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Editorial Board Member of *World Journal of Gastroenterology*, Ki Mun Kang, MD, PhD, Chairman, Professor, Department of Radiation Oncology, College of Medicine, Gyeongsang National University, 79 Gnam-ro, Jinju 52727, South Korea. jsk92@gnu.ac.kr

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Progress in elucidating the relationship between *Helicobacter pylori* infection and intestinal diseases

Shunji Fujimori

ORCID number: Shunji Fujimori
[0000-0002-6214-2595](https://orcid.org/0000-0002-6214-2595).

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Shunji Fujimori, Department of Gastroenterology, Chiba Hokusoh Hospital, Nippon Medical School, Chiba 270-1694, Japan

Corresponding author: Shunji Fujimori, AGAF, MD, PhD, Director, Department of Gastroenterology, Chiba Hokusoh Hospital, Nippon Medical School, 1715, Kamagari, Inzai, Chiba 270-1694, Japan. s-fujimori@nms.ac.jp

Abstract

Helicobacter pylori (*H. pylori*) infection causes changes to the intestinal flora, such as small intestinal bacterial overgrowth, and increases gastric acid secretion-stimulating gastrointestinal hormones, mainly gastrin, due to a decrease in gastric acid caused by atrophic gastritis. In addition, the cellular components of *H. pylori* travel through the intestinal tract, so the bacterial infection affects the immune system. Therefore, the effects of *H. pylori* infection are observed not only in the stomach and the proximal duodenum but also in the small and large intestines. In particular, meta-analyses reported that *H. pylori*-infected individuals had an increased risk of colorectal adenoma and colorectal cancer. Moreover, a recent study reported that the risk of developing colorectal cancer was increased in subjects carrying *H. pylori* vacuolating cytotoxin A antibody. In addition, it has been reported that *H. pylori* infection exacerbates the symptoms of Fabry's disease and familial Mediterranean fever attack and is involved in irritable bowel syndrome and small intestinal ulcers. On the other hand, some studies have reported that the frequency of ulcerative colitis, Crohn's disease, and celiac disease is low in *H. pylori*-infected individuals. Thus, *H. pylori* infection is considered to have various effects on the small and large intestines. However, few studies have reported on these issues, and the details of their effects have not been well elucidated. Therefore, additional studies are needed.

Key Words: *Helicobacter pylori*; Intestine; Colorectal cancer; Intestinal bacterial overgrowth; Inflammatory bowel disease; Intestinal ulcer

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Core Tip: *Helicobacter pylori* (*H. pylori*) infection causes abnormalities in the intestinal flora and increases gastric acid secretion-stimulating gastrointestinal hormones. In

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addition, the cellular components of *H. pylori* travel through the intestinal tract, causing an effect of bacterial infection on the immune system. Meta-analyses reported that colorectal adenoma and cancer increase in *H. pylori*-infected individuals, and this bacterium has also been reported to be involved in several other diseases. On the other hand, *H. pylori* infection is considered to suppress inflammatory bowel disease. However, few studies have reported on these issues, and further elucidation is required.

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INTRODUCTION

It is well known that *Helicobacter pylori* (*H. pylori*) infection causes atrophic gastritis, gastric ulcer, duodenal ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Many studies have reported that *H. pylori* infection might affect not only the stomach and the proximal duodenum but also the intestinal tract on the anal side. For example, meta-analyses reported that colorectal adenomas and colorectal cancers are more common in *H. pylori*-infected individuals[1-3]. In addition, studies have reported that the symptoms of Fabry's disease are exacerbated[4] and that attacks of familial Mediterranean fever (FMF) are increased[5] in *H. pylori*-infected individuals. Moreover, studies have reported that small intestinal ulcerative lesions in patients are significantly more common in *H. pylori*-infected individuals[6]. Furthermore, it has been suggested that *H. pylori* infection may cause irritable bowel syndrome[7]. On the other hand, the frequencies of ulcerative colitis[8,9], Crohn's disease[8-10], and celiac disease[11] are low in *H. pylori*-infected individuals.

Thus, *H. pylori* infection causes neoplastic and ulcerative lesions not only in the stomach and proximal duodenum but also in a wide range of locations that range from the distal duodenum to the large intestine. Furthermore, *H. pylori* infection is associated with abnormal pathology of immune diseases and abnormal intestinal motility. In the stomach and duodenal bulb where the gastric mucosa is found, various diseases occur due to *H. pylori* infection. Direct infection of the anal side of the duodenum to the large intestine does not occur without ectopic gastric mucosa, such as the Meckel diverticulum[12]. Therefore, the causes of abnormalities of the intestinal tract on the anal side are presumed to be due to *H. pylori* infection; these causes include the effects of *H. pylori* components, abnormalities of the intestinal flora, the effects of immune responses, and the effects of gastrointestinal hormones such as gastrin. In this paper, the effects of *H. pylori* infection on the small and large intestines will be examined and discussed.

EFFECTS OF *H. PYLORI* COMPONENTS

H. pylori DNA is detected in the lowest portion of the small intestine as a bacterial component of *H. pylori*, and this bacterial component is excreted in the stool[13]. Utilizing the fact that bacterial components are excreted in stool, *H. pylori* infection can now be confirmed by a stool test. Studies have reported that the bacterial component of *H. pylori* promotes DNA synthesis in a small intestinal cell line (IEC-6), as evaluated by the labeling index[14]. Similarly, the cancer-related CagA-positive strain of *H. pylori* has been confirmed to stimulate DNA synthesis in IEC-6 epithelial cells *in vitro*, regardless of its ability to produce vacuolating cytotoxin A (VacA) toxin[15].

Butt *et al*[16] recently reported an increased risk of developing colorectal cancer in individuals carrying serum antibodies against VacA of *H. pylori*. Rassow *et al*[17] reported in a review that VacA forms chloride (Cl⁻) channels that enter the cell and mitochondrial membranes, and VacA causes loss of mitochondrial membrane potential, mitochondrial fragmentation, formation of reactive oxygen species, autophagy, cell death and gastric cancer. Since Cl⁻ channel abnormalities are involved in cystic fibrosis, which is known to be associated with colorectal cancer, this VacA-induced Cl⁻ channel abnormality may be involved in colorectal cancer[18]. Because

Butt *et al*[16] did not directly examine the bacterial cell components of the intestinal tract but examined serum antibodies, the effect of bacterial components could not be determined. However, blood antibodies are unlikely to be carcinogenic. Therefore, bacterial cell components have a high probability of being involved. Whether VacA may be the cause of colorectal carcinogenesis has not been resolved. However, bacterial cell components, such as VacA, can travel through the intestinal tract and could be associated with colon tumors. Thus, *H. pylori* bacterial components that travel through the intestinal tract have a significant likelihood of affecting the intestinal tract.

CHANGES IN THE INTESTINAL FLORA

When atrophic gastritis due to *H. pylori* infection progress, the gastric acid concentration decreases, and the bactericidal ability of the stomach diminishes. The bacterial flora in the stomach changes drastically[19]. This causes abnormalities in the intestinal flora. *H. pylori* often infects the stomach at a young age and significantly reduces the post-infection *Firmicutes* to *Bacteroidetes* ratio at the phylum level[20]. Successful eradication of *H. pylori* increases the amount of *Bifidobacterium* in the intestinal flora [21]. A relationship between *H. pylori* and small intestinal bacterial overgrowth (SIBO) has been reported[22]. SIBO is involved in many gastrointestinal and systemic diseases, and SIBO may be the cause of the increased rate of FMF attack in *H. pylori*-infected individuals[5].

In a systematic review and meta-analysis, Shah *et al*[23] reported a link between irritable bowel syndrome (IBS) and SIBO. Although the authors reported that the overall quality of the evidence was low in the analysis, the relationship between IBS and SIBO had long been strongly suspected. Even recently, there was a report that SIBO plays an important role in IBS[24]. It was also reported that *H. pylori* eradication improves IBS[25]. In the future, *H. pylori* eradication treatment may become an important treatment strategy for IBS patients with *H. pylori* infection.

It has been suggested that dysbiosis may be associated with colorectal carcinogenesis[26], and research on this front is progressing. *H. pylori* causes dysbiosis, including SIBO, which may be the cause of colorectal cancer. Further research could determine whether *H. pylori*-induced dysbiosis is associated with colorectal cancer.

Additionally, intestinal mucosal permeability has been reported to be enhanced in *H. pylori*-infected individuals[27]. We hypothesize that this hyperpermeability of the intestinal mucosa is combined with abnormalities in the intestinal flora, resulting in an increase in small intestinal ulcerative lesions[6]. However, there are very few reports examining the relationship between *H. pylori* infection and the intestinal flora, so future studies are required.

EFFECTS OF GASTROINTESTINAL HORMONES

H. pylori gastritis causes atrophic gastritis and reduces gastric acid secretion. Therefore, the blood gastrin concentration increases. A study in rats reported that *H. pylori* infection altered the levels of gastrin, cholecystokinin, and substance P, resulting in increased colonic motility[28]. This finding suggests the possibility that *H. pylori* infection could cause gastrointestinal motor dysfunction. *H. pylori* infection may also cause IBS due to its effects on gastrointestinal hormones.

Moreover, intestinal tract hormones, especially gastrin, are assumed to cause overgrowth in the large intestinal mucosa and to be closely related to large intestinal tumor development[29]. In addition, progastrin, not gastrin, levels are reported to be high in patients with colorectal cancer[30]. In colorectal cancer, the gastrin receptor is overexpressed, and gastrin-binding capacity is increased 10-fold over that in normal colonic epithelium[31]. It has also been reported that the expression of gastrin and its receptor promotes the progression from colorectal adenoma to cancer[32]. In mice, gastrin treatment enhanced colon cancer cell growth and invasion and decreased oxidative stress and apoptosis[33]. Additionally, G-protein coupled receptor 56, which is expressed in colonic stem and cancer cells, is upregulated in transgenic mice overexpressing human progastrin[34]. Thus, although it is experimentally likely that gastrin is involved in colon tumors, a recent patient study found that gastrin was not associated with colon tumors[35]. At this time, it appears that gastrin and VacA could be potential factors in the development of colorectal tumors due to *H. pylori* infection.

Table 1 Effects and factors of diseases in which *Helicobacter pylori* may affect the small and large intestines

| Disease | Impact | Major factors suspected of being involved |
|--------------------------|--------------|---|
| Colon adenoma | Increase | Bacterial component, gastrin |
| Colon cancer | Increase | Bacterial component (especially VacA), gastrin, dysbiosis |
| Small intestinal ulcer | Increase | Mucosal permeability increased, dysbiosis |
| Irritable bowel syndrome | Involvement | Gastrointestinal hormones, SIBO |
| Ulcerative colitis | Decrease | Host immune response, antibacterial drug use |
| Crohn's disease | Decrease | Host immune response |
| Fabry's disease | Exacerbation | SIBO |
| FMF attack | Increase | SIBO |
| Celiac disease | Decrease | Immunological effects |

SIBO: Small intestinal bacterial overgrowth; FMF: Familial Mediterranean fever; VacA: Vacuolating cytotoxin A.

IMMUNITY EFFECTS

H. pylori activates various innate immune system functions[36]. The immune system, especially Peyer's patches in the small intestine, may play an important role in *H. pylori*-induced gastritis because there are reports that gastritis is not induced in *H. pylori*-infected mice lacking Peyer's patches. Peyer's patch dendritic cells phagocytose coccoid forms of *H. pylori*. *H. pylori* transforms into a sphere in the anaerobic small intestine and stimulates the host's immune system *via* Peyer's patches[37]. Most likely, because of the involvement of this immune system response, a meta-analysis has recently evaluated the association between *H. pylori* infection and systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophic gastritis, and autoimmune pancreatitis. This study suggested that infection with more virulent strains of *H. pylori* (such as CagA positive) may increase the risk of autoimmune diseases[38]. In other words, *H. pylori* infection may be involved in intestinal diseases such as ulcerative colitis and Crohn's disease.

However, the frequency of ulcerative colitis and Crohn's disease is lower in *H. pylori*-infected individuals[8-10]. Meta-analyses have concluded that the risk of inflammatory bowel disease (IBD) is lower in *H. pylori*-infected individuals[39,40]. Furthermore, recent studies have reported that eradication of *H. pylori* under the age of 18 increases the risk of IBD[41]. In other words, *H. pylori* infection may be a potentially protective factor against the development of IBD[42].

In addition, lymphoma is a neoplastic disease of the immune system, and the fact that gastric MALT lymphoma is relieved by *H. pylori* eradication is well known. Small intestinal MALT lymphoma has been shown to be curable by eradication of *H. pylori*[43]. In particular, a study has reported that *H. pylori* eradication is effective in stage 1 MALT lymphoma[44]. However, it is unclear how *H. pylori* is involved in MALT lymphoma in the small intestine.

CONCLUSION

Multiple studies have reported that *H. pylori* has an effect on neoplastic lesions, ulcerative lesions, autoimmune diseases, and the abnormal gastrointestinal motility of the small intestine and large intestine. Table 1 summarizes the diseases in which *H. pylori* may affect the small and large intestines. Unfortunately, the wording in Table 1 is ambiguous because it is not known exactly how *H. pylori* is involved in these diseases. Although there are generally still few reports on this topic, the most advanced of these is the link between colorectal tumors and *H. pylori* infection. These studies show that *H. pylori* infection is involved in the increased rates of colorectal adenoma and cancer. The involvement of gastrin has been suspected as the reason for this increase in colorectal adenoma and cancer; however, recent studies have reported the involvement of bacterial cell components, such as VacA. In addition to the effects of bacterial components and gastrointestinal hormones, *H. pylori* infection may have various effects on the small and large intestines by causing abnormalities in the

intestinal flora and immunological effects. Few studies have reported on this topic, so more studies are needed in the future.

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