Review Article

H. pylori and Cardiovascular Diseases

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Abstract

Helicobacter pylori (*H. pylori*) does not cause only peptic ulcer, gastritis, dyspeptic symptomatology, low-grade mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma, it is also reported to be associated with many extragastrointestinal manifestations, such as hematological diseases, dermatologic diseases and cardiovascular diseases (CVD). Because certain microbial agents including *H. pylori* play important roles in atherosclerosis induced CVD. The mechanisms underlying atherosclerosis induced by *H. pylori* are inflammation, coagulation, oxidative stress, lipid-lipoprotein metabolism, insulin resistance, obesity, endothelial dysfunction and hyperhomocysteinemia. This review summarized the literatures on the association of cardiovascular manifestations with *H. pylori* infection, and provided information about the etiopathogenesis of this association.

Keywords: *H. pylori*; Atherosclerosis; Cardiovascular diseases

Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative microaerophilic bacillus with heterogeneous morphology. *H. pylori* produces urease, an enzyme that produces ammonia. This creates pH greater than gastric mucous and allows it to survive [1,2]. Warren and Marshall were awarded the Noble prize in 2005 for their discovery of *H. pylori* and its role in gastritis and peptic ulcer disease.

H. pylori is a bacterium that occurs worldwide with a prevalance specially it is common in developing countries. *H. pylori* infection causes peptic ulcer, gastritis, dyspeptic symptomatology, low-grade mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma and the association between *H. pylori* infection and gastric disease has been well established [3,4]. In fact it has been classified as a type 1 carcinogen by the World Health Organization. Additionally recent studies showed that there is a significant association between the *H. pylori* and extragastric disease such as iron deficiency anemia [5], Henoch-Schönlein Purpura [6], immune thrombocytopenic purpura [7], chronic urticaria [8], hepatocellular carcinoma [9], laryngeal cancer [10], insulin resistance [11], metabolic syndrome [12] and asthma [13].

Coronary heart disease (CHD) is the most prevalent cause of death in the industrialized world and a significant cause of morbidity and mortality in the developing countries and atherosclerosis is one of the important factors affecting cardiovascular diseases (CVD) including CHD. Clarification of the atherosclerosis etiopathology is very important to prevent and treat for minimize its consequences. But up to now, exact mechanism of this process still remains a challenge.

There are lots of chronic atrophic gastritis (CAG) investigations about association between *H. pylori* and CVD [14-16]. In some of investigations, it was suggested that gastric damage due to *H. pylori* causes CVD. Chronic infection with *H. pylori* strongly increases the risk of CAG which causes vitamin B12 deficiency that was found responsible for CVD. Because deficiency of vitamin B12 is one of the causes of hyperhomocysteinemia [17-19]. In the other studies, it was found that endothelial dysfunction occurs in *H. pylori* positive subjects [20,21]. Inflammatory cytokines are also important for *H. pylori* induced CVD. Insulin resistance, coagulation activation, distribution in lipid and lipoprotein metabolism, platelet activation, increased oxidative stress and obesity (metabolic syndrome) are the other major factors of *H. pylori* induced CVD.

This review aimed to summarize the literatures on the cardiovascular manifestations of *H. pylori* infection and to weigh the evidence of its role in these conditions.

Mechanisms of *H. pylori* induced atherosclerosis

H. pylori **and inflammatory cytokines:** Recent studies showed that inflammation is one of the main risk factor for atherosclerosis induced CVD [21,22]. Inflammation induces atherosclerosis and CVD via changes in cardiovascular risk factors, such as increasing coagulation factors, lipid factors and proinflammatory cytokines like C reactive protein (CRP) [23], tumor necrosis factor- α (TNF-α) [24], interleukin-6 (IL-6) [25], IL-18 [26,27]. *H. pylori* is not only cause an inflammation in gastric mucosa, but low-grade systemic inflammation is also found in *H. pylori* infected person. The main of this is increasing in production of proinflammatory cytokines such as IL-6 and IL-18.

One of the most important pathways in promoting inflammation is the activation of the nuclear factor kappa-B (NF-κB) pathway which mediates tissue inflammation by activating pro-inflammatory cytokines such as IL-6, TNF-alpha and IL-1 [28]. Cag-A, an antigen which is produces by *H. pylori* is important for *H. pylori*-induced inflammation. Recent studies showed that Cag-A plays a role in NF-κB activation [29]. Also NF-κB activation might be independent of Cag-A [30-32], and it may be suggested that NF-κB plays a major role in the transactivation of inflammatory cytokines' genes in response to *H. pylori* infection.

IL-18 is an important cytokine released from epithelial cells and monocytes during *H. pylori* infection [33-35]. Because increased expression of IL-18 in serum and human atherosclerotic plaques was reported [27,36] it was suggested that IL-18 has a pathogenic role in atherosclerosis. Also IL-6 is an important cytokine in atherosclerosis pathogenesis. Because it stimulates acute phase reactant production such as CRP from liver. CRP increases in *H. pylori* infection. It contributes atherosclerotic plaque formation activiting of endothelial cells and increasing coagulation cascade [37-39]. A high-sensitivity CRP (hs-CRP) test measures low levels of CRP in blood and it is a marker of low grade inflammation. In recent studies, hs-CRP was found to be increased in atherosclerosis [40,41].

H. pylori **and activation of coagulation:** Plasminogen activator inhibitor-1 (PAI-1) and PAI-2 are serine protease inhibitors (serpin) and they inhibit tissue plasminogen activator and urokinase which activates plasminogen and therefore fibrinolysis [42]. PAI-1 and -2 have an active role in thrombosis during atherosclerosis formation and they prevent fibrinolysis by inhibiting plasminogen activation. There is a positive correlation between elevation of blood PAI-1 levels and death rate in patients with CHD [43].

In one study, Keates et al. [44] found that PAI-1 mRNA and protein levels are higher in gastritis patients with *H. pylori* infection than the uninfected gastritis patients. *H. pylori* infected gastric epithelial cells upregulate PAI-1 mRNA and protein production. Another study by Varro et al. [45] showed that PAI-2 which increases in *H. pylori* infected gastric epithelial cells induces the release of IL-8 and the activation of cyclooxygenase-2.

Fibrinojen is an acute phase reactant that increases in the inflammation and helps in the formation of blood clots. In one study by Longo-Mbenza et al. [46] related to prevention of the metabolic syndrome insulin resistance and the atherosclerotic diseases in Africans infected by *H. pylori* infection and treated by-antibiotics, they found fibrinogen levels were higher in *H. pylori* infected subjects than in healthy controls. Furthermore after the treatment of *H. pylori* with antibiotics, fibrinogen levels decreased. Inflammation induced higher fibrinogen levels in *H. pylori* may contribute the thrombotic complications of atherosclerosis.

H. pylori **and oxidative stress:** Oxidative stress is a condition occured due to an imbalance between the systemic manifestation of reactive oxygen species (ROS) and antioxidants in the biological system. The ROS upregulate atherosclerotic events namely cell infiltration, migration, adhesion and platelet activation. Also ROS oxidize cellular biomolecules including lipids, proteins and nucleic acids causing endothelial impairments [47].

H. pylori infection creates an oxidative microenvironment with release of proinflammatory, toxic, vasoactive substances and ROS. There are some studies about increased ROS and decreased antioxidant defense mechanism in *H. pylori* infected patients [48,49]. Due to oxidative stress, oxidation of low density lipoprotein cholesterol (LDL-C), lipid peroxidation and DNA oxidation and expression of adhesion molecules increase. Furthermore, vascular smooth muscle proliferation and migration, and endothelial apoptosis are induced by ROS. All of them contribute atherosclerosis process [50].

H. pylori **and lipid-lipoprotein metabolism:** Generally chronic infections cause atherosclerosis via distributed lipid and lipoprotein metabolism. In literature, there are some studies found that *H. pylori* seropositivity was associated with lower high density lipoprotein cholesterol (HDL-C), higher triglyceride (TG) and total cholesterol (TC) [47,51]. The main reason of these changes in lipid-lipoprotein metabolism is the inflammation which is caused by *H. pylori* infection. As mentioned above, chronic infections cause inflammation by increasing expression of inflammatory cytokines such as TNF-α. It was shown that TNF-α inhibits lipoprotein lipase which provides fatty acid to allows the passage from blood to the tissues. This is resulted in mobilization of TGs from tissue to blood circulation and thus elevated triglyceride in circulation is observed. After *H. pylori* treatment with antibiotics, decreasing LDL-C, TG, TC levels and increasing HDL-C levels show that *H. pylori* eradication is important for prevention of CVD [11,47].

H. pylori **and insulin resistance:** Insulin resistance is a condition in which cells fail to respond to the normal actions of the insulin hormone. Common insulin resistance as observed in obesity and type 2 diabetes mellitus results from a complex interaction of environmental and inherited factors and progresses chronically.

At the cellular level, stimulation by insulin activates tyrosine kinase of the insulin receptor, which stimulates insulin receptor substrate phosphorylation followed by activation of some complex pathways. Obesity, family history, oxidative stress, are the factors for the pathogenesis of insulin resistance. Also infection and systemic inflammation are risk factors for insulin resistance. Recent studies suggest that infection of *H. pylori* may be one of the major risk factor for improving insulin resistance, diabetes complications and CVD [12,51-53], It was shown that eradication of *H. pylori* decreased insulin resistance calculated with homeostasis model assessment for insulin resistance. Thus authors have suggested that *H. pylori* eradication may prevent coronary artery disease [12]. But there is controversial data for this association [54-56]. The conflicting results regarding the association between *H. pylori* infection and insulin resistance and its abnormalities could be explained in part by the varying virulence of *H. pylori* strain type.

H. pylori **and obesity:** Obesity is a medical condition in which excess body fat has accumulated to the extent. Obesity is becoming a global epidemic and there is a dramatic increasing in obesity in both children and adults in the past 10 years. Especially abdominal obesity may have a negative effect on health, leading to CVDs [57-59].

The adipose tissue is not simply a passive fat storehouse, it has important endocrine functions such as synthesizing and releasing into the bloodstream variety of peptides and nonpeptide compounds that play important roles in cardiovascular homeostasis. Adipose tissue is also a significant source for lots of molecules involving TNF-α, IL-6, plasminogen activator inhibitor-1, resistin [60,61].

The circulating concentrations of plasminogen activator inhibitor-1, angiotensin II, CRP, fibrinojen and TNF-α are all related to body mass index [62,63]. In one in vivo study, 30% of the total circulating concentrations of IL-6 originate from adipose tissue [57,64]. IL-6 modulates CRP production in the liver, and it can start acute coronary syndrome (ACS) [65]. Obese individuals show an increased susceptibility to infections with different pathogens. Zhang et al. [66] and Longo-Mbenza and coworkers [46] found association of H. pylori seropositivity with higher weight.

In contrary to these findings, in forty-nine studies with data from 10 European countries, Japan, the US and Australia showed that there is an inverse correlation between *H. pylori* prevalence and rate of overweight/obesity in the developed countries. Thus, decrease of the *H. pylori* colonisation in recent decades could be related to the obesity endemic observed in the developed countries [67]. This result is

consistent with previous observations in controlled trials that after successful *H. pylori* eradication patients experience a significant increase in weight that was not observed in control subjects who had placebo instead of *H. pylori* eradication [68].

***H. pylori* and endothelial dysfunction**: The endothelium is a fundamental element of vascular health because it regulates vascular tone and vascular homeostasis. Endothelial dysfunction known as impairment of endothelial physiology is early step in the atherosclerosis, and it is an important factor in the progression of atherosclerotic cardiovascular disease [69]. As an endocrine tissue, endothelium regulates balance between vasodilation and vasoconstriction [70] by releasing vasodilator hormones such as nitric oxide and prostacyclin, and vasoconstrictory H_2 hormones such as endothelin-1, angiotensin II and prostaglandin H_2 [71].

Oxidative stress and vitamin deficiency, especially vitamin B12 deficiency, appear to be the most common underlying mechanism for the development of endothelial dysfunction. Inflammation is another common underlying mechanism of endothelial dysfunction and there seems to be a causal relationship between oxidative stress and inflammation [72]. CRP, an acute phase inflammatory protein directly contributes to the early phase of atherosclerosis by deposition on the intima and directly affects nitric oxide (NO) bioavailability and this causes oxidative stress, endothelial dysfunction, and intimal hyperplasia. In one study, there was an association between *H. pylori* infection and endothelial dysfunction and the treatment of *H. pylori* infection improved the endothelial dysfunction [21]. Adachi et al. [73] found a significant association between the *H. pylori* infection and arterial stiffness in young subjects.

***H. pylori* and hyperhomocysteinemia:** Among several cardiovascular risk factors, vitamin deficiency is emerging as a candidate. Atrophic gastritis which is induced by *H. pylori* infection may cause malabsorption of vitamin B12 and folic acid that are important vitamins in homocysteine metabolism. As a result, deficiency of these vitamins may result in hyperhomocysteinemia. High homocysteine levels are associated with impaired endothelial-dependent vasodilation. Homocysteine causes endothelial dysfunction by reducing NO synthesis, activating platelet and coagulation, impairing fibrinolysis and leading to chronic inflammation [74].

In some - studies, it was observed that serum in homocysteine levels in *H. pylori* infected patients were higher than the control groups [75,76]. Increasing homocysteine levels in *H. pylori* infected subjects may contribute CVD.

Cardiovascular manifestations in *H. pylori* infection

Peripheral arterial disease (PAD): PAD is known as narrowed arteries except heart and brain vessels and it has a significant association with coronary artery disease and cerebrovascular disease such as acute ischemic stroke [77-79]. But there have been limited studies about the association between the H. pylori and PAD. In one study authors found that *H. pylori* had a significant influence on the occurence of PAD. Bloemenkamp et al.[80] suggested that *H. pylori* infection was a risk factor for PAD in young women population.

***H. pylori* and stroke:** There has been increasing evidence about association between the stroke and chronic infections like *H. pylori*. *H. pylori* can cause ischemic stroke by facilitating the formation of atherosclerotic plaque. In one study, chronic infection leads an increase of carotid plaque thickness and stroke [81]. Heushmann et al. [82] found that there was a significant association between chronic H.

pylori infection and stroke caused by small artery occlusion, but totally elevated *H. pylori* antibodies were not associated with ischemic stroke. Another study showed that *H. pylori* incidence was higher in the patients than in the controls [83]. In a comprehensive study, 17 332 patients with *H. pylori* infection and 69 328 controls identified and then were followed up until the occurrence of ischemic stroke or until censored. Authors determined that the cumulative incidence of nonembolic ischemic stroke was significantly higher in *H. pylori* infected patients than in patients without *H. pylori* infection [84]. Diomedi et al.[85] showed that there was an association between *H. pylori* infection and poorer short term clinical outcomes and greater carotid intima media thickness in stroke patients [85]. On the other hand, Jang et al. [86] found conflicting results. They showed that H. pylori infection was not associated with small vessel disease in the brain.

***H. pylori* and Acute Coronary Syndrome:** ACS refers to a group of clinical conditions such as unstabil angina, ST elevation myocardial infarction (STEMI) and non-ST elevation MI (NSTEMI) due to decreased blood flow in the coronary arteries. Izadi et al. [87] showed that *H. pylori* infection in the coronary arterial wall was associated with atherosclerotic plaque formation by increasing blood LDL-C and TC.

Aceti et al. [14] found that CHD was significantly associated with *H. pylori* infection and anti-Cag-A positivity. In another study found that Cag-A levels were higher in unstable patients than the stable angina patients and healthy controls. Cag-A antigens localized inside coronary atherosclerotic plagues specimens from both unstable and stable patients [88]. Another study showed that patient died of acute MI had higher *H. pylori* seropositivity [89]. In one study, there was a significant association between *H. pylori* seropositivity and MI [90]. Kinjo et al. [91] found that *H. pylori* seropositivity was associated with acute MI in younger patients but not in older than 55 years. But there are conflicting results. Schöttker et al. [92] studied with 9 953 older adults and found that *H. pylori* infection and Cag-A positivity were not associated with CVD or mortality. In another study there was a negative association between the *H. pylori* and risk of MI [93].

Cardiac syndrome X: The patients with cardiac syndrome X have angina pain in their chest and ST segment depression on stress exercise test without coronary angiogram pathology. The pathogenesis of this syndrome is not well known, but one of the pathogenetic mechanism in cardiac syndrome X may be endothelial dysfunction [94-96]. One study showed that chronic inflammation in *H. pylori* infected patients causes increased CRP, IL-1 levels and these can conduce endothelial dysfunction which may play a pathogenetic role in cardiac syndrome X [97]. Eskandarian et al. [98] found that the prevalence of *H. pylori* infection is higher in cardiac syndrome X patients than the healthy control groups. In a preliminary study, fifty percent of cardiac syndrome X patients had *H. pylori* seropositivity and controls groups had no *H. pylori* seropositivity [99].

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