

**Helicobacter pylori**: Does it add to risk of coronary artery disease

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a known pathogen implicated in genesis of gastritis, peptic ulcer disease, gastric carcinoma and gastric lymphoma. Beyond the stomach, the organism has also been implicated in the causation of immune thrombocytopenia and iron deficiency anemia. Although an area of active clinical research, the role of this gram negative organism in causation of atherosclerosis and coronary artery disease (CAD) remains enigmatic. CAD is a multifactorial disease which results from the atherosclerosis involving coronary arteries. The major risk factors include age, diabetes mellitus, smoking, hypertension and dyslipidemia. The risk of coronary artery disease is believed to increase with chronic inflammation. Various organisms like Chlamydia and Helicobacter have been suspected to have a role in genesis of atherosclerosis via causation of chronic inflammation. This paper focuses on available evidence to ascertain if the role of *H. pylori* in CAD causation has been proven beyond doubt and if eradication may reduce the risk of CAD or improve outcomes in these patients.

**Key words:** Extra gastric; Coronary artery disease; *Helicobacter pylori*; Atherosclerosis; Inflammation

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**Core tip:** Coronary artery disease (CAD) is a multifactorial disease and inflammation plays an important role in Atherogenesis. *Helicobacter pylori* (*H. pylori*) is speculated to be one organism which may incite the inflammatory response thereby predisposing infected individuals to CAD. This paper looks at clinical evidence in relation to *H. pylori* infection and CAD and also examines the evidence of effects of eradication of *H. pylori* on CAD and its risk factors.

Sharma V, Aggarwal A. *Helicobacter pylori*: Does it add to risk of coronary artery disease. *World J Cardiol* 2015; 7(1): 19-25

Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/19.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.19

**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*), first identified by Marshall and Warren in 1982, is a ubiquitous gram negative bacterium. A mixture of serendipity and diligent research lifted the veil off this enigmatic organism which was first
thought to be Campylobacter like. The Easter holidays of 1982 had ensured that the culture plates were not destroyed after 48 h of absence of growth and led on to the discovery of *H. pylori*. However, it was after much perusal that the scientific community accepted the bacterium-ulcer-cancer dogma eventually culminating in the 2005 Nobel Prize. Over years it has become clear that this bacterium is responsible for many disease other than the gastric diseases. In the stomach *H. pylori* is implicated in the causation of chronic gastritis, peptic ulcer (gastro-duodenal), gastric MALTOMA (mucosa associated lymphoid tissue lymphoma) and gastric adenocarcinoma. It is also associated with certain extragastric disorders like immune thrombocytopenia and iron deficiency anaemia. Although the role of these in causation of gastric injury has emerged in recent times, the role of *H. pylori* and its virulence factors in causation of atherosclerosis and coronary artery disease is not entirely clear as yet. The present review will focus on the relationship between this bacterium and the coronary artery disease.

**THE BACTERIUM**

*H. pylori* have an inherent ability to survive in the gastric epithelium where they reside in the mucous layer and remain protected from the gastric acid. Urease, an enzyme abundantly present in this flagellate organism, helps create an alkaline environment to help in survival in the otherwise acidic environment. While most infected individuals remain unaffected, others develop a myriad of clinical manifestations ranging from gastritis to gastric cancer. What fuels and drives the pathogenesis of these varied clinical spectrums is not completely understood. While it is estimated that around half the world's population harbours infection with *H. pylori*, only a fraction of the infected manifest with the implicated diseases. The various factors implicated in disease causation following infection by *H. pylori* include both the bacterial virulence factors and the host response to the infection. The bacterial virulence factors include BabA (bacterial binding and inflammation), lipopolysaccharide (interaction with toll-like receptors and mediation of inflammation), Cag pathogenicity island (heightened inflammatory response to infection) and vacA toxin (impaired host responses). The host responses which affect the outcome of infection include interleukin (IL)-1β (certain polymorphisms associated with careino genesis), activation of nuclear factor (NF)-κB, IL-8 levels, recruitment of neutrophils, macrophages and oxidative injury and TH1 cell response may all mediate tissue injury and reaction to *H. pylori* infection.

**CORONARY ARTERY DISEASE: A MULTIFACTORIAL DISEASE**

Coronary artery disease (CAD) is a multifactorial disease manifesting in a number of clinical presentations including angina, myocardial infarction and heart failure. The CAD is primarily a result of coronary atherosclerosis for which a multitude of risk factors are implicated including hyperlipidemia, smoking, diabetes mellitus, lack of physical activity, male gender, increasing age, obesity amongst others. There is a growing acknowledgement of inflammatory factors including C-reactive protein in prediction of increased risk of CAD. *H. pylori* has also been implicated by some to have a role in predisposition to cardiac risk and causation of CAD. Indeed, in a polymerase chain reaction (PCR) based study for detection of *H. pylori* in the coronary plaques of patients who underwent coronary artery bypass grafting (CABG), 29.5% patients had a detectable *H. pylori* on PCR. Also there was serological evidence of infection in 53.3% of these 105 patients. Therefore the infection by *H. pylori* may play a role in plaque rupture and causation of ischemic heart disease. Interestingly, cytotoxin associated gene A (Cag-A) may also play a role in the pathogenesis of CAD as results of one study suggest that anti-Cag-A antibody titres were higher in patients with CAD vis-à-vis normal subjects. Also patients with anti-Cag-A positivity had more severe lesions of CAD. It is believed that the chronic inflammation associated with chronic infections may result in progressive atherosclerotic disease eventually manifesting as CAD.

**CAD AND H. PYLORI**

**Epidemiological evidence**

A number of reports have evaluated the role of *H. pylori* in causation of CAD. In a report on 120 patients who underwent coronary angiography, the prevalence of serologically detectable evidence of *H. pylori* infection was more in patients with angiographically documented CAD (> 50% stenosis in at least one coronary artery). The evidence of infection was found in 70% patients with single vessel disease, 76.3% patients with double vessel disease but only in 50% individuals with no CAD. Coronary artery calcium is believed to be a marker of atherosclerosis and its progression a predictor of CAD events. The correlation of coronary artery calcium (CAC) with various pathogens is conflicting. In a report on 201 asymptomatic subjects, the antibodies to heat shock protein 65 correlated with CAC score as also with evidence of *H. pylori* infection. Another large study from South Korea which evaluated 2029 individuals for *H. pylori* antibody and coronary artery calcification score found that *H. pylori* seropositivity was different amongst those with and those without CAC. This association was more evident in patients with early coronary atherosclerosis. However another report about presence of *H. pylori* infection in a large cohort of individuals who underwent repeat CAC assessment, the presence of *H. pylori* infection (IgG to *H. pylori*) did not correlate with development or progression of CAC. In a report comparing patients with CAD and healthy controls, seropositivity for *H. pylori* infection was significantly higher.
in patients of CAD (59%) vis-à-vis the healthy controls (39%) [14]. Similar reports from India also corroborate that *H. pylori* sero-positivity was much higher in patients with CAD when compared with asymptomatic controls [15-17]. Few reports have indicated, to the contrary, that there is no significant association between *H. pylori* infection and CAD. In a report from Asian Indian families which evaluated role of multiple pathogens in causation of CAD, while CMV infection appeared to elevate the risk of CAD infection with *H. pylori* did not increase the risk [18]. In a large Japanese study to assess seroprevalence of *H. pylori* in CAD and asymptomatic controls no significant differences were detected between the two groups [19]. However when a subgroup of patients younger than 55 years was analysed the seroprevalence of *H. pylori* antibody was higher in cases than controls (58.7% and 43.3%, respectively) [19]. Another report about incidence of CAD in elderly individuals who were assessed for *H. pylori* infection at baseline and followed up for 10 years indicated that *H. pylori* positivity was not associated with increased incidence of CAD [20]. As described previously, PCR based studies of the coronary plaque have been done and have detected *H. pylori* DNA in them. In a controlled study of atheromatous plaques of 46 patients who underwent CABG, 22 (47.8%) showed *H. pylori* DNA while none of the controls who underwent coronary artery biopsy had PCR detectable *H. pylori* [21]. Aortic biopsies from areas free of atheromatous plaque have also been reported to be positive in a significant number of patients with CAD but none of the controls [22]. Table 1 summarises the recent studies reporting about association of *H. pylori* with CAD.

CAG-A AND CAD

As previously mentioned, role of Cag-A has also been evaluated as a predisposing factor for occurrence of coronary artery disease [23]. In a study of cardiac peptides including Brain Natriuretic Peptide in 103 patients with non-ST elevation myocardial infarction and their relation with *H. pylori* infection, it was found that individuals infected with Cag-A positive strains of *H. pylori* had higher levels of BNP in the serum [24]. BNP is a marker of heart failure and may predict a more serious course of the disease thereby suggesting that *H. pylori* infection with Cag-A positive strains may lead to an adverse outcome. Interestingly, IL-6 levels were also found to correlate with the Cag-A status. This suggests that the inflammatory response to Cag-A positive *H. pylori* may mediate atherogenesis in a subgroup of patients with CAD [25]. However other reports indicate that Cag-A positivity does not vary significantly between angiographically positive and negative group of individuals. In a report of 112 consecutive individuals who underwent coronary angiography, the Cag-A positivity did not affect the severity of CAD [26]. In a large study including 505 patients with CAD and 1025 matched controls, neither the prevalence of *H. pylori* infection was increased in the diseased subjects nor did the presence of Cag-A positive strains predict higher likelihood of CAD [27]. In a large population based report on 685 individuals, merely the presence of infection by *H. pylori* did not correlate with serum markers of inflammation. However those seropositive for Cag-A positive strains had increased values of common carotid artery intima-media thickness and the risk of atherosclerosis was enhanced by CRP positivity [28]. Another report also indicated that Cag-A positive strains appeared to raise the risk of CAD while merely the presence of *H. pylori* infection was not significantly different between cases and controls [29].

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Table 1  Recent reports on association of *Helicobacter pylori* infection with coronary artery disease

| Ref.            | Population (number of subjects) | Diagnosis of CAD | Association between *H. pylori* infection and CAD |
|-----------------|---------------------------------|-----------------|-----------------------------------------------|
| Shmauely et al [20] | CAD (173) vs Controls (123)    | Myocardial Perfusion imaging | Yes |
| Vafaeimanezh et al [21] | CAD (62) vs Controls (58)      | Angiographic     | No association with Cag-A |
| Laek et al [22]  | 5744 individuals, Age 45-84 yr, average follow-up of 2.4 yr | Newly detectable coronary artery calcium (CAC) | No correlation with CAC development |
| Mundkur et al [23] | CAD and controls (433 each) from South Asians | Angiography | None |
| Padmaravti et al [24] | Acute myocardial infarction vs Controls | ECG, enzymes | None |
| Tewari et al [25]  | 200 CAD cases and controls     | ECG, treatment records | Yes |
| Grdanoska et al [26] | Acute coronary syndrome (64), CAD (53), controls (35) | ECG, enzymes | Yes |
| Grub et al [27]   | Controls (30), CAD (52) and CAD with rheumatic diseases (67) | Patients referred for CABG | None |
| Park et al [28]   | 2029 subjects                  | CAC              | Yes |
| Al-Ghamdi et al [29] | CAD (90) and controls (15)     | ECG, angioigraphy | Yes |
| Azarkar et al [30] | Controls (78) and myocardial infarction (73) | ECG, enzymes | Yes |
| Khodaii et al [31] | Myocardial infarction (500) and controls (500) | ECG, enzymes | Cag-A positivity also correlates with CAD |

CAD: Coronary artery disease; Cag-A: Cytotoxin associated gene A; ECG: Electrocardiography; CAC: Coronary artery calcium; CABG: Coronary artery bypass grafting; *H. pylori*: *Helicobacter pylori*. 

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of homology between bacterial and eukaryotic HSP may result in molecular mimicry and collateral immune damage from immune response primarily directed against infectious agents[39]. The host reaction to the H. pylori lipopolysaccharide (LPS) may also be a risk factor for atherosclerosis[40]. Figure 1 depicts the predominant mechanisms purported to play a role in genesis of H. pylori-related CAD.

**EFFECT OF ERADICATION**

The prognostic role of H. pylori infection has also been assessed in acute CAD. In 433 patients of acute coronary syndrome (ACS) the seroprevalence of H. pylori infection was determined using IgG and IgA serology. Those infected with H. pylori had an increased risk of short term adverse outcomes during the first month of follow-up[49]. Another report which evaluated role of eight pathogens on occurrence future events in patients diagnosed to have angiographic evidence of CAD. Serological evidence of H. pylori infection predicted an increased risk of future events and mortality in these 1018 patients and increase in pathogen burden also affected long term outcome[40]. An interesting study evaluated the role of H. pylori eradication on coronary artery lumen reduction in patients who underwent percutaneous intervention for CAD. A higher loss of coronary lumen was noted in those patients who had serological evidence of H. pylori infection. Also, eradication of H. pylori attenuated this reduction in lumen of the coronary artery vis-à-vis the placebo group[40]. Another report by the same group provides similar findings but it is not clear if the report was based on different patients[40]. This small but elegant study opens debate about possible benefit of H. pylori eradication in attenuating further atherosclerotic process which is driven primarily by inflammatory mediators. In a study assessing the effect of H. pylori eradication on coronary risk factors in 48 patients, no differences were observed in pre and post-treatment fasting sugars, lipid profile and levels of tissue-plasminogen activator, fibrinogen, plasminogen activator inhibitor-1 and D-dimer levels[49]. However a larger study of 496 patients and reporting about pre and post- H. pylori eradication profile, the eradication of H. pylori seemed to increase HDL levels and reduce the levels of C reactive protein and those of fibrinogen. This suggests that attenuation of inflammatory response is likely to occur after H. pylori eradication[40]. In a report documenting the effects of H. pylori eradication on insulin resistance in 159 patients using homeostasis model assessment of insulin resistance, the insulin resistance measured six weeks post-eradication was lower than the baseline. The study also reported changes in lipid profile including an increase in HDL levels and a fall in LDL levels with H. pylori eradication[50]. Another report also indicates that the H. pylori eradication may increase HDL levels and lead to reduction of CRP levels[52]. Table 2 depicts various studies reporting about the effects of H. pylori eradication on CAD and its risk
factors.

**ATHEROGENESIS BEYOND CORONARY ARTERIES**

In contrast to CAD, data is scarce on the relation between *H. pylori* infection and stroke. A meta-analysis found that Cag-A-positive *H. pylori* increases the risk of both ischemic stroke and coronary heart disease[83].

A case-control study of 150 patients by Yang et al[56] in 2011 does not reveal any strong association between chronic *H. pylori* infection and ischemic stroke. However, another study by Pan[55] suggested lowering of inflammatory markers and decrease in cerebral infarction readmission rates in patients of stroke with positive urease test treated with (conventional therapy + anti- *H. pylori* therapy). Wu et al[57] suggested role of increased expression of CD62p on platelets and increase in clotting indexes in pathogenesis of stroke in *H. pylori* positive patients.

A meta-analysis of 13 studies including 4041 participants indicated that positive anti-*H. pylori* IgG, anti-Cag-A IgG and (13)C-urea breath test were significantly associated with increased risk of IS, respectively, and positive anti-Cag-A IgG was more effective for predication of IS risk[53].

But a formal meta-analysis of ten prospective observational studies indicated no strong association between *H. pylori* infection and stroke, neither in those with cytotoxin-associated gene-A-positive infection[50].

All in all, the evidence supporting the role of *H. pylori* in causation of CAD is equivocal and interventions aimed at *H. pylori* eradication have not shown conclusive evidence of benefit in eradicating the organism vis-à-vis cardiovascular outcomes. Perhaps multicentre randomised trials comparing eradication of *H. pylori* in large populations at risk of CAD and then follow-up to determine risk of CAD may answer this question.

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