Cross-sectional Study

Evaluating the relationship between *Helicobacter pylori* infection and carotid intima-media thickness a cross sectional study

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A R T I C L E  I N F O

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A B S T R A C T

Introduction: *Helicobacter pylori* is a gram-negative spiral bacterium that is frequently found in the human stomach. Significant association has been reported between Cytotoxin associated gene A (CagA)-positive *Helicobacter pylori* strains and coronary heart disease. The aim of the present study is to investigate the carotid intima-media thickness as an indicator of atherosclerosis in people with *Helicobacter pylori* infection.

Methods: This study was done on patients who underwent upper GI endoscopy and biopsy, and after obtaining conscious consent underwent ultrasound of the right and left carotid arteries for measuring carotid intima-media thickness (CIMT) and blood tests.

Results: In this study, 90 patients who underwent upper GI endoscopy were examined in three groups: negative *H. pylori* negative, positive cagA and negative cagA. The right, left and average of CIMT in cagA-positive group were significantly higher than the other two groups (p < 0.05). However, the average of CIMT was not significantly different between men and women. Also, the hsCRP average level in positive cagA group was significantly higher than other groups (p < 0.05).

Conclusion: Our findings suggest that there is an increase in CIMT values in patients with *H. pylori* infection, especially in cases of positive cagA. The positive cagA group showed significantly higher levels of hs-CRP, as a marker of elevated inflammatory response. Therefore, *H. pylori* infection, especially cagA-positive strains and its associated systemic inflammatory response can be considered as a contributing factor in atherosclerosis and cardiovascular disease.

1. Introduction

*Helicobacter pylori* is a spiral gram-negative bacterium that normally colonizes in human gastric epithelium. At least 50% of the world population is infected with this bacteria, which is much higher in developing countries such as Iran that is estimated at up to 90 percent. Lots of studies showed the strong relation between this infection and chronic gastritis, peptic ulcer and gastric carcinoma [1]. These studies showed the relation between infection and some diseases like metabolic disorders such as diabetes [2], Neurological disorders especially stroke [3], Psychiatric complications [4], Gynecological diseases like Hyperemesis gravidarum [5], Pre-eclampsia [6], Infertility [7], eye deseases Glaucoma [8], skin diseases like Chronic resistant urticaria[9], alopecia areata [10] and Behcet’s syndrome [11], Ear, nose and throat benign diseases [12], and Malignant deseases like laryngeal carcinoma [13], lung cancer [14], hematologic disorders like iron deficiency anemia [15] and Idiopathic thrombocytopenic purpura [16] Hepatobiliary system disorders [17] and cardiovascular disease.

Patients with *H.pylori* infection show high systemic inflammatory symptoms that are with the increase in number of neutrophils and basophils and cytokines and vasoactives [18]. All of these are involved in pathogenicity of extragastic diseases. Atherosclerosis is a chronic inflammatory diseases of arteries [19]. Some researches have proved the relation between infectious pathogens like chlamydia pneumoniae [20], cytomegalovirus [21] and helicobacter pylori and athrosclerosis in coronary and carotid artery [22]. Virulence of pathogens can be an important indicator of their potential for damage and atherosclerosis. The most invasive strains of Helicobacter pylori produce high molecular
weight toxins which called Vacuolating cytotoxin A (VacA) and cause the vaculozation of gastric epithelia cells. This toxin can damage the gastric epithelial cells and lead to a local inflammation response. There is an immunogenic protein with VacA which called Cytoxtoxin associated gene A (CagA). Positive CagA serologically is a common method for H. pylori infection diagnosis [23]. Zhang L et al., in 2019 had a study in which 13,168 patients went under carotid ultrasonic examination and urea breath test for H.pylori. Examinations showed that H.pylori increased the risk of atherosclerosis in men [24]. Dong, X et al., in 2018 showed that carotid intima thickness in patients with positive H.pylori was higher than negative H.pylori patients. They concluded that H.pylori infection had a correlation with carotid intima thickness and caused the carotid artery thickness [25].

Since the exact relation between atherosclerosis and H.pylori infection was not clear, in this study carotid intima-media thickness (CIMT) as an atherosclerosis indicator was assessed in patients with H.pylori infection.

2. Material and methods

90 patients who underwent the endoscopy in 2018–2019 were included in the cross sectional study. Demographic and clinical variables like age, gender, and BMI, cardiovascular disease family record, blood pressure, diabetes, smoking, and peptic ulcer record were evaluated[26] (Fig. 1).

Atherosclerosis risk factors like total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), fasting blood sugar (FBS), and high sensitive C-reactive protein (hsCRP) were assessed in blood samples of patients. Gastroduodenoscopy was done for positive H.pylori infection and the sample was taken from the gasteric antrum. Hematoxylin and Eosin (H&E) and Giemsa staining and also urea fast test were done in this sample. If these tests were negative, Helicobacter pylori infection was considered negative. In addition, H.pylori culture was done for positive H.pylori patients. Firstly Samples were cultured in a proper culture medium. Then H.pylori DNA was extracted and the CagA gene was detected by the PCR method. On this basis, patients were divided into three groups on the basis of positive/negative H.pylori and CagA. CIMT was evaluated by ultrasonography method for all patients. Measured IMT in the common left/right carotid artery was recorded as the final CIMT. CIMT and hsCRP as the general inflammation markers were compared in H.pylori patients with positive and negative CagA and control groups.

2.1. Statistical analysis

Data were analyzed by SPSS version 20.0 software. For assessing of normal distribution, Kolmogorov–Smirnov test was done. Parametric test like ANOVA and independent t-test was used for significance assess. P-value <0.05 was considered significant.

2.2. Ethical considerations

The study was approved by the ethics committee of Khashan University of medical science, with ID IR.KAUMS.MEDNT.REC.1397.50. Patients were sure that their information was private and there was no interruption or additional cost in their treatment.

3. Results

This study was done in order to evaluate the relation between H. pylori infection and carotid intima-media thickness (CIMT). 65.6% of patients were women and 34.4% were men. The average age of patients was 46.10 ± 15.236. The average age of women was 47.22 ± 14.835 which is higher than the other group. But according to the independent t-test, there is no significant difference between two groups.

The most common reason for endoscopy was dyspepsia (67.8%) and after that people with abdominal pains and heart burn were frequent. The average of fasting blood sugar was 93.00 ± 8.41 mg/dl, triglyceride was 148.02 ± 5543 mg/dl, total cholesterol was 191 ± 40.93 mg/dl, LDL was 115.30 ± 25.16 mg/dl, HDL was 46.37 ± 12.89 mg/dl,fasting blood pressure was 118.72 ± 17.26 mmHg, diastolic blood pressure 73.89 ± 12.40 mmHg, BMI 25.18 ± 3.63 kg/m² and hsCRP was 4.27 ± 3.05 mg/l. The average of right CIMT in patients with H.pylori was 0.729 ± 0.190 mm and according to the ANOVA test, it was significantly higher than the other group (p < 0.05) (Table 1).

![Fig. 1. Flowchart of patients who entered the cross sectional study.](image-url)
In H. pylori patients with positive cagA, the average of right CIMT was 0.85 ± 0.142 mm and according to the independent t-test was significantly higher than the other group. The average of left CIMT in patients with positive cagA was 0.825 ± 0.127 mm. The average of both CIMT in patients with positive cagA was 0.837 ± 0.130 mm and independent t-test showed that it was significant (p < 0.05) (Table 2).

According to the ANOVA test, the average of right/left/both CIMT in H. pylori patients with positive cagA were significantly higher than the negative cagA patients and patients without H. pylori infection (Table 3) (see Table 4).

Right CIMT in women was higher than men and the average was 0.674 ± 0.210 mm. But this difference, according to the independent t-test, was not significant. Left CIMT was higher in men and the average was 0.699 ± 0.201 mm. This difference was not significant. The average of both CIMT was higher in women (0.668 ± 0.195) but it wasn’t significant. The average of hsCRP in patients with H. pylori infection and positive cagA was 6.85 ± 3.26 mg/L in patients with H. pylori and negative cagA was 3.95 ± 1.97 ml/l and in patients without H. pylori infection was 2.02 ± 1.37. According to the ANOVA test, this difference was significant (p < 0.05).

In terms of spearman correlation, there was a significant relation between age and both side CIMT and the average of both CIMT, between the BMI and both side CIMT and the average of both CIMT, between cardiovascular diseases and left CIMT and the average of both side CIMT, between triglyceride level and cagA, between total cholesterol and H. pylori infection, between LDL and left CIMT, between HDL and left CIMT, between H. pylori infection and both side CIMT and the average of both side CIMT, between H. pylori infection and cagA, between cagA and both side CIMT and the average of both side CIMT, between cag and H. pylori infection, between hsCRP level and cagA, between hsCRP and H. pylori infection (Table 4).

The average of age (49.97 ± 14.35 years old), triglycerid level (166.27 ± 55.43 mg/dl), HDL (47.867 ± 13.61 mg/dl), LDL (119.49 ± 23.95 mg dl), BMI (25.70 ± 3.77 kg/m²) in patients with H. pylori and positive cagA and the average of FBS (94.167 ± 9.37 mg/dl) in H. pylori and negative cagA patients were higher but according to the ANOVA test, they weren’t significant.

The average of total cholesterol (205.27 ± 44.47 mg/dl), systolic blood pressure (127.5 ± 16.44 mmHg) and diastolic blood pressure (77.33 ± 12.71 mmHg) were significantly higher in patients without H. pylori infection (p < 0.05) (Table 5).

4. Discussion

The current study evaluated the relation between H. pylori infection and CIMT in 90 patients who underwent the endoscopy. The results showed that right/left/both sides CIMT in people with H. pylori infection was significantly higher than the other groups. Right/left/both sides CIMT in people with H. pylori infection and positive cagA was significantly higher than the other groups. Right/both sides CIMT in people with H. pylori infection and positive cagA was significantly higher than without-infection group. Left CIMT in these people was higher but this difference was not significant. Right/both sides CIMT in people with infection and negative cagA was higher than people without infection but it wasn’t significant. Right/both sides CIMT was higher in women and left CIMT was higher in men. But this difference was not significant.

The average of hsCRP in H. pylori and positive cagA was significantly higher. Atherosclerosis risk factors such as high blood pressure, diabetes and cholesterol level had no disturbing effects on the results.

Wu, Y., et al., in 2013 had a study on the effect of YKL-40 Overexpression on plaque instability in carotid atherosclerosis with CagA-positive Helicobacter pylori infection. They proved that in H.pylori and positive cagA patients, YKL-40 overexpression resulted to more severe atherosclerosis clinical symptoms [27]. In terms of the relation between atherosclerosis risks and H. pylori infection, these findings were related to the current study but YKL-40 expression was not evaluated in this study.

In a study which was done by Longo-Mbenza, B., et al., in 2012, it was indicated that there were relation between cardiovascular diseases risk factors and carotid plaque and stroke and H. pylori infection. Also there were significant relation between the infection severity in males and cardiovascular diseases [28]. These findings don’t agree with this study in terms of the relation between the infection and gender. Park, M. J., et al., in 2011 in a study showed that patients with H. pylori infection were at the higher risk of coronary arteries atherosclerosis due to the common cardiovascular risk factors [29]. This study indicated the same results. Niccoli, G., et al., in 2010 proved that anti-CagA antibody in patients with Coronary artery disease were higher than the patients with normal coronary arteries. They also indicated that there was a significant correlation between anti-cagA antibody levels and atherosclerosis levels. In addition, positive cagA patients had higher levels of coronary artery disease than negative cagA patients. Therefore they suggested there is significant relation between H. pylori infection with positive cagA and atherosclerosis risks [30]. The current study also indicated this.

Table 1

| Artery          | H. pylori | Number | Minimum | Maximum | Average | Standard deviation | P-value |
|-----------------|-----------|--------|---------|---------|---------|--------------------|---------|
| Right carotid   | positive  | 60     | 0.36    | 1.15    | 0.729   | 0.202              | 0.000   |
|                 | negative  | 30     | 0.31    | 0.79    | 0.549   | 0.168              |         |
| Left carotid    | positive  | 60     | 0.37    | 1.10    | 0.718   | 0.183              | 0.000   |
|                 | negative  | 30     | 0.34    | 0.93    | 0.559   | 0.162              |         |
| Both carotid    | positive  | 60     | 0.365   | 1.12    | 0.723   | 0.190              | 0.000   |
|                 | negative  | 30     | 0.325   | 0.86    | 0.554   | 0.160              |         |

* P-value <0.05 was considered significant.

Table 2

| Artery          | CagA    | number | minimum | maximum | average | Standard deviation | Independent t-test p-value |
|-----------------|---------|--------|---------|---------|---------|--------------------|---------------------------|
| Right carotid   | positive | 30     | 0.42    | 1.15    | 0.850   | 0.142              | 0.032                     |
|                 | negative | 30     | 0.36    | 0.98    | 0.609   | 0.182              |                           |
| Left carotid    | positive | 30     | 0.44    | 1.10    | 0.825   | 0.127              | 0.021                     |
|                 | negative | 30     | 0.37    | 0.95    | 0.611   | 0.169              |                           |
| Both carotid    | positive | 30     | 0.43    | 1.12    | 0.837   | 0.130              | 0.023                     |
|                 | negative | 30     | 0.365   | 0.96    | 0.610   | 0.172              |                           |
The present study is consistent with the significant association between gen and a protein contained in coronary atherosclerotic plaques [31]. Coronary instability mediated by antigen mimicry between CagA anti-relation. Franceschi, F., et al., in 2009 suggested that an intense immune response to CagA-positive Helicobacter pylori infection might be important for coronary instability mediated by antigen mimicry between CagA antigen and a protein contained in coronary atherosclerotic plaques [31]. The present study is consistent with the significant association between the increased risk of atherosclerosis and CagA-positive Helicobacter pylori, as well as the association between CagA-positive and high immune response measured here by hsCRP.

Table 3
The average of CIMT in patient with H.pylori and positive/negative cagA and without H.pylori.

| Artery          | CagA          | Number | Minimum | Maximum | Average | Standard deviation | P-value |
|-----------------|---------------|--------|---------|---------|---------|--------------------|---------|
| Left carotid    | Non-infected  | 30     | 0.34    | 0.93    | 0.559   | 0.162              | 0.000   |
|                 | Positive cagA | 30     | 0.44    | 1.10    | 0.825   | 0.127              |         |
|                 | Negative cagA | 30     | 0.37    | 0.95    | 0.611   | 0.169              |         |
|                 | Non-infected  | 30     | 0.325   | 0.86    | 0.554   | 0.160              | 0.000   |
|                 | Positive cagA | 30     | 0.43    | 1.12    | 0.837   | 0.13               |         |
|                 | Negative cagA | 30     | 0.365   | 0.96    | 0.610   | 0.172              |         |

* P-value < 0.05 was considered significant.

Table 4
Spearman correlation of variables.

| Variables                  | Right CIMT   | Left CIMT   | Both CIMT | H.pylori infection | cagA | hsCRP |
|----------------------------|--------------|-------------|-----------|--------------------|------|-------|
| Age                        | 0.425        | -0.016      | 0.474     | -0.005             | 0.155| 0.062 |
| BMI                        | 0.270        | 0.038       | 0.09      | 0.057              | 0.132| -0.038|
| diabetes                   | 0.007        | -0.045      | -0.032    | -0.155             | -0.089| -0.153|
| Cardiovascular diseases    | 0.175        | 0.215       | 0.208     | 0.120              | 0.069| 0.013 |
| High blood pressure        | 0.116        | 0.164       | 0.128     | -0.204             | -0.034| -0.118|
| Hyperlipidemi              | 0.127        | 0.129       | 0.110     | -0.055             | 0.000| 0.090 |
| Triglycerid level          | 0.116        | 0.080       | 0.100     | 0.191              | 0.264| 0.069 |
| Total cholesterol          | 0.133        | 0.178       | 0.150     | -0.050             | 0.128| 0.106 |
| LDL                        | 0.122        | 0.215       | 0.161     | -0.018             | 0.105| 0.121 |
| HDL                        | 0.188        | 0.232       | 0.201     | 0.026              | 0.019| 0.003 |
| Fasting blood sugar        | -0.056       | -0.006      | -0.037    | -0.053             | -0.078| 0.043 |
| Helicobacter pylori infection | 0.615        | 0.559       | 0.597     | 1.000              | 0.500| 0.539 |
| cagA                       | 0.638        | 0.592       | 0.624     | 0.866              | 1.000| 0.518 |
| hsCRP                      | 0.439        | 0.392       | 0.412     | 0.610              | 0.518| 1.000 |

* P-value < 0.05 was considered significant.

Table 5
The average of variables in patients with H.pylori and positive/negative cagA and without H.pylori.

| Variables                  | Non-infected | Positive cagA | Negative cagA | P-value |
|----------------------------|--------------|---------------|---------------|---------|
| Age                        | 46.97±       | 49.97±        | 41.37±        | 0.592   |
| Total cholesterol          | 140±45.8     | 166.27±       | 137.8±        | 0.085   |
| HDL                        | 45.34±       | 47.867±       | 45.91±        | 0.734   |
| LDL                        | 13.06±       | 13.61±        | 12.28±        | 0.071   |
| Total cholesterol          | 205.27±      | 198.87±       | 170.4±28.1±   | 0.002   |
| Total cholesterol          | 44.47±       | 40.76±        | 40.76±        | 0.734   |
| HDL                        | 119.7±       | 119.49±       | 106.72±       | 0.071   |
| LDL                        | 25.29±       | 23.95±        | 24.79±        | 0.416   |
| Total cholesterol          | 93.46±9.25   | 91.38±6.27±   | 94.167±       | 0.416   |
| BMI                        | 24.87±3.76   | 25.70±3.77±   | 24.97±3.41    | 0.629   |
| Systolic blood pressure    | 127.5±       | 118.5±        | 110.17±       | 0.000   |
| Diastolic blood pressure   | 16.44±       | 16.14±        | 15.11±        | 0.009   |

* P-value < 0.05 was considered significant.

5. Conclusion

It was concluded that Helicobacter pylori infection especially in case of positive CagA caused the right/left CIMT increase but the difference between two genders was not significant. Also there were higher levels of inflammation in Helicobacter pylori and positive CagA patients and atherosclerosis risk factors as confusing factors couldn’t cause the significant difference. So it was concluded that Helicobacter pylori infection with positive CagA and its inflammation is an important factor in atherosclerosis and cardiovascular diseases.

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Availability of data and materials

The dataset used in this study is available with the authors and can be made available upon request.

Authors’ contributions

All the authors participated in the study design. HRT, RM, MRM and MNJ collected and documented the data and assisted in preliminary data analysis. HHK and MNJ wrote the initial draft. HRT and HHK participated in draft revision, data analysis and editing of the final draft.

Consent for publication

Not applicable.
Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declared that they have no competing interests.

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Abbreviations

CIMT Carotid intima-media thickness
IMT Intima-media thickness
H pylori Helicobacter pylori
LDL Low-density lipoprotein
HDL High-density lipoprotein
TG Triglyceride
FBS Fasting blood sugar
csCRP High sensitive C - reactive protein
CagA Cytotoxin associated gene A

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102659.

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