

Flow mediated dilation and carotid intima media thickness in patients with chronic gastritis associated with *Helicobacter pylori* infection

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ABSTRACT – Background – Endothelial dysfunction is one of the early stages of vascular diseases. **Objective** – The aim of this study was to investigate the endothelial dysfunction markers in patients with chronic gastritis associated with *Helicobacter pylori* (*H. pylori*) infection. **Methods** – By a cross sectional study, basic and clinical information of 120 participants (40 patients with positive *H. pylori* infection, 40 patients with negative *H. pylori* infection and 40 healthy people) were analyzed. Carotid intima media thickness and flow-mediated dilation levels were measured in all patients and controls. Soluble vascular cell adhesion molecule-1 (sVCAM-1) and intercellular adhesion molecule-1 (ICAM-1) were measured with Elisa for all subjects. IgG level was assessed in chronic gastritis patients. **Results** – The flow-mediated dilation level in patients with positive *H. pylori* infection ($0.17\% \pm 0.09$) was significantly lower than those with negative *H. pylori* infection ($0.21\% \pm 0.10$, $P < 0.05$) and compared to the control group ($0.27\% \pm 0.11$, $P < 0.05$). Carotid intima media thickness level in patients with positive *H. pylori* infection (0.58 ± 0.13 mm) was significantly higher than those with negative *H. pylori* infection (0.48 ± 0.32 mm, $P < 0.05$) and compared to the control group (0.36 ± 0.44 mm, $P < 0.05$). The mean level of sICAM-1 in positive *H. pylori* infection group (352.16 ± 7.54 pg/mL) was higher than negative *H. pylori* infection group (332.64 ± 8.75 pg/mL = 0.75) and compared to the control group (236.32 ± 12.43 pg/mL, $P < 0.05$). A direct relationship was revealed between flow-mediated dilation and carotid intima media thickness changes and between sICAM-1 and sVCAM-1 associated with the level of *H. pylori* IgG in chronic gastritis. **Conclusion** – The levels of flow-mediated dilation, carotid intima media thickness and sICAM-1 were higher among patients with positive *H. pylori* infection. Patients with chronic gastritis associated with *H. pylori* infection are at risk of endothelial dysfunction due to flow-mediated dilation and carotid intima media thickness abnormalities and increased level of sICAM-1 and sVCAM-1.

HEADINGS – Gastritis. *Helicobacter pylori*. Endothelial growth factors. Carotid intima-media thickness.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that causes one of the most common chronic infections in human. This microorganism is a known pathogen associated with chronic gastritis, peptic ulcer disease (PUD), gastric carcinoma and gastric lymphoma. However, the clinical effects of this pathogen is beyond of the stomach and the epidemiological studies suggested an association between *H. pylori* infection and atherosclerosis or vascular diseases. The role of *H. pylori* and its virulence factors involved in the pathogenesis of atherosclerosis has not been identified so far⁽¹⁸⁾. Atherosclerosis as a chronic inflammatory disease is a multifactorial inflammatory phenomenon and it is known that some pathogens is associated with chronic infection can induce inflammation⁽¹²⁾. In the case of *H. pylori* infection, the organism after colonization, by activating proinflammatory signaling pathways such as nuclear factor kappa B (NF- κ B)⁽⁸⁾, can cause the production and release of the proinflammatory cytokines such

as CRP, mRNA and protein expression of tumor necrosis factor alpha (TNF α) and interleukin⁽¹⁷⁾. Systemic effect of this inflammatory process is a basic hypothesis of the association between *H. pylori* infection and extragastrintestinal (GI) diseases⁽¹⁵⁾. The inflammatory cytokines especially CRP are independent risk factor for CVD, so that it is known that inflammatory cytokines can induce function and structural vessel abnormalities in the arterial wall, by many mechanisms, such as changes in the serum lipid levels, and metabolism and production of oxidative stress. Endothelial dysfunction plays a key role in the pathogenesis of atherosclerosis, that refers to the lack of ability in endothelium to providing vascular homeostasis⁽⁴⁾. The endothelial dysfunction is a consequence of overproduction of vasoconstrictors and dysregulation of hemostasis, inflammation and thrombosis in endothelium of vascular wall⁽²⁰⁾. Activation of vascular endothelium causes an upregulation of different markers including soluble vascular cell adhesion molecule-1 (sVCAM-1) and intercellular adhesion molecule 1 (ICAM-1) that have direct relationship with the severity of

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atherosclerosis⁽¹⁶⁾. In addition to these markers, some non-invasive procedures such as flow mediated dilation (FMD) and carotid intima media thickness (CIMT) can be indicators of atherosclerosis⁽¹⁹⁾. As mentioned previously, inflammation is a common feature of *Helicobacter pylori* and atherosclerosis⁽¹⁵⁾; however, in reality there is no study to indicate the atherogenic mechanisms of *H. pylori* and evidences are available only based on epidemiological studies. Therefore, this study aimed to investigate the relationship between *H. pylori* infection and serologic markers related to *H. pylori* with blood markers of endothelial dysfunction such as ICAM-1 and VCAM-1 and markers related to atherosclerosis such as CIMT and FMD in patients with chronic gastritis associated with *H. pylori* infection.

METHODS

Study protocol

This case-control study was performed among 120 participants who showed some gastrointestinal manifestations such as dyspepsia and attended to the gastroenterology clinics, for routine checks or endoscopy, in Ilam city, West of Iran, during May and November 2015. For all of participants, a detailed history including the starting time of signs and symptoms, duration of disease, past medical history and predisposing factors such as smoking, alcoholism, medication used especially Nonsteroid Anti-inflammatory Drugs (NSAID) was obtained. Patients with chronic diseases such as cardiovascular, endocrine, hematologic and respiratory disorders, pregnancy or lactation and hormone replacement therapy (HRT), antibiotic use in the previous 6 weeks, previous attempts at *H. pylori* eradication, previous gastric surgery or a previous history of alcohol consumption or drug abuse were excluded from the study. For better comparison of the results, the control group was selected among subjects who had no history of atherosclerotic risk factors or confirmed diseases. Also, controls did not show any dyspepsia symptom, or did not report a history of antibiotics, bismuth, proton pump inhibitors or NSAID application during the past 8 weeks. The Ethics Committee of Ilam University of Medical Sciences confirmed the study, and a written informed consent was obtained from each participant. All clinical procedures were performed according to the principles expressed in the Helsinki declaration.

Detection of *H. pylori* infection

H. pylori infection was detected via cultivation of two biopsy samples taken from antrum of stomach in a transport medium (Portagerm pylori, bioMe'rieux, Marc l'Etoile, France) and Urease Breath Test (UBT) viaa CLOtest (Tri-Med Specialities, Osborne Park, Western Australia). In addition, two biopsy samples were taken from antrum and corpus of stomach for histopathologic assessment. Three different tests including UBT, histology and cultivation of *H. pylori* were performed for confirmation of infection and if the results of all tests were positive, the patient was considered as an infected individual for *H. pylori*.

Endoscopic evaluations

All participants were inspected by the same upper Olympus (GIF-V) endoscopic apparatus. Endoscopy was performed by a gastrointestinal subspecialist and the biopsy needle as well

as the apparatus were sterilized for each patient separately. All patients were sedated by 10% oral xylocaine spray and 5.5-7 mg midazolam intravenously and samples of biopsies were taken by the same needle and the same method. Endoscopy was done at a lying position on the left side and after macroscopic evaluations, the needed biopsy samples were taken from the different parts of the stomach.

Histology

In this study, histological assessment was performed according to the Sydney System for the classification of gastritis. Hematoxylin-Eosin (H&E) staining was performed for the *H. pylori* diagnosis and histological findings. For confirming the presence of *H. pylori* "Giemsa" stain was also done. Identification of rods and curved gram-negative organisms in the mucosal surface in the pit of stomach with $\times 40$ zoom of light microscope was precisely sought by expert individuals. The existence of at least five bacilli per microscopic field was necessary for confirmation. Infiltration of lymphocytes and plasma cells in the lamina propria were considered as signs of chronic gastritis and neutrophil infiltration was considered as sign of active gastritis. The presence of goblet cells and replacement of mucosal cylindrical cells by absorption cells was considered as a sign of intestinal metaplasia⁽¹⁷⁾.

FMD assay

FMD measurement was performed by ultrasound imaging with 18-MHz linear array transducer on M-mode (Acuson S3000; Siemens). All measurements were performed at the morning and all patients had 30 minutes rest and were inhibited to consume coffee or a special diet.

Carotid intima media thickness assay

CIMT assessment was performed for all participants using B-mode ultrasonography (Esaote, MylabTM 70 Co., Italy) using a high-resolution, 18-MHz linear array transducer. All measurements were performed by a radiologist who was blinded to the clinical conditions of patients. According to a previous study, the CIMT of both left and right common carotid arteries was measured only once, and the CIMT value was calculated by averaging the measurements of left and right common carotid IMT.

Laboratory assay

After a fasting of 12 hours, 10 mL of blood sample from brachial vein was collected from all participants. Samples were centrifuged for 5 minutes at 4000 rpm and then were frozen and stored at -70°C until the time of assessment. sICAM-1 and sVCAM-1 levels were measured with sandwich enzyme immunoassay technique (Elisa) kits (Bender medical systems GmbH Vienna, Austria).

Statistical analysis

Data analysis was performed by SPSS 19) SPSS Inc, Chicago, USA) software. The results were expressed as mean \pm SD for quantitative variables and or frequencies for qualitative variables. The normality of data was assessed by Kolmogorov-Smirnov test. The Student's *t*-test and the chi-square test were applied for comparison of the results. A level of equal or less than 0.05 was considered statistically significant for all variables.

RESULTS

Basic information of subjects

Basic and clinical findings of subjects are showed in Table 1. In the control group, 21 (52.5%) participants were male and 19 (47.5) were female. In the *H. pylori* positive group, 18 (45%) patients were male and 22 (55%) were female. Twenty three (57.5%) patients of the *H. pylori* negative group were male and 17 (42.5%) were female. There wasn't any significant difference between three studied groups for gender ($P=0.876$). Mean \pm standard deviation (SD) for age among control, negative and positive *H. pylori* groups were 47.21 ± 7.54 , 46.52 ± 5.52 and 45.64 ± 8.32 years respectively ($P=0.943$). Five (12.5%) participants in the control group, six (15%) patients in the positive and seven (17.5%) patients in the negative *H. pylori* groups reported alcohol consumption ($P=0.245$). Also, four (10%) participants in the control group were current smokers and 10 (25%) others were passive smokers. In the positive *H. pylori* group, six (15%) patients and 12 (30%) patients and in the negative *H. pylori* group 8 (20%) patients and 9 (22.5%) patients were current and passive smokers respectively ($P=0.032$). NSAID was applied by 12 participants in the control group, 16 (40%) patients in the positive *H. pylori* and 14 (35%) patients in the negative *H. pylori* groups respectively ($P=0.042$). The frequencies of atrophy, metaplasia and dysplasia among the positive *H. pylori* group were 12 (30%), 10 (25%) and 14 (35%) respectively and among the negative *H. pylori* group these figures were 15 (37.5%), 7 (17.5%) and 13 (32.55%) respectively. Mean \pm SD of IgG in the positive and negative *H. pylori* groups

were 87.54 ± 12.32 IU/mL and 14.32 ± 6.43 IU/mL respectively with a high significant difference ($P=0.000$).

Relationship between endothelial dysfunction and *H. pylori*

The level of endothelial dysfunction among both negative and positive *H. pylori* groups is showed in Table 2. Mean \pm SD of FMD in the control group ($0.27\% \pm 0.11$) was significantly higher in comparison with the positive ($0.17\% \pm 0.09$, $P=0.034$) and negative *H. pylori* groups ($0.21\% \pm 0.10$, $P=0.041$). Also, the mean \pm SD of CIMT in the positive *H. pylori* group (0.58 ± 0.13 mm) was significantly higher than that in the control (0.36 ± 0.44 mm, $P=0.021$) and negative *H. pylori* groups (0.48 ± 0.32 mm, $P=0.040$). Mean \pm SD of CIMT in the chronic gastritis patients with negative *H. pylori* was significantly higher than that for participants in the control group ($P=0.037$). Mean \pm SD of sICAM-1 in the chronic gastritis patients with positive and negative *H. pylori* was significantly higher than that for participants in the control group (332.64 ± 8.75 pg/mL, 352.16 ± 7.54 pg/mL, 236.32 ± 12.43 pg/mL, $P=0.000$, respectively). Level of sICAM-1 in positive *H. pylori* group was higher than that in the negative *H. pylori* group but this difference was not significant ($P=0.053$). Mean \pm SD of sVCAM-1 in patients with positive *H. pylori* (731.43 ± 21.34 pg/mL) was significantly higher than that in the negative *H. pylori* patients (665.45 ± 17.54 pg/mL, $P=0.001$) as well as those in the control group (456.54 ± 24.32 , $P=0.000$). Also the level of sVCAM-1 in the negative *H. pylori* group was significantly higher than that in the control group ($P=0.000$).

TABLE 1. Basic characteristics of participants

Variable	Control n=40	<i>H. pylori</i> positive n=40	<i>H. pylori</i> negative n=40	Overall P
Sex, n (%)				0.876
Male	21 (52.5)	18 (45)	23 (57.5)	
Female	19 (47.5)	22 (55)	17 (42.5)	
Age, years	47.21 ± 7.54	45.64 ± 8.32	46.52 ± 5.52	0.943
BMI, kg/m ²	25.65 ± 5.43	27.54 ± 3.65	26.13 ± 4.76	0.354
Alcohol, n (%)	5 (12.5)	6 (15)	7 (17.5)	0.245
Current smoking n (%)	4 (10)	6 (15)	8 (20)	0.032
Passive smoking n (%)	10 (25)	12 (30)	9 (22.5)	
NSAID, n (%)	12 (30)	16 (40)	14 (35)	0.042
Atrophy, n (%)	-	12 (30)	15 (37.5)	0.467
Mataplesia, n (%)	-	10 (25)	7 (17.5)	0.345
Dysplasia, n (%)	-	14 (35)	13 (32.5)	0.233
IgG (IU/mL)	-	87.54 ± 12.32	10.32 ± 6.43	0.000

BMI: body mass index; NSAID: nonsteroid anti-inflammatory drugs.

TABLE 2. Compression the level of endothelial dysfunction markers in patients with chronic gastritis associated with *H. pylori* infection

Variable	Control	<i>H. pylori</i> positive	<i>H. pylori</i> negative
FMD, %	0.27 ± 0.11	0.17 ± 0.09 ^a	0.21 ± 0.10 ^{a,b}
CIMT, mm	0.36 ± 0.44	0.58 ± 0.13 ^a	0.48 ± 0.32 ^{a,b}
sICAM-1 (pg/mL)	236.32 ± 12.43	352.16 ± 7.54 ^a	332.64 ± 8.75 ^a
sVCAM-1 (pg/mL)	456.54 ± 24.32	731.43 ± 21.34 ^a	665.45 ± 17.54 ^{a,b}

FMD: flow mediated dilation; CIMT: carotid intima media thickness; Sicam-1: soluble inter cellular adhesion molecule-1; Svcam-1: soluble vascular cell adhesion molecule; a: $P < 0.05$ compared to control group; b: $P < 0.05$ compared to *H. pylori* positive.

Relationship between IgG level with markers of endothelial dysfunction

Figure 1 shows the correlation between markers of endothelial dysfunction and the level of IgG as the serological marker of *H. pylori* infection. Based on the results, the level of IgG had a revers correlation with FMD, so that by increasing the serum level of IgG, the level of FMD was reduced, but this correlation was not significant ($P=0.247$). Regardless to FMD, the level of CIMT increased with increasing the serum level of IgG ($P=0.563$).

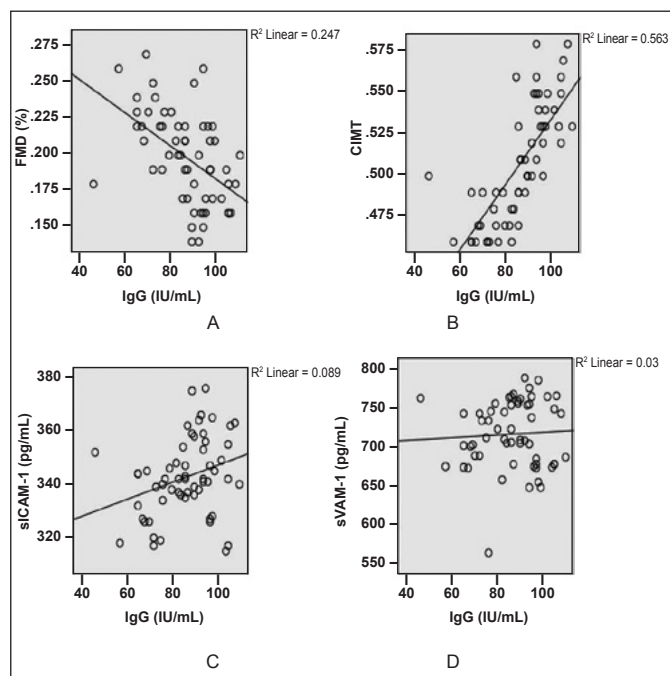


FIGURE 1. Association between endothelial dysfunction markers and *H. pylori* IgG in patients with chronic gastritis associated with *H. pylori* infection. FMD: flow mediated dilation; CIMT: carotid intima media; sICAM: soluble inter cellular adhesion molecule-1; sVCAM: soluble vascular cell adhesion molecule; FMD: flow mediated dilation, CIMT: carotid intima media; sICAM: soluble intera cellular adhesion molecule-1; sVCAM: soluble vascular cell adhesion molecule.

DISCUSSION

The aim of this study was to assess the endothelial dysfunction in patients with chronic gastritis associated with *H. pylori* infection. Some blood markers such as sICAM-1 and sVCAM-1 as well as some vascular markers such as FMD and CIMT were measured in this study. Endothelial dysfunction is a key component of maintaining structure and vascular function through various mechanisms⁽⁹⁾. According to the results, changes of FMD in patients with positive *H. pylori* infection showed significant differences with FMD changes in healthy subjects as well as those with negative *H. pylori* infection. Although many studies have reported a relationship between *H. pylori* infection and coronary artery diseases and also vascular events such as atherosclerosis, but these studies were cross sectional or epidemiological reports⁽⁵⁾ and there is not a specific study to investigate the effects mechanism of *H. pylori* infection on vascular changes. This study showed the relationship between *H. pylori* infection and FMD changes and

endothelial dysfunction during chronic gastritis disease for the first time. Another interesting finding in results was the FMD changes in patients with *H. pylori* infection was significantly lower than those in patients without *H. pylori* infection. Also, early changes in the endothelial dysfunction were higher among chronic gastric patients compared to healthy controls, but these changes in the patients with chronic gastritis associated with *H. pylori* infection were higher than those in the chronic gastritis without *H. pylori* infection and healthy people. Due to lack of similar studies, we could not compare the results of this study with other findings. Blum and colleagues reported that *H. pylori* eradication could improve endothelial dysfunction according to attenuated FMD and ankle brachial index after 3 months⁽³⁾. This study also revealed a reverse correlation between FMD changes and the serum level of IgG as a serological marker of *H. pylori* infection, for the first time. In a study by Ozdogru and colleagues, the relationship between IgG titer and the extent of coronary artery disease was reported among patients with angiography proven coronary artery disease (CAD) as well as those with acute coronary syndrome (ACS)⁽¹⁴⁾, while Hara and colleagues have rejected this kind of association⁽⁶⁾. This study showed a direct association between CIMT and IgG titer in chronic gastritis associated with *H. pylori* infection compared to the healthy subjects and furthermore compared to patients with negative *H. pylori* infection. CIMT is an indicator of structural changes in vascular wall and measuring this marker can predict future risk of cardiovascular events⁽¹³⁾. Fortunately, some studies have limitedly investigated the association between CIMT and *H. pylori* infection⁽¹⁰⁾. For example, Akbas and colleagues reported that the CIMT among positive *H. pylori* subjects was significantly higher than that in those with negative *H. pylori* infection⁽¹⁾. Findings of this study were in accordance with the results of Akbas et al. Of course, our study was relatively different from Akbas study, so this study compared chronic gastric patients either with or without *H. pylori* infection with the healthy subjects. Nevertheless, Altintas and colleagues reported that carotid intima-media thickness was higher among positive *H. pylori* patients with atrophic gastritis compared to positive *H. pylori* patients with non-atrophic gastritis but their difference was not significant⁽²⁾. In addition, we have shown a direct linear correlation between the CIMT rate and the serum level of IgG that this finding has not been reported so far. Another important aspect of this study was assessment of blood markers associated with endothelial dysfunction such as sICAM-1 and sVCAM-1 in patients with chronic gastritis associated with *H. pylori* infection. We showed that the levels of sICAM-1 and sVCAM-1 in chronic gastritis patients associated with *H. pylori* infection were significantly higher compared to those without *H. pylori* infection. In addition, the level of these two markers in chronic gastritis patients with or without *H. pylori* infection was significantly higher in comparison with healthy individuals. According to Mori's study, *H. pylori* infection, directly, induced expression of ICAM-1 during culturing of gastric epithelial cells in a NF-kappa B-dependent manner⁽¹¹⁾. In another study, findings showed a significant role of ICAM-1 and VCAM-1 in leukocyte-endothelial interaction among patients with chronic gastritis associated *H. pylori* infection without E-selectin upregulation⁽⁷⁾. This finding was in accordance with our results. We showed that a direct association between serum level of IgG and increasing level of ICAM-1 and VCAM-1 in chronic gastritis patients. This result was not reported so far and this issue was performed by this study for the first time. As it was previously mentioned, there

are few studies to show the changes in the endothelial dysfunction markers among chronic gastritis patients and we showed a completely elaborated endothelial dysfunction in patients with chronic gastritis. We showed that these dysfunctions were exacerbated in the presence of *H. pylori* infection. One of the limitations of our study was a small sample size of participants, mostly due to narrow criteria in the selection of patients for inclusion. Considering the role of *H. pylori* in the endothelial dysfunction, if the effects of *Helicobacter pylori* eradication on improving of endothelial function to be evaluated by the clinical trials studies, better results could be expected about the pathogenesis of this disease. In addition, new therapeutic strategies for endothelial dysfunction in chronic gastritis disease associated with *H. pylori* infection may be achieved.

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Authors' contributions

Judaki A and Rahmani A contributed to data analysis, interpretation of the results and drafted the manuscript. Rahmani A participated in manuscript preparation. Hafezi Ahmadi MR, Mis Ghavam S and Asadollahi KH participated in data collection. Norozi S contributed to the design of the study and participated in the clinical work and manuscript preparation. All authors have read and approved the article for publication.

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RESUMO – Contexto – A disfunção endotelial é um dos estágios iniciais de doenças vasculares. **Objetivo** – O objetivo deste estudo foi investigar os marcadores de disfunção endotelial em pacientes com gastrite crônica associada com infecção por *Helicobacter pylori* (*H. pylori*). **Métodos** – Através de estudo cruzado seccional, foram analisadas informações básicas e clínicas de 120 participantes (40 pacientes com infecção pelo *H. pylori*, 40 pacientes sem infecção pelo *H. pylori* e 40 pessoas saudáveis). A espessura da camada íntima-média da carótida e níveis de dilatação mediada por fluxo foram medidos em todos os pacientes e controles. A adesão da molécula-1 solúvel (sVCAM-1) à célula vascular e da molécula de adesão intercelular-1 (ICAM-1) foram medidas pelo método Elisa para todas os indivíduos. O nível de *H. pylori* IgG foi avaliado em pacientes de gastrite crônica. **Resultados** – O nível de dilatação mediada por fluxo em pacientes com infecção positiva pelo *H. pylori* foi significativamente menor do que em aqueles com infecção negativa ($0,17\% \pm 0,09$) X ($0,21\% \pm 0,10$) $P < 0,05$ e em relação ao grupo controle ($0,27\% \pm 0,11$) $P < 0,05$. O nível da espessura da íntima-média da carótida em pacientes com infecção positiva pelo *H. pylori* foi significativamente maior ($0,58 \pm 0,13$ mm) do que aqueles com negativa ($0,48 \pm 0,32$ mm) $P < 0,05$ e em relação ao grupo controle ($0,36 \pm 0,44$ mm) $P < 0,05$. O nível médio de sICAM-1 grupo de infecção *H. pylori* positiva ($352,16 \pm 7,54$ pg/mL) foi maior do que o grupo de infecção negativa ($332,64 \pm 8,75$ pg/mL = 0,75) e em relação ao grupo controle ($236,32 \pm 12,43$ pg/mL) $P < 0,05$. Revelou-se uma relação direta entre a dilatação mediada por fluxo e alterações da espessura da íntima-média da carótida e sICAM-1 e sVCAM-1, associada com o nível de *H. pylori* IgG em gastrite crônica. **Conclusão** – Os níveis de dilatação mediada por fluxo, da espessura da íntima-média da carótida e sICAM-1 foram maiores entre os pacientes com infecção positiva pelo *H. pylori*. Pacientes com gastrite crônica associada a infecção por *H. pylori* correm o risco de disfunção endotelial, devido à dilatação mediada por fluxo e anormalidades da espessura da íntima-média da carótida e aumento do nível de sICAM-1 e sVCAM-1.

DESCRITORES – Gastrite. *Helicobacter pylori*. Fatores de crescimento endotelial. Espessura íntima-media carotídea.

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