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MINIREVIEWS

Impact of *Helicobacter pylori* infection on gut microbiota

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Abstract

A number of studies have revealed the association between *Helicobacter pylori* (*H. pylori*) infection and the gut microbiota. More than half of the investigations on the impact of *H. pylori* on the gut microbiota have been the sub-analyses of the influence of eradication therapy. It was observed that *H. pylori* eradication altered gut microbiota within a short period after eradication, and majority of the alterations took a long period of time to reverse back to the original. Changes in the gut microbiota within a short period after eradication may be attributed to antibiotics and proton pump inhibitors. Modification of gastric acidity in the stomach caused by a long-term *H. pylori* infection alters the gut microbiota. Analysis of the gut microbiota should be conducted in a large population, adjusting for considerable biases associated with the composition of the gut microbiota, such as age, sex, body mass index, diet and the virulence of *H. pylori*.

Key Words: *Helicobacter pylori*; Gut microbiota; Atrophic gastritis; Eradication; Proton pump inhibitor

Core Tip: *Helicobacter pylori* (*H. pylori*) eradication alters gut microbiota within a short period after eradication; this is attributed to antibiotics and proton pump inhibitors. However, most of these alterations reverse back to baseline levels over a long period of time. Modification of acidity in the stomach with mucosal atrophy caused by *H. pylori* infection alters the gut microbiota. As the human gut microbiome is diverse among individuals, a large population size is needed to study. Adjustment of biases associated with the composition of the gut microbiota is also crucial for accurate evaluation of the association between *H. pylori* infection and the gut microbiota.

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INTRODUCTION

In recent years, a number of studies related to gut microbiota have been published, shedding light on the association between gut microbiota and human health. The human microbiota consists of as many as 10-100 trillion symbiotic microbial cells harbored in the intestinal tract of every person[1]. The gut microbiota plays a pivotal role of in the metabolic, physiological, and immunological systems of the human body [2], and its structure is closely associated with an individual's health and past illnesses [3].

Accordingly, research on the association between *Helicobacter pylori* (*H. pylori*) infection and the microbiota has also increased[4]. Most of the studies, including our previous studies that revealed the influence of *H. pylori* infection on the gut microbiota, have focused on the gastric microbiota, while only a few studies have investigated the gut microbiota harbored in the intestinal tract of patients with *H. pylori* infection[5,6]. Subsequently, some published studies have revealed new findings and have improved our understanding of this phenomenon. Therefore, the current review aims to summarize the recent evidence on the influence of *H. pylori* infection on the gut microbiota, while focusing on the gut microbiota in the intestinal tract, and to discuss the mechanisms underlying the *H. pylori* mediated alterations in the gut microbiota.

H. PYLORI AND GUT MICROBIOTA

More than half of the investigations on the impact of *H. pylori* on the gut microbiota have been the sub-analyses of the influence of eradication therapy on the gut microbiota[7-11] (Table 1). Two earlier studies were based on in situ hybridization and bacterial culturing using fecal samples. A study showed that the gut microbiota of *H. pylori*-positive patients was characterized by an increase in the growth of acid-tolerant *Lactobacillus acidophilus*[7]. Another study found that the total amount of *Anaerobes* and *Clostridia* present in *H. pylori*-positive patients was significantly lower as compared to that of *H. pylori*-negative subjects[8]. Subsequent studies were based on the analysis of the fecal 16S rRNA. The analysis of the fecal 16S rRNA from 70 *H. pylori*-positive subjects and 35 *H. pylori*-negative subjects showed a decrease in the abundance of *Clostridia* as well as total anaerobes in the fecal samples of *H. pylori*-positive individuals[9]. In a study on young adults, the microbial diversity of the gut microbiota was higher in patients infected with *H. pylori* than in healthy controls. Moreover, at the phylum level, the relative abundance of *Proteobacteria* significantly increased in patients infected with *H. pylori*[10]. In contrast, only the study by Martín-Núñez *et al*[11] revealed that in comparison with uninfected individuals, the alpha diversity of gut microbiota was significantly lower in patients infected with *H. pylori*. In these studies, the composition of the gut microbiota between subjects infected and uninfected was not the primary endpoint. Moreover, the number of subjects taken into consideration was relatively small. As the diversity of the human gut microbiome varies among individuals, a large population size is needed.

A few studies have been conducted to investigate the influence of *H. pylori* infection on the gut microbiota[5,6,12,13]. Our large population study performed using 16S rRNA amplification from fecal samples revealed that *Lactobacillus* in the human gut microbiota may be influenced by *H. pylori* infection[5]. In a small-sample study, Dash *et al*[12] showed that the gut microbiota of *H. pylori*-infected individuals were enriched with members of *Succinivibrio*, *Coriobacteriaceae*, *Enterococcaceae*, and *Rikenellaceae* families. Furthermore, several studies have suggested that the composition of the human gut microbiota changes with age, body mass index (BMI), and sex[14-16]. Therefore, we excluded the influence of these factors using the propensity score matching, which has not been considered in previous studies. We compared 214 *H. pylori*-positive subjects and 214 matched *H. pylori*-negative subjects from a large population study and found a higher gut microbial diversity and a different gut microbiota composition in subjects with *H. pylori*[6]. Furthermore, at the genus level,

Table 1 Studies for the influence of *Helicobacter pylori* infection on gut microbiota

Ref.	Study groups *H. pylori* (+) *vs* (-)	Aim	Main findings for *H. pylori* positive subject
Bühling *et al*[7], 2001	51 *vs* 27	Sub analysis for eradication study	*L. acidophilus* ↑
Myllyluoma *et al* [8], 2007	39 *vs* 19	Sub analysis for eradication study	*Clostridia* ↓, *Anaerobes* ↓
Chen *et al*[9], 2018	70 *vs* 35	Sub analysis for eradication study	Diversity ↑, *Nitrospirae* ↓, the relative abundance of 19 pathways were significantly different between *H. pylori*-negative and *H. pylori*-positive patients
Iino *et al*[5], 2018	226 *vs* 524	Analysis of microbiota without eradication	*Lactobacillus* ↑
He *et al*[10], 2019	10 *vs* 7	Sub analysis for eradication study	Diversity ↑, *Proteobacteria* ↑
Iino *et al*[6], 2020	214 *vs* 214	Analysis of microbiota without eradication	Diversity ↑, *Haemophilusu* ↑, *Streptococcus* ↑, *Gemella* ↑, *Actinomyces* ↑
Martín-Núñez *et al* [11], 2019	40 *vs* 20	Sub analysis for eradication study	Diversity ↓, *Oscillospira* ↓
Dash *et al*[12], 2019	12 *vs* 48	Analysis of microbiota without eradication	Diversity ↑, *Succinivibrio* ↑, *Coriobacteriaceae* ↑, *Enterococcaceae* ↑, *Rikenellaceae* ↑, *Candida glabrata* ↑
Frost *et al*[13], 2019	212 *vs* 212	Analysis of microbiota without eradication	Diversity ↑, *Prevotella* ↑, *Bacteroidetes* ↓, *Parasutterella* ↑, *Holdemanella* ↑, *Betaproteobacteria* ↑, *Pseudoflavonifractor* ↓, *Alisonella* ↑, *Howardella* ↑

Helicobacter pylori: *H. pylori*.

the abundance of *Actinomyces*, *Gemella*, *Streptococcus*, and *Haemophilus* was significantly higher in the gut microbiota of *H. pylori*-infected subjects. Another recent study conducted by Frost *et al*[13] assessed the microbiota composition of 212 *H. pylori*-positive subjects and 212 matched negative controls. Similar to our study, all control samples were matched with respect to age, sex, BMI, alcohol consumption, smoking, proton pump inhibitor (PPI) usage, history of peptic ulcer disease, and dietary habits. This study demonstrated that *H. pylori* infection was associated with alterations in fecal microbiota and an overall increase in fecal microbial diversity. A later study on the long-term effects of *H. pylori* eradication demonstrated that the structure of the gut microbiota is more closely associated with subject-specific parameters, such as age or BMI, than with the eradication therapy itself[17]. Therefore, adjusting for biases associated with the composition of the gut microbiota is crucial for accurate evaluation of its composition. Diet is a key modifiable factor affecting the composition of the gut microbiota[18]. However, only one study has addressed this parameter[13].

THE INFLUENCE OF *H. PYLORI* ERADICATION ON GUT MICROBIOTA

A number of published studies have investigated the changes in the gut microbiota after *H. pylori* eradication. A recent systematic review of 24 articles examining the effect of *H. pylori* eradication on the gut microbiota revealed that most studies identified a significant decrease in the alpha diversity of the gut microbiota within a short period after eradication but no further alterations were observed for over 6 mo after *H. pylori* eradication[19]. Additionally, the abundance of *Proteobacteria* increased during a short-term follow-up whereas that of *Lactobacillus* decreased; *Enterobacteriaceae* and *Enterococcus* increased during the short-term and interim follow-up. Moreover, a more recent study evaluating the long-term effects of *H. pylori* eradication found out that the composition of the gut microbiota was restored to baseline status over the 2 years after eradication, and the relative abundances of the microbial species at the genus level before and after eradication did not differ significantly[17]. However, modest differences in the taxonomic composition were observed before and after eradication. The findings of this study where diversity of the microbiota tends to decrease in the short period after eradication and returns to baseline thereafter, it was consistent with the findings of most studies[9,10,20-26]. However, the taxonomic composition before and after eradication varied among the studies[21,22]. Some studies demonstrated that the relative abundance of all genera was restored to baseline

levels. Other studies revealed notable changes at the genus level[10,24-26]. Thus, it may be assumed that after the microbial diversity returns to baseline, the levels of each strain might demonstrate minor variations following the eradication of *H. pylori*.

THE MECHANISMS UNDERLYING *H. PYLORI* INFECTION INDUCED GUT MICROBIOTA

Although the mechanisms underlying *H. pylori* infection associated alterations in gut microbiota are still unknown, some studies have suggested possible contributing factors; these included host immune responses, virulence factors, physical contact and modification of gastric acidity[4,27]. A previous study performed using a transgenic *Drosophila* model revealed that the virulence factor, cytotoxin-associated gene A (CagA), of *H. pylori* may contribute to gut microbiota dysbiosis[28]. CagA, which is translocated into host epithelial cells after bacterial attachment, impairs cell polarity and affects host signaling pathways, thereby promoting inflammation[29]. Vacuolating cytotoxin A (VacA) is also an important virulence factor of *H. pylori*. VacA is a secreted toxin that lead to damages of gastric epithelial cells, and promotes cell death[30]. CagA and VacA counter-regulate each other to manipulate host cell responses[31]. CagA and VacA can alter the gastric microbiota and immune phenotypes previously attributed to *H. pylori* infection in the stomach[28]. Therefore, CagA and VacA have been associated with important requirements for long-term sequelae in humans. As such, ongoing crosstalk between *H. pylori* and gastric commensal microbiota may affect the host immune response. The altered host immune response may also modulate the gut microbiota[9,32]. A previous review suggested the possibility of a direct interaction of *H. pylori,* which migrates from the stomach towards the intestinal tract, with the local gut microbiota[4]. However, this hypothesis is yet to be proven. In fact, in our previous study, the presence of *H. pylori* in the intestinal tract was found to be rare even in subjects with *H. pylori* infection[6]. Therefore, the influence of *H. pylori* in the intestine on gut microbiota seems to be limited.

Modification of gastric acidity as a result of *H. pylori* infection is one of the variable effects on altered gut microbiota. PPIs, which decrease gastric acidity, affect the gut microbiota[33,34]. Reduced gastric acid promotes the passage of acid-sensitive bacteria and changes the intestinal environment[35]. Similar to the interference with the action of PPIs, *H. pylori* can regulate gastric luminal acidity. *H. pylori* infection is generally acquired during childhood and persists for life unless eradicated by treatment. In the initial stages of *H. pylori* infection, acute gastritis temporarily leads to impaired gastric acid secretion[36]. In later stages, a significant decrease in gastric acid secretion is observed in individuals who develop severe atrophic gastritis[36,37]. Previous studies investigating the gut microbiota following PPI administration detected an increase in the *Lactobacillus* population in the gut microbiota[33,34]. We evaluated *Lactobacillus* according to the degree of gastric atrophy in subjects with and without *H. pylori* infection[5]. The relative abundance of *Lactobacillus* in the human gut microbiota significantly increased after the development of severe atrophic gastritis. In another study, after adjusting for biases, we demonstrated that among *H. pylori*-infected subjects, a significant increase in the abundance of the genus *Streptococcus* was observed in subjects with severe atrophic gastritis[6]. These results support the hypothesis that severe atrophic gastritis reduces gastric acid secretion and affects the composition of the gut microbiota, similar to the results of PPI administration. Most previous studies examining the association between *H. pylori* infection and gut microbiota have not considered the influence of gastric mucosal atrophy. However, atrophic gastritis may be an important mechanism associated with the changes in the gut microbiota induced by *H. pylori* infection.

In previous studies, although *H. pylori* eradication was observed to alter gut microbiota within a short period, most of the changes induced tended to return to baseline levels over a long periods after eradication therapy[9,10,20-26]. The changes in the gut microbiota within a short period after eradication may be attributed to antibiotics and PPIs that were administered for *H. pylori* eradication. This finding was represented by a study that demonstrated a decrease in gut microbial diversity within a short period after eradication therapy in both patients with and without successful eradication[38]. The changes in the diversity within a short period after eradication may be attributed to the eradication therapy itself. Hence, the influence of eradication therapy on the gut microbiota would diminish over a long period of time. After eradication, the influence of host immune responses towards *H. pylori,* virulence factors, and physical contact with *H. pylori* could decrease or disappear. In contrast, the

modification of gastric acidity depends on the degree of mucosal atrophy. Hence, after *H. pylori* eradication, gastric acid secretion gradually improves in patients without gastric mucosal atrophy[39]. However, this improvement is not observed in patients with severe atrophic gastritis[40]. Further studies demonstrating minor changes in the gut microbiota over a long period need to be conducted using a large number of subjects with severe atrophic gastritis. Especially after *H. pylori* eradication, mechanisms other than gastric acid modification would not have a significant impact on the gut microbiota.

CONCLUSION

Although all the studies demonstrated a compositional change in the gut microbiota of *H. pylori*-infected patients, the results of these studies were not consistent with each other. This incompatibility may be attributed to several factors. Although remarkable variations are observed in the gut microbiota among individuals, the sample size considered in these studies was relatively small, and subjects were included regardless of biases associated with the composition of the gut microbiota, such as, age, gender, BMI and diet. Therefore, an analysis of gut microbiota in a large population should be conducted while adjusting to considerable biases. Particularly, it is necessary to evaluate of the degree of atrophic gastritis, which is associated with gastric acid production, when investigating the influence of *H. pylori* infection on the gut microbiota. Additionally, the virulence of *H. pylori* differs depending on the status of CagA. The prevalence of CagA-positive *H. pylori* infection varies, and the prevalence of the most virulent strain, eliciting the East Asian-type CagA phenotype, is dependent on geographical area[41]. Therefore, the investigation of the influence of *H. pylori* infection on the gut microbiota may yield different results depending on the area in which the study is conducted. Future studies should consider these points and predict the mechanisms underlying *H. pylori* infection induced changes in the gut microbiota.

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