World Journal of Cardiology

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DOI: 10.4330/wjc.v7.i1.19

World J Cardiol 2015 January 26; 7(1): 19-25
ISSN 1949-8462 (online)

REVIEW

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

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Author contributions: Sharma V and Aggarwal A contributed to this paper.
Conflict-of-interest: No conflicts.

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Telephone: +91-98-11060025
Received: October 17, 2014
Peer-review started: October 20, 2014
First decision: November 27, 2014
Revised: December 14, 2014
Accepted: December 29, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

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

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*[1]. However, it was after much perusal that the scientific community accepted the bacterium-ulcer-cancer dogma eventually culminating in the 2005 Nobel Prize[2]. 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 extra-gastric disorders like immune thrombocytopenia and iron deficiency anaemia[3,4]. 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 carcinogenesis), 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[5]. There is a growing acknowledgement of inflammatory factors including C-reactive protein in prediction of increased risk of CAD[6]. *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[7]. Therefore the infection by *H. pylori* may play a role in plaque rupture and causation of ischemic heart disease. Interestingly, cytotoxin asso-ciated gene A (Cag-A) may also play a role in the path-ogenesis 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[8]. It is believed that the chronic inflammation associated with chronic infections may result in progressive atherosclerotic disease eventually manifesting as CAD[9].

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[10]. 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[11]. 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[12]. This association was more evident in patients with early coronary atherosclerosis[12]. 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[13]. In a report comparing patients with CAD and healthy controls, sero-positivity for *H. pylori* infection was significantly higher

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
Shmuely *et al*[23]	CAD (173) *vs* Controls (123)	Myocardial Perfusion imaging	Yes No association with Cag-A
Vafaeimanesh *et al*[10]	CAD (62) *vs* Controls (58)	Angiographic	Yes
Laek *et al*[13]	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*[18]	CAD and controls (433 each) from South Asians	Angiography	None
Padmavati *et al*[24]	Acute myocardial infarction *vs* Controls	ECG, enzymes	None
Tewari *et al*[15]	200 CAD cases and controls	ECG, treatment records	Yes
Grdanoska *et al*[25]	Acute coronary syndrome (64), CAD (53), controls (35)	ECG, enzymes	Yes
Grub *et al*[26]	Controls (30), CAD (52) and CAD with rheumatic diseases (67)	Patients referred for CABG	None
Park *et al*[12]	2029 subjects	CAC	Yes
Al-Ghamdi *et al*[27]	CAD (50) and controls (15)	ECG, angiography	Yes
Azarkar *et al*[28]	Controls (78) and myocardial infarction (73)	ECG, enzymes	Yes
Khodaii *et al*[29]	Myocardial infarction (500) and controls (500)	ECG, enzymes	Yes 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 by-pass grafting; *H. pylori*: *Helicobacter pylori*.

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[8]. 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[30]. 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 atherogeneis in a subgroup of patients with CAD[30]. 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[31]. 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[32]. 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[33]. 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[34]. An

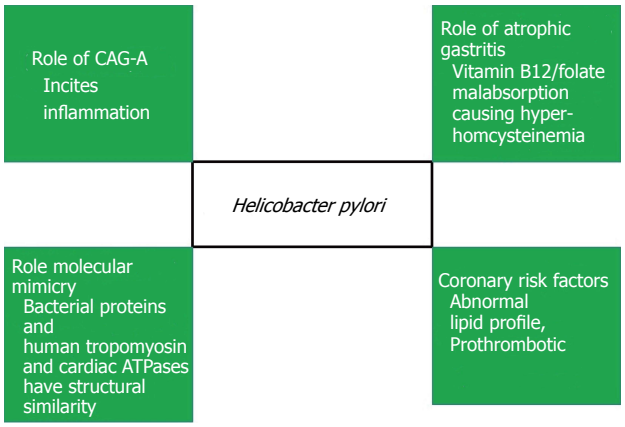

Figure 1 Postulated mechanisms of Atherogenesis in *Helicobacter pylori* infection.

interesting study reported about sero-prevalence of anti-Cag-A antibodies across a spectrum of presentations which included controls, stable and unstable angina and found that anti-Cag A titres were significantly higher in patients with unstable angina[35].

MECHANISMS BEHIND ATHEROGENESIS

One report has studied the association of atrophic gastritis with CAD. Atrophic gastritis is believed to be the end result of chronic gastric inflammation including that related to *H. pylori* infection. Decrease in serum pepsinogen I and a low Pepsinogen I / Ⅱ ratio points to the diagnosis of atrophic gastritis. In this intriguing report based on a population based study, Senmaru *et al*[36] reported that prevalence of CAD was higher in the patients having atrophic gastritis (5.8%) when compared with individuals not having atrophic gastritis (2.8%). Atrophic gastritis may result in malabsorption of Vitamin B12 and Folate and result in increased homocysteine levels. Hyper-homocysteinemia is a recognised risk factor for CAD[37]. One report has also suggested structural homology between bacterial proteins and human tropomyosin and cardiac ATPases thereby providing insight into molecular mechanism involved in the cardiac injury due to anti-*H. pylori* inflammatory response[30]. *H. pylori* has also been associated with dyslipidemia. In a Japanese study on 6289 subjects, infection with *H. pylori* was associated with low HDL and elevated LDL levels[38]. Other reports have also provided similar evidence[39]. Cag-A positive strains also exhibit elevated levels of highly sensitive CRP, oxidized LDL and apolipoprotein B all of which may participate in the pathogenesis of atherosclerosis[40]. There is also a suggestion that *H. pylori* may have a prothrombotic role which may also increase the associated risk of atherosclerotic diseases. The bacterium may promote aggregation of platelets by binding to the von-Willibrand factor[41]. Infection with *H. pylori* may stimulate an inflammatory response against heat shock protein (hsp60) which may drive a helper T cell (TH1) response and increase the risk of atherosclerosis[42]. The high degree of homology between bacterial and eukaryotic HSP may result in molecular mimicry and collateral immune damage from immune response primarily directed against infectious agents[43]. The host reaction to the *H. pylori* lipopolysaccharide (LPS) may also be a risk factor for atherosclerosis[44]. 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[45]. 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[46]. 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[47]. Another report by the same group provides similar findings but it is not clear if the report was based on different patients[48]. 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[50]. 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[51]. 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

Table 2 Effect of *Helicobacter pylori* eradication on coronary artery disease

Ref.	Population	Intervention	Results
Kowalski *et al*[47,48]	40 patient with single vessel CAD and *H. pylori* infection	All underwent PTCA and 20 each received eradication or placebo	Attenuated reduction mean coronary artery lumen at 6 mo in those undergoing eradication
Lu *et al*[49]	*H. pylori* positive individuals	Testing of coronary risk factors before and after *H. pylori* eradication	No change in sugar, lipid and fibrinolytic parameters with eradication
Pellicano *et al*[50]	*H. pylori* positive individuals	Testing of coronary risk factors before and after *H. pylori* eradication	Improvement in HDL-C, reduction in CRP and fibrinogen levels. Elevation in BMI and diastolic blood pressure
Gen *et al*[51]	*H. pylori* positive individuals	Testing for insulin resistance, lipid profile and CRP before and after eradication	Improvement in insulin resistance, lipid abnormalities and CRP levels
Kanbay *et al*[52]	*H. pylori* positive individuals	Testing for lipid profile and CRP before and after eradication	Increase in HDL and reduction in CRP with successful eradication

CAD: Coronary artery disease; CRP: C-reactive protein; HDL: High density lipoprotein; PTCA: Percutaneous transluminal coronary angioplasty; *H. pylori*: *Helicobacter pylori*.

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[53].

A case-control study of 150 patients by Yang *et al*[54] 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*[56] 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[57].

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[58].

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 deterimine risk of CAD may answer this question.

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