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REVIEW

Role of *Helicobacter pylori* infection in pathogenesis of atherosclerosis

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Abstract

Though a century old hypothesis, infection as a cause for atherosclerosis is still a debatable issue. Epidemiological and clinical studies had shown a possible association but inhomogeneity in the study population and study methods along with potential confounders have yielded conflicting results. Infection triggers a chronic inflammatory state which along with other mechanisms such as dyslipidemia, hyper-homocysteinemia, hypercoagulability, impaired glucose metabolism and endothelial dysfunction, contribute in pathogenesis of atherosclerosis. Studies have shown a positive relations between Cytotoxic associated gene-A positive strains of *Helicobacter pylori* and vascular diseases such as coronary artery disease and stroke. Infection mediated genetic modulation is a new emerging theory in this regard. Further large scale studies on infection and atherosclerosis focusing on multiple pathogenetic mechanisms may help in refining our knowledge in this aspect.

Key words: Atherosclerosis; Coronary artery disease; *Helicobacter pylori* ; Infection; Stroke

Core tip: Though a century old hypothesis, infection as a cause of atherosclerosis is still a debatable issue. Clinical and epidemiological studies had shown a possible association, however in-homogeneity in the study population and methodology has yielded conflicting results. We performed a literature search on MEDLINE electronic database using keywords such as *Helicobacter pylori* (*H. pylori*), infection, atherosclerosis, coronary artery disease, myocardial infarction, stroke, cerebro-vascular disease and peripheral arterial disease using MeSH terms, to review this subject. The association between *H. pylori* and atherosclerosis is not strong and a causal role is not yet established. Large scale studies on infection and atherosclerosis focusing on multiple pathogenetic mechanisms may help in refining our knowledge in this aspect.

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INTRODUCTION

Though a century old hypothesis, infection is still debated as a cause of atherosclerosis[1]. Infection triggers a chronic inflammatory state which along with other mechanisms such as dyslipidemia, hyperhomocysteinaemia, hypercoagulability, impaired glucose metabolism and endothelial dysfunction contribute in pathogenesis of atherosclerosis. Studies have shown a positive relations between Cytotoxic associated gene-A (Cag-A) positive *Helicobacter pylori* (*H. pylori*) strains with vascular diseases such as coronary artery disease (CAD) and stroke. Infection mediated genetic modulation is a new emerging theory in this regard. Minick and Fabricant's work on infection and atherosclerosis in animal model had made the ground for revolutionary research in this field[2,3]. Chronic infection triggers T1 Helper cell (Th1) mediated inflammatory reaction, which plays a crucial role in atherosclerosis. Markers of infection and inflammation were also studied as the risk factors for atherosclerosis[4-6]. An association between infection and atherosclerosis was established following detection of infectious agents from arterial vessels, positive immunehistochemistry studies, detection of microbial DNA sequences in atherosclerotic plaques by PCR method, positive serological response with higher titres in infected patients, and a positive correlation of infection with atherosclerotic burden and dyslipidaemia[7-23]. The microbial agents that have been implicated in the etiopathogenesis of atherosclerosis are presented in Table 1, Figure 1.

This review has been divided into two parts. Part Ⅰ elucidates different mechanisms of *H. pylori* related atherosclerosis and relevant studies. Part Ⅱ reviews the literature about *H. pylori* association with atherosclerotic diseases such as CAD, stroke and peripheral arterial disease (PAD).

MECHANISMS OF *H. PYLORI* RELATED ATHEROSCLEROSIS

Development of CAD in patients without conventional risk factors suggests a possible role of an additional unexplored mechanism. The evolution of atherosclerosis in the background of chronic inflammatory milieu involves multiple pathways (Table 2, Figure 1). Some of these pathways will be discussed in following section.

H. pylori and endothelial dysfunction

Infection related chronic vascular inflammation can result in endothelial dysfunction. Tousoulis *et al*[24] first proposed an inflammatory mechanism for endothelial dysfunction. C-reactive protein (CRP) and inflammatory adhesion molecule such as intracellular adhesion molecule-1 (ICAM-1) are elevated in patients with *H. pylori* infection, suggesting a possible link between infection and endothelial dysfunction[25].

Table 1 Microbial agents associated with atherosclerosis

Bacteria	Viruses
Chlamydia pneumonia	H simplex virus type 1 and 2
Helicobacter pylori	Cytomegalovirus
Helicobacter cinaedi	Epstein- Barr virus
Hemophilus influenza	
Mycoplasma pneumonia	

Chronic infection triggers release of inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α), which affects microvascular vasomotor functions, resulting into vasoconstriction and endothelial dysfunction. Coskun *et al*[26] studied a possible relation between *H. pylori* infection in children and endothelial dysfunction as a precursor for future atherosclerosis. There was no significant association between *H. pylori* seropositivity and CRP levels with flow mediated vasodilation. Another evidence is about increase prevalence of slow flow in the major epicardial coronary arteries in patients with *H. pylori* infection[27]. The possible mechanism of slow flow was endothelial dysfunction secondary to raised homocysteine levels. *H. pylori* infection causes malabsorption of vitamin B12 and folic acid and thus increases serum homocysteine levels. Evrengul *et al*[27] reported a mean TIMI frame count of coronary flow as 46.3 ± 8.7 and 24.3 ± 2.9 in patients with and without *H. pylori* infection, respectively. An association between *H. pylori* infection and functional vascular disorders such as cardiac syndrome-X, migraine and primary Reynaud phenomenon provides evidence about its role in endothelial dysfunction and atherosclerosis[28-32].

Chronic inflammation

Presence of chronic, persistent inflammation provides a vital clue for infectious theory of CAD. Chronic *H. pylori* infection induces a pro-inflammatory state, resulting into an increase in cytokines levels such as TNF-α, Interleukins (IL-1, IL-6, IL-8), gamma interferon, coagulant factors - fibrinogen, thrombin and soluble adhesion molecules such as intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1)[33-35]. Eradication of *H. pylori* infection by use of antibiotics leads to reduction in cytokines levels[34,36]. These evidences suggest that *H. pylori* induced inflammatory cascade plays an active role in atherosclerosis. Activated T lymphocytes and macrophages following cytokines release induce proliferation of smooth muscle cells and extracellular matrix, which plays a crucial role in pathogenesis of atherosclerosis. It also stimulates metalloproteinases production, which causes rupture of atheroma cap and leads to acute coronary syndromes. However, a large population based study failed to support the association between *H. pylori* and increased inflammatory cytokines[37].

Recent research has unveiled novel molecular

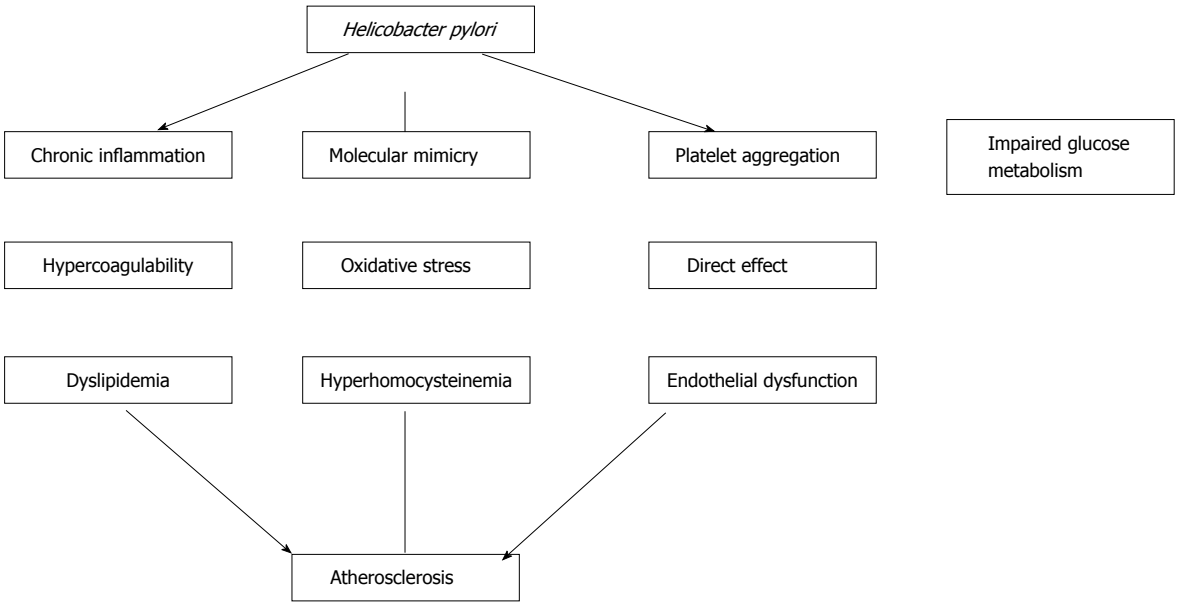

Figure 1 Theories of infection related atherosclerosis.

Table 2 Mechanisms of *Helicobacter pylori* related atherosclerosis

Induction of inflammatory response secondary to chronic infectious state
Endothelial damage
Chronic low grade activation of coagulation cascade
Dysregulation of lipid metabolism resulting in increased total cholesterol and triglyceride levels and reduced high density lipoprotein levels
Hyperhomocysteinaemia

While the proponents support the possible association[52,70,104], the opponents refute this hypothesis[46,71,105].

mechanisms of *H. pylori* mediated inflammation[38-41]. *H. pylori* infection exerts an immune-inflammatory reaction by activating cyclooxygenase enzyme-2 (COX-2), which causes increase production of prostaglandin (PGE_2) and nitric oxide (NO). *H. pylori* cell wall lipopolysaccharide (LPS) triggers toll-like receptor-4, which activates various secondary mediators such as mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase, c-Jun N-terminal kinase (JNK) and p38 kinase resulting in enhanced stimulation of *NOS* and *COX-2* gene expression[38,39]. LPS-induced activation of MAPK cascade is also associated with epidermal growth factor receptor (EGFR) transactivation which is a key protein regulating cellular proliferation, differentiation, migration and modulation of apoptosis[41]. Gherlin, a peptide hormone activates NO synthase, thereby inhibiting *H. pylori* LPS induced activation of COX-2 and other inflammatory pathways[40].

H. pylori and hyper-homocysteinaemia

H. pylori causes atrophic gastritis, which is associated with malabsorption of vitamin B12 and folic acid. Deficiency of these vitamins causes hyper-homocysteinaemia due to interruption of re-methylation pathway[42-45]. Hence, it may have a role in the pathogenesis of premature atherosclerosis[45]. In a study by Kutluana *et al*[45], carotid intima media thickness was found to be higher in patients with *H. pylori* related atrophic gastritis. In this study, *H. pylori* positive patients had significantly higher homocysteine levels compared to controls (14.17 ± 9.24 μmol/L *vs* 9.81 ± 3.42 μmol/L, $P = 0.01$). Senmaru *et al*[46] reported a higher prevalence of CAD in atrophic gastritis (5.8% *vs* 2.8%). Torisu *et al*[47] had shown an association between increased pulse wave velocity, a preclinical marker of atherosclerosis with atrophic gastritis. Apart from hyper-homocysteinaemia, other mechanisms are reduced ghrelin levels and induction of chronic pro-inflammatory cascade resulting into endothelial damage[46,47]. However, Bloemenkamp *et al*[48] did not support the hypothesis about *H. pylori* infection induced hyper-homocysteinemia and atherosclerosis.

H. pylori and dyslipidemia

H. pylori infection is associated with lower HDL cholesterol (HDL-C) and higher total cholesterol (TC), LDL cholesterol (LDL-C) and triglyceride levels. Higher apolipoprotein-B and lower apolipoprotein-A (apo-A) levels were also reported[11]. Murray *et al*[49] demonstrated that women with *H. pylori* infection had lower HDL-C ($P = 0.006$). Another study had also shown significantly lower HDL-C levels in

infected patients[11]. Niemelä *et al*[50] and Laurila *et al*[22] reported an increase triglyceride levels in *H. pylori* positive patients. These alterations in lipid homeostasis proved to be significant even after adjusting co-variables such as socioeconomic class, body weight, age and diabetic status[22,51]. de Luis *et al*[52] showed that eradication of *H. pylori* decreases apo-A and increases HDL-C. Other studies had also shown reduction in TC, LDL-C levels and increase in HDL-C, apo-AI and apo-AII levels following *H. pylori* eradication[53-55]. However, this association was not supported by few other authors[56-59].

H. pylori, impaired glucose metabolism and metabolic syndrome

Gillum *et al*[60] reported a significant association of *H. pylori* seropositivity with CAD in diabetic males. de Luis *et al*[51] showed that CAD and cerebrovascular diseases were significantly more seen in *H. pylori* infected diabetic patients. Yoshikawa *et al*[61] suggested that *H. pylori* seropositivity increases brachial-ankle pulse wave velocity, a marker of atherosclerosis, in patients with impaired glucose metabolism. Aydemir *et al*[62] reported that *H. pylori* positive subjects had higher homeostatic model assessment-insulin resistance (HOMA-IR) levels (2.56 ± 1.54 *vs* 1.73 ± 1.1, $P < 0.05$), a surrogate of insulin resistance, as compared to *H. pylori* negative controls. Aslan *et al*[63] had shown that paraoxanase, a marker of oxidative stress is well correlated with HOMA-IR levels and is significantly elevated in *H. pylori* positive patients. Regarding role of *H. pylori* eradication therapy in improvement of glucose tolerance, Gen *et al*[64] reported that HOMA-IR level significantly reduced after successful therapy, whereas Park *et al*[65] did not show any significant reduction. Polyzos *et al*[66] in his systematic review concluded that available evidences indicate a potential association between *H. pylori* infection and insulin resistance. Gunji *et al*[67] reported that *H. pylori* infection was significantly and independently associated with metabolic syndrome. A recent study by Ando *et al*[68] revealed that eradication of *H. pylori* increases circulating adiponectin levels and might be helpful in prevention of metabolic syndrome. Naja *et al*[69] suggested no association between *H. pylori* infection and metabolic syndrome or impaired glucose tolerance.

H. pylori, hypertension and arterial stiffness

Migneco *et al*[70] demonstrated a significant reduction in blood pressure after eradication of *H. pylori* in hypertensive subjects. The possible association of *H. pylori* with arterial stiffness was initially reported by Adachi and Yoshikawa. Adachi *et al*[71] reported that carotid pulse wave velocity was higher in seropositive subjects. Yoshikawa *et al*[61] similarly reported a higher brachial-ankle pulse wave velocity in seropositive patients with impaired glucose metabolism. The possible association of *H. pylori* and arterial stiffness tends to be more in younger subjects, whereas in the elderly arterial stiffness is more often due to aging[72]. Honda *et al*[73] demonstrated that *H. pylori* infection did not affect the age related progression of arteriosclerosis over a 4 years follow-up period.

EVIDENCE OF ASSOCIATION BETWEEN *H. PYLORI* AND ATHEROSCLEROSIS

H. pylori and CAD

Demonstration of an association between *H. pylori* and CAD is always challenging. Both conditions are more prevalent in the population, increases with age and are related to socioeconomic status. The following section reviews the evidence of *H. pylori* association with CAD.

Numerous studies have shown that CAD patients have a higher prevalence of *H. pylori* infection[74-77]. Vijayvergiya *et al*[77] demonstrated that CAD patients had higher IgG seropositivity as compared to controls (42% *vs* 23%, $P = 0.06$). Franceschi *et al*[78] found that *H. pylori* Cag-A was significantly associated with acute coronary events (OR = 1.34; 95%CI: 1.15-1.58, $P = 0.0003$). Niemelä *et al*[50] showed that the association between CAD and *H. pylori* infection was not strong. A meta-analysis revealed that there is a little association between *H. pylori* infection and stroke, but the strength of association was greater for Cag-A positive strains[79]. *H. pylori* was shown to be associated with premature CAD even in patients without conventional cardiovascular risk factors[80,81]. A number of studies had shown a negative association between *H. pylori* and CAD which include serological[82,83] and histological studies[84-86]. A negative association is even reported in long term follow-up studies[87]. The Australian Busselton health study comprising of 1612 healthy subjects demonstrated negative association between infection and CAD or stroke[88]. Danesh *et al*[89] in his meta-analysis of five prospective studies reported no significant association of *H. pylori* infection with CAD (RR = 1.13). Association of *H. pylori* infection and outcome of CAD treatment had also been studied. Schiele *et al*[90] found that *H. pylori* infection was not a risk factor for restenosis after percutaneous coronary angioplasty. Limnell *et al*[91] had shown an inverse relationship between *H. pylori* infection and coronary bypass graft occlusion. Results from Caerphilly heart disease study suggested that Cag-A seropositivity had no relations with CAD or CAD related mortality[92].

H. pylori has been associated with cardiac syndrome X, *i.e.*, angina pectoris with normal epicardial coronaries[28-30]. The proposed mechanism is chronic endothelial dysfunction. Eskandrian *et al*[28] reported a higher prevalence of *H. pylori* positivity in syndrome X patients compared to controls (95% *vs* 47.5%). Patients with syndrome X were found to be more commonly associated with *H. pylori* Cag-A positivity and elevated IL-1 and TNF-α[93]. Lanza *et al*[94] has

also described association of inflammation, infectious burden and vascular dysfunction. Assadi *et al*[30] reported 15% of patients with syndrome X had urea breath test (UBT) positivity for *H. pylori* while none of the patients with chronic stable angina or controls had UBT positivity.

H. pylori and acute myocardial infarction

H. pylori induced inflammatory reaction is possibly responsible for plaque instability and platelet aggregation in acute coronary syndrome patients. Danesh *et al*[95] demonstrated a higher prevalence of *H. pylori* infection (42% *vs* 24%, OR = 1.75) in young acute myocardial infarction (AMI) survivors. Alkout *et al*[96] showed a higher titre of *H. pylori* IgG titre in patients who died of AMI (151 ng/mL *vs* 88 ng/mL, p= 0.034). Kahan *et al*[97] reported a higher prevalence of *H. pylori* seropositivity in recent myocardial infarction patients as compared to controls (68% *vs* 53%, OR = 1.36). This remained significant even after adjusting for other CAD risk factors like age, sex, smoking and hypertension. Kinjo *et al*[98] suggested that *H. pylori* infection was significantly associated with AMI in younger patients (age < 55 years, OR = 2.7) but not in those with age of > 55 years. Frazer *et al* showed a higher prevalence of *H. pylori* infection in AMI patients compared to control (41.6% *vs* 34.5%; $P = 0.038$)[99].

Similar to CAD, negative associations is also been reported between *H. pylori* and myocardial infarction. Zhu *et al*[100] hypothesised that *H. pylori* infection could not lead to CAD or myocardial infarction. Murray *et al*[101] had shown a negative association between *H. pylori* and risk for myocardial infarction. Pellicano *et al*[102] reported a negative association between cytotoxic *H. pylori* strains and myocardial infarction, with insignificant anti-Cag-A antibody seropositivtiy between cases and controls (33.8% *vs* 26.8%).

H. pylori Cag-A positivity - Is the risk greater?

Cag-A positivity has raised a curiosity in the infectious theory of atherosclerosis. Several studies had shown a significant relationship between Cag-A strain and CAD or stroke. Carriers of Cag-A positive strains had a higher risk for stroke (OR = 2.99) and carotid plaque instability (OR = 8.42)[103]. De Bastiani *et al*[104] showed increased prevalence of Cag-A seropositivity and ischemic stroke. Rasmi *et al*[93] reported a positive relation between Cag-A seropositivity and cardiac syndrome-X. Huang *et al*[105] revealed that Cag-A positive strains enhanced atherosclerosis in CAD patients by modifying oxidised LDL levels and high sensitive C-reactive protein (hsCRP) levels. Kowalski[36] showed that Cag-A positivity was significantly associated with greater coronary artery lumen loss and restenosis after percutaneous coronary artery stenting. He also demonstrated that *H. pylori* eradication significantly attenuate reduction in coronary artery lumen after coronary artery stenting[36]. But various authors had denied the excess risk of Cag-A positive strains with atherosclerosis. Koenig *et al*[106] demonstrated a similar prevalence of Cag-A seropositivity in CAD patients and healthy subjects. Whincup *et al*[107] in his prospective study comprising of 505 patients and 1025 healthy subjects had clearly shown that there was no significant association of seropositivity with CAD. Murray *et al*[101] reported negative association between the virulent *H. pylori* Cag-A strains and acute myocardial infarction.

H. pylori and stroke

By catalysing atherosclerotic pathways, *H. pylori* infection may be a risk factor for ischemic stroke. Single infectious agent is weakly linked to stroke but cumulative chronic infectious exposures, or "infectious burden", have been associated with the risk of stroke. The adjusted hazard ratio demonstrating the risk of association between *H. pylori* and stroke was 1.13, whereas that of infectious burden and stroke was 1.39[108]. The possible mechanisms include macrophage activated plaque destabilization, increased expression of various adhesion molecules and inflammatory cytokines, localized hypercoagulability, altered gene expression, and a molecular mimicry. Markus *et al*[109] found a higher prevalence of *H. pylori* seropositivity in stroke cases compared to controls. There was an association between *H. pylori* infection and large vessel disease and lacunar stroke irrespective of other confounding factors. Another study by Grau *et al*[110] demonstrated an association between *H. pylori* seropositivity and ischemic stroke. Elkind *et al*[111] suggested that that chronic infectious burden results in increase carotid plaque thickness and stroke. A retrospective study reported higher incidence of ischemic stroke in patients with *H. pylori* infection than in non-infected group (14.8 *vs* 8.45 per 1000 person years)[112]. Diomedi *et al*[113] showed that Cag-A positive *H. pylori* infection was associated with poorer short term clinical outcomes and greater carotid intima media thickness in stroke patients. Increased risk of stroke in Cag-A positive *H. pylori* patients may be due to enhanced plaque vulnerability[103,114]. In one of the studies, the positive correlation between *H. pylori* and stroke was confounded by socioeconomic class[115]. A study on chronic bacterial infection and stroke demonstrated that elevated anti- *H. pylori* antibody was not significantly associated with ischemic stroke[116].

H. pylori and peripheral arterial disease

Studies about association of *H. pylori* infection with peripheral arterial disease (PAD) are limited. Bloemenkamp *et al*[117] demonstrated infection as a novel risk factor for PAD in young women. A case control study on infection and PAD in young women suggested that *H. pylori* infection was positively correlated with PAD only in those with high CRP levels[118]. Sawayama *et al*[119] reported a significantly higher prevalence of *H.*

pylori infection in PAD cases than in controls (79.7% *vs* 44.8%; $P < 0.01$).

CONCLUSION

Overall the association between *H. pylori* and CAD is not strong and a causal role is yet to be established. Future studies on larger scale may possibly establish a stronger link between the two. If it gets established, there can be drastic reduction in burden of CAD by managing *H. pylori* infection. Proponents of infectious theory will have a real challenge in the years to come because establishing a definite causal role of *H. pylori* in CAD will be a nightmare due to the existence of numerous confounding factors. Opponents may continue to criticise the infectious theory of CAD because of lack of strong scientific evidence.

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