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Heart Disease Due to Infections: the *Helicobacter pylori*

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Traditional cardiovascular risk factor, such as hyper cholesterolemia, smoking, diabetes, and hypertension, do not necessarily explain the incidence of heart disease. Several less substantiate risk factors may contribute significantly to cardiovascular Pathogenesis. *H. pylori* is a gram-negative, microaerophilic, spiral bacterium that occurs naturally, and inhabits the mucus layer that covers the gastric epithelial cells. This Short review deals with the heart disease due to infection, *H. pylori*.

Key words: *H. Plyori*, heart disease

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In recent years, observational studies in humans have provided intriguing hints linking certain viral and bacterial infections to coronary heart disease (CHD) (Gura, 1998; Libby *et al*., 1997; Lip and Beevers, 1997). Mechanistic studies suggested that gene products of infectious agents may acts directly on the vascular cells. Nevertheless, an important question is, whether infectious agents can exert vasculopathic effects without infecting vascular cells. For example, the atherogenic changes seen in infected endothelial and smooth muscle cells can be caused by systemic inflammation due to chronic infection and activation of circulating inflammatory cells. It is also possible that infectious agents currently showing weak associations with vascular disease, as well as with infectious agents which were not previously associated with atherogenesis, may contribute to vascular pathogenesis. Rupprecht *et al*. (2001) analyzed infectious burden with 8 pathogens in 1018 CHD patients and found that only Epstein-Barr virus, *Helicobacters pylori* and herpes simplex virus type 2 were independently associated with the potential death from CHD.

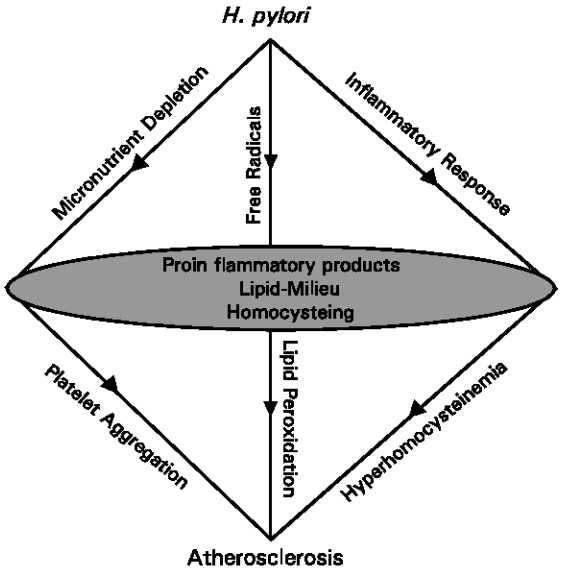
H. pylori originally thought to be a member of the genus Campylobacter, occurs naturally and inhabits the mucus layer that covers the gastric epithelial cells (Dekigai *et al*., 1995). It is a gram-negative, microaerophilic, spiral bacterium that possesses a powerful enzyme, urease. Urease protects this organism and allows it to survive in an acidic environment by producing ammonia that increases the pH in immediate vicinity (Booth, 1985). The ammonia gas is toxic to gastric and other epithelial cells resulting in hypochlorhydria in the stomach (Suzuki *et al*., 1992). *H. pylori* is commonly accepted as the etiological agent of type B gastritis and as a major contributor to peptic ulcer disease (Graham, 1989). Several specific virulence factors such as cytotoxin-associated gene A (cagA) and vacuolating cytotoxin A (vacA) as well as other noxious substances including ammonia, lipopolysaccharide (endotoxin), platelet activating factor (PAF), nitric oxide (NO), have been implicated in gastritis (Perri *et al*., 1999; Cover and Blaser, 1996). Chronic inflammation, atrophic gastritis, intestinal metaplasia, impaired micronutrient absorption (ascorbic acid and vitamin B_{12} in particular) combined with hypergastrinemia in the stomach, excessive reactive oxygen species (ROS) and epithelial cell proliferation have all been associated with gastric cancer due to *H. pylori* (Blaser, 1992; Correa, 1995; Konturek *et al*., 1999). Consequently we found a state of oxidative stress, as defined by an excessive pro-oxidant, i.e., ROS, activity with concomitant inadequate/compromised antioxidant protection, in *H. pylori* infected human subjects (Khaled and Sarker, 1998). Oxidative state, at least in terms of lipid per oxidation, plays a greater role in the pathogenesis of heart disease (Khan and Baseer, 2000).

Sung and Sanderson (1996) and Markle (1997) hypothesized possible mechanisms of association of *H. pylori* infection and CHD involving hyperhomocysteinemia which is caused by the over-production of total homocysteine (tHCY) (Goraham, 1997). Basic etiological factors for homocysteine formation are the following:

a) Nutritional deficiencies of folic acid, vitamin B_{12} and/or vitamin B_6.
b) There could be a faulty transport protein for any of the above vitamins/cofactors.
c) There may be a genetic component. For example, the genetically heterozygous loss of cystathionine β-synthase in the transsulfuration pathway results in the disease homocystinuria. This disease causes profound cardiovascular disease. Another genetic disease affecting tHCY levels in plasma is a mutation of the methylene tetrahydrofolate reductase (MTHFR) gene, which results in a thermolabile enzyme, the end result of which is a large reduction of methyl groups being made available to the remethylation pathway, and the subsequent build-up of homocysteine.

Soon after Sung and Sanderson (1996) proposed their hypothesis, a handful of investigators claimed that no such association of tHCY could be found in CHD patients infected with *H. pylori* (Whincup *et al*., 1997; Saxena *et al*., 1997; Leung *et al*., 2001). In the absence of many other pieces of information, particularly patients' dietary habits, Menge *et al*. (2000) commented that the proposed link between tHCY and *H. pylori* needed further investigations. For example, if the patients with and without *H. pylori* infection did have adequate and/or equal intake of the above mentioned nutrients, these observations might have been confounded. Additionally, Chambers *et al*. (2000) reported tHCY-induced abnormal endothelial function in humans due to the deficiency of the above mentioned B vitamins. Interestingly, such adverse effects due to tHCY were reversed by supplementation with vitamin C (Chambers *et al*., 1999). We and others have shown that *H. pylori* is capable of depleting these micro nutrients in humans (Carmel *et al*., 1994; Khaled *et al*., 1997).

Lip *et al*. (1996) reported an important finding that the body mass index (BMI), an approximate measure of body fatness, was significantly higher in *H. pylori* seropositive than seronegative patients with CHD; (BMI 28.4 $\pm$ 4.2 vs 26.2 $\pm$ 3.2 p = 0.019). Mendall *et al*. (1997) also reported a strong association between BMI and TNF-alfa in *H. pylori* infected CHD patients. Recently, we, found a significant difference in TNF-alfa and TBARS (thiobarbitoric acid reacting substance, as an index of lipid per oxidation) between *H. pylori* positive and negative healthy human subjects with similar BMI (Khaled and Mahalanabis, 2000). Interestingly, *H. pylori* infection has also been found to modify serum lipid, particularly triglyceride (TG), concentrations (Laurila *et al*., 1999) and higher serum TG is associated with higher lipid per oxidation, a known risk factor for CHD (Khan and Baseer, 2000). Recently, it has been well documented that the level of lipid per oxidation increased linearly with increased levels of tHCY (Welch and Loscalzo, 1998). After having described our and others studies on *H. pylori*, related to its associations with heart disease, probable mechanisms of *H. pylori* actions could be visualized by mapping its pathways as depicted in the diagram below.



The circulating lipid-milieu in this diagram is a major host factor. This host factor could be exacerbated either by the host's visceral fat/TG and/or by *H. pylori* infection and/or by the host's dietary habits. Per oxidation of this lipid-milieu, leading to atherosclerosis, could be induced by some inflammatory/

proinflammatory products as generated by *H. pylori*. Hyperhomocysteinemia, as a consequence of *H. pylori* infection, is also capable of inducing atherosclerosis either by per oxidation of the lipid milieu and/or by promoting platelet aggregation. Depletion of antioxidant protection, as created by this bacterium, could very well facilitate development and/or aggravate incidence of atherosclerosis in humans. Prospective scientific investigations in this direction will be necessary to substantiate this model of *H. pylori* actions associated with the induction and/or progression of CHD in humans.

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