Relationship Between Helicobacter pylori Infection and Arteriosclerosis

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Abstract: It is reported that Helicobacter pylori (H. pylori) infection may be linked to non-digestive tract diseases, such as arteriosclerosis including dyslipidemia, diabetes, obesity, hypertension, and cardiovascular disease. Therefore, we reviewed recent studies available in PubMed dealing with the mechanisms of arteriosclerosis due to H. pylori infection and the effects of H. pylori eradication. Conventional studies suggested that H. pylori infection may increase the risk of arteriosclerosis. A large interventional study is required to clarify the causal relationships and the effects of bacterial eradication.

Keywords: Helicobacter pylori infection, arteriosclerosis, hypertension

Introduction

While it is widely known that Helicobacter pylori (H. pylori) may cause gastritis, gastric ulcer, gastric cancer, gastric lymphoma, idiopathic thrombocytopenic purpura, and iron-deficiency anemia, this infection may also be involved in non-digestive tract diseases such as chronic urticaria, Alzheimer’s disease, Parkinson’s disease, atrial fibrillation, liver diseases, Behçet’s disease, hyperemesis gravidarum, infertility, glaucoma, alopecia areata, and arteriosclerosis disease including dyslipidemia, diabetes, obesity, hypertension, chronic kidney disease and cardiovascular disease. Several reports have indicated a relationship between H. pylori and acute coronary syndrome, which suggests that H. pylori infection is a risk factor for cardiovascular disease (CVD); moreover, patients with H. pylori infection show an approximately 3-times higher risk of coronary artery disease than do healthy individuals. Furthermore, in a study of H. pylori patients below 65 years of age, who were categorized into bacterial eradication or non-eradication groups, the eradication group showed a significantly lower incidence of coronary heart disease during a 1-year follow-up period. H. pylori infection was found to be an independent risk factor for carotid artery plaque and stroke.

A relationship between H. pylori infection and lifestyle-based diseases has also been suggested. Associations of H. pylori infection with hypercholesterolemia, low levels of high-density lipoprotein-cholesterol (HDL-C), and high levels of low-density lipoprotein-cholesterol (LDL-C) have been reported. Several studies have found that H. pylori is associated with insulin resistance and diabetes mellitus. Furthermore, H. pylori infection has been reported to be positively correlated with body mass index (BMI). Among patients with chronic kidney disease, the risk of developing end-stage renal disease is 3.72-times higher for H. pylori-infected individuals than for patients without the infection. Hypertension has also been associated with H. pylori...
infection.\textsuperscript{15} \textit{H. pylori}-positive hypertensive patients show significantly higher arterial blood pressure than that of hypertensive patients without the infection.\textsuperscript{21} Furthermore, the eradication of \textit{H. pylori} has been reported to improve hypertension.\textsuperscript{22,23}

Conversely, findings related to arteriosclerosis accompanied by \textit{H. pylori} infection vary,\textsuperscript{5,36–39} and the relationship between both pathologies remains unclear. Moreover, while the precise nature of this relationship is still unclear, it is important to update this information because the eradication of \textit{H. pylori} may be beneficial for treatment of arteriosclerosis. To fill current gaps in knowledge, we reviewed recent studies on the mechanisms of arteriosclerosis due to \textit{H. pylori} infection and the effects of \textit{H. pylori} eradication.

**Methods**

We performed a detailed review of the recent literature to study the relationship between \textit{H. pylori} infection and arteriosclerosis. A literature screen was conducted by reviewing PubMed. We screened the following keywords: “Helicobacter pylori infection,” and/or “eradication” with “arteriosclerosis,” “hypertension,” “dyslipidemia,” “diabetes,” “obesity,” and “cardiovascular disease.” We examined the mechanism of arteriosclerosis by \textit{H. pylori} infection and the role of eradication of \textit{H. pylori} for arteriosclerosis. Moreover, we present a narrative review of the literature obtained from these screenings as brief summary. We have described the mechanism of disease onset in detail and the most recent information on the relationship between \textit{H. pylori} infection and arteriosclerosis.

**Helicobacter pylori Infection and Arteriosclerosis**

\textit{H. pylori} may influence the development of arteriosclerosis due to hypertension, as suggested in previous reports.\textsuperscript{15,21–23} Two possible explanations may account for the higher incidence of hypertension in \textit{H. pylori}-positive patients. Firstly, high-salt intake, which is a known risk factor for hypertension, favors the colonization of \textit{H. pylori}.\textsuperscript{40–42} Moreover, experiments in mice have shown that high-salt intake facilitates the formation of \textit{H. pylori} colonies.\textsuperscript{40} Another study revealed that high-salt intake increases the surface mucous cell mucin with an affinity to \textit{H. pylori}, decreases the \textit{H. pylori}-resistant gland mucous cell mucin, and damages the gastric mucosal gel layer.\textsuperscript{41} As further proof, the 1991 EUROGAST study, which examined global \textit{H. pylori} infection rates, revealed that the Akita region in Japan had the highest \textit{H. pylori} infection rate (70%).\textsuperscript{42} Akita is located in the Tohoku region, where the diet is known for being particularly high in salt intake compared to the rest of Japan. The high \textit{H. pylori} infection rate in Akita, a developed prefecture with elevated standards of hygiene, suggests a relationship between \textit{H. pylori} infection rate and the high-salt diet.\textsuperscript{43} Therefore, the incidence of hypertension in a region with high-salt intake may be more closely associated with \textit{H. pylori} presence than with \textit{H. pylori} absence, although this most likely depends also on the levels of hygiene and sociocultural factors.\textsuperscript{44,45}

Secondly, since epidemiological research\textsuperscript{46} indicates that \textit{H. pylori} infection may be a new risk factor for CVD, the higher prevalence of hypertension in patients with \textit{H. pylori} infection may be a result of the existence of factors specific to \textit{H. pylori} that also play a role in arteriosclerosis. Possible mechanisms by which atherosclerosis could be caused by \textit{H. pylori} have been reported (Box 1).\textsuperscript{23,27} \textit{H. pylori} infection was reported associated with increased prevalence of metabolic syndrome, CVD, and high levels of fibrinogen, total cholesterol, uric acid, and blood glucose.\textsuperscript{26,47} Moreover, \textit{H. pylori} causes persistent long-term infections\textsuperscript{48} that lead to chronic inflammation,\textsuperscript{27,49,50} platelet activation,\textsuperscript{28,51} dyslipidemia,\textsuperscript{14,15,52} glucose intolerance,\textsuperscript{16–18,53} hyperhomocysteinemia,\textsuperscript{27,54} increased resorption of sodium due to elevated ammonia levels in the digestive tract,\textsuperscript{23} direct invasion of the vascular walls,\textsuperscript{55,56} and reaction in atheromas.\textsuperscript{28}

Additionally, chronic inflammation due to \textit{H. pylori} infection activates a variety of chemical mediators that have been linked to endothelial dysfunction.\textsuperscript{49} Specifically, \textit{H. pylori} increases the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, gamma interferon, fibrinogen, thrombin, intercellular adhesion molecule, and vascular cell adhesion molecule; these inflammatory cytokines directly or indirectly damage the vascular walls, thereby causing arteriosclerosis.\textsuperscript{57–59}

**Box 1 Possible Mechanisms by Which Atherosclerosis May Be Caused by Helicobacter pylori**

| Chronic inflammation |
| Platelet aggregation |
| Hypercoagulability |
| Dyslipidemia |
| Impaired glucose metabolism |
| Hyperhomocysteinemia |
| Excessive fluid and salt retention |
| Direct effect |
| Endothelial damage |
| Oxidative stress |
| Molecular mimicry |

**Note:** Adapted from Nasrat et al\textsuperscript{73} and Vijayvergiya et al.\textsuperscript{27}
**H. pylori** also causes an immune response through the activation of cyclooxygenase enzyme-2 (COX-2), which increases the production of prostaglandin and nitric oxide (NO). Lipopolysaccharide (LPS) on the **H. pylori** cell wall activates Toll-like receptor-4, which activates secondary mediators, such as mitogen-activated protein kinase, extracellular signal-regulated kinase, c-Jun N-terminal kinase, and p38 kinase, and further stimulates NO synthase and COX-2 gene expression. This immune response to LPS could also increase the risk of atherosclerosis.

Another mechanism related to chronic inflammation is the antigen cross-reactivity of **H. pylori**, which has been shown to activate an autoimmune response that causes vascular endothelial damage. Antigenic cross-reactivity between human heat shock protein and **H. pylori** has been reported to cause coronary artery calcification and atherosclerosis; as well as the activation of helper T-cells.

CagA (cytotoxin-associated gene A) is a very important **H. pylori** virulence factor associated with a greater inflammatory response. After CagA undergoes tyrosine phosphorylation in gastric epithelial cells, it can induce a variety of cellular responses, including cell proliferation, cell movement, and suppression of cell death. CagA-positive **H. pylori** patients showed a higher risk of CVD and stroke. CagA, at a molecular level, mimics human tropomyosin and cardiac adenosine triphosphatase that can cause myocardial damage; it also promotes secretion of cytokines that induce severe inflammation and atherosclerotic destabilization. Moreover, CagA was reported to promote atherosclerosis by increasing the levels of COX-1 and COX-2 in the vascular endothelium, thus promoting prostacyclin production, platelet activation, and increased levels of oxidized LDL-C, high-sensitivity C-reactive protein (CRP), and Apolipoprotein B.

**H. pylori** infection has been reported to induce thromboxane, which activates platelets and promotes their binding to the Von Willebrand factor, causing platelet aggregation and destabilization of atherosclerotic plaques. Furthermore, TNF-α, interferon-α, IL-6, and IL-1, which are activated due to **H. pylori** infection, in turn, activate lipoprotein lipase, which can affect lipid metabolism and result in dyslipidemia.

In relation to glucose intolerance, **H. pylori**-positive patients have elevated levels of the oxidative stress marker paraoxonase, suggesting a relationship between this infection and oxidative stress. Additionally, atrophic gastritis due to **H. pylori** infection leads to vitamin B12 and folic acid deficiency, which results in hyperhomocysteinemia, and damages the vascular endothelial cells. Increased ammonia in the intestinal tract and the accompanying intestinal spasms are induced through **H. pylori** infection, which can damage absorption within the digestive tract and result in increased resorption of sodium through the kidney, causing hypertension.

Invasion of **H. pylori** into atheromas has been observed using PCR. Direct **H. pylori** colonization in the arterial walls has also been suggested. In addition, **H. pylori** reacts with monocytes and activates the proliferation of fibroblasts in atheromas. Therefore, **H. pylori** has been linked to atherosclerosis through a variety of mechanisms, thus potentially causing hypertension. **H. pylori** infection may independently be involved in atherosclerosis and hypertension through mechanisms that differ from the classical well-known causes of atherosclerosis.

**H. pylori** eradication results in a variety of reported outcomes in patients. This holds true for atherosclerosis-related disease; according to recent research (Table 1), outcomes include increased HDL-C, apolipoprotein AI, apolipoprotein AII, and BMI levels, as well as higher diastolic blood pressure, decreased levels of CRP, fibrinogen, total oxidant status, LDL-C, total cholesterol, triglycerides, insulin resistance, BMI, blood pressure, coronary artery lumen, and coronary heart disease and improved endothelial dysfunction (Table 2). Although there might be favorable effects of treating **H. pylori** on atherosclerosis, in some studies the effects of **H. pylori** eradication on sugar, lipid and fibrinolytic parameters, inflammatory parameters and platelet activation markers were not confirmed. The contradictory results for BMI and blood pressure might be related to the study design; the effects of **H. pylori** eradication are controversial.

The incidence of **H. pylori** infection is influenced by social, economic, cultural, regional, and sanitary factors. Large, long-term, prospective, randomized controlled, interventional studies are required to elucidate the role of eradication for **H. pylori** infection.

**Conclusion**

**H. pylori** infection may increase the risk of atherosclerosis through mechanisms other than those classically associated with the disease. A large interventional study is required to clarify the causal relationships and effects of bacterial eradication.
Table 1 Recent Research Regarding the Role of Eradication of *Helicobacter pylori* in the Evolution of Atherosclerosis-Related Disease

| First Author (Reference No.) | Year | Country | Subjects | Outcome |
|-------------------------------|------|---------|----------|---------|
| Kowalski et al. | 2001 | Germany | 100 patients with coronary artery disease vs 100 patients without | Mean coronary artery lumen reduction in patients undergoing percutaneous coronary angioplasty + *Helicobacter pylori* eradication therapy was significantly (p<0.05) smaller compared to percutaneous coronary angioplasty + placebo-treated. |
| Lu et al. | 2002 | Taiwan | 48 patients with gastric *H. pylori* infection | Coronary risk factors including fasting sugar, lipid and fibrinolytic profiles were not changed after successful *H. pylori* eradication treatment. |
| Yusuf et al. | 2002 | United Kingdom | 40 patients over the age of 65 years presenting with symptomatic ischemic heart disease vs age-matched control group of 21 patients | The fibrinogen level decreased significantly after eradication treatment of *H. pylori* in patients with raised fibrinogen levels (p<0.01). |
| Elizalde et al. | 2004 | Spain | 487 received eradication treatment vs 199 did not receive eradication treatment | *H. pylori* eradication has no influence on blood lipids or fibrinogen levels. |
| Migneo et al. | 2003 | Italy | 72 hypertensive patients vs 70 normotensive controls | A significant reduction in blood pressure after eradication of *H. pylori* in hypertensive subjects. |
| Elizalde et al. | 2004 | Spain | 92 patients with recent acute coronary syndromes | There was not any change in inflammatory parameters or platelet activation markers after *H. pylori* eradication in patients with acute coronary syndrome. |
| Scarnaglia et al. | 2004 | Austria | 87 patients with duodenal ulcers | A significant increase was observed in high-density lipoprotein (HDL) cholesterol, apolipoprotein AI, and apolipoprotein AII after eradication. |
| Kanbay et al. | 2005 | Turkey | 78 patients with *H. pylori* antigen positivity, 57 patients with *H. pylori* eradication vs 21 patients without *H. pylori* eradication | Increase in HDL-C and reduction in CRP with successful eradication (p<0.05). |
| Pellicano et al. | 2006 | Italy | 496 patients with *H. pylori*-positive dyspepsia and/or peptic ulcer were studied after cure of the bacterium | HDL-C increased (p=0.02) while C reactive protein and fibrinogen levels diminished (p=0.0001) significantly. BMI and diastolic blood pressure increased in a significant (p=0.032 and p=0.039 respectively) manner compared to baseline. |
| Kebapcilar et al. | 2009 | Turkey | In 33 patients, *H. pylori* infection was successfully eradicated | Soluble CD40 ligand, and total oxidant status levels were significantly decreased after *H. pylori* eradication. |
| Gen et al. | 2010 | Turkey | 88 patients with *H. pylori* infection vs 71 patients without *H. pylori* infection | Improvement in insulin resistance, lipid abnormalities and CRP levels with *H. pylori* eradication (p<0.05). |
| Nazligul et al. | 2011 | Turkey | 30 patients with *H. pylori* infection | After eradication treatment, serum myeloperoxidase activity and total oxidant status were significantly lower. |
| Blum et al. | 2011 | USA | 31 dyspeptic patients were diagnosed as *H. pylori* positive using histopathological evaluation. 11 dyspeptic patients were negative to *H. pylori* (controls). | *H. pylori* eradication can improve endothelial dysfunction (p=0.001) significantly. |
| Jalalzadeh et al. | 2012 | Iran | 59 patients negative for *H. pylori* vs 39 patients positive for *H. pylori* | In hemodialysis patients positive for *H. pylori*, 6 months after eradication of *H. pylori*, the BMI was significantly decreased (p=0.001). The mean serum albumin level, cholesterol, and blood urea nitrogen were also significantly decreased after the eradication. |
| Nasr et al. | 2015 | Saudi Arabia | 99 middle-aged male patients on treatment for essential hypertension and positive for *H. pylori* dyspepsia | Most patients of the study (90.9%) were able to discontinue medication and maintain normal blood pressure values after *H. pylori* eradication. |

(Continued)
Table 1 (Continued).

| First Author (Reference No.) | Year | Country | Subjects | Outcome |
|------------------------------|------|---------|----------|---------|
| Wang                         | 2018 | Taiwan  | In patients with peptic ulcer disease, 3164 patients with \textit{H. pylori} eradication vs 3164 patients without \textit{H. pylori} eradication | There was significant difference observed in composite end-points for coronary heart disease and death in early eradication subgroup compared to those without eradication (0.16% vs 0.57%, p=0.0133). |
| Iwai                         | 2019 | Japan   | 163 patients with \textit{H. pylori}-associated chronic gastritis | \textit{H. pylori} eradication therapy increased the HDL cholesterol level significantly (p=0.001). |

Table 2 Change in Atherosclerosis Markers After Eradication of \textit{Helicobacter pylori}

| Clinical Parameter | Reference: First Author (Reference No.) |
|--------------------|-----------------------------------------|
| Increased          | Pellicano\textsuperscript{74}, Gen\textsuperscript{75}, Kanbay\textsuperscript{76}, Scarnagl\textsuperscript{77}, Iwai\textsuperscript{78} |
| HDL-C              | Scarnagl\textsuperscript{77} |
| Apolipoprotein AI, apolipoprotein All | Pellicano\textsuperscript{74} |
| BMI                | Pellicano\textsuperscript{74} |
| Diastolic blood pressure | Pellicano\textsuperscript{74} |
| No Change          | Lu\textsuperscript{85} |
| Blood sugar        | Lu\textsuperscript{85}, Elizalde\textsuperscript{86} |
| Lipid and fibrinolytic parameters | Elizalde\textsuperscript{87} |
| Inflammatory parameters and platelet activation markers | Elizalde\textsuperscript{87} |
| Decreased          | Pellicano\textsuperscript{74}, Gen\textsuperscript{75}, Kanbay\textsuperscript{76} |
| CRP                | Pellicano\textsuperscript{74}, Yusuf\textsuperscript{79} |
| Fibrinogen         | Pellicano\textsuperscript{74}, Yusuf\textsuperscript{79} |
| Total oxidant status levels | Kebapci\textsuperscript{80}, Nazligil\textsuperscript{81} |
| LDL-C              | Gen\textsuperscript{75} |
| Total Cholesterol  | Gen\textsuperscript{75}, Jalalzadeh\textsuperscript{82} |
| Triglyceride       | Gen\textsuperscript{75} |
| Insulin resistance | Gen\textsuperscript{75} |
| BMI                | Jalalzadeh\textsuperscript{82} |
| Blood pressure     | Migneco\textsuperscript{22}, Nasrat\textsuperscript{23} |
| Coronary artery lumen | Kowalski\textsuperscript{83} |
| Coronary heart disease | Wang\textsuperscript{79} |
| Improved           | Blum\textsuperscript{84} |

Abbreviations

CVD, cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; BMI, body mass index; TNF, tumor necrosis factor; IL, interleukin; COX, cyclooxygenase enzyme; LPS, lipopolysaccharide; NO, nitric oxide; CagA, cytoxin-associated gene A; CRP, C-reactive protein.

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Author Contributions

YF: Conceptualization; YF, MK, JY, TY, AN, RI, HT, and YS: Data curation; YF: Formal analysis; YF: Investigation;
YF: Methodology; YF: Project administration; YF: Supervision; YF: Validation; YF: Roles/Writing; YF: original draft; YF: Writing; YF: review & editing. All authors read and approved the final manuscript.

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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