Serological evidence of association between *Helicobacter pylori* infection and coronary artery disease

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Abstract:

**Background:** Studies have reported relationship between chronic *Helicobacter pylori* infection and coronary artery disease (CAD). The cytotoxin-associated gene A product (CagA) is an immunodominant protein which indicates infection with virulent *H. pylori* strains. Significant associations of CagA-positive *H. pylori* strains with coronary artery disorders have been widely reported. *H. pylori* is also known to produce different heat shock proteins (HSPs) which can stimulate the production of specific antibody against microbial proteins and capable of eliciting autoimmune reaction against human tissue expressing HSPs such as vascular endothelial cells. The objectives of this study are to investigate the association between *H. pylori* and CagA with coronary atherosclerosis and CAD, and to determine the possible role of *H. pylori* HSP60 protein in increasing the risk of CAD development.

**Methods:** This study included 70 patients with stable angina and 70 age and gender-matched controls. Each group was evaluated by clinical history, physical examination, cardiac echocardiography (ECHO) and electrocardiography (ECG) with and without exercise. Fasting blood glucose, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG) were estimated by automated enzymatic methods. *H. pylori* IgG, CagA IgG and HSP60 IgG were measured by enzyme-linked immunosorbent assay (ELISA) for both groups.

**Results:** The seroprevalence of *H. pylori* infection was high in both groups; 75.7% in case and 68.6% in control (p=0.346). Serum IgG levels were significantly higher for CagA (p=0.028) and HSP60 (p<0.001) in cases than in controls. There was significant association between *H. pylori* and CagA IgGs in cases (p=0.007) but no association in controls (p=0.700). Higher HSP60 IgG level was significantly associated with both positive *H. pylori* IgG (p<0.001) and CagA IgG (p<0.001) in cases but no significant association was found with *H. pylori* (p=0.815) or CagA (p=0.332) IgG levels in the control group. Serum values were significantly higher for TC (p<0.001), TG (p<0.001) and LDL (p=0.004) while value for HDL was significantly lower (p<0.001) in *H. pylori* IgG-positive subjects (case and control).

**Conclusion:** There is serological evidence that *H. pylori* infection may pose a significant risk factor for CAD. Since *H. pylori* can be eliminated by specific treatment, this may be a good preventive approach for CAD.

**Key words:** *H. pylori*, coronary artery disease, CagA, HSP60, serology.

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Abstrait:

Contexte: Des études ont montré un lien entre l’infection chronique à *Helicobacter pylori* et la maladie coronarienne. Le produit du gène A associé à la cytotoxine (CagA) est une protéine immunodominante qui indique une infection par des souches virulentes de *H. pylori*. Des associations significatives de souches de *H. pylori* CagA-positives avec des troubles coronariens ont été largement rapportées. *H. pylori* est également connu pour produire différentes protéines de choc thermique (HSP) capables de stimuler la production d’anticorps spécifiques contre les protéines microbiennes et capables de provoquer une réaction auto-immune contre les HSP exprimant le tissu humain, telles que les cellules endothéliales vasculaires. Les objectifs de cette étude sont d’étudier l’association entre *H. pylori* et CagA avec l’athérosclérose coronarienne et la coronaropathie, et de déterminer le rôle possible de la protéine *H. pylori* HSP60 dans l’augmentation du risque de développement de coronaropathie.

Méthodes: Cette étude a inclus 70 patients présentant une angine de poitrine stable et 70 témoin de même âge et de même sexe. Chaque groupe a été évalué par antécédents cliniques, examen physique, échocardiographie cardiaque (ECHO) et électrocardiographie (ECG) avec et sans exercice. La séroprévalence de l’infection à *H. pylori* était élevée dans les deux groupes; 75,7% en cas et 68,6% en contrôle (p=0,346). Les taux sériques d’IgG étaient significativement plus élevés pour CagA (p=0,028) et HSP60 (p<0,001) chez les sujets témoins. Il avait une association significative entre les IgG anti- *H. pylori* et CagA dans les cas (p=0,007), mais aucune association chez les témoins (p=0,700). Un taux plus élevé d’IgG HSP60 était associé de manière significative à la fois aux IgG positives pour *H. pylori* (p<0,001) et aux IgG anti-CagA (p<0,001), mais aucune association significative n’a été constatée avec *H. pylori* (p = 0,815) ou CagA (p=0,332). Taux d’IgG dans le groupe témoin. Les valeurs sériques étaient significativement plus élevées pour le CT (p<0,001), le TG (p<0,001) et le LDL (p=0,004), tandis que les valeurs pour le HDL étaient significativement plus basses (p<0,001) chez les sujets positifs pour *H. pylori* IgG.

Conclusion: Il existe des preuves sérologiques que l’infection à *H. pylori* peut constituer un facteur de risque significatif de coronaropathie. Étant donné que *H. pylori* peut être éliminé par un traitement spécifique, cela peut constituer une bonne approche préventive pour la coronaropathie.

Mots clés: *H. pylori*, maladie coronarienne, CagA, HSP60, sérologie.

Introduction: *Helicobacter pylori* infection is one of the most widespread infections worldwide, affecting half the population of the world. The bacterium causes chronic gastritis, peptic ulcer and gastric cancer (1). The infection stimulates both cell mediated and humoral immune system with elevation of basophils and polymorphs (2), and increased concentration of local and systemic vasoactive cytokines (3). These reactions are not restricted to the digestive tract (4) but also involved many extra gastrointestinal manifestations including haematological disorders (idiopathic thrombocytopenic purpura and unexplained iron deficiency anemia), neurological disorders (stroke, Parkinson and Alzheimer’s diseases), obesity and skin diseases (5,6).

Several studies have reported relationship between chronic *H. pylori* infection and coronary artery disease (CAD), highlighting its role in the pathogenesis of coronary vascular disorders (7). The cytotoxin-associated gene A (CagA) product is an immunodominant protein which indicates infection with virulent *H. pylori* strains. Some studies have reported significant associations of CagA-positive *H. pylori* strains with coronary artery disorders (8).

*Helicobacter pylori* have been detected in human atherosclerotic plaques by immunohistochemistry and polymerase chain reaction (9), and particularly in patients undergoing coronary bypass grafting (10). Chronic *H. pylori* infection is believed to induce low-grade constant inflammatory response with release of mediators that causes vascular endothelial damage through recruitment of monocytes and T-lymphocytes to the vascular wall, even in the absence of the pathogen. Therefore, chronic *H. pylori* infection does not only induce coronary atherosclerosis but can activate acute coronary rupture (11).

A variety of systemic effects including atherosclerosis can be induced by chronic infection in several different manners through increasing circulating cytokine (interleukins 1 and 6) production and formation of the acute-phase products such as C-reactive protein and white blood cells. Also, chronic infection can stimulate the immune system with production of antibodies against the infecting pathogen (12). Furthermore, pathogens can stimulate proliferation and migration of smooth muscle.
cells, accumulation of lipid, and formation of several pro-coagulants, with inhibition of endothelial cell apoptosis (13).

Heat shock proteins (HSPs) represent well conserved protein families sharing wide sequence homology amongst various species, from bacteria to humans (14). Exposure to stressful stimuli such as sudden increase in temperature, hypoxia, infection, inflammation, mechanical stress, and oxidizing agents can induce or up-regulate production of HSPs (14). These proteins play essential roles in the bacterial growth at different temperatures and protection against a variety of injurious factors (15). *H. pylori* are known to produce different HSPs that stimulate the production of specific antibodies (16). Due to high sequence homology of HSPs, autoimmune reaction directed against bacterial HSPs as well as human (such as vascular endothelium) HSPs, could occur (17).

The objectives of this study are to; (i) determine association between *H. pylori* and CagA protein with CAD; (ii) investigate the possible role of *H. pylori* in CAD by estimating its specific HSP60 IgG levels in patients with CAD and healthy subjects and (iii) determine association between *H. pylori* and known risk factors for CAD.

**Methodology:**

**Subjects (case and control)**

This case control study was conducted over a period of six months (January to June 2019), and included 70 patients (cases) with stable angina selected by stratified random sampling among patients admitted to the cardiology unit or attending the cardiology outpatient clinic of Mansoura University Hospital, Egypt. Clinical history, physical examination, cardiac echocardiography (ECHO), and electrocardiography (ECG) with and without exercise, were done for each subject. The cases had signs and symptoms of angina at exercise ECG with more than 2mm ST segment depression. The controls were 70 age and gender-matched patients randomly selected from units other than cardiology who had no feature of CAD (negative tread mill test).

**Exclusion criteria**

The exclusion criteria for both case and control subjects were; (i) significant kidney insufficiency (creatinine more than 1.5 mg/dL), (ii) significant hypothyroidism/hyperthyroidism (serum thyroid stimulating hormone level more than 4.5IU/mL or free thyroxine more than 2ng/dL), (iii) significant C-reactive protein elevation (more than 10mg/L) and (iv) persons with any history of intake of antibiotics for *H. pylori* infection during the last 3months.

**Ethical approval**

The study was approved by Institutional Review Board of the Faculty of Medicine, Mansoura University, Egypt. All subject participants gave informed consent for the study.

**Clinical and laboratory evaluations of case and control subjects**

Subjects in both groups were evaluated for hypertension (indicated by systolic blood pressure ≥140mmHg, diastolic blood pressure of ≥90mmHg (or antihypertensive medication), body mass index (BMI), and smoking (patients who had stopped smoking for 10 years or less were classified as smokers). Approximately 10ml of venous blood was collected from each subject with the serum separated and stored in aliquots at -80°C until specific tests were done.

**Determination of serum glucose and lipids**

Fasting blood glucose (FBG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG) were measured by enzymatic methods in an automated chemistry analyzer (Toshiba TBA-120 FR, Toshiba Medical Systems, Japan).

**Determination of *H. pylori* infection IgG**

The level of serum IgG to *H. pylori* O antigen was determined by a commercial enzyme-linked immunosorbent assay (ELISA) (Euroimmun, Germany). The value of upper limit of normal range for *H. pylori* specific IgG level for the assay kit is 22units/mL.

**Determination of *H. pylori* CagA IgG**

The level of serum IgG to *H. pylori* CagA protein was serologically detected by a commercial ELISA assay (Radim Diagnostics, Germany). The value of upper limit of normal range for *H. pylori* CagA specific IgG levels for the assay kit is 15units/mL.

**Determination of *H. pylori* HSP60 IgG**

The level of serum IgG to *H. pylori* HSP60 was serologically detected by a commercial ELISA assay (Elabscience Biotechnology, China). The detection range of the kit was from 78.13-5000 pg/mL.

**Statistical analysis**

Statistical analysis was performed with the Statistical Package for the Social Sciences software version 17.0 (SPSS Inc., Chicago, IL, USA). The association between two variables...
was evaluated using Chi-square or Fisher Exact tests for categorical variables and Student t tests for continuous variables, with \( p<0.05 \) considered significant.

**Results:**

This study was conducted on 70 patients who had stable angina, with mean age of 58.9 years, and 70 controls with a comparable mean age of 57.7 years \( (p=0.426) \). The cases (36 males, 34 females) were gender-matched with the controls (40 males, 30 females) \( (p=0.497) \). The mean BMI of cases and controls were 30.4 and 29.8 respectively \( (p=0.251) \). There were no significant differences between the case and control subjects regarding history of smoking \( (p=0.319) \), hypertension \( (p=0.122) \), diabetes mellitus \( (p=0.231) \) or fasting blood glucose \( (p=0.074) \).

The prevalence of *H. pylori* infection was 75.7% in the case and 68.6% in control subjects \( (p=0.346) \). On the other hand, CagA IgG \( (p=0.028) \) and HSP60 IgG \( (p<0.001) \) values were significantly higher in cases than in controls (Table 1).

| Parameter                  | Control (n=70) | Case (n=70) | \( p \) value |
|----------------------------|----------------|-------------|---------------|
| Age (years)                | Mean ± SD      | 57.7 ± 9.2  | 58.9±9.6      | 0.426          |
| Age range (years)          |                | 41 – 72     | 45 – 75       |               |
| Gender                     |                |             |               |               |
| Male                       | n (%)          | 40 (57.1)   | 36 (51.4)     | 0.497          |
| Female                     | n (%)          | 30 (42.9)   | 34 (48.6)     |               |
| BMI (kg/m2)                | Mean ± SD      | 29.8 ±3.0   | 30.4±3.5      | 0.251          |
| Smoking                    | n (%)          | 14 (20.0)   | 19 (27.1)     | 0.319          |
| DM                         | n (%)          | 14 (20.0)   | 22 (31.4)     | 0.122          |
| FBG (mg/dL)                | Median (range) | 107.5 (78-256) | 110.5 (85-350) | 0.074          |
| Hypertension               | n (%)          | 26 (37.1)   | 33 (47.1)     | 0.231          |
| *Helicobacter pylori* IgG  | n (%)          | 48 (68.6)   | 53 (75.7)     | 0.346          |
| CagA IgG                   | n (%)          | 31 (44.3)   | 44 (62.9)     | 0.028*         |
| HSP60 IgG                  | Median (range) | 839 (550-4837) | 3365 (1187-5298) | <0.001*        |

\* = significant difference
Association of Helicobacter pylori with coronary artery disease

Table 2: Association of CagA IgG with Helicobacter pylori IgG in case and control subjects

|                  | Control (n=70) | p value | Case (n=70) | p value |
|------------------|----------------|---------|-------------|---------|
|                  | H. pylori IgG negative (n=22) | H. pylori IgG positive (n=48) | H. pylori IgG negative (n=17) | H. pylori IgG positive (n=53) |
| CagA IgG         |                |         |             |         |
| Negative         | 13 (59.1)      | 26 (54.2) | 0.700       | 11 (64.7) | 15 (28.3) | 0.007* |
| Positive         | 9 (40.9)       | 22 (45.8) |             | 6 (35.3)  | 38 (71.7) |       |

* = significant difference

![CagA IgG Negative](image1)

Fig. 1: Association of CagA IgG with H. pylori IgG in case and control subjects

There was significant association of H. pylori and CagA IgGs in the case (p=0.007) but no such association in the control (p=0.700) (Table 2 and Fig 1). Higher anti-HSP60 antibodies level was significantly associated with positive H. pylori IgG (p<0.001) and CagA IgG (p<0.001) in the case but no significant association was found with H. pylori IgG (p=0.815) or CagA IgG (p=0.332) in the control group (Table 3, Figs 2 and 3). The serum levels were significantly higher for TC (p<0.001), TG (p<0.001), and LDL (p=0.004) in H. pylori IgG-positive than H. pylori IgG-negative subjects (case and control) while HDL value was significantly lower (p<0.001) in H. pylori IgG-positive subjects (Table 4).
Table 3: Association of HPS60 IgG with H. pylori and Cag A IgGs in case and control subjects

| Parameter   | Control (n=70) | p value | Case (n=70) | p value |
|-------------|---------------|---------|-------------|---------|
| H. pylori IgG |               |         |             |         |
|-negative (n=22) | Median  | 962.5   | 794 | 0.815 | 2698 | 3658 | <0.001* |
|              | Range         | 550-4398 | 550-4837 | 1187-3827 | 1187-5298 |
| CagA IgG      |               |         |             |         |
|-negative (n=39) | Median  | 839     | 1445 | 0.332 | 2765 | 3876 | <0.001* |
|              | Range         | 550-4398 | 560-4837 | 1187-3265 | 1576-5298 |

*= significance difference

Fig. 2: Association of HPS60 IgG with H. pylori IgG in case and control subjects

Fig. 3: Association of HPS60 IgG with CagA IgG in case and control subjects

Table 4: Association of Helicobacter pylori IgG with lipid profiles in case and control subjects

| Parameter   | Control (n=70) | p value | Case (n=70) | p value |
|-------------|---------------|---------|-------------|---------|
| TG (mg/dL)  |               |         |             |         |
|-negative (n=22) | median  | 50      | 42-76 | <0.001 | 49 | 42-102 | 130 | 50-145 | <0.001 |
|              | range         | 76-234  |         |         | 50-166 | 182 | 135-330 | <0.001 |
| TC (mg/dL)  |               |         |             |         |
|-negative (n=22) | median  | 116     | 94-195  | <0.001 | 129 | 50-166 | 182 | 135-330 | <0.001 |
|              | range         | 94-220  |         |         | 160 | 160-272 | 230 | 124-340 | 0.004 |
| LDL (mg/dL) |               |         |             |         |
|-negative (n=22) | median  | 23.5    | 12-154  | <0.001 | 200 | 160-272 | 230 | 124-340 | 0.004 |
|              | range         | 16-165  |         |         | 160 | 160-272 | 230 | 124-340 | 0.004 |
| HDL (mg/dL) |               |         |             |         |
|-negative (n=22) | median  | 55      | 52-59  | <0.001 | 55 | 48-57 | 47 | 38-55 | <0.001 |
|              | range         | 44-52  |         |         | 50-164 | 182 | 135-330 | <0.001 |
Discussion:

CAD has been considered one of the extra gastrointestinal diseases associated with H. pylori infection (18). In this study designed to determine, by serology, association between H. pylori and CAD, the cases were carefully matched for age, gender and important risk factors for CAD such as history of smoking, hypertension and diabetes mellitus, with the controls. In our study, H. pylori IgG was high in both case and control groups (p=0.346). Studies done on the association between H. pylori infection and cardiovascular diseases have been mostly carried out with the serological H. pylori IgG test because it is rapid, inexpensive and non-invasive (19, 20). However, there have been contradictory reports between serology and occurrence of CAD. While some researchers have reported non-significant association between H. pylori seropositivity and CAD (21,22), others have reported significant association (19,20). These conflicting reports may be explained by the fact that antibody testing cannot differentiate recent and past infection (23). Therefore, serological test is usually performed to study only association between the occurrence of H. pylori infection and CAD (19).

In this study, CagA IgG was significantly detected in cases more than controls (p=0.028), and there was significant association of H. pylori and Cag A IgGs in the cases (p=0.007) but not in the controls (p=0.700). It has been reported that patients with CAD are more prone to infection by CagA positive H. pylori strains with more rigorous clinical manifestations (24). This may be due to the exaggerated inflammatory reaction in CagA-positive H. pylori infection from increased systemic levels of interleukin (IL)-1β, IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α), which tend to exert injurious damage to the vascular endothelial cells (11). In addition, elevated levels of thrombin factor and pro-thrombin subunits F1+2 in patients with both CAD and CagA positive H. pylori strains have been reported (25). Moreover, antibodies against CagA show cross-reactivity with vascular wall antigens, providing a potential role of CagA in vascular wall inflammation (26).

The serum HSP60 IgG level in our study was significantly higher in cases than in controls (p<0.001) and higher anti-HSP60 antibodies level was significantly associated with both H. pylori and CagA IgGs positivity in the case but no such significant association in the control group. This may suggests an association between H. pylori HSP60 and development of CAD. Consistent with the hypothesis of Wick and coworkers (27), atherosclerosis can be associated with high levels of HSP antibodies because of an autoimmune response directed against endothelial tissue expressing high levels of HSP in response to traumatic stimuli such as local infections, cytokines, elevated LDL, or other stressful conditions. Another explanation is that both bacterial toxic metabolites and the concommitant inflammatory response can change the epithelial HSP such that immune tolerance to self HSP is lost, with production of autoantibodies which cross-react with H. pylori HSPs (11). Latif et al., (28) found a strong similarity between HSP60 and heavy chain of cardiac myosin, therefore, cross-reaction between related epitopes could result in autoimmune.

In our study, H. pylori IgG-positive subjects had significantly elevated TG, TC and LDL levels and significantly lower HDL level than those with H. pylori IgG-negative ones. Some researchers have reported that chronic H. pylori infection changes the lipid profile. Rahman et al., (29) and Lee et al., (30) reported significantly lower levels of HDL in patients with H. pylori infection with and without CAD. Jia et al., (31) reported that H. pylori infection may lower HDL levels with predisposition to coronary atherosclerosis. Kim et al., (32) also reported that LDL cholesterol level was significantly higher in H. pylori infected patients, and increasing H. pylori severity increased LDL levels, which is the most important risk factor for atherosclerosis. Therefore, atherogenic lipid (elevated LDL and decreased HDL) profile has been reported in H. pylori infected compared to un-infected patients (33). However, other researchers have reported that lipid profile was not affected by H. pylori infection and therefore not considered as a risk factor for CAD (34).

Conclusion:

There is serological evidence that H. pylori infection may pose a significant risk factor for CAD. Since H. pylori can be eliminated by specific treatment, this may be a good preventive approach for CAD.

Conflicts of interest:

Authors declare non financial conflicts of interest in this study
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