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Extra-digestive Manifestations of *Helicobacter pylori* Infection – An Overview

Sue K. Park

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Abstract

Helicobacter pylori (*H. pylori*) is well known as a group I human gastric cancer carcinogen by the International Agency for Research on Cancer. Although an exact causal relation‐ ship is unclear, *H. pylori* is expected to have been associated with non-digestive abnormal condition and/or diseases, such as metabolic syndrome, atherosclerosis and cardiovascu‐ lar diseases, which have substantially lots of prior studies; adaptive immune response – related disorders, such as autoimmune thyroid diseases (ATDs), urticaria, atopy and asthma; and the other extra-digestive diseases, such as chronic obstructive pulmonary disease (COPD), migraine, anemia and hyperemesis gravidarum. This chapter overviews several groups of extra-digestive diseases by *H. pylori* infection and discusses the role of *H. pylori* in relation to the diseases in the viewpoint of causality.

Keywords: *Helicobacter pylori*, non- digestive diseases, overview, causality, relationship

1. Introduction

Helicobacter pylori (*H. pylori*), gram- negative spiral or curved bacillus, was discovered in 1982 by two pathologists, Barry Marshall and Robin Warren, the 1982 Nobel Prize awardees. Almost all patients had active chronic gastritis or gastroduodenal ulcer and thus the bacteria got attention as an important etiological factor of these diseases. Ironically, back to the past, Freedburg and Barron had first found the spiral organisms among gastrectomy patients in 1940, but the bacteria were forgotten for a long time due to failure to replication in other studies.

H. pylori is an established cause of chronic active or superficial gastritis, gastroduodenal ulcer disease, gastric adenocarcinoma and the mucosa-associated lymphoid tissue (MALT) lym‐ phoma. The International Agency for Research on Cancer (IARC), a suborganization of the World Health Organization (WHO), classified the *H. pylori* as a group I human gastric cancer

carcinogen (the meaning of definite carcinogen) in 1994. *H. pylori* chronic infection to gastric tissue results in carcinogenic environment or causes chronic inflammation, which leads to gastric carcinogenesis. Chronic *H. pylori* infection also induces gastric lymphoid follicles and trigger MALT lymphomagenesis of lymphoid expansion, which leads to MALT lymphoma.

Although only a few people (1–3%) with *H. pylori* chronic infection develop gastric cancer, *H. pylori* explains a 60–90% of gastric cancer in studies of population attributable fraction (PAF) estimation.

Prior studies showed that *H. pylori* is also expected to be associated with extra-digestive diseases. The first group of diseases is abnormal metabolic profiles such as insulin resistance, diabetes, hypertension, obesity and dyslipidemia, which are the components of metabolic syndrome. Consequently, the abnormal profiles are complexly influenced to increase the risk for cardiovascular diseases by atherosclerosis and vascular dysfunction. The second group of diseases is adaptive immune response–related disorders, such as autoimmune diseases including autoimmune thyroid diseases (ATDs), atopic disease, urticaria and asthma. The other group is on elusive knowledge, such as COPD, glaucoma, migraine, anemia and hyperemesis gravidarum.

The suggested mechanism, despite of inconclusive causal relationship, is as follows: Chronic *H. pylori* infection induces chronic inflammation, a complex biological response of the tissues to *H. pylori*. Inflammatory factors including cytokines interleukin (IL) and tumor necrosis factor (TNF), especially induced from chronic, low-grade inflammation, on the infection-inflammation pathway are common in pathogenesis of gastritis, atherosclerosis, metabolic syndrome, obesity and diabetes. These inflammatory factors produced in the inflamed gastric mucosa are continually secreted into the circulation, and they can affect metabolic profiles.[1] Therefore, chronic, low-grade inflammation by chronic *H. pylori* infection may induce extra-gastric diseases due to the effect of *H. pylori*–induced cytokines.

H. pylori infection and its transmission were related to low socioeconomic status (SES) such as poor hygiene, water contamination, and non-healthy lifestyles such as poor diet, smoking and physical inactivity. Usually people who were tested with *H. pylori* infection are those in middle SES class and over, and therefore, non-gastric diseases are also diagnosed in this class. Poor hygiene hypothesis seems to be no more proper for these populations in the association of *H. pylori* infection with non-gastric diseases.

Therefore, this chapter introduces extradigestive diseases by *H. pylori* infection and discusses critical issues in the *H. pylori* role in extradigestive diseases in the viewpoint of causality of *H. pylori* infection for these diseases.

2. Dyslipidemia

Dyslipidemia, such as high total cholesterol and/or triglyceride concentration or low high-density lipoprotein (HDL) level, is a component for metabolic syndrome (MetS). Abnormal lipid profile in *H. pylori*–infected subjects has been reported in several studies. A review paper

for dyslipidemia using 8 related articles[1] showed that *H. pylori* infection patients had higher levels of plasma total cholesterol, low-density lipoprotein (LDL)-cholesterol and/or triglyceride, but lower levels of high-density lipoprotein (HDL)-cholesterol relative to non-infected patients. These conditions were significantly replicated in 5,077 Japanese men only in a large population study for *H. pylori* eradication therapy, but failed to replicate it in women due to small number of woman patients.[1, 2] However, Satoh et al. showed significant associations between *H. pylori* infection and LDL or HDL levels only in male subjects and there was no significant association between *H. pylori* seropositivity and triglyceride concentration in the same study.[2] It is postulated that overexpression of various cytokines, such as IL-6 and TNF-*α* by *H. pylori* infection, may stimulate production of fatty acids by activating lipoprotein lipase in adipose tissue. Successful eradication treatment of *H. pylori* may induce an increase of HDL and decrease of LDL and triglycerides, but the alteration of blood lipid profiles before and after eradication therapy is not consistent in the total five observational studies and clinical trials.[1]

3. Hypertension

Hypertension is a component of MetS. Various cytokines induced by *H. pylori* infection in gastric mucosa may stimulate the hypothalamus and brain stem, which leads to sympathetic activation by secretion of cortisol and adrenaline. The subsequent pathway may induce the high blood pressure.[3] Although Harvey et al. reported the significantly positive association of *H. pylori* infection with hypertension in the community-based Bristol helicobacter project with the 10,537 subjects, the relationship is likely to be the result by residual confounding factors. Although a paper for African people showed decreased levels of blood pressure levels after three weeks of *H. pylori* eradication treatment,[4] it is likely to be not causally related because the study is not placebo controlled and remains misclassification bias because *H. pylori* test is not performed after treatment.

4. Insulin resistance and diabetes

Insulin resistance (IR) is one of important componnents on type 2 diabetes mellitus (DM) pathogenesis. In a systematic review published in 2011, a significantly high homeostatic model assessment-insulin resistance (HOMA-IR) score in *H. pylori*–infected population than non-infected population was reported in seven cross-sectional analyses.[5] In two non-randomized trials for *H. pylori* eradication therapy, a study showed a beneficial effect of *H. pylori* eradication therapy with decreased IR score in successfully eradicated patient group, but the other study failed to prove it. The potential mechanisms are suggested as follows: Lipopolysaccharides from *H. pylori* link to the activation of Toll-like receptors (TLRs), expressed mainly in macrophages and dendritic cells, which results in energy harvesting, fat accumulation and consequently IR.[6] And higher inflammatory cytokines can inhibit insulin action on its receptor

through phosphorylation of serine residues on the insulin receptor and consequently induce insulin insensitivity and resistance.[5]

However, despite of statistical association between *H. pylori* infection and IR, there is continually arguing among investigators. The reasons are due to inconsistent result in comparison of IR status in pre– and post–*H. pylori* eradication therapy in a systematic review.[5] There were three non-randomized trials: two reported beneficial effects of *H. pylori* eradication therapy in decreasing IR score,[7] but the others [8] reported non-association and non-changes in the levels of IR in pre- and post-therapy regardless of eradication treatment.[5-7]

Three meta-analysis papers were reported up to date. In a meta-analysis using 41 diabetes and non-diabetes comparison studies in 2013, *H. pylori* infection was reported to be higher in patients with diabetes compared with non-diabetic patients,[9] and in the other meta-analysis using 13 case-control studies published in the same year, *H. pylori* infection was also associated with a 2-fold higher risk for diabetes among 13 case-control studies and at 1.6-fold higher risk for diabetic nephropathy among 6 case-control studies.[10] Both meta-analyses showed the action of *H. pylori* infection was stronger in type 2 diabetes than in type 1 diabetes.[9, 10]

The first prospective cohort study, published in 2012, of 782 diabetes-free subjects with 5-year follow-up presented that *H. pylori*–infected subjects had 2.7-fold higher risk for type 2 diabetes relative to non-infected people.[10, 11] However the other prospective cohort study, published in 2012, with 10-year follow-up did not show significant association between *H. pylori* infection and DM.[10–12] Moreover, meta-analysis of two cohort studies did not show any relationship.

The inconsistency across the studies is due to non-overcoming reverse causation and recall bias. The positive result in the first cohort study may be due to the finding secondary to the higher proportion of other risk factors of diabetes in *H. pylori*–infected group relative to non-infected group. Considering the results of the two cohort studies, it can be inferred that the significant effect of *H. pylori* infection on the development of diabetes may exist in only earlier life within 5-year follow-up and disappear or weaken due to risk factors of diabetes for long-term follow-up. Thus, the debate in causality for the association between *H. pylori* infection and diabetes has been still around.

5. Obesity

Although changes in ghrelin, a peptide hormone produced in the gastrointestinal tract, in relation to appetite or weight gain and in leptin, a hormone secreted from adipose tissue, in relation to inhibition of hunger and storage of triglycerides in adipocytes are suggested to be associated between obesity and *H. pylori* infection, there was inconsistent association across prior observational studies. Although the data regarding association between obesity and *H. pylori* infection are uncommon, most of the studies are cross-sectional design, non-overcoming reverse causation. The prior results are controversial across studies such as positive relationship (more obese in *H. pylori* infected people relative to non-infected people) and non-relationship.[1] Body mass index (BMI) after successful *H. pylori* eradication is expected to be

decreased. However two non-randomized[13, 14] and a randomized placebo-controlled trial studies showed that BMI after successful *H. pylori* eradication was rather increased.[12]

6. Metabolic syndrome

The metabolic syndrome (MetS) is a group of five components: central obesity (waist circumference ≥102cm or 40 inches in male and ≥ 35 inches in female); high blood pressure (≥130/85 mmHg, and fasting plasma glucose ≥6.1 mmol/L); triglyceride dyslipidemia (triglyceride levels ≥1.7mmol/L); HDL-cholesterol dyslipidemia (high density lipoprotein-C (HDL-C) <40mg/dl in male and <50mg/dL in female); and hyperglycemia (fasting plasma glucose ≥6.1 mmol/L). By the standard of the US National Cholesterol Education Program Adult Treatment Panel III (NCEP III), MetS requires at least three of the five components. Many studies concerned the association between *H. pylori* infection and extradigestive manifestation. Relation of *H. pylori* infection with the MetS was evaluated in several studies.

Nabiour et al. first evaluated the association between *H. pylori* infection and MetS in 2006.[13] Compared with the group not infected by *H. pylori*, the group with *H. pylori* infection showed 1.5-fold significantly elevated risk for the MetS in both men and women. Association between *H. pylori* eradication treatment and remission of the MetS was evaluated to investigate the effect of *H. pylori* infection on the pathogenesis of the MetS. According to the study among Black people by Longo-Mbenza et al.,[4] three components such as plasma glucose, systolic and diastolic blood pressure and HDL-cholesterol levels were significantly improved compared with baseline values after three weeks of *H. pylori* eradication treatment. However, the two studies are cross-sectional small-numbered design; it is not obvious whether the observed difference is due to the anti-inflammatory or confounded effects by other risk factors than *H. pylori* eradication effects.[4] Also prior studies for the association of *H. pylori* infection for each MetS component failed to show its clear relationship. Therefore, further cohort studies with larger sample size need to be performed to confirm the relationship between MetS and its components and *H. pylori* infection, especially infection to highly virulent *H. pylori* such as CagA-strain.

7. Atherosclerosis and related diseases

Recent data have implicated *H. pylori* in atherosclerosis. Atherosclerosis, arteriosclerotic vascular disease, is a condition of artery wall thickness by complex pathogenesis of invasion and accumulation of white blood cells (WBCs) and proliferation of intimal smooth muscle cells by fatty fibrinogen plaque. It occurres due to chronic inflammation of WBCs and is promoted by residues of dead cells, including cholesterol and triglycerides. It can increase cardiovascular and cerebrovascular morbidity and mortality.

Biologically, *H. pylori* infection to gastric tissue can induce inflammatory cytokines, such as c-reactive protein (CRP), IL-series including 1, 6, 18, etc, and TNF-α, which leads to systemic

inflammation. *H. pylori* infection can modify asymmetric dimethylarginine (ADMA) and inhibit absorption of vitamin B_{12} and folic acid in stomach, which also causes hyperhomocysteinemia.

Moreover, a virulent *H. pylori* strain, vacuolating cytotoxin A (VacA)-secreting *H. pylori*, infection can directly stimulate hyperhomocysteinemia. Cross-reaction between *H. pylori* antigens such as cytotoxin-associated gene A (CagA) and heat shock proteins (HSPs) produces autoimmune response by realizing it as a molecular mimicry of autoimmune antigen. Systemic inflammation by cytokine reaction, cytokines themselves as pro-atherogenic mediators, prohyperhomocysteinemia and autoimmune response complexly affect, thereby causing dysfunctional microvessels and inducing growth of vascular epithelial cells. *H. pylori* infection can also increase dyslipidemia, oxidative stress, and platelet aggregation. Subsequently these processes complexly induce and aggravate atherosclerosis.[14, 15] Additionally, pro-atherogenic cytokines activate hypothalamus and brain stem, which subsequently increase sympathetic hormones such as cortisol and adrenalin and result in hypertension, insulin resistance and dyslipidemia. These sequential pathological conditions finally lead to the cardiovascular diseases such as ischemic heart disease and ischemic stroke.[17, 18]

A prior case-control study of atherosclerosis measured by carotid intima-media thickness showed that *H. pylori*–infected people had higher carotid intima-media thickness than non-infected people and *H. pylori* infection increased the risk for atherosclerosis.[14] A prospective cohort study for 5-year follow-up showed the CagA-strain–infected group had much higher changes in intima-media thickness of common carotid arteries (IMT-CCA) and even developed new atherosclerotic lesions.[16] This study suggests that *H pylori* infection, in particular the more virulent *H. pylori* infection of CagA-strain, can be associated with atherosclerosis risk, perhaps due to an enhanced immune inflammatory response.

In contrast, the link between *H. pylori* infection and ischemic heart disease and stroke seems to be still left as unresolved issue due to divergent results. There are two meta-analyses for ischemic heart disease and two meta-analyses for coronary heart disease (CHD) events or death up to date. For ischemic heart disease, the meta-analyses of 10 case-control studies published in 2006 and of 26 case-control studies published in 2015 presented that *H. pylori* infection was associated with 1.87-fold and 2.1-fold higher risk for ischemic heart disease, respectively.[17, 18] Liu et al.'s summary risk was consistent, regardless of ethnicity and age (range 1.75–2.29).[18] For CHD, a meta-analysis of 15 case-control studies, published in 2008, presented that CagA had a 2.1-fold higher risk for CHD (Zhang et al.), and the other meta-analysis of 3 cohort studies, published in 2008, also presented a 1.26-fold higher risk for CHD (Pasceri et al., 2006). However, most recent meta-analysis, published in 2015, of 19 prospective cohort studies reported a debatable result: the significant effect was weaker (only 11% increase in the risk of CHD) and existed in only patients' early lives within follow-up of 5 years and the association was not seen at 10-year follow-up due to masking effect by CHD risk factors (Sun).

Meta-analyses for ischemic stroke, two published in 2008 and one in 2006, respectively, summarized results from case-control and cross-sectional studies and reported an increasing risk for ischemic stroke by *H. pylori* infection (Wang et al., 2008, a 1.6-fold higher risk by *H. pylori* infection including CagA; Pasceri et al., 2006, a 2.4-fold higher risk by CagA strain infection; Zhang et al., 2008, a 2.7-fold higher risk by CagA strain infection). However, a recent

meta-analysis of six cohort studies and four nested case-control/case-cohort studies failed to prove the association (Yu), regardless of CagA virulence, study design, number of pathogens, and study quality (Yu). Case-control or cross-sectional designs have a higher possibility in overwhelming risk by their small size and consequently selection bias and insufficient adjustment for confounders. Therefore, the summary risk in meta-analysis of prior case-control and cross-sectional studies may be augmented relative to real risk value. Association between *H. pylori* infection and the risk of ischemic stroke up to date seems to be inconclusive.

8. Adaptive immune response relating disorders

Autoimmune disease develops when adaptive immune response induced by *H. pylori*–infected cells develops and autoantibodies are pronouncing against self-antigens, such as thyroid antigens,[19] circulating IgE or alpha-chain of the high-affinity IgE receptor.[20] Autoimmune diseases by *H. pylori* infection, autoimmune thyroid diseases (ATDs) and chronic urticaria (CU) have been reported. For ATDs, a meta-analysis of seven observational studies involving a total of 862 patients, published in 2013, indicated that *H. pylori* infection, especially CagA, was associated with 1.92-fold higher risk for total ATDs, and there is no heterogeneity and publication bias. In subgroup analysis, *H. pylori* infection was at 4.35-fold higher risk for Graves' disease, while Hashimoto's thyroiditis was not associated with *H. pylori* infection.[19]

For urticaria, a meta-analysis of nine case-control studies with high quality indicated that *H. pylori* infection was at 1.36-fold higher risk for CU (no heterogeneity and publication bias).[20] However, both meta-analyses fundamentally did not overcome the possibility of confounders and the problem of reverse causation and bias in meta-analysis using case-control studies, although the findings suggest *H. pylori* potentially plays a part in the development of ATDs and CU.[22, 23]

For atopy/allergic disease, a meta-analysis of 17 case-control studies performed in Western countries, published in 2014, showed a significant inverse association of *H. pylori* infection, perhaps by link of a better hygiene related to decrease of *H. pylori* infection and the large spreading of atopic diseases.[21] The mechanism of allergy is different from ATD. *H. pylori* infection may evoke immune tolerance, which is an overactive Th2 response by lack of the Th1 response, which facilitates persistent infection and inhibits allergic T-cell responses.[21] This mechanism is applied to asthma. A meta-analysis, published in 2012, of five case-control studies failed to show an association between *H. pylori* infection and asthma,[22] while the other meta-analysis, published in 2013, of 14 case-control and cross-sectional studies showed the opposite result, which is a significant reduced risk for asthma by *H. pylori* infection (OR=0.84), but had significant heterogeneity across studies.[23]

9. Other extra-digestive diseases

For COPD and CB, a meta-analysis, published in 2015, of 16 studies demonstrated that *Th. pylori* infection had a 2.07-fold and 1.57-fold increased risk for Chronic obstructive pulmonary

disease (COPD) and chronic bronchitis (CB) risk, respectively. CagA-strain *H. pylori* infection had much higher risk for COPD up to 3.46-fold. There are no heterogeneity and publication bias.[24] Although *H. pylori* infection on the etiology of CB and COPD remains controversial, two hypothetical mechanisms are suggested: 1) *H. pylori* infection may cause direct lung tissue damage, which leads to COPD and chronic bronchitis; 2) *H. pylori* infection triggers both diseases through sequential reaction of inflammatory cytokines.[24]

For migraine, a meta-analysis[25], published in 2014, of five cross-sectional studies showed that *H. pylori* infection had significantly 1.92-fold higher risk. However there are heterogeneity and publication bias across studies. Despite of its inconclusive result, the suggested mechanism is that *H. pylori* infection in stomach triggers inflammation, which stimulates the gastrointestinal neuroendocrine cells to secrete neuroendocrine peptides because migraine originates from the gastrointestinal organ. This sequential process may result in migraine by the brain-gut axis.[25]

For iron deficiency anemia (IDA), a meta-analysis,[26] published in 2010, of 15 case-control studies showed that *H. pylori* infection had significantly 2.22-fold higher risk. However, *H. pylori* eradication therapy in five RCTs was not efficient in improving hemoglobin and ferritin levels.[26] Both meta-analysis results had a publication bias and heterogeneity across the studies. The association is not causally related because IDA is specifically related to *H. pylori* infection and confounded by other risk factors.

For hyperemesis gravidarum (HG), a meta-analysis,[27] published in 2015, of 32 cross-sectional and case-control studies demonstrated a significantly 3.34-fold higher risk by *H. pylori* infection; however, there is heterogeneity across the studies. Hypothetical pathogenic mechanism is that *H. pylori* infection induces oxidative stress status by increasing reactive oxygen species (ROS) and decreasing plasma antioxidants, such as vitamin C and antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CT) and glutathione peroxidase (GSH-Px).[27]

10. Summary and Conclusion

Most studies for extra-digestive diseases up to date are cross-sectional or case-control studies, with small sample size. There are several cohort studies, but the results are diverse. Cross-sectional or case-control designs are more susceptible to bias than cohort or clinical trial design. *H. pylori* infection was diagnosed by different methods up to date, which cause different *H. pylori* infection prevalence according to each assay method and affect heterogenous meta-analysis result across studies. Therefore, evidence as to what impact the *H. pylori* infection, especially highly virulent *H. pylori* infection such as CagA-strain infection, would have on the development of extra-digestive diseases concerned in lots of prior studies seems to be inconclusive. Large-scale, multicenter-based prospective cohort or clinical trial studies are still required to clarify the etiology between H. pylori and extra-digestive diseases because of the limited number of studies included in meta-analysis, their small sample sizes and inclusion of study design with low quality on causality reasoning evidence.

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