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Helicobacter pylori and cardiovascular disease

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Abstract. – *Helicobacter pylori* (*H. pylori*) is one of the most common infections in human. The association between *H. pylori* and gastrointestinal diseases including peptic ulcer, chronic gastritis, mucosa associated tissue lymphoma (MALT) and gastric cancer is well known. However it was also suggested that *H. pylori* was linked to various extra-gastrointestinal disorders such as diabetes mellitus and coronary artery disease. In this review we summarized the association between *H. pylori* and cardiovascular disease.

Key Words:
H. pylori, Cardiovascular disease, Inflammation, Atherosclerosis, CagA.

Introduction

Cardiovascular disease (CVD) including coronary artery disease (CAD), stroke and peripheric artery disease (PAD) are the leading causes of mortality and morbidity in the world[1]. Due to the high burden of these diseases, massive studies have been conducted to clarify the risk factors of CVD. Despite the developments in the prevention of CVD, there is still a gap between the prevalence of CVD and the risk factor distribution. Classical risk factors (hypertension, diabetes mellitus, smoking, dyslipidemia) failed to explain all of the cases of CVD.

As atherosclerosis is a multi-step process that inflammation takes place in all steps, it has been suggested that chronic infection can contribute to this process. Helicobacter pylori (*H. pylori*) is one of the most common infections in human. Association of *H. pylori* and gastrointestinal diseases including peptic ulcer, chronic gastritis, mucosa associated tissue lymphoma (MALT) and gastric cancer is well known[2]. Additionally it was also indicated that *H. pylori* was linked to various extra-gastrointestinal diseases such as diabetes mellitus and coronary artery disease[3]. Large number of studies have been designed to assesss the relationship between *H. pylori* and CVD but this relationship still remains controversial. This paper reviews the studies investigating *H. pylori* infection and CVD association, and also possible mechanisms by which this chronic infection contributes to atherosclerosis.

Pathophysiology of Atherosclerosis

Atherosclerosis is the definition of the thickening of the medium and large artery vessels. This thickening occurs in a dispersed way. In the earlier era of the research on atherosclerosis; it was believed that accumulation of lipid constituted the atheroma plaque, but today evidence suggests that three components are involved in the atheroma plaque; celluler components (smooth muscle cell and macrophages), connective tissue matrix, extracellular lipid, and intracellular lipid that accumulates within macrophages[4]. Inflammatory stimuli pertubate the endothelial function. These inflammatory stimuli, which consist of hypertension, dyslipidemia, smoking, obesity, diabetes mellitus, are also considered as risk factors for CVD today. After this trigger, many adhesion molecules, cytokines and growth hormone take part in this process, and in the end a fibrous plaque which consist of the above-mentioned components, develop. Acute coronary syndrome occurs if the fibrin plaque ruptures and platelets aggregate on it. Inflammation plays a crucial role in all these steps of the development of CVD[5].

Systemic Response to H. pylori Infection

H. pylori is a Gram negative micro-aerophilic spiral shaped bacterium. *H. pylori* colonizes the antral mucosa of stomach. After the colonization; *H. pylori* recruits the neutrophils and monocytes to the infected area and triggers the release of pro-inflammatory and pro-coagulant cytokines.

Release of these cytokines and their systemic effects on other organs of the organism is the base of the idea of the association of between *H.*

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pylori and extra-intestinal diesases. Given the gap between the high prevalence of CVD and its risk factors, the idea that other unknown factors should play role in the pathogenesis of CVD comes to mind. Chronic infections have been suggested as an example of the possible inflammatory risk factors for CVD. After *Chlamydia pneumonia* was proposed as a risk factor for CVD; it was also hypothesized that *H. pylori* could also promote CVD[6].

H. Pylori and Coronary Artery Disease

The first study compared 111 patients with angiographically proven CAD and age- and sex-matched controls in terms of *H. pylori* infection. *H. pylori* seropositivity was significantly different between these two groups. The difference was still significant after adjustment for possible confounders[7]. This case control study raised concerns about this relationship. In the following years many case-control and sero-epidemiologic studies, that aimed to assess the correlation between *H. pylori* and CAD, were published. These studies couldn't provide a strong evidence regarding this association, because investigations that found positive correlations[8-10] have been contradicted by the others with little or no associations[11,12]

After this period; a systematic review was needed to clarify the relationship between *H. pylori* and coronary artery disease. One review revealed that there were more than twenty epidemiologic studies that aimed to search this relationship. Studies with small populations tend to show high odds ratios while case-control studies with large number of patients did not show this association after adjustments for classical risk factors for CAD[13]. Same authors also conducted a meta-analysis that aimed to clarify relationship between *H. pylori* infection and risk factors for CAD. No strong correlation was found between *H. pylori* infection and body mass index, high blood concentration, blood pressure, lipid concentrations and hematological factors[14].

As uncertainty went on about the relationship between *H. pylori* and CVD, authors continued their researches. Case-control and cross-sectional studies were conducted after the above-mentioned review did not determine whether *H. pylori* was related to CVD or not. Majority of these studies that were published between 1998 and 2013 can be found in Table I. Heterogeneity of these researches makes it impossible to reach a clear conclusion. Papers that reported high odds ratios can be blamed as potential cofounders like low socio economic status, gender and ethnicity affected the studies' results. But most of these reports gave their results after the adjustment for classical risk factors for CVD and these potential cofounders. Coronary artery disease definition was also inconsistent. Patients with acute myocardial infarction, chronic stable angina, unstable angina or only history of CAD and electrocardiogram changes can be inclusion criteria. Absence of the patient enrollment criteria among these studies can be the cause of the wide difference among the studies.

The conflicting results of case-control studies were tested with well-designed population-based cohort studies. Blood samples of the individuals were stored before the clinical appearance of CAD and risk factors of CAD were evaluated. *H. pylori* positivity was measured in these stored samples. Individuals suffered from myocardial infarction or clinical forms of CAD, or died due to CAD were compared with age- and sex-matched controls from the cohort, in order to prevent sampling errors and selection bias.

The first prospective cohort study recruited 135 patients with ischemic heart disease and age- and sex-matched 136 controls from a longitudinal study of cardiovascular disease that recruited 7735 middle aged man randomly selected from 24 towns of Britain[15]. Odds ratio was 1.8 (95% CI: 1.1-3.0). After adjustment for social class, town, smoking habitus, blood pressure and glucose, odds ratio was decreased to 1.3. Death due to CVD was moderately related to *H. pylori* positivity in this study (odds ratio 1.6 after adjustment for cofounders). One prospective study[16], which was designed to evaluate the relationship between *H. pylori* and CVD among elderly population, did not find an association between *H. pylori* and CVD. Furtheremore, *H. pylori* did not relate to all cause or CVD death.

Another prospective cohort study[17] compared *H. pylori* positivity between 648 deaths from ischemic disease and age- and sex-matched controls selected from a prospective study of professional men aged between 35 and 64 years in Britain. There was no significant difference and also mortality did not change due to *H. pylori* positivity (OR: 1.06, 95% CI: 0.86-1.31). The largest study ever done did not determine an association. Consequent prospective cohort studies[18] also reiterate the previous findings (Table II). A meta-analysis conducted in 1999 revealed no association either.

Table I. Case control studies about the relationship between *H. pylori* and CVD.

Author	Year	Patient	Association	
J. Rengstrom	1998	97 patients with CAD vs controls	No association	Scandinavian origin, *H. pylori* seropositivty is low
F. Zito	1999	101 myocard infarctus vs control	Odds ratio (OR): 1,4 after adjustment	Fibrinogen is also increased (B2 allele has effect)
M.J. Quinn	1999	488 patients undergoing elective coronary angiography	OR 1.3, 95% confidence interval 0.83 to 2.16	
J. Danesh	1999	Case control study of myocardial infarction at young ages and study of sibling pairs with one member affected and the other not	OR ratio: 1.75 after adjustment	Sibling study did not show significant difference
M. Smieja	2001	171 consecutive patients presenting with myocardial infarction or unstable angina (coronary care unit patients), or with previous angina or myocardial infarction (angiography suite patients), vs control	No association with *H. pylori*	Serology for CP, *H. pylori*, CMV, adenovirus, and hepatitis A virus were also measured
G. Di Tano	2000	206 incident cases of acute myocardial infarction	No significant difference was observed in the frequency of *H. pylori* antibodies in acute myocardial infarction patients and in the control group (43.3 vs 41.5%, p = NS, odds ratio-OR 1, 95% confidence interval-CI 0.7-1.6).	CP was associated with myocard infarction
C.J. Tsai	2000	Cases (n = 165) were defined as those who had at least one coronary artery lesion occupying at least 50% of the luminal diameter on coronary angiography. Patients who had normal coronary angiography were selected as controls (n = 127)	Nonsignificant (odds ratio 0.59, 95% CI 0.32-1.09, p = 0.09)	
R. Pellicano	1999	44 consecutive male patients, aged 40-65 years, admitted for acute myocardial infarction to the Coronary Care Unit at Novi Ligure Hospital in northern Italy.vs age- and sex-matched controls	OR: 2.36 (95% confidence interval 1.08-5.31) association (+)	Only male patients
R. Pellicano	1999	212 consecutive male patients, aged 40-65 years, admitted for AMI vs controls	Association (+)	Only male patients in three Italian towns
J. De Backer	2002	446 out of 16307 men at work, aged 35-59 years, had antecedents of myocardial infarction, CABG or PTCA or had prominent Q/QS waves on their resting ECG	No asscoiation	Community based case-control, also measured CMV, CP, EBV
K. Hara	2001	60 healthy individuals that served as control subjects, and 21 patients with acute myocardial infarction (AMI), 34 with old myocardial infarctions (OMI), 35 with effort angina (AP) and 41 with vasospastic angina (VSA)	*H. pylori* IGA titer were higher in acute myocardial infarction patients than the others	

Table continued

Table I *(Continued)*. Case control studies about the relationship between *H. pylori* and CVD.

Author	Year	Patient	Association	
M. Kowalski	2001	100 patients with coronary artery disease (subgroup 1) and 100 patients without (subgroup II)	Association (+)	Also association with CagA
H. Osawa	2001	Three hundred and four patients who underwent consecutive coronary arteriography were investigated	Association (+)	Japanese population
K. Kinjo	2002	618 individuals with acute myocardial infarction vs 967 controls	No association for overall population	But in subjects younger than 55 years, there was association (58.7% vs 43.3%, $p = 0.009$).
D. Rajasekhar	2002	117 patients with UA and CSA	Association (+)	
Pellicano, R	2003	32 consecutive patients with unstable angina vs age and sex matched control	The odds ratio was 3.82 (95% CI 1.27 to 12.04)	
T.S. Altannavch	2003	Patients with unstable angina pectoris, 52 of them having type 2 diabetes mellitus, and in a matched control group	No association	CMV and CP were associated with unstable angina
X.J. Cai	2003	Fourty-five patients with at least one coronary artery stenosis > 50% and 33 control subjects with negative coronary angiography	Association (+)	CP and *H. pylori* was associated with CVD but CMV was not associated
A.G. Fraser	2003	341 patients with a recent myocardial infarction and 831 community controls	No association	CP was not with myocardial infraction
M. Miyazaki	2006	33 male patients with acute coronary syndromes (ACS)	No association	CagA was also measured, no association
J. Sheehan	2005	Patients with AMI	No association	CMV, CP and herpes were not associated AMI
A. Vcev	2006	Coronary artery disease (n = 90) and control group (n = 90)	No association	No association with risk factors
I. Ozdogru	2007	353 patients with angiographically proven CAD, which contains 3 different subgroups: 163 patients with Myocardial infarction (MI), 106 patients with unstable angina and 84 patients with stable angina Control group included 163 subjects with angiographically proven normal coronary arteries	No association	*H. pylori* IgG antibody levels may be correlated with the extent of CAD
S.W. Jin	2007	Patients with CAD	No association	*H. pylori* was diagnosed with endoscopic biopsy
G.S.Tamer	2009	152 patients (group I, 73 patients with acute coronary syndrome; group II, 79 patients with chronic stable angina) and 22 control subjects	Association (+)	*H. pylori* did not differ between acute coronary syndrome and chronic stable angina
Z. Khodaii	2010	500 patients with AMI and 500 control individuals without any evidence of clinical CVD	Association (+)	CagA was also associated with CAD

(+): Present, AMI: acute myocardial infarction, CP: *Chlamydia pneumoniae*, CMV: *Cytomegalovirus*, CVD: cardiovascular disease, CAD: Coronary artery disease. NS: nonsignificant, CABG: coronary arteri bypass, PTCA: percutaneous coronary angiography, UA: unstable angina, CSA: coronary stable angina.

Table II. Prospective cohort studies about the association between *H. pylori* and CVD.

Author	Year	Patient	Association
J.M. Ossewarde	1997	First MI vs control	No association
K.A. Coles	2003	Patients with CAD and stroke vs control	Odds ratio: 1.2 (no association)
H.L. Witherell	2003	Patients with first MI vs control	Odds ratio: 1.9 (but not evident after adjustment for education)
A.W. Haider	2002	Patients form Framingham Heart Study participants (CAD vs controls)	Odds ratio: 1.09 (attenuated after adjustment)
A.R. Folsom	1998	Patients with CAD vs controls (men and women)	Odds ratio: 1.03
M. Roivainen	2000	Patients with AMI or coronary death vs control	No association

Although half of the world's population is infected with *H. pylori*; all individuals infected with *H. pylori* did not develop peptic ulcer, gastric cancer or clinical symptoms. Cytotoxin associated gen A toxin (CagA) is one of the important virulence factor that is coded by CagA pathogenity island. *H. pylori* strains with CagA elicit systemic immune response stronger than CagA sero-negative strains and cause more serious gastric damage by releasing pro-inflammatory cytokines. CagA sero-positive strains have stronger association with peptic ulcer, gastric carcinoma than CagA sero-negative strains[19].

As provoked inflammation can be an etiological factor for CAD, and studies have failed to demonstrate a clear association between *H. pylori* and CAD; researchers were interested in possible relationship between more virulent strains and CAD. First case-control studies examined the relationship between virulent strains and CAD conducted in late 90's after understanding the effect of CagA positive strains on enhanced inflammation. 88 individuals with CAD, compared with age- and sex-matched controls, revealed 3.8 fold increase in risk of CAD in CagA sero-positive individuals[20]. A larger study only focused on acute myocardial infarction (AMI), showed 1.2 fold increase in risk of AMI but odds ratio increased to 1.8 in patients aged < 65, and 2.25 in patients age < 55[21]. As *H. pylori* seropositivity prevalence increases in elderly population, this finding can explain the contribution of *H. pylori* infection to CAD after conflicting results of studies that did not take into account genetic diversity of *H. pylori*. But not all case-control studies reiterated the previous findings. 312 patients with chronic stable CAD and 479 control subjects were assessed for CagA seropositivity. After fully adjustment there was no association between CAD and CagA seropositivity[22].

A meta-analysis investigated the association between *H. pylori* strains bearing CagA and CAD. Only case-control studies that compared patients with CAD and age-, sex-matched controls, performed adjustments for confounding risk factors, had valid diagnosis of CAD and used valid diagnostic tools for *H. pylori* and CagA seropositivity were assessed. After combining and analysis of 15 studies, the review yielded a OR of 2.11 for overall population. In this review, also Chinese and Caucasian populations were assessed separately and both of two populations had significant relationship between CAD and CagA seropositivity[23].

Limitations of case-control studies and methodological differences between them do not enable us to make a decision whether virulent strains of *H. pylori* are linked to CAD or not. Thereafter, prospective cohort studies were carried out. British Regional Heart Study that was used previously to assess the relation between *H. pylori* seropositivity and CAD[15], was used once more to determine the relationship between CAD and virulent *H. pylori* strains this time. Among 7753 men, 642 had major CAD events. Among 642 individuals, 135 were selected for the previous above-mentioned prospective study. Remaining 505 patients were compared with age- and sex- matched controls. This study did not find a strong relationship between CagA seropositivity and neither CAD nor its risk factors (blood pressure, lipid profile, homocysteine level, fibrinogen) after adjustment for confounding factors including socioeconomic status[24]. Subsequent studies continued the uncertainty about the relationship between CagA seropositivity and CAD[25-28]. Prospective studies aimed to assess the relationship between CagA and CAD can be found in Table III.

H. pylori and Stroke

Stroke is one of the leading causes of mortality and morbidity, and has a high prevelance that can not be explained with classical risk factors. Considering that atherosclerosis is an inflammatory

Table III. Prospective studies aimed to assess the relationship between CagA and CAD.

Author	Year	Patient	Association
P. Whinchup	2000	Patients with major cardiac event vs control from British Regional Heart Study	No association
A.F. Stone	2001	Patients with CAD vs control from the Caerphilly prospective heart disease study	No association
R.K. Singh	2002	Patients with cardiac event from west of Scotland coronary prevention study. vs control	OR: 1.5
B. Schottker	2012	Patients with primary MI vs controls from German cohort (Esther study)	No association
M. Smieja	2003	Patients with cardiac event vs controls from HOPE study	No association

CAD: Coronary artery disease; CagA: cytotoxin associated gene A.

process, stroke may be trigered by the inflammation caused by *H. pylori* or Chlamydia infections.

The above-mentioned population based cohort study also assessed the relationship between stroke and *H. pylori*. There was no statistical significant relationship was found after adjustment for social class, however diagnosis of stroke was determined by death certificates and general practice[15]. First study that used valid diagnostic tools like MR, CT, carotid artery doppler ultrasonography, which investigated stroke subtypes was published in 1998. *H. pylori* seropositivity was found to be related to cerebrovascular disease independently, the relation was strongest with large artery disease. Adjustment for confounding factors, including social class, did not change the results[29]. Again Heuschmann et al[30] investigated the relationship between *H. pylori* seropositivity and ischemic stroke types. Interestingly, *H. pylori* was related to small artery occlusion, but not to large artery atherosclerosis. These results could stem from small number of cases. Cardiac embolism was not related to *H. pylori* infection in this study. This finding is plausible because most of the cardiac embolism develop from atrial fibrillation and valvular heart disease. On the other hand, a recent study[31] contradicted previous data, with its negative findings of association between *H. pylori* seropositivty and ischemic stroke subtypes.

It is plausible that *H. pylori* strains bearing CagA can contribute to the pathogenesis of ischemic stroke. Studies that take into account the genetic diversity of *H. pylori* can enlighten this question. A meta-analysis that reviewed case-control studies retrieved ten studies that were eligible for inclusion criteria. There was 2.66 fold increased risk of stroke for individuals infected with *H. pylori* bearing CagA strains. CagA negative strains did not reveal such a finding. Furthermore, subgroups of Chinese and Caucasian populations were not different from each other[32]. A recent meta-analysis[33] that aimed to investigate whether chronic *H. pylori* infection was related to ischemic stroke or not, and to investigate predictive value of anti-*H. pylori* IgA, anti-CagA IgG and 13 (C) urea breath test, revealed that seropositivity for *H. pylori* and CagA was strongly related to the risk of ischemic stroke, and also positivity of urea breath test was related to the risk of ischemic stroke. Seropositivity for CagA can predict the risk of stroke more effectively than other diagnostic tools.

Prospective cohort studies have failed to reiterate findings of case-control studies. One prospective cohort study found an odds ratio of 1.13 (95% CI: 0.68-1.89) while this study did not take into account CagA bearing strains also subtypes of stroke. Another prospective study from ESTHER cohort also investigated the association between risk of stroke, *H. pylori* seroposivity and CagA seropositivity. Neither CagA negative nor CagA positive *H. pylori* had predictive effect on stroke risk[27].

Peripheral Artery Disease

There are inconsistent data about PAD and *H. pylori* infection. Limited number of studies have been carried out to address this question. 69 patients with PAD and 143 age- and sex-matched controls with hyperlipidemia were compared. Patients with PAD had higher *H. pylori* positivity ratio than controls (79.7% *vs* 44.8%; $p < 0.01$)[34].

Postulated Mechanisms for H. Pylori Infection and Atherosclerosis

Low grade systemic inflammation differs from acute illness of infection. Human immune system cannot eliminate *H. pylori* from gastric mucosa,

thus infection persists and is suggested to cause low grade systemic inflammation. Relationship between chronic *H. pylori* infection and extragastrointestinal diseases is actually based on this theory. Although systemic inflammatory markers, like high sensitive C-reactive protein (hsCRP), serum amyloid have been suggested as predictive risk factors for CAD. There are conflicting data about serum levels of hsCRP, cytokines like TNF-α and IL-6. One study[35] revealed that inflammation that played an important role in atherosclerosis was unrelated to *H. pylori* infection. But some of the population-based studies reported that hsCRP levels of *H. pylori* infected individuals, were higher than those of the *H. pylori* negative individuals[9,36].

It can be expected that CagA-bearing *H. pylori* strains stimulate the release of higher levels of hsCRP. But some of the population-based case-control studies did not determine such a finding. hsCRP levels did not differ among the individuals with and without CagA strains[22,24,26]. A recent case-control study[37] investigated the prevalence of CagA seropositivity among patients with CAD and controls, found higher levels of hsCRP in CagA positive patients, and also IL-6 was correlated with hsCRP.

One plausible mechanism is alteration in lipid profile of individuals with *H. pylori* infection. An epidemiological study[38] that enrolled 6289 Japanese subjects without CAD, reported higher low-density lipoprotein cholesterol (LDL-C) levels and lower High-density lipoprotein cholesterol (HDL-C) in men with *H. pylori* infection. Odds ratios of *H. pylori* infection were also significant. But this finding did not reiterate in females. Another study showed that *H. pylori* sero-positive individuals had significantly higher levels of LDL-C and total cholesterol, and also Sydney classification score for activation and inflammation was correlated with LDL-C and total cholesterol[39].

There is a consistency about this issue because small pilot studies[40,41] that investigated the effect of *H. pylori* eradication on lipid profile reported an increase in HDL-C levels and decrease in levels of total cholesterol, LDL-C after eradication therapy. But some of the population-based cohort studies[24,26] have failed to clarify the alterations of lipid profile in *H. pylori* infection.

Autoimmunity was also postulated as another possible mechanism for atherosclerosis pathogenesis. Heat shock proteins (Hsps) are group of proteins whose production was induced by infection, inflammation, mechanical stress, and hypoxia[42]. They have an essential role in the protection of cell from such stressful stimuli[43]. As their sequences were homologous among different species, it can be hypothesized that systemic antibody response to Hsps can elicit an inflammatory response against arterial wall because of the cross-reactivity between Hsps and arterial wall proteins. *H. pylori* produces a Hsps, whose molecular weight is approximately 60 kilodalton (KD)[44]. A case control-study revealed that IgG antibody to Hsp60 were increased in patients diagnosed with CAD both in CagA positive and CagA negative group. This study[45] also showed that CagA prevalence in patients with CAD was higher than controls.

Another postulated mechanism for autoimmunity was the crossreactivity between CagA antigen and vascular wall proteins. This mimicry triggers an inflammatory response to vascular wall by which atherosclerosis needs to develop. One study reported that anti CagA antibody titer was corelated with CAD extent. Furtheremore, this study revealed that anti-CagA antibody titer was the only independent predictor of the extent of the disease[46].

Last step of the chronic *H. pylori* infection is atrophic gastritis. As inflammation continues, gastric glandular cells changes into intestinal-type cells and fibrous tissue. Relationship between *H. pylori* infections with CVD can be attributed to the development of atrophic gastritis, because absorption of vitamin B12 is altered. Malabsorption of vitamin B12 causes high levels of homosystein that is regarded as a risk factor for CVD[47]. Some studies[48,49] reported that atrophic gastritis was associated with atherosclerosis. On the other hand, one population based cohort study have reported that there was no association between atrophic gastritis and coronary artery disease[27].

Previous exposure of an individual to chronic infections is regarded as a risk factor for CVD. Actually *Chlamydia pneumoniae* (CP) is the pioneer of the infectious agent that was investigated for this issue. Total pathogen burden or total infectious burden is a paradigm that can be defined as total sum of the previous chronic infection exposure[50] *Cytomegalovirus* (CMV), hepatitis A, herpes simplex virus-1 and 2 are the other pathogens that were investigated. Number of the infectious agents exposed previously have been attributed to the risk of subsequent CVD events. In a study[51] that measured serum levels of CMV,

H. pylori, HSV 1 and HSV 1, revealed that individuals exposed to more than 3 infections had increased risk for CAD (OR: 3.83 CI: 0.84-17.43). Another study[52] demonstrated that %50 of the patients with CAD were exposed to more than 4 chronic infections. However, prospective studies[53] that were designed to clarify the risk factors for CVD, and whose subjects were enrolled before the disease development, reported that total pathogen burden had a weak association with CVD.

Another possible mechanism for the pathogenesis of atherosclerosis, is the relationship between chronic *H. pylori* infection and glucose metabolism. As diabetes mellitus is a classical risk factor for coronary artery disease, impairment in glucose metabolism due to *H. pylori* infection may be an etiologic factor for atherosclerosis in individuals infected with *H. pylori*. Diabetic patients with chronic *H. pylori* infection, suffered from CAD and cerebrovascular disease more than individuals without *H. pylori* infection[54]. Another study[55] did not reiterate this finding, *H. pylori* seropositivity did not differ among the patients suffered from unstable angina with and without diabetes mellitus.

In the development of atherosclerosis, platelet aggregation and activation is the most important step that causes clinical symptoms. Several animal models showed that *H. pylori* infection elicits platelet aggregation via increasing the rolling of leukocytes and aggregation of platelet and leukocytes. Some strains of *H. pylori* bind to von Willebrand factor and interact with glycoprotein 1b to form platelet aggregation[56]. One prospective study that recruited patients from a large population cohort reported that von Willebrand levels were associated with the risk of myocardial infarction, and *H. pylori* seropositivity was also correlated to von Willebrand factor values[57].

Direct effect of *H. pylori* on the vascular wall is an intriguing issue. As *H. pylori* is an intracellular organism, it can invade macrophages and reach the vascular site away from its primary colonization site. Direct involvement of *H. pylori* can also elicit inflammation which is essential for the development atherosclerosis. Some other studies[58,59] reported the presence of *H. pylori* DNA in the atheroma plaques.

H. pylori may continue its effect on inflammation after myocardial infarction. One study[60] reported that patients with infected with *H. pylori* infection showed a significantly higher expression of the adhesion molecule LFA-1 on neutrophils than *H. pylori* negative patients. Another study[61] reported that eradication of *H. pylori,* protect the coronary artery lumen from reduction after percutanous coronary angioplasty. However, another work[62] that aimed to investigate the relationship between serologic markers of *H. pylori*, CP and CMV and late cardiac events after myocardial infarctus, revealed no association between late cardiac events and *H. pylori* seropositivity. A prospective cohort study[63] that aimed to evaluate the effect of *H. pylori* positivity on future cardiovascular events reported that *H. pylori* contributed to the progression of CVD. *H. pylori* positive patients with AMI suffered from recurrence of unstable angina, AMI, coronary angioplasty more than *H. pylori* negative patients with AMI after one year. But such an association cannot be determined after 3 years of follow up.

Conclusions

Despite many investigations, the relationship between CVD and *H. pylori* infection is still a matter of debate. A small number of case-control studies highlighted a possible association, but large cohort studies did not show these findings. The idea of a higher level of inflammation may cause extraintestinal disease arose after the discovery of CagA, which is one of the virulence factors of *H. pylori.* CagA triggers a more serious inflammation in gastric mucosa. But studies investigated the association between CagA seropositivity and atherosclerosis did not did not find an evidence.

Global burden of cardiovascular disease leads researches to clarify new risk factors for atherosclerosis. Despite the developments in controlling classical risk factors, there are still challenges in the epidemiology of cardiovascular disease. Possible chronic infections related to atherosclerosis, are easy to treat and may contribute to the control of CVD. *H. pylori* infection can still be a risk factor for atherosclerosis. However genetic diversity, host factors like polymorphisms of cytokines, geographic area must be taken into account in the designs of new studies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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