resistance [22], increased TG, and decreased HDL-C levels lead to inflammatory conditions [23] and obesity is also associated with inflammation [18]. The investigations have shown that the elimination of *H. pylori* infection leads to a decrease in inflammatory cytokines, which indicates a link between *H. pylori* infection and inflammation [24].

In a meta-analysis, Upala *et al.* demonstrated that *H. pylori* infection is related to systolic BP [25]. This study also showed that systolic BP in MetS patients with positive *H. pylori* infection was significantly higher than in MetS patients with negative *H. pylori* infection. As in the present investigation, hypertension was the inclusion criteria for all subjects with MetS, this observation indicates that *H. pylori* infection induces a significant increase in systolic BP in these patients.

These inflammatory conditions in MetS patients with *H. pylori* infection provide the basis for endothelial dysfunction and progression to atherosclerosis [26]. Activation of blood inflammatory cells also results in the oxidation of LDL-C, which is one of the early stages of atherosclerosis [27]. Oxidized LDL-C increases the expression of E-selectin and ICAM-1 [28]. Studies have also shown that there is a significant relationship between *H. pylori* infection and increased ICAM-1 [29], however, in this study, no association between E-selectin and ICAM-1 was found between MetS patients with positive and negative *H. pylori* infection. NO and EN-1 are markers involved in regulating CAM expression on endothelial cells in response to inflammatory stimuli [30]. Low levels of NO play an essential role in patients with MetS [31]. Another study found that measurement of dimethyl arginine (as a potent inhibitor of endogenous nitric oxide synthase) before and

after the eradication of *H. pylori* infection showed a significant decrease of dimethyl arginine after infection eradication. The results of the current study indicate that *H. pylori* infection induces endothelial dysfunction and atherosclerosis through increased dimethyl arginine and inhibition of endothelial nitric oxide synthase [32]. In this study,  $\text{NO}_2^-$  and  $\text{NO}_3^-$  levels were higher in MetS patients with positive *H. pylori* infection than in MetS patients with negative *H. pylori* infection, which indicates a decrease in NO levels due to increased metabolites that can play a role as an endothelial dysfunction marker. NO as a vascular regulator conflicts with the ET-1, and the imbalance between these two markers results in impaired endothelial function [33]. Expression of ET-1 gene, which produces preproET-1, is increased by internal mediators such as cytokines. On the other hand, NO inhibits ET-1 expression [34]. In the present study, plasma concentrations of ET-1 in MetS patients with positive *H. pylori* infection were higher than in those with negative *H. pylori* infection which is one of the characteristics of endothelial dysfunction.

## 5. Conclusion

Therefore, it can be concluded that in this study, from four markers that influence endothelial dysfunction process, MetS patients with positive *H. pylori* infection is influenced by inflammatory conditions and consequently increases ET-1 and decreases NO.

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## Ethical Considerations

The research design of this study was approved by the ethics committee (1390.869) of Urmia University of Medical Sciences.

## Competing Interests

The authors declare no conflict of interest.

## Availability of Data and Material

The data and material of this study are available from the corresponding author upon request.

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