Helicobacter pylori Infection and Atherosclerosis: a Systematic Review

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Abstract- *Helicobacter pylori* (*H. pylori*) is a spiral-shaped gram negative bacterium that naturally colonizes the human gastric epithelium. In recent years, large evidence has come to the literature strongly proposing causal link between *H. pylori* and extra gastric disorders. Cardiovascular system is one of the extra gastric organs that can be affected by *H. pylori* infection. The first evidence suggestive of such an association comes from seroepidemiological evaluations, but histopathological and eradication studies have strongly confirmed existence of a causal association between *H. pylori* infection and cardiovascular events.

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Introduction

Helicobacter pylori (*H. pylori*) is a spiral-shaped gram negative bacterium that has been found to naturally colonize the human gastric epithelium and numerous reports support a causal relation between this infection and chronic gastritis, peptic ulceration, and gastric carcinoma (1,2).

In recent years, large evidence has come to the literature strongly proposing causal link between *H. pylori* and extra gastric disorders. There are evidences suggestive of a link between *H. pylori* and metabolic disorders including diabetes mellitus (3), neurological disorders, especially stroke events (4), psychiatric complications (5), gynecological disorders, from hyperemesis gravidarum (6) to pre-eclampsia (7) and infertility (8), ophthalmological diseases like glaucoma (9), dermatologic diseases including resistant chronic urticaria (10), alopecia areata (11) and Behçet's disease (12), ear, nose, and throat (E.N.T.) diseases from benign disorders (13) to malignancies like laryngeal carcinoma (14) and lung cancer (15), hematologic disorders from iron deficiency anemia (16) to idiopathic thrombocytopenic purpura (ITP) (17), several disorders of hepatobiliary system (18,19) and cardiovascular diseases.

Overwhelming evidence suggests that chronic *H. pylori* infection plays a role in the initiation, progression and outcome of vascular diseases (20-22). Although treatment is not always definite (23), seroepidemiological and eradication studies have showed a causal association between *H. pylori* infection and cardiovascular events (24) and mortality (25), but histopathological evaluations of atherosclerotic vascular injuries more strongly confirmed such associations (22).

On the other hand, well-known risk factors of atherosclerosis formation including homocysteinemia (26) and hyperlipidemia (27) have also been shown to have associations with *H. pylori* infection. In this article, we aimed to review the existing literature on associations between *H. pylori* infection and cardiovascular disorders.

Seroepidemiological evidence for the role of *H. pylori* infection in developing cardiovascular disease

Several studies have investigated that whether serological evidence for *H. pylori* infection has any predictive value for the development of cardiovascular disorders. The first data on any association between these two conditions comes from seroepidemilogical evaluations. Longo-Mbenza *et al*., (24) prospectively followed 205 individuals with cardiovascular risk factors and evaluated their *H. pylori* IgG. After 10 years of follow-up, *H. pylori* IgG positive patients were independently more likely to develop acute coronary syndromes including incident angina pectoris

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(multivariate OR = 3.5, 95% CI: 1.6-16; $P < 0.0001$) and myocardial infarction (multivariate OR 7.2, 95% CI 3.1-18; $P < 0.0001$) than IgG negative subjects. Park *et al*., (28) in a population-based study on 2029 individuals from Korea showed that the presence of *H. pylori* seropositivity was independently associated with coronary artery calcification score (P=0.049; OR 1.23; 95% CI 1.001 to 1.51).

Al-Ghamdi *et al*., (29) also showed that *H. pylori* specific IgG antibodies were significantly higher among patients with coronary artery disorders. There is also other serologic evidence for an association between *H. pylori* infection and atherosclerosis. Arabski *et al*., (30) suggested that Anti-*H. pylori*-ureB antibodies may be involved in the initiation of atherosclerosis. Torisu *et al*., (31) showed that pulse wave velocity (PWV) or cardio-ankle vascular index were significantly higher in *H. pylori* positive young participants.

In a case-control study of 384 individuals from India, subjects with cardiovascular diseases were significantly more likely to be positive for either *H. pylori* IgA or IgG (32). In another case-control study from Turkey, Tamer *et al*., (33) reported that rate of *H. pylori* IgG seropositivity was significantly higher in patients with a history of coronary artery disease than that in controls. Sawayama *et al*., (34) in a case-control study from Japan showed that *H. pylori* seropositivity was significantly higher in patients with peripheral vascular diseases. Nikolopoulou *et al*., (35) in a similar study from Greece reported similar findings to the previous study. However, another study with similar methodology from Turkey revealed controversial data, suggestive of no association between *H. pylori* IgG seropositivity and atherosclerosis (36). Similar finding has been reported by Folsom *et al.,* (37) in a 3.3 year cohort sample of 498 subjects, and by Regnström *et al*., (38) and Ossewaarde *et al*., (39) in two case-control studies.

Yoshikawa *et al*., (40) suggested that glucose impairment contributes in the cardiovascular injury to *H. pylori*-positive subjects either in young (r=0.203, P <0.0001) or older subjects (50-69 years, r=0.099, P= 0.0009), while Goyal *et al*., (41) in a case-control study showed that in cardiovascular patients without conventional risk factors for atherosclerosis, *H. pylori* IgG seropositivity rate was comparable to healthy blood donors. Both of the mentioned articles suggest that *H. pylori* seropositivity is a predictor of cardiovascular disease only in the presence of other conventional risk factors. On the other hand, Altannavch *et al*., (42) showed that *H. pylori* seropositivity in either diabetic or nondiabetic patients were not a predictor of cardiovascular disease. In dialysis population, Lentine *et al*., (43) found no significant association between *H. pylori* seropositivity and cardiovascular events.

To investigate the association between *H. pylori* infection and early stages of atherosclerosis, Saijo *et al*., (44) evaluated arterial stiffness defined by brachial-ankle pulse wave velocity (PWV) and correlated it to *H. pylori* seropositivity. Authors found that in Younger male subjects, *H. pylori* seropositivity (odds ratio (OR) 1.27 (95% confidence interval, 1.05-1.52) was significantly related to a high value of PWV, while this association was not found for older males or females. Consistent with this study, Ongey *et al*., (45) reporting from a population-based German study indicated that the sero-prevalence of *H. pylori* and their combination was not associated with the prevalence of cardiovascular diseases. It has also been suggested that *H. pylori* seropositivity is associated with enhanced platelet activation in patients with intermittent claudication (46). *H. pylori* stool antigen has also been related to the intensity of atherosclerotic disease in cardiovascular patients with more severe vasculopathy in the infected patients (Adiloglu, reff188). In a study on young women, Bloemenkamp, *et al*., (47) showed a significant correlation between *H. pylori* infection and peripheral arterial disease 1.6 (95% CI 1.1-2.2).

IgG antibodies against *H. pylori* has also been significantly associated with advanced atherosclerosis (≥2 vascular regions) measured by coronary angiography and/or carotid artery duplex sonography, in a study by Espinola-Klein *et al*., (48). Kahan *et al*., (49) in a case-control study of 200 subjects reported a significant association between *H. pylori* seropositivity and having history of acute myocardial infarction in univariate analysis. Multivariate analysis showed that this relation is independent of conventional risk factors (odds ratio 1.35 with 95% confidence interval 1.01-1.83, P=0.046). On the other hand, Jia *et al*., (50) provided controversial evidence suggesting no association between *H. pylori* seropositivity and cardiovascular diseases.

Endothelial dysfunction as early stage of atherogenesis and *H. pylori*

A study in children by Coskun *et al*., (51) showed that *H. pylori* IgG seropositivity has no relation to endothelial dysfunction. Khairy *et al*., (52) in a study on young men showed that anti-*H. pylori* seropositivity does not predict endothelial dysfunction. Similar findings have been reported on adult individuals as well

(53). Prasad *et al*., (54) although found a significant relation between *H. pylori* infection and endothelial dysfunction, in multivariate analysis, *H. pylori* infection has lost its significance. However, a study by Liuba *et al*., (55) based on a mouse model survey suggested that Co-infection with *Chlamydia pneumoniae* and *Helicobacter pylori* results in vascular endothelial dysfunction.

Antibodies to heat shock proteins (HSP)-60 and/or -65 are considered risk factors for atherosclerosis and they have been proposed as diagnostic markers for atherosclerosis and cardiovascular risk (56). Moreover, these antibodies have been reported to mediate endothelial toxicity (57).

Besides, *H. pylori* is supposed to induce its atherogenic effects through HSPs (58), and this risk enhancement is independent of other inflammatory factors (59). Serum concentrations of anti-(hsp) 60 auto-antibodies are reported to be significantly higher in patients with more severe cardiovascular disease, and less in those who undergone successful coronary artery bypass grafting (60). Although there are studies suggesting that anti-(hsp) 60 antibodies are higher in atherosclerotic patients, even when both case and control groups are anti-*H. pylori* antibody negative (61).

Effects of *H. pylori* Eradication and cardiovascular system

Knowing the association between *H. pylori* infection and atherosclerosis formation, it would be logical to think that treatment of *H. pylori* infection might be associated with an improvement in the cardiovascular risk. In fact, several studies have suggested such a relation. Wu *et al*., (62) in a rabbit model showed that the treatment of *H. pylori* infection decreases factors associated with atherosclerosis. Literature also suggests that eradication treatment of *H. pylori* favorably affects oxidative stress (63,64), myeloperoxidase activity (63) and fat mass (64), which are important biomarkers in pathogenesis of atherosclerosis.

Aydemir *et al*., (65) detected significant decrease in serum ADMA levels, another biomarker of atherosclerosis for patients in whom *H. pylori* has been eradicated. Kanbay *et al*., (66) treated 78 stool-*H. pylori* antigen positive patients and observed CRP levels decreased and HDL levels increased in the group that *H. pylori* had been eradicated, but no significant difference has been found in the patients in whom *H. pylori* had not *been eradicated after treatment.*

Eradication of *H. pylori* infection has also been suggested to improve blood pressure values in hypertensive patients (67). It has also been proposed that *H. pylori* eradication attenuate the reduction in coronary artery lumen after percutaneous transluminal coronary angioplasty while eradication therapy had no effect on serum lipid profile and homocysteinemia (68). Successful eradication of *H. pylori* has been reportedly associated with a significant improvement in endothelial dysfunction, and early stages of atherosclerosis formation (58, 69). Despite all the above-mentioned favorable effects reported to be associated with the eradication of *H. pylori*, there are also controversial reports suggesting no beneficial effect of *H. pylori* eradication on acute phase reactants (70).

Epidemiology of *H. pylori* DNA detection within atherosclerotic plaques

Although seroepidemiologic evidence of associations between *H. pylori* infection and atherosclerosis is overwhelming, they do not provide direct data for the existence of such a relationship. However, in more recent studies, with the detection of *H. pylori* within the coronary and carotid arterial walls using histopathological evaluations and polymerase chain reaction (PCR), very strong evidence came out corroborating initial data provided by seroepidemiological studies suggesting associations between *H. pylori* infection and atherosclerosis. In a previous study of ours, we found that a 29.5% of coronary atherosclerotic plaques achieved from patients undergoing coronary artery bypass grafting are colonized by *H. pylori* infection, detected through PCR tests (22). Jha *et al*., (71) also reported comparable rates of infection with 33.5% and 27.2% coronary & carotid arterial wall infection rates, respectively, confirmed by PCR test in their series.

Similar methodology in 18 Italian patients represented no individual positive PCR for *H. pylori* from carotid endoartherectomy specimens (72). Hagiwara *et al*., (73) in his study on 50 carotid endartherectomy patients also found no *H. pylori* positive specimen. Comparable finding has been reported by Latsios *et al*., (74) in a study on 83 carotid atherosclerotic plaque specimens in which only 2 (2.4%) were positive for *H. pylori*. No plaque specimen in a study by Dore *et al*., (75) was PCR positive for *H. pylori*. Similar finding is reported by Kaklikkaya *et al.* in a Turkish study on aorta-iliac atherectomy specimens (76).

On the other hand, Kilic *et al*., (77) in a study from Turkey found *H. pylori* in 48.2% atherosclerotic and 19.6% non-atherosclerotic vascular wall specimens with a significantly higher *H. pylori* infection rate in

atherosclerotic specimens of coronary artery and abdominal aorta, but no significant difference in carotid artery. Putting together, we conclude that *H. pylori* institution within arterial walls of the coronary artery and aorta can serve as a predictor of atherosclerosis formation, but this association cannot be observed for carotid artery; although there are controversial reports as well. Arias *et al*., in a study from Argentina reported 83% *H. pylori* infection rate in carotid atherosclerotic plaques, but we should consider that the study was not comparative.

Moreover, Kaplan *et al*., (78) reported that 17.3% of carotid artery plaques were positive for *H. pylori* PCR while no positive specimen was found from healthy aorta specimens, but we should note that the control specimens were not achieved from the same artery (carotid). Moreover, one should not think that in all studies investigating *H. pylori* infection in coronary artery plaques the microorganism has been found. Sulewska *et al*., (79) in a study from Poland reported no positive case of *H. pylori* infection within coronary arterial walls of patients undergone CABG.

But Russu *et al*., (80) studying atherosclerotic plaques from different arteries reported that 22.2% of the specimens were positive for *H. pylori* PCR, but similar study in Turkey revealed 37% *H. pylori* positive rate (81). However, in aortic aneurysm plaque specimens, *H. pylori* was found in none of the 51 patients evaluated (82). An important issue in concluding all these controversial data is that PCR test is not performed perfectly all over the world, and several studies have reported low sensitivity and specificity of this test (83).

Role of CagA, VacA

The virulence of *H. pylori* infection can be a crucial determinant of its atherogenic ability. Vacuolating cytotoxin gene A is the most virulent *H. pylori* strain that has been associated with an increased local inflammatory response and also it can cause severe damage to the gastric epithelium (84). One of the proteins associated with VacA is the cytotoxin associated gene A (CagA) and seropositivity to CagA has been broadly used to detect infections with virulent *H. pylori* strains (85). In this section, we review studies investigating effects of *H. pylori* strains on three major arteries, separately:

Coronary artery

The severity of coronary atherosclerosis has also been associated with CagA positivity. Huang *et al*., (86) in a cross-sectional study of 159 coronary artery disease patients reported that the severity of the coronary atherosclerosis was significantly increased in CagA+ *H. pylori* group. Niccoli *et al*., (87) studied 40 coronary artery disease patients and compared their data with 20 normal controls. The anti-CagA antibody titer was not only significantly higher in patients with CAD compared to normal controls, but also a significant correlation was found between anti-CagA antibody titer and extent score (R=0.35).

Multivariate analysis showed an independent correlation between anti-CagA antibody titer and the extent of coronary atherosclerosis (OR 0.051). Acute coronary events have also been associated with seropositivity to CagA; Franceschi *et al*., (88) in a meta-analysis of 4241 cases reported that seropositivity to CagA was significantly associated with the occurrence of acute coronary events (OR 1.34; 95% CI 1.15-1.58). The same findings are reported by another meta-analysis with OR of 2.11 (95% CI 1.70, 2.62) (89). While Chimienti *et al*., (90) failed to detect any significant effect of Cag A positive *H. pylori* infection on the lipid profile of 211 healthy volunteer blood donors. Consistent with this study, Chmiela *et al*., (91) reported no difference in the prevalence of anti-CagA IgG in the coronary heart disease patients compared to controls. In a large cohort study, Kowalski reported that CagA IgG significantly was found more frequently in CAD group than in controls (85% *vs.* 36%; OR 2.5, 95% CI 1.1-5.6) (68).

Murray *et al*., (92) conducted a case-control study in 259 patients with myocardial infarction and the same population size of healthy controls and tested them for CagA positivity. Although in univariate analysis, CagA seropositivity was more frequently observed in cases than in control groups (OR 1.41; 95%CI 1.00, 1.99), multivariate analysis after adjustments for conventional risk factors and demographics eliminated the significance level (OR 1.16; 95%CI 0.79, 1.70). Infection with cagA positive *H. pylori* strains has surprisingly been inversely associated with cardiovascular mortality by Schöttker *et al*., in a cohort study (HR 0.62; CI 0.41-0.94) (21), and in a cross-sectional population based study of 1179 type 2 diabetic patients by Schimke *et al*., (93).

Carotid artery

In a study on 64 patients and 65 controls, CagA antibody titers were significantly higher in symptomatic patients with advanced carotid stenosis (OR 8.8; 95%CI 5.8-32.7) compared to either asymptomatic patients (4.7; 2.1-8.8) or the control

group (5.0; 2.2-7.9) (93).

Immunoreactivity between monoclonal CagA antibodies and antigens nested within the atherosclerotic specimens was significantly higher among symptomatic patients compared to asymptomatic patients (97.0 *vs.* 74.2%) (94). In a 3 years prospective cohort of 68 CagA positive stroke patients and 102 CagA negative patients, Kaplan-Meier survival analysis, CagA-positive patients showed a significantly higher risk for stroke recurrence than CagA-negative ones (45.6% *vs*. 17.6%; $P < .001$). Difference in the rate of recurrent stroke between the two groups persisted after Cox regression analysis taking into account possible confounding factors (hazard ratio=3.5; 95% CI 1.9-6.4; $P<0.001$) (95). Zhang *et al*., (89) in a meta-analysis of 26 studies reported that patients with anti-CagA positive strains of *H. pylori* infection had a trend of increasing the risk of ischemic strokes (OR 2.68, 95% CI 2.20, 3.27).

A prospective population-based study of 684 subjects revealed that either incident measures or changes (through 5 years) of carotid artery intima-media thickness were significantly higher in subjects seropositive to CagA than their counterparts infected with CagA-negative *H. pylori* strains. As well, there was a direct relation between anti-CagA antibody levels and both intima-media thickness and atherosclerosis risk, which was consistent to CRP levels. Pietroiusti *et al*., evaluated CagA seropositivity in 138 patients with large-vessel stroke (Group A), in 61 patients with cardiometabolic stroke (Group B), and in 151 healthy control subjects. They reported that after multivariate analysis, the prevalence of CagA-positive strains was higher in group A than in group B (OR 3.04, 95% CI 1.43 to 6.49) and higher in group A than in the control group (OR 4.3, 95% CI 2.12 to 8.64) (97).

In a population-based cross-sectional study of 983 normal individuals in the UK, Markus *et al*., (98) reported that amongst *H. pylori* seropositive individuals, those infected with the CagA strain were more likely to have enhanced carotid intima-media thickness after controlling for age and sex (OR 0.0256, 95%*CI*: 0.001-0.050), although further adjustments eliminated the significance level. Nevertheless, a recent meta-analysis suggested that the positive anti-Cag A IgG is predictive for ischemic stroke risk (OR 2.33 (95% *CI*: 1.76-3.09) (4).

Aortic artery

A prospective cohort study of 188 subjects by Shmuely *et al.,* (99) revealed that CagA-positive *H. pylori* seropositivity remained an independent factor significantly associated with risk of developing aortic atheroma (OR 4.4; 95% CI, 1.4-14.7; P=0.01). Nyberg *et al*., (100) in a case-control study of 119 patients with abdominal aortic aneurysm and 36 controls failed to show any connection between *H. pylori* CagA seropositivity and abdominal aortic aneurysm rupture. *H. Pylori* VacA has a more important role than CagA in the development of two aneurysms especially in ruptured ascending aortic aneurysm (101).

In this comprehensive review of the literature, we reviewed studies with controversial findings, so having a conclusion that satisfies all the reviewed manuscripts seems hard. However, based on the findings of the majority of the articles either on seropositivity to *H. pylori* infection or histopathological evidence to it, literature suggests that *H. pylori* infection can promote the process of atherosclerosis both in the general population, and in patients undergoing coronary intervention, and eradication therapy of the pathogen can attenuate the promotion of atherosclerosis in the latter patient population. Moreover, CagA seropositivity has been associated with atherosclerosis and vascular events both in the coronary and/or carotid arteries, although there are controversial data, as well.

On the other hand, surprisingly, CagA positivity was protective against cardiovascular mortality. In aortic lesions, CagA positivity was associated with higher atherosclerosis rate, but no association with aortic rupture has been reported. VacA has been reported to have a stronger association with aortic rupture than cagA strains. Moreover, *H. pylori* positivity has been associated with disturbance in lipid profile and elevated CRP - but not with homocysteine levels - as predictors of atherosclerosis formation and progression, nonetheless these findings are in most cases controversial.

Table 1 summarizes data of some of the major studies on this latter issue. Finally, we suggest prevention and treatment of *H. pylori* infection, especially CagA positive strain ones, in high-risk individuals to decrease the risk of cardiovascular diseases. Treatment strategies are most important in patients who undergo surgical interventions to repair the atherosclerotic artery.

Table 1. *H. pylori* and its effects on some conventional risk factors of atherosclerosis

Risk factors		Findings [study reference]
HDL	-	Serum HDL was significantly lower in the HP-seropositive group (24).
	-	No association with *H. pylori* infection (102).
	-	HDL was significantly lower in seropositive patients [50]
	-	HDL was significantly lower in the atrophic gastric patients [31]
	-	Significant increase after *H. pylori* eradication [66]
	-	Lower mean value for *H.* pylori-seropositive group, after adjusting for age [104]
	-	Not affected by *H. pylori* eradication [68]
	-	No significant difference regarding patients' *H. pylori* IgG-positivity [51]
	-	Significantly decreased levels in *H.* pylori seropositive patients [103].
	-	No significant difference in males with positive IgG and IgA antibody titers for *H. pylori* [105]
	-	In multivariate analysis, *H. pylori* infection was associated with high LDL cholesterol level (>140 mg/dL) [OR 3.11; 95% CI 1.36-7.02] [102].
LDL	-	Higher in *H. pylori* positive patients [106]
	-	No significant change after *H. pylori* eradication [66]
	-	Higher mean value for *H. pylori*-seropositive group, after adjusting for age [104]
	-	Increased levels in *H*-pylori positive subjects [90]
	-	Not affected by *H*-pylori eradication [68]
	-	Significantly elevated by CagA+*H. pylori* infection [86]
	-	No significant difference regarding patients' *H. pylori* IgG-positivity [51]
	-	Higher in *H. pylori* positive patients [106]
	-	No significant change after *H. pylori* eradication [66]
	-	Higher mean value for *H. pylori*-seropositive group, after adjusting for age [104]
Total cholesterol	-	Increased levels in *H. pylori* positive [90]
	-	Not affected by *H. pylori* eradication [68]
	-	Significantly elevated by CagA+ *H. pylori* infection [86]
	-	No significant difference regarding patients' *H. pylori* IgG-positivity [51]
	-	Significantly increased levels in *H. pylori* seropositive patients [103].
	-	Significant increase in males with positive IgG and IgA antibody titers for *H. pylori* [105]
	-	No association with *H. pylori* infection [102].
	-	*H. pylori* specific IgG was positively correlated with triglyceride level [29]
	-	Serum TG levels of *H. pylori* positive subjects were significantly higher than negatives [107]
Triglyceride	-	Higher TG in *H. pylori* positive patients [103]
	-	Higher mean value for *H. pylori*-seropositive group, after adjusting for age [104]
	-	Not affected by *H. pylori* eradication [68]
	-	No significant difference regarding patients' *H. pylori* IgG-positivity [51]
	-	Significantly increased levels in *H. pylori* seropositive patients [103].
	-	Significant increase in males with positive IgG and IgA antibody titers for *H. pylori* [105]
Homocysteine	-	Not affected by *H. pylori* eradication [68]
	-	No significant difference regarding patients' *H. pylori* IgG-positivity [51]
	-	No significant association with *H. pylori* positivity [108]
CRP	-	They also found that CagA positive patients had significantly higher levels of CRP [97]
	-	Significant decrease after *H. pylori* eradication [66]
	-	Significantly elevated by CagA+ *H. pylori* infection [86]
	-	No significant difference regarding patients' *H. pylori* IgG-positivity [51]
	-	No significant correlation was observed between CRP levels and HP-LgG level titers [36].
	-	The hsCRP levels did not vary with *H. pylori* IgG status [43].
Apolipoprotein B	-	Significant increase in CagA+ *H. pylori* group [86].
	-	Higher values after multivariate analysis for *H. pylori* seropositive group [104]
	-	Higher but not statistically significant in *H. pylori* antibody positive cases [109]

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