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,¹ idiopathic thrombocytopenic purpura,² and iron-deficiency anemia,² this infection may also be involved in non-digestive tract diseases such as chronic urticaria,³ Alzheimer's disease,⁴ Parkinson's disease,⁵ atrial fibrillation,⁶ liver diseases,⁷ Behçet's disease,⁸ hyperemesis gravidarum,⁹ infertility,¹⁰ glaucoma,¹¹ alopecia areata,¹² and arteriosclerosis disease¹³ including dyslipidemia,^{14,15} diabetes,^{16–18} obesity,^{19,20} hypertension,^{15,21–23} chronic kidney disease²⁴ and cardiovascular disease.^{24–29} Several reports have indicated a relationship between *H. pylori* and acute coronary syndrome,²⁵ which suggests that *H. pylori* infection is a risk factor for cardiovascular disease (CVD);^{24,26,27} moreover, patients with *H. pylori* infection show an approximately 3-times higher risk of coronary artery disease than do healthy individuals.²⁸ 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.²⁹ *H. pylori* infection was found to be an independent risk factor for carotid artery plaque and stroke.²⁶

A relationship between *H. pylori* infection and lifestyle-based diseases has also been suggested. Associations of *H. pylori* infection with hypercholesterolemia,¹⁴ low levels of high-density lipoprotein-cholesterol (HDL-C), and high levels of low-density lipoprotein-cholesterol (LDL-C) have been reported.¹⁵ Several studies have found that *H. pylori* is associated with insulin resistance¹⁶ and diabetes mellitus.^{17,18} Furthermore, *H. pylori* infection has been reported to be positively correlated with body mass index (BMI).¹⁹ 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.²⁴ Hypertension has also been associated with *H. pylori*

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infection;¹⁵ *H. pylori*-positive hypertensive patients show significantly higher arterial blood pressure than that of hypertensive patients without the infection.²¹ Furthermore, the eradication of *H. pylori* has been reported to improve hypertension.^{22,23}

Conversely, findings related to arteriosclerosis accompanied by *H. pylori* infection vary,^{5,30–39} 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 *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 *H. pylori* infection and the effects of *H. pylori* eradication.

Methods

We performed a detailed review of the recent literature to study the relationship between *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 *H. pylori* infection and the role of eradication of *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 *H. pylori* infection and arteriosclerosis.

Helicobacter pylori Infection and Arteriosclerosis

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

Secondly, since epidemiological research⁴⁶ indicates that *H. pylori* infection may be a new risk factor for CVD, the higher prevalence of hypertension in patients with *H. pylori* infection may be a result of the existence of factors specific to *H. pylori* that also play a role in arteriosclerosis. Possible mechanisms by which atherosclerosis could be caused by *H. pylori* have been reported (Box 1).^{23,27} *H. pylori* infection was reportedly associated with increased prevalence of metabolic syndrome, CVD, and high levels of fibrinogen, total cholesterol, uric acid, and blood glucose.^{26,47} Moreover, *H. pylori* causes persistent long-term infections⁴⁸ that lead to chronic inflammation,^{27,49,50} platelet activation,^{28,51} dyslipidemia,^{14,15,52} glucose intolerance,^{16–18,53} hyperhomocysteinemia,^{27,54} increased resorption of sodium due to elevated ammonia levels in the digestive tract,²³ direct invasion of the vascular walls,^{55,56} and reaction in atheromas.²⁸ Additionally, chronic inflammation due to *H. pylori* infection activates a variety of chemical mediators that have been linked to endothelial dysfunction.⁴⁹ Specifically, *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.^{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 al²³ and Vijayvergiya et al.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).²⁷ 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.^{60,61} This immune response to LPS could also increase the risk of atherosclerosis.⁶²

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.⁶³ Antigenic cross-reactivity between human heat shock protein and *H. pylori* has been reported to cause coronary artery calcification and atherosclerosis;^{64,65} as well as the activation of helper T-cells.⁶⁶

CagA (cytotoxin-associated gene A) is a very important *H. pylori* virulence factor associated with a greater inflammatory response.^{67,68} 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.⁶⁹ CagA-positive *H. pylori* patients showed a higher risk of CVD and stroke.^{27,70,71} CagA, at a molecular level, mimics human tropomyosin and cardiac adenosine triphosphatase that can cause myocardial damage;^{72,73} it also promotes secretion of cytokines that induce severe inflammation and atherosclerotic destabilization.⁵⁰ Moreover, CagA was reported to promote arteriosclerosis by increasing the levels of COX-1 and COX-2 in the vascular endothelium, thus promoting prostacyclin production, platelet activation,⁵⁰ and increased levels of oxidized LDL-C, high-sensitivity C-reactive protein (CRP), and Apolipoprotein B.⁷²

H. pylori infection has been reported to induce thromboxane, which activates platelets²⁸ and promotes their binding to the Von Willebrand factor, causing platelet aggregation and destabilization of atherosclerotic plaques.⁵¹ 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.⁵²

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.⁵³ 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.²⁷ 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.²³

Invasion of *H. pylori* into atheromas has been observed using PCR.⁵⁵ Direct *H. pylori* colonization in the arterial walls has also been suggested.⁵⁶ In addition, *H. pylori* reacts with monocytes and activates the proliferation of fibroblasts in atheromas.²⁸ Therefore, *H. pylori* has been linked to arteriosclerosis 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 arteriosclerosis.

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,^{74–78} apolipoprotein AI, apolipoprotein AII,⁷⁷ and BMI levels,⁷⁴ as well as higher diastolic blood pressure,⁷⁴ decreased levels of CRP,^{74–76} fibrinogen,^{74,79} total oxidant status,^{80,81} LDL-C,⁷⁵ total cholesterol,^{75,82} triglycerides,⁷⁵ insulin resistance,⁷⁵ BMI,⁸² blood pressure,^{22,23} coronary artery lumen,⁸³ and coronary heart disease²⁹ and improved endothelial dysfunction⁸⁴ (Table 2). Although there might be favorable effects of treating *H. pylori* on arteriosclerosis, in some studies the effects of *H. pylori* eradication on sugar,⁸⁵ lipid and fibrinolytic parameters,^{85,86} inflammatory parameters and platelet activation markers⁸⁷ were not confirmed. The contradictory results for BMI and blood pressure might be related to the study design;⁷⁴ 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 arteriosclerosis 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 I 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 ⁸³	2001	Germany	100 patients with coronary artery disease vs 100 patients without	Mean coronary artery lumen reduction in patients undergoing percutaneous coronary angioplasty + <i>Helicobacter pylori</i> eradication therapy was significantly ($p<0.05$) smaller compared to percutaneous coronary angioplasty + placebo-treated.
Lu ⁸⁵	2002	Taiwan	48 patients with gastric <i>H. pylori</i> infection	Coronary risk factors including fasting sugar, lipid and fibrinolytic profiles were not changed after successful <i>H. pylori</i> eradication treatment.
Yusuf ⁷⁹	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 <i>H. pylori</i> in patients with raised fibrinogen levels ($p<0.01$).
Elizalde ⁸⁶	2002	Spain	487 received eradication treatment vs 199 did not receive eradication treatment	<i>H. pylori</i> eradication has no influence on blood lipids or fibrinogen levels.
Migneco ²²	2003	Italy	72 hypertensive patients vs 70 normotensive controls	A significant reduction in blood pressure after eradication of <i>H. pylori</i> in hypertensive subjects.
Elizalde ⁸⁷	2004	Spain	92 patients with recent acute coronary syndromes	There was not any change in inflammatory parameters or platelet activation markers after <i>H. pylori</i> eradication in patients with acute coronary syndrome.
Scarnagi ⁷⁷	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 ⁷⁶	2005	Turkey	78 patients with <i>H. pylori</i> antigen positivity, 57 patients with <i>H. pylori</i> eradication vs 21 patients without <i>H. pylori</i> eradication	Increase in HDL-C and reduction in CRP with successful eradication ($p<0.05$).
Pellicano ⁷⁴	2009	Italy	496 patients with <i>H. pylori</i> -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 ⁸⁰	2009	Turkey	In 33 patients, <i>H. pylori</i> infection was successfully eradicated	Soluble CD40 ligand, and total oxidant status levels were significantly decreased after <i>H. pylori</i> eradication.
Gen ⁷⁵	2010	Turkey	88 patients with <i>H. pylori</i> infection vs 71 patients without <i>H. pylori</i> infection	Improvement in insulin resistance, lipid abnormalities and CRP levels with <i>H. pylori</i> eradication ($p<0.05$).
Nazligul ⁸¹	2011	Turkey	30 patients with <i>H. pylori</i> infection	After eradication treatment, serum myeloperoxidase activity and total oxidant status were significantly lower.
Blum ⁸⁴	2011	USA	31 dyspeptic patients were diagnosed as <i>H. pylori</i> positive using histopathological evaluation. 11 dyspeptic patients were negative to <i>H. pylori</i> (controls).	<i>H. pylori</i> eradication can improve endothelial dysfunction ($p=0.001$) significantly.
Jalalzadeh ⁸²	2012	Iran	59 patients negative for <i>H. pylori</i> vs 39 patients positive for <i>H. pylori</i>	In hemodialysis patients positive for <i>H. pylori</i> , 6 months after eradication of <i>H. pylori</i> , 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.
Nasrat ²³	2015	Saudi Arabia	99 middle-aged male patients on treatment for essential hypertension and positive for <i>H. pylori</i> dyspepsia	Most patients of the study (90.9%) were able to discontinue medication and maintain normal blood pressure values after <i>H. pylori</i> eradication.

(Continued)

Table 1 (Continued).

First Author (Reference No.)	Year	Country	Subjects	Outcome
Wang ²⁹	2018	Taiwan	In patients with peptic ulcer disease, 3164 patients with <i>H. pylori</i> eradication vs 3164 patients without <i>H. pylori</i> 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 ⁷⁸	2019	Japan	163 patients with <i>H. pylori</i> -associated chronic gastritis	<i>H. pylori</i> eradication therapy increased the HDL cholesterol level significantly ($p=0.001$).

Table 2 Change in Atherosclerosis Markers After Eradication of *Helicobacter pylori*

	Clinical Parameter	Reference: First Author (Reference No.)
Increased	HDL-C	Pellicano ⁷⁴ , Gen ⁷⁵ , Kanbay ⁷⁶ , Scarnagi ⁷⁷ , Iwai ⁷⁸
	Apolipoprotein AI, apolipoprotein AII	Scarnagi ⁷⁷
	BMI	Pellicano ⁷⁴
	Diastolic blood pressure	Pellicano ⁷⁴
No Change	Blood sugar	Lu ⁸⁵
	Lipid and fibrinolytic parameters	Lu ⁸⁵ , Elizalde ⁸⁶
	Inflammatory parameters and platelet activation markers	Elizalde ⁸⁷
Decreased	CRP	Pellicano ⁷⁴ , Gen ⁷⁵ , Kanbay ⁷⁶
	Fibrinogen	Pellicano ⁷⁴ , Yusuf ⁷⁹
	Total oxidant status levels	Kebapcila ⁸⁰ , Nazligul ⁸¹
	LDL-C	Gen ⁷⁵
	Total Cholesterol	Gen ⁷⁵ , Jalalzadeh ⁸²
	Triglyceride	Gen ⁷⁵
	Insulin resistance	Gen ⁷⁵
	BMI	Jalalzadeh ⁸²
	Blood pressure	Migneco ²² , Nasrat ²³
	Coronary artery lumen	Kowalski ⁸³
	Coronary heart disease	Wang ²⁹
Improved	Endothelial dysfunction	Blum 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, cytotoxin-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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