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Review Article

Helicobacter pylori and cardiovascular complications: a mechanism based review on role of *Helicobacter pylori* in cardiovascular diseases

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ABSTRACT

Heart disease comprises a wide class of cardiovascular abnormalities, including ischemic heart disease, myocardial infarction, atherosclerosis, and coronary artery disease. It is the leading cause of death all over the world. Several traditional and novel risk factors, such as infectious and noninfectious agents, have been associated with heart disease. Out of these, *Helicobacter pylori* has been recently introduced as an important etiological factor for heart disease. Numerous seroepidemiological findings observed *H. pylori* antibodies in the blood of a patient with cardiovascular complications. The bacteria survive in the epithelial cells of gastric organs and cause digestive complications. Excess inflammatory pathogenesis and prognosis stimulate an immune response that further causes significant disturbances in various factors like cytokines, fibrinogen, triglycerides, high density lipoprotein, C-reactive protein, heat shock protein, and white blood cell count, and provoke a number of problems such as atherosclerosis and prothrombic state, and cross-reactivity which eventually leads to heart diseases. *H. pylori* releases toxigenic nutrients, chiefly vacuolating cytotoxin gen A (Vac A) and cytotoxin associated gene A (Cag A), of which Cag A is more virulent and involved in the formation of cholesterol patches in arteries, induction of autoimmune disorder, and release of immune mediated response. Although numerous mechanisms have been correlated with *H. pylori* and heart disease, the exact role of bacteria is still ambiguous.

1. Introduction

Introduction of heart disease to the medical community has been a focus of debate, due to the continuously increasing rate of mortality in developed and developing countries.[1–3] Heart diseases or cardiovascular diseases describe several heart disorders, including elevated blood pressure, coronary artery disease, and blockage of the arteries. A number of diseases related to the heart and blood vessels can come under the umbrella of heart.[4] Diverse risk factors such as hypertension, increased lipid level, obesity, diet with high

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fat, physical inactivity, diabetes, and stress conditions are generally associated with it. Certain microorganisms such as *Chlamydia pneumoniae*, *Cytomegalovirus*, Epstein-Barr virus, human immunodeficiency virus, Herpes simplex, and *Helicobacter pylori* contribute in the development of heart diseases and are considered as risk factors and infectious.[5–8]

H. pylori infection has been reported as an important cause of chronic gastrodigestive ulcers, however the epidemiological study based on discovery of bacteria during the past two decades has suggested that the higher prevalence of *H. pylori* infection might be involved in the pathogenesis of heart disease.[9–13] In recent years, a theory has been proposed that a bacterium is one of the potential mechanisms that can cause direct and indirect effects on heart disease. Inflammatory and immunological events provoked by the *H. pylori* infection are the main underlying causes of the heart disease.[14–16] The effect of infection on cardiovascular physiology can be direct and indirect. The direct effect includes endothelial injury, dysfunction through circulating endotoxins, smooth muscle proliferation, and local inflammation, whereas the indirect effect includes proinflammatory, hypercoagulability, atherogenic action, production of cross reactive antibodies, oxidation of low density lipoprotein, molecular mimicry, oxidative modification as well as nutrient/vitamin malabsorption and metabolic disturbances such as excess ammonia production.[17–23] Recent studies suggested that a highly virulent strain of *H. pylori* [cytotoxin associated gene A (Cag A) strain] was more strongly associated with the risk of heart diseases which was confirmed by the presence of anti *H. pylori* antibodies through seroprevalence.[24,25] The objective of the present review is to highlight all possible mechanisms responsible for heart disease in relation with *H. pylori* infection.

1.1. *H. pylori*

The presence of a spiral-shaped bacterial microorganism was described by Professor W. Jaworski at Cracow in Jagiellonian University, Kraków, Poland. Later, Marshall and Warren[27] cultured an organism from a gastritis patient which was not exactly the same as any previous species; it perhaps belonged to the *Campylobacter* genus, so they named it "pyloric campylobacter" which was later changed to *Campylobacter pylori*, and after that, it was named *H. pylori* due to its distinct morphogenic structural and genetic features. It has a heterogeneous morphology and normally it is present in a helicoidal, spiral, or curved shape, while in aged culture it is observed in coccoid form.[26–32]

H. pylori is a unipolar and microaerophilic bacterium. It contains five major outer membrane protein families. The largest family is putative adhesions whereas the other four families include porins, iron, transporters, flagellum-associated proteins, and proteins of unknown function. As it is a Gram-negative bacterium, its outer membrane consists of phospholipids and lipopolysaccharides and it also contains cholesterol glucosides, which are found in a few other bacteria. The high motility of the bacteria is due to the presence of two to six lophotrichous flagella. These sheathed flagellar filaments are composed of two copolymerized flagellins; flagellin A and flagellin B.[33–37] They are about 0.5–1 mm in diameter and 2.5–5.0 mm long. They require about 5% oxygen (O_2) and 5–10% carbon dioxide (CO_2). *H. pylori* produces oxidase, catalase, and urease enzymes. The ability of the bacteria to survive in the harsh environment of the stomach is because of urease synthesis, a powerful enzyme which converts urea, a chemical made by stomach cells, to carbon dioxide and ammonia. This in turn creates a protective environment to the bacteria, by neutralizing acidity in the mucus surrounding the bacteria.[38–42] The variability among strains of *H. pylori* is due to the availability of multiple bacterial genome sequences. It is one of the most genetically diverse species of bacteria, as it produces a wide range of toxins. Due to high virulent factors, it has been linked with many diseases. These virulent factors mainly include vacuolating cytotoxin gene A (Vac A) production and Cag A. About 50% of *H. pylori* strains produce Cag A which has been specifically linked to heart disease. These toxigenic nutrients of *H. pylori* cause inflammation to host cells and strong cellular damage, and rapidly stimulate host factors such as interleukins (ILs; IL-1, IL-2, IL-6, IL-8, and IL-12), interferon-gamma, tumor necrosis factor-α, T and B lymphocytes, and phagocytic cells, thereby increasing chances of heart disease.[43–48]

1.2. *Association between H. pylori and heart diseases*

Several studies have ruled out and it has been suggested that *H. pylori* infection is not only linked to gastroduodenal conditions, but also extragastroduodenal conditions such as heart disease. The bacterial role in several diseases has been studied on the basis of serological surveillance.[49–54] Although these studies have too many biases, for the awareness of the people regarding this asymptomatic infection, a hypothesized theory has been made using epidemiological and pathological studies which might be responsible for heart disease.

H. pylori is one of the most widespread infections in the world. Although *H. pylori* infection is common, it is difficult to identify. The delayed diagnosis of infection exaggerates numerous problems, thus, epidemiological studies are generally preferred to recognize the incidence of *H. pylori* infection. Several studies have been executed for evaluating *H. pylori* incidences and prevalence, transmission of infection, and associated risk factors responsible for the infection. It has been evident that the prevalence of infection was erratic from region to region, between the socioeconomic and ethnic groups. Three main factors, namely rate of acquisition of infection (incidences), the rate of loss of infection; and prolonged prevalence of the bacterial infection and eradication are mainly responsible for *H. pylori* infection in the community.

The prevalence of infection is about 60–70% in adults and increases with age, while in children it is 20–30%. Its prevalence is greater in men than in women and many studies have shown that nonHispanic blacks and Hispanics are more prone to infection than the White population.[55–59] The exact mode of *H. pylori* infection transmission is not clear, but several transmission mechanisms have been suggested such as direct transfer from person to person (via fecal-oral or oral-oral routes), epidemiological factors (food borne, water borne), and some zoonotic transmission (primates, domestic cats, and sheep). It is specifically seen in poorly sanitized people, in crowded living conditions, and with diminished hygiene.[60–67]

2. Pathological mechanism

No single factor could account for infection related heart diseases, as the infection is a multifactorial process. Several potential mechanisms and pathways allied with *H. pylori* contribute in infection-induced cardiovascular complications. Fig. 1 briefly focuses on different mechanisms by which *H. pylori* contributes to heart diseases.

Inflammation is a protective multistep process of the immune system. Repeated exposure to *H. pylori* infection leads to failure of the inflammation process and inability to combat progress of infectious agents, which leads to a number of diseases such as heart disease and cancer. This continuous over stress causes weakening of the body.[68–72] Chronic stimulation of inflammatory responses due to bacterial infection in gut and gastric organs further produces induction of dyslipidemia, increases the levels of fibrinogen, stimulates release of C-reactive protein, escalates blood leukocytes and homocysteine, induces hypercoagulability, stimulates immune cross-reactivity, increases proinflammatory cytokines (ILs, lymphocytes) and other cytotoxic agents. This dramatic rise in the production of various proinflammatory and inflammatory metabolites affects blood vessel motility and provokes endothelial dysfunctioning, which results in blocking of arteries, thereby increasing the chances of heart attack. It has been reported that C-reactive protein is a potential indicator of disease associated with the heart and may play a crucial role in vessel mortality. Bacterial infection also enhances the release of IL-8, a small peptide (chemokine) secreted by various cell types, which serves as a potent inflammatory mediator recruiting and activating neutrophils such as T and B lymphocytes. Thus, chronic *H. pylori* infection results in disturbed immune response, which ultimately contributes to cardiovascular abnormalities including coronary artery diseases.[73–75]

Increased inflammation and cellular damage caused by adhesion of *H. pylori* infection in the body may increase the release of toxins such as Cag A and Vac A. Recently, it has been revealed that Cag A positive strain has been linked to *H. pylori*-associated heart disease more virulently than the Cag-A negative strain. It has been observed that Cag A strains enhance the activity of cycloxygenase-1 and -2 in vascular endothelial cells. Also, Cag A-induced inflammation may encourage the immune-mediated release of cytokines such as IL1–12, monocytes, macrophages (tumor necrosis factor α), and T and B lymphocytes, thereby causing heart disease or heart shock. Also, an autoimmune reaction could be postulated which includes cross-reactivity between anti-Cag A antibodies and vascular wall antigens, suggesting that these antibodies may contribute to the activation of inflammatory cells within atherosclerotic lesions.[76–80]

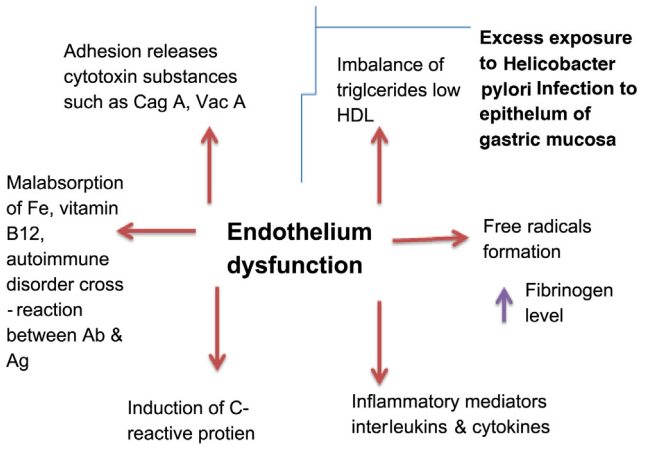

Fig. 1 – *Helicobacter pylori* infection induced immune response
HDL, high density lipoprotein.

H. pylori infection exaggerates disturbances in the metabolism of lipid and lipoprotein. Triglyceride levels usually rise and the level of high density lipoprotein-cholesterol decreases. This could be due to the involvement of cytokines, especially tumor necrosis factor-α, which inhibits lipoprotein lipase and enhances free radical generation. This in turn facilitates the oxidation of low density lipoprotein, which is a key event in atherosclerosis. Free radicals also provoke activation of platelet and leukocyte chemotaxis, and might be responsible for thrombus formation. Increased release of various factors such as fibrinogen, C-reactive protein, tumor necrosis factor, IL-6, and white blood cell count might induce a prothrombotic state.[81–83]

Some studies revealed that *H. pylori* also decreases absorption of iron through reduction of the ferric to the ferrous form. Generally, this reaction is enhanced by ascorbic acid, but in the presence of *H. pylori* infection, decreases its concentration. It has been suggested that there is a competition between the bacteria and host for iron, as it is an essential element for growth. Thus, starvation of iron results in pernicious anemia, which further leads to the reduction in the number of circulating red blood cells, bleeding, and malabsorption of vitamin B12.[84,85]

H. pylori burden contains a protein on the arterial cell surface that is similar to the heat shock protein-60 found in endothelial cells. Therefore, an immune response to *H. pylori* may induce immune cross-reaction between human and bacterial heat shock protein-60, which in turns leads to an autoimmune reaction and local inflammation of the artery.[86] There is also speculation regarding the role of *H. pylori* in atherosclerotic plaque development, because some studies have found bacterial deoxyribonucleic acid in arterial plaques where it forms patches of infection, which results in heart disease.[86]

3. Conclusion

Infection of *H. pylori* bacteria infection is directly or indirectly involved in the development of cardiovascular diseases. Several serological based findings have revealed the active role of *H. pylori* in heart diseases. Activation of inflammatory mediators, proinflammatory factors, release of toxins, abnormal lipid metabolism, altered iron metabolism, and autoimmune reaction are the leading mechanisms of *H. pylori*, which contributes in cardiovascular anomalies. The chief leading role in the cause of heart disease is the improper functioning of the immune system, both at the cellular and systemic level. Most of these findings are based on serological

findings. Further studies are needed to recognize the exact involvement of *H. pylori* in these diseases.

Conflicts of interest

We declare that we have no conflicts of interest.

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