



# The Association of *Helicobacter pylori* Infection with Endothelial Dysfunction in Pediatric Patients

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## Abstract

**Objectives:** The aim of this study was to evaluate endothelial dysfunction in pediatric patients with *Helicobacter pylori* infection.

**Methods:** In a cross sectional study, 50 children between six and twelve years old were evaluated for *Helicobacter pylori* infection by a histopathologic specimen. C-reactive protein (CRP) and Interleukin -12 of all subjects was checked. Endothelial dysfunction was evaluated by echocardiography of brachial artery and through measuring flow mediated dilatation (FMD).

**Results:** Mean of FMD level was significantly higher in children with *H. pylori* infection (P value: 0.04). Interleukin-12 (IL-12) was higher in children with *H. pylori* infection (P value: 0.04). Linear regression showed a positive association of *Helicobacter pylori* infection and endothelial dysfunction (beta = 0.3, P value = 0.08).

**Conclusions:** Children with *Helicobacter pylori* infection have more endothelial dysfunction independent of IL-12.

**Keywords:** Child, Endothelial Dysfunction, *Helicobacter pylori*

## 1. Background

*Helicobacter pylori* (*H. pylori*) are gram-negative bacilli with worldwide prevalence, especially in developing countries (1, 2). The association of gastrointestinal tract diseases and *H. pylori* has been well-documented (3). New researches mentioned about the association of this gram-negative microorganism and other diseases, such as iron deficiency anemia, Henoch-schonlein purpura, immune thrombocytopenia purpura, and metabolic syndrome (4-7).

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in the adult population worldwide (8, 9). Researchers have attempted to find the exact mechanisms of CHD, yet this has been challenging. One of the hypothesized mechanisms is inflammatory processes (10). The hypothesis of infectious cause of CHD has been evaluated. Findings showed that pneumonia (11), chronic infection by chlamydia, and cytomegalovirus (12) can be associated with coronary heart disease, through inflammatory response change. *Helicobacter pylori* is another microorganism, which can cause chronic infection and low inflammatory response by producing pro-inflammatory

cytokines, such as Interleukin (IL)-12 and C-reactive protein (CRP) (13, 14).

Vascular endothelium dysfunction is another cause of coronary heart disease (15, 16). Different mechanisms, such as vitamin deficiency, hormonal dysregulation, and inflammatory processes have been suggested as causes of endothelial dysfunction (17, 18). Data from a number of researches show the possible association between *H. pylori* infection and endothelial dysfunction, through producing inflammatory cytokines, such as IL-6 (10, 19). Data suggested that coronary artery disease begins during childhood (20), while infections with microorganisms that can cause chronic infection, especially *H. pylori*, also occur more in children. Therefore, in the present study, the researchers evaluated the association of one the prevalent childhood infections and endothelial dysfunction of children as a two assumed causes of coronary disease.

## 2. Methods

### 2.1. Subjects

In a cross sectional study, 50 children between six and twelve years old, who were eligible for upper gastrointesti-

nal endoscopy (21), and parental consent for participation were selected by simple random sampling. Patients were admitted to the hospital the day before the endoscopy. Children's weigh, height, and BMI were measured with a standard method (21).

### 2.2. Laboratory Analysis

After eight hours of fasting, blood samples were taken for checking high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), and cholesterol (Chol), by the enzymatic method. C-reactive protein and interleukin-12 (IL-12) were also measured by the enzyme-linked immunosorbent assay (Sta biopharma, Singapore).

Upper gastrointestinal endoscopy was done and two biopsy samples were obtained from the antrum. Biopsies were evaluated by histopathology and urea breath test for *H. pylori* detection (22).

### 2.3. Endothelial Function Evaluation

Endothelial function was checked by flow mediated dilatation (FMD). This was measured by MEDISON EKO 7, equipped with vascular software for two-dimensional (2D) imaging, built with the guidelines of the International Brachial Artery Reactivity Task Force (23, 24).

### 2.4. Data Analysis

SPSS (version 21, Chigaco, IL, USA) was used for statistical analysis. P values equal and less than 0.05 were considered statistically significant for all analysis. Height, TG, Chol, HDL, LDL, and FMD had a normal distribution and One-Sample Kolmogorov-Smirnov test was used for the analysis. Mann-Whitney test was used for values with non-normal distribution (Age, body mass index, and FMD). Logistic regression test was used for adjusting IL-12.

## 3. Results

Fifty children, aged between six and twelve years were evaluated. Overall, 36 children were negative for *H. pylori* and 14 patients were positive.

The basic characteristics of children is presented in Table 1.

Mean FMD level was  $21.60 \pm 23.21$  and  $7.6 \pm 15.70$  in children with and without *H. pylori* infection (P value: 0.02). Therefore, this finding showed a significant abnormal endothelial dysfunction in children with *H. pylori* infection.

Table 1. Basic Characteristics of Children<sup>a</sup>

Variable	Group		P Value
	With HP	Without HP	
Age	9.17 ± 4.0	7.63 ± 4.11	0.26
Height	130.64 ± 24.77	123.05 ± 28.01	0.38
Weight	29 ± 16.25	27.38 ± 15.71	0.61
BMI	15.8 ± 3.43	16.56 ± 3.22	0.43
TG	115 ± 21.41	111.3 ± 21.61	0.60
CH	198.8 ± 34.51	180 ± 30.81	0.06
HDL	58.57 ± 11.75	53.83 ± 11.71	0.20
LDL	115.28 ± 27.08	102.52 ± 26.32	0.13

Abbreviations: CH, cholesterol; HDL, high -density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

<sup>a</sup>Values are expressed as mean ± SD.

Data show that the IL-12 level was 1.5 times more in patients with *H. pylori* infection, and analysis showed a significant difference in this group ( $233.92 \pm 206.66$  versus  $142.41 \pm 150.0$ ) (P value: 0.04).

The mean level of CRP in children with *H. pylori* was  $1.35 \pm 1.53$  and in children without *H. pylori* infection was  $1.42 \pm 1.56$  (P value: 0.81).

Logistic regression test showed that children with *H. pylori* infection had significantly more endothelial dysfunction (P value: 0.02) and this association is independent of IL-12 level (Table 2).

## 4. Discussion

The findings showed significantly higher level of flow mediated dilatation in children with *H. pylori* infection. Also, IL-12 level was significantly higher in children with *H. pylori* infection. *Helicobacter pylori* infection predicts more severe FMD level, independent of IL-12.

Recent studies showed intelukin-12 influences vascular health. Ikonomidis et al. showed that inhibition of

Table 2. Predictors of Flow Mediated Dilatation Level

Variable	FMD	
	Standardized $\beta$	P Value
<b>Model 1</b>		
HP	0.32	0.02
<b>Model 2</b>		
HP	0.381	0.008
IL-12	-0.251	0.74

Abbreviations: FMD, flow mediated dilatation; HP, *Helicobacter pylori*; IL-12, interleukin-12.

IL-12 causes improvement of coronary and arterial function (25). Other study findings showed the association of interleukin-12 with early atherosclerosis in a healthy population (26). Guiney et al. (27) showed that *H. pylori* infection produces more interleukin-12 than interleukin-10 and interleukin-2. The current findings showed that patients with *H. pylori* infection have significantly higher IL-12 level. However, IL-12 level in the patients is not associated with FMD. One of the causes of this finding is the low sample size of the patients. On the other hand, some studies showed that the effect of *H. pylori* on vascular endothelium may be directly through changing proliferation and apoptosis of endothelial cells (22, 28). Studies have shown that *H. pylori* can cause hyperhomocysteinemia by malabsorption of vitamins B12 and B6. Hyperhomocysteinemia causes malfunction of vascular endothelium (29). Therefore, in accordance with the current results, the effect helicobacter may be independent of producing inflammatory cytokines, such as IL-12.

C-reactive level in the current study patients was not significantly higher in children with *H. pylori* infection; this result is in line with Coskun et al.'s study (20), and it may be due to the method for CRP check. The current researchers did not use hsCRP level check, which is more sensitive. Another cause of this finding is due to duration of infection, which is lower in children than adults (29). Finally, the absence of an association between CRP level and endothelial dysfunction in children with *H. pylori* infection may be due to the direct cause of this microorganism on platelet aggregation and oxidative stress (30, 31).

In conclusion, children with *H. pylori* infection have more endothelial dysfunction, independent of IL-12.

In the present study, the researchers evaluated *H. pylori* infection in histopathologic examination. This method is more precise than checking anti-*H. pylori* antibodies, which was done in other studies.

One of the study limitations was the sample size. Another limitation was that this study could not show that infection with *H. pylori* is recent or chronic.

## Footnote

**Ethical Considerations:** The study was reviewed by Ethical Committee of Isfahan University of Medical Sciences.

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