

## Association of helicobacter pylori infection with severity of coronary heart disease

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### Abstract

**BACKGROUND:** There are few literatures evaluating the association between cytotoxin-associated gene A (CagA) positive strains of *Helicobacter pylori* (HP) and the severity of coronary heart disease (CHD). This study was designed to investigate this association.

**METHODS:** Medical and drug history of 112 consecutive patients who were candidate for coronary angiography were taken. Fasting blood samples were obtained to measure C-reactive protein (CRP), anti *Helicobacter pylori* immunoglobulin G (anti-HP IgG), anti-CagA antibody (Ab) and interleukine-6 (IL6). According to angiography reports, participants were divided into patients with mild (n = 69) and with severe CHD (n = 36). To measure the association between CagA positive strains of HP with the severity of CHD, multivariate logistic regression tests were used by adjusting age, sex, history of diabetes mellitus (DM), dyslipidemia (DLP), and/or hypertension (HTN), CRP status and IL-6 level.

**RESULTS:** The analysis was concluded on 105 subjects. HP infection and CagA Ab were not significantly higher compared to the patients with severe and mild CHD (P = 0.28 and P = 0.68, respectively). Colonization of CagA positive HP did not significantly associate with severity of CHD (OR 1.05, 95% CI 0.33-3.39).

**CONCLUSION:** Colonization of CagA positive HP was not an independent risk factor for severe coronary heart disease.

**Keywords:** *Helicobacter Pylori*, CagA, Coronary Heart Disease, Severity.

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### Introduction

Diabetes, blood hypertension, dyslipidemia and smoking have been known as the risk factors for atherosclerosis process which lead to coronary heart disease (CHD).<sup>1</sup> Data show that severity of CHD is different in various patients but the exact risks which affect on the severity of atherosclerosis process is still not obvious,<sup>2,3</sup> while various researchers suggested some cardiovascular risk factor as responsible for the severity of CHD.<sup>2,3,4</sup>

Chronic inflammation was recently introduced as a risk factor of CHD,<sup>5</sup> and it was mentioned that vascular injury, inflammation, and thrombosis cause atherosclerosis while the stimulus that generate the inflammatory response has remained unclear.<sup>6</sup> A number of studies suggested some infectious pathogens like *Chlamydia pneumoniae*, and cytomegalovirus as pathogenesis which induce

immune responses in their host and trigger the development of atherosclerosis.<sup>7,8</sup> On the other hand, the other studies which were conducted on *Helicobacter pylori* (HP) at the same time has shown the role of this gram-negative bacteria in extra gastrointestinal (GI) disorders in addition to GI diseases.<sup>9,10</sup> CHD is one of the extra GI diseases which some studies showed the association of HP infection with it.<sup>11,12</sup>

HP has different virulent types and a special strain of this bacterium which creates cytotoxin-associated gene A (CagA) is highly virulent and is associated with severe damage of the gastric epithelium and enhances local inflammatory response.<sup>13</sup> It was documented that local inflammatory and immune responses against HP in GI can induce systematic immune response.<sup>14</sup> Some studies have explored the role of CagA positive strain of this pathogen in CHD<sup>15,16</sup> but

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its exact role on severity of CHD is not obvious, so we evaluated the association of CagA positive strain of HP with the severity of CHD.

## Materials and Methods

### Study Population

This cross-sectional study was performed in Isfahan Chamran Heart Hospital from September 2010 to April 2011. One hundred and twelve consecutive positive patients who were candidate for coronary angiography and signed informed consent were selected for this study. All subjects completed a semi-structured questionnaire regarding their past medical and drug history. Accordingly, patients with infectious processes within 2 weeks prior to the catheterization, heart failure, hepatic dysfunction, autoimmune disease, thyroid dysfunction and adrenal dysfunction as well as patients who consumed any kinds of glucocorticoids were excluded. Finally, 105 patients met the inclusion criteria of the study. Present study was reviewed and approved by the Ethical Committee of Islamic Azad University, Najaf Abad Branch.

### Biochemical Measurements

All participants' fasting blood sample were taken to measure C-reactive protein (CRP), anti-helicobacter pylori immunoglobulin G (anti-HP IgG), anti-HP CagA immunoglobulin G antibody (anti-CagA Ab) and interleukine-6 (IL6). Eliza method was used to measure the level of IL-6 and anti-HP IgG. The immune quantitative method by latex agglutination was used to detect CRP status. IL-6  $\geq 14.1$  was considered as high IL-6.

### Coronary Angiography and severity measurement

Coronary angiography was carried out by left-heart catheterization and arteriography using Judkins

method.<sup>17</sup> For detecting severity of CHD, the percent of involvements of each artery was obtained according to angiography data and then changed to decimal numbers. The decimal numbers of arteries were added together and if the sum was  $\geq 1.5$  participants were classified as severe CHD and if this number was  $< 1.5$  patients were considered as mild CHD.<sup>18</sup>

### Data analyses:

Statistical analyses were carried out using SPSS software (version 16.0, Chicago, IL, USA). Unpaired student t-tests were used for comparing continuous variable. Chi-square test for discrete variables was used. To compare the association between CagA positive HP infection with severity of CHD, logistic regression test was employed. The association was first adjusted for age and sex then for sex, age, history of diabetes mellitus (DM), and/or dyslipidemia, and/or hypertension. Finally, it was adjusted for aforementioned factors in addition to IL-6 and CRP level.

## Results

Thirty six patients out of 105 participants had severe CHD and 62 had mild coronary artery involvements. Baseline characteristics of study population were presented in table 1. CRP level were significantly higher in patients with severe CHD ( $P = 0.04$ ). Also, patients with severe CHD had significantly higher level of IL-6 ( $P = 0.01$ ). HP infection and CagA Ab were not significantly higher in patients with severe CHD compared to mild CHD ( $P = 0.28$  and  $P = 0.68$ , respectively). Table 2 shows the association of CagA Ab with severity of CHD. Colonization of CagA positive HP did not significantly associate with severity of CHD (OR 1.05, 95% CI 0.33-3.39).

**Table 1.** Baseline characteristics of study population

	Patients with mild CHD n = 69	Patients with severe CHD n = 36	P
Age (mean $\pm$ SD)	59.05 $\pm$ 10.5	62.36 $\pm$ 9.5	
Female (%)	25(36.2%)	12(33.3%)	0.8
History of DM (%)	14(20.3%)	12(33.3%)	0.07
History of DLP (%)	25(36.2%)	19(52.8%)	0.05
History of HTN (%)	23(33.3%)	17(47.2%)	0.08
HP positive (%)	17(47.2)	30(43.4%)	0.28
CagA positive (%)	10(27.7)	17(24.63)	0.65
CRP level (%)	7(10.1%)	8(22.2%)	0.04
IL-6 $\geq 14$ (%)	4 (30.8%)	9(69.2%)	0.01

DM: Diabetes mellitus, DLP: Dyslipidemia, HTN: Hypertension, CRP: C-reactive protein, IL-6: Interlukine-6, HP: Helicobacter pylori, CagA: Cytotoxin-associated gene A

**Table 2.** The association of infection with *Helicobacter pylori* CagA positive with the severity of coronary heart disease

	OR (95% CI)	P
Unadjusted model	1.02 (0.45-2.29)	0.96
Adjusted model 1*	0.69 (0.63-3.35)	0.43
Adjusted model 2†	1.18 (0.27-5.05)	0.81
Adjusted model 3**	1.05 (0.33-3.39)	0.92

\* Adjusted for age and sex

† Adjusted for age and sex plus history of diabetes mellitus and/or hypertension and/or dyslipidemia

\*\* Adjusted for age and sex plus history of diabetes mellitus and/or hypertension and/or dyslipidemia plus C-reactive protein status and Interlukine-6 level

CagA: Cytotoxin-associated gene A

### Discussion

Present study evaluated the role of CagA positive HP on severity of CHD and found that CagA positive HP was not an independent risk factor for sever CHD.

According to our knowledge, there are few literatures which evaluated the HP and the association of its virulent type with the severity of CHD. Niccoli et al. in a case-control study in line with our findings showed CagA positive strains of HP did not associate with stenosis score of coronary artery involvements.<sup>15</sup> Another population based study in china demonstrated that HP infection was not associated with the severity of coronary atherosclerosis.<sup>19</sup>

In a review article<sup>16</sup> it was suggested that infection with CagA positive strains of HP is associated with atherosclerotic disease like coronary heart disease. One meta-analysis by Pasceri et al.<sup>20</sup> showed small but significant association between CHD and virulent CagA positive type of HP. Mechanisms which could explain the association of CagA positive type of HP infection are as follows;<sup>21,22,23</sup> first, increasing the level of COX-1 and COX-2 in vascular endothelium which lead to prostacycline generation ad finally cause platelet aggregation. Second, these types of HP cause strong inflammatory responses which influence release of especial cytokines which play a role in atherosclerosis process. Third, cross-reactivity between antigens of vascular wall and anti-CagA Ab has shown that this immune mechanism might lead to plaque destabilization.

As we mentioned before, our findings in line with some other studies could not show the significant association of CagA positive strains of HP with severity of CHD while we explained studies and mechanisms which justified this association. Hence,

two possible reasons for such inconsistency could be speculated. First, while CHD was induced by infection with this virulent type of HP, it may not play a role in the progression of atherosclerosis.<sup>19</sup> Second, the score which was used here for detecting CHD severity indicated the severity of lesions which occurs in late phase of atherosclerosis process, but the inflammation of this virulent type of HP contributes to early stage of atherosclerosis process.<sup>24</sup>

This study had some limitations such as its cross-sectional design and small sample size. The explained method for detecting severity of coronary artery involvements instead of Gensini score must be considered as another limitation of present study too. In conclusion, in the present study, a significantly independent association between CagA positive HP and severity of CHD was not found.

### Conflict of Interests

Authors have no conflict of interests.

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