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Helicobacter pylori and Extragastroduodenal Disorders

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Introduction

Peptic ulcer disease and gastric maligancydiseases are well known related to *Helicobacter pylori* (*H.pylori*) infection, and further studies have shown the *H.pylori* infection possible role in several extragastric disoders. There are many reports related to metabolic syndrome, cardiovascular disease and colon adenoma, in which *H. pylori* may possibly play a potencial factor. Different mechanisms of action have been proposed, ranging from the induction of an inflammatory process to the occurrence of molecular mimicry mechanisms in the human microbiota. This review summarizes the results of the most relevant studies published on these three popular topics metabolic syndrome, cardiovascular disease and colon adenoma associated with *H.pylori* infection.

During the past years, several studies performed have supported the possible role for *H. pylori* infection in the pathogenesis of several extragastric diseases. As well known , *Helicobacter pylori* (H. pylori) infection is confirmed to correlate with chronic gastritis, peptic ulcer disease, Mucosa Associated Lymphoid Tissue (MALT)-lymphoma, precancerous changes in the stomach (atrophy, intestinal metaplasia), and gastric cancer [1]. In addition, the persistence of a pathogen in an environment long thought to be sterile also resulted in insights into the pathogenesis of chronic diseases. Many of these H. pylori-host interactions have similarities with the interactions between the gut flora and the gastrointestinal tract and may serve as paradigms for the interactions between bacteria and their hosts [2]. This chronic infection has the local production and systemic diffusion of proinflammatory cytokines, which may influence the remote organic systems and result in extragastric manifestations [3]. *H. pylori* could influence the process of carcinogenesis in organs other than the stomach is gaining increasing attention.

Some epidemiologic studies report a significant link between *Helicobacter pylori* infection and certain cardiovascular disease risk factors, suggesting that chronic inflammation caused by *H. pylori* promotes atherosclerosis and cardiovascular disease [4-6]. A large Japanese population study also revealed that infection with *H. pylori* was significantly and independently associated with metabolic syndrome through alterations in several metabolic parameters, and eradication of *H. pylori* might have a role in preventing metabolic syndrome [7]. Besides, *H. pylori* infection and elevated HbA1c has reported a synergistic effect on the risk for colon adenoma and carotid artery plaque formation [8]. This review article is aimed at summarizing the most relevant studies about metabolic syndrome, cardiovascular disease and colon adenoma.

Helicobacter pylori and Metabolic Syndrome

Metabolic syndrome is characterized by a cluster of metabolic abnormalities including hypertension, hyperlipidemia, and hyperglycemia, in combination with visceral obesity [9]. Additionally, the status of insulin resistance is also thought to be a potential risk factor for metabolic syndrome [10]. A possible role of *H. pylori* in diabetes mellitus (DM) has been fully investigated, and higher *H. pylori* re-infection rate in DM patients than in general population has been shown [11].

A large study from Japan(totally 5,095 cases including 3,854 men and 1,241 women) reported that the prevalence rate of *H. pylori* infection was significantly higher in cases with metabolic syndrome than the rate in those without metabolic syndrome (38.6 % vs 28.0 %, P < 0.001) [6]. The result also found that *H. pylori* seropositivity was significantly associated with higher systolic blood pressure, lower high-density lipoprotein (HDL)-cholesterol level, and higher LDL-cholesterol level by multiple linear regression analysis. It confirmed a significant association between *H. pylori* serostatus and metabolic syndrome. Another Taiwan study reported that chronic *H. pylori* infection is significantly associated with high levels of glycated hemoglobin HbA1c and type 2 DM in patients over 65 years old (p =0 .001) and decreased levels of insulin and insulin sensitivity in subjects under 45 years old (p = 0.05) [12]. Similar results were obtained in a study showing a positive correlation between *H. pylori* infection and nephropathy in DM patients [13]. In a study enrolling total of 1791 (49.2% males, 50.8% females) of the studied population with multiple logistic regression analysis, *H. pylori* infection [OR = 1.50 (1.12–2.00); p = 0.007] showed a significant association with the metabolic syndrome in men and [OR = 1.45 (1.09–1.94); 0.01] in women [14]. Chronic subclinical inflammation is increasingly recognized as a part of the insulin resistance syndrome [15,16]. Dysregulation of the inflammatory axis predicts the development of insulin resistance and type 2 diabetes mellitus. Insulin resistance and another inflammatory state, atherosclerosis, share similar pathophysiological mechanisms, mainly due to the actions of the two major proinflammatory cytokines, TNF-alpha and IL-6 [17]. In contrast, *H. pylori* eradication has being observed significantly improved blood pressure, glucose level, and lipid profile in men, suggesting a potential role of *H. pylori* in atherosclerosis and metabolic syndrome [18]. WAN, Zhengce, et al also reported *H. pylori* infection was associated with an increased prevalence of hypertension (OR, 1.23; 95% CI, 1.04- 1.46). In addition, compared with participants not infected with H. pylori, those with *H. pylori* infection had an increase of 0.735 mmHg (95% CI, 0.101-1.369) for diastolic blood pressure and 0.723 mmHg (95% CI, 0.034-1.413) for mean arterial pressure [19]. A recent large cross-sectional study in Israel were accessed for 147,936 individuals 25–95 years of age who performed the urea breath test during 2002–2012, which *H. pylori* infected persons had increased likelihood of metabolic syndrome: adjusted odds ratio 1.15 (95% confidence intervals (CI) 1.10–1.19). Metabolic syndrome appeared significantly increased in relation to *H. pylori* infection and gastric and duodenal ulcers [20]. These findings suggest that *H. pylori* long-term gastric inflammation might play a role in metabolic homeostasis.

Helicobacter pylori and Cardiovascular Disease

Cardiovascular disease and all-cause mortality are increased in men with the metabolic syndrome, even in the absence of baseline CVD and diabetes [21]. Because inflammation has been shown to play a key role in the destabilization of atherosclerotic plaques. Nakagawa et al. disclosed that high serologic IL-6 levels are significantly associated with *H. pylori* infection, possibly playing a role in ischemic heart disease [22]. Sealy-Jefferson et al. demonstrated that antibody levels to *H. pylori* predicted the incidence of strokes in a Mexican–American population (OR: 1.58; 95% CI: 1.09–2.28) [23]. Carotid artery plaque is also strongly associated with CVD, and a study showed hyperglycemia combined with *H. pylori* infection was an increased risk factor for synchronous colorectal adenoma and carotid artery plaque formation.[8] Kowalski et al. found that patients infected with CagA-positive *H. pylori* show significantly greater coronary artery lumen loss and arterial re-stenosis after PTCA with stent implantation ,and *H. pylori* eradication significantly attenuates the reduction in lumen of the coronary artery lumen in CAD patients after PTCA. In addition, the identification of DNA in atherosclerotic plaques of patients with severe CAD supports the hypothesis that *H. pylori* infection (especially CagA positive) may influence the development of atherosclerosis [24]. Besides, a trend of decrease in coronary heart disease(CHD) occurrence after early *H. pylori* eradication in addition to the significant decrease in composite end points for CHD and death, and the significantly lower cumulative CHD rate in younger patients < 65 years old with *H. pylori* treated within one year was found in a large cohort study(total of 208196 patients with peptic ulcer diseases (PUD) from the years of 2000 to 2011) such as big data from the Taiwan National Health Insurance Research Database, suggested that there was positive association between *H. pylori* eradication and CHD [25].

Both *Helicobacter pylori* and Chlamydia pneumoniae infections are associated with coronary heart disease, and odds ratios for abnormal electrocardiograms were 3.82 (95% confidence interval 1.60 to 9.10) and 3.06 (12.33 to 7.01) in men seropositive for *H.pylori* and C.pneumoniae, respectively, after adjustment for a range of socioeconomic indicators and risk factors for coronary heart disease [26]. Another recent research revealed seroprevalence of specific IgG antibodies for C. pneumoniae and *H. pylori* showed significant increase in C. pneumoniae IgG and *H. pylori* IgG positivity among 80 patients with previously diagnosed to have CAD compared to control (P value <0.001 and 0.015, respectively) [27]. In the similar studies, the association of adult coronary heart disease with H pylori seropositivity suggests that the early childhood environment may be important in determining the risk of CHD in adult life.

Helicobacter pylori and Colon Adenoma

There are more articless that support the biological convicing of this association with *Helicobacter pylori* and colon adenoma or colorectal cancer (CRC). A 2006 meta-analysis of elevan papers that analsyed this association found that those infected with *H. pylori* have an odds ratio of 1.4 for CRC [28]. Chen et al. [29] in a meta-analysis demonstrated that *H. pylori* infection indeed increases the risk of colorectal adenoma and adenocarcinoma (OR: 1.49; 95% CI: 1.30–1.72). Compared with normal gastric

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mucosa, *H. pylori* gastritis arises more frequently among patients with hyperplastic polyps, adenomatous polyps, advanced adenomas, villous adenomas or adenomas with high-grade dysplasia, and adenocarcinomas [30]. In the recent study, Kim et al who suggested *Helicobacter pylori* infection is an independent risk factor of colorectal neoplasm for any adenoma and advanced neoplasm, and the odds ratio (OR) (95% confidence interval [CI]) was 1.32 (1.07-1.61) and 1.90 (1.05-3.56) in participants with *H. pylori* infection and without *H. pylori* infection, respectively [31]. Furthermore, HU, Kuang-Chun, et al reported synergistic effect of hyperglycemia and *Helicobacter pylori* infection status on colorectal adenoma risk, which showed the prevalence of adenoma was increased with elevated HbA1c levels regardless of *H. pylori* status. The odds ratio (OR) for adenoma was 1.44 (95% confidence interval [CI], 1.20 to 1.73) if *H. pylori* was present or 1.68 (95% CI, 1.05 to 2.70) in patients who were H. pylori–negative but had HbA1c ≥7.0%. If both conditions were present, the OR was 4.79 (95% CI, 2.92 to 7.84). A 1% increase in HbA1c was associated with an increased prevalence of adenoma by 42.4% in H. pylori–positive subjects [32]. A similar mechanism underlying carotid artery plaque and colon adenoma formation may be related to chronic inflammation. Chiu et al. also found that elevated C-reactive protein levels were associated with colon adenoma [33]. H. pylori-related chronic gastritis could be involved in an increased risk of colorectal neoplasm that appears to be enhanced by the progression of gastric atrophy and the presence of active inflammation [34]. In detail mechanism about the connection between *H. pylori* infection and colorectal adenoma survey, Grivennikov et al. found colorectal adenoma in both human and mouse models had increased the amounts of interleukin (IL-23 and IL-17) via some bacterial products as endotoxin [35]. Endotoxin including a complex of lipopolysaccharide is part of outer membrane of gram-negative bacterium. Although *H. pylori* is not alone gram-negative bacterium in gut microbiota, other organisms (e.g., Bacteroides spp.) were belong gram-negative bacterium too. As noted above, *H. pylori* might be an indicator of changes in human microbiota. This finding might support the theory that *H. pylori* infection may have a role in the pathogenesis of colon adenoma.

Conclusion

There are more evidences about *H. pylori* infection may not be only a local gastric disease. Due to active inflammation and changing in human microbiota, more studies showed that metabolic syndrome, cardiovascular disease and colon adenoma have already been recognized as being associated with *H. pylori* infection. Besides, the synergistic effect of *H. pylori* infection with metabolic, atherosclerosis, and carcinogenesis pathway raises the question of whether eradicating *H. pylori* infection might reduce the prevalence of the diseases. The benefit of *H. pylori* eradication was not only in decreasing gastric malignancy disease but also reducing metabolic and cardiovascular disease, colorectal adenoma probability.

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