The Effect of *Helicobacter pylori* Eradication on the Gastrointestinal Microbiota in Patients with Duodenal Ulcer

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**ABSTRACT**

**Background:** Recent reports have indicated that *Helicobacter pylori* (*H. pylori*) might have an effect on gastrointestinal flora; moreover, gastric commensal bacteria have been observed in the development of duodenal ulcer (DU). **Aims:** In our study, we aimed to evaluate the effect of *H. pylori* eradication on gastrointestinal flora in DU patients. **Methods:** A case-control study was performed at Jiangsu Shengze Hospital between December, 2013 and April, 2014. The patients received antibiotic eradication therapy if *H. pylori* testing was positive. At least four weeks after cessation of the eradication therapy, a repeat gastroscopy was performed to collect biopsies again in the same position. Gastric mucosa samples and feces specimens were collected to extract bacteria DNA and then to quantify by real-time polymerase chain reaction (PCR). **Results:** After the eradication of *H. pylori*, an increase of *Lactobacillus* group, *Clostridium leptum* subgroup, *Enterobacteria* and a decrease of *Clostridium coccoides* subgroup were found in the antrum. In the corpus, the number of bacteria in the *Lactobacillus* group was increased and the expression of *Clostridium coccoides* subgroup was significantly down-regulated. In the feces samples, only the number in the *Lactobacillus* group was increased. Moreover, the distribution was significantly different between female and the male patients. **Conclusions:** The presence of *H. pylori* in the stomach suppressed the colonization with *Lactobacillus* group, *Clostridium leptum* subgroup and *Enterobacteria*. Gender might affect the distribution and/or recolonization of the bacteria in DU patients. **Key words:** gastrointestinal micro-ecology – *Helicobacter pylori* – Duodenal ulcer – *Lactobacillus*. **Abbreviations:** DU: duodenal ulcer; GI: gastrointestinal; GIN: gastrointestinal neoplasia; GU: gastric ulcer; PPI: proton pump inhibitors; UBT: urea breath test.

**INTRODUCTION**

The human gastrointestinal (GI) microbiota contains a complex ecosystem of hundreds, even thousands of microbial species (the human microbiome) [1].

The harsh gastric environment has led to assumptions that the human stomach did not harbor a complex micro-ecology until the discovery of *Helicobacter pylori* (*H. pylori*), which is a microaerophilic, gram-negative spiral bacterium. It is estimated that *H. pylori* is present in the gastric mucosa in more than 50% of humans [2] and generates the main pathogenesis of chronic gastritis, peptic ulceration, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [3-5].

However, limited to the cultivation of gastric juice or mucosal biopsies, little is known about other members of the human gastric microbial ecosystem, because most natural microbes are not cultured by using standard methods. Recently, molecular-based techniques were introduced, which offer us a more detailed insight into the complex microbial communities molecularly [6]. Quantitative real time PCR using 16S ribosomal RNA gene (16s rRNA) primers is useful for the determination of the bacterial composition of the microbiota [7, 8].

Many studies put the emphasis on the links between GI micro-ecology and some systemic diseases, and currently, there is strong evidence for microbiota involvement in peptic ulceration, although little is known about the specific causative microorganisms. For example, germfree rats injected with indomethacin did not develop symptoms of inflammation and ulceration [9]. Furthermore, when indomethacin was co-administered with broad-range antibiotics or antimicrobials,
experimental animals did not develop gastric ulcers (GU) [10-12].

Some studies have suggested that *H. pylori* competitively inhibited other microbiota such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* in gastric mucosa in vivo and *in vitro* [13, 14]. The effect of *H. pylori* eradication on other microbiota has never been studied in duodenal ulcer (DU) patients.

As reported, it was estimated that six independent bacterial phylogenetic groups are representing approximately 90% of the faecal bacterial RNA in the healthy adult. These are *Clostridium cocoides*, *Clostridium leptum*, *Bacteroides*, *Bifidobacterium*, *Enterobacteria*, and *Lactobacillus* [15].

Based on the fact that the GI microbiota involved in the occurrence and development of DU and the effect of *H. pylori* eradication on gastric and fecal ecology remain largely unknown, we conducted a 16s rRNA-based analysis to investigate the potential effect of *H. pylori* eradication on the *Lactobacillus* group, *Clostridium cocoides* subgroup, *Clostridium leptum* subgroup, *Prevotella*, *Enterobacteria* and *Bacteroides* fragilis group. And in order to exclude the influence of proton pump inhibitors (PPIs) or antibiotics on this GI flora, we recollected samples at least four weeks after the cessation of the eradication therapy of *H. pylori*.

**METHODS**

**Study sample**

Forty patients suspected of DU referred to the Jiangsu Shengze Hospital, Jiangsu, China, between December, 2013 and April, 2014 were recruited for the study, and written informed consent was obtained from each participant at gastroscopy. All the patients were diagnosed with a DU with at least 0.3×0.4 cm in size. Thirty patients with chronic antral gastritis served as controls. All the study patients were newly diagnosed with DU and did not have a history of drug use in the month prior to this test, such as antacids, antibiotics, antimicrobial agents or probiotics. Other GI organic diseases, digestive tract surgery, diabetes, excessive drinking or any other diseases that could change the gastric and intestinal ecology were excluded. *H. pylori* infection status was determined by the rapid urease test of mucosal biopsy, stool antigen test, and 13C-urea breath test (13C-UBT). At least one positive result was considered as confirmation of infection.

The study was approved by the Ethics Committee of the First Affiliated Hospital, Nanjing Medicine University, China, and written informed consent was obtained from each participant (Ethics No. 2013-SR-159).

**Treatment**

Antibiotic *H. pylori* eradication therapy was achieved with rabeprazole 20 mg twice daily (Jiangsu Hausho Pharmaceutical Co., Ltd.), colloidal bismuth pectin for suspension three times daily (Hunan HuNaDa Pharmaceutical Co., Ltd.), clarithromycin 500 mg twice daily (Jiangsu Hengrui Medicine Co., Ltd.) and amoxicillin 1 g twice daily (Hong Kong Federation Pharmaceutical Co., Ltd.) for 10 days and then continued for two weeks with rabeprazole 20 mg daily in DU patients. During the treatment, alcohol, spicy food, vinegar, yogurt and other food that might have changed the gastrointestinal micro-ecology were prohibited. At least 4 weeks after cessation of the eradication therapy, a repeat gastroscopy and 13C-UBT were performed in each patient.

**Data collection and variables**

Patient information and consent forms were provided, containing name, sex, age, height, weight, body mass index (BMI), address, habit or history of smoking and alcohol, history of diseases such as cardiovascular disease, respiratory disorder, diabetes, digestive system disease especially peptic ulcer and family history of gastric cancer, *H. pylori* infection and eradication, as well as whether they received antibiotics or antacids later than one month before inclusion in the study, drug allergy especially to antibiotics such as clarithromycin and amoxicillin. Symptoms were also collected, such as abdominal pain, abdominal distention, acid reflux, belching.

**Samples collection**

During endoscopy, one antrum biopsy (2-3 cm proximal to the pylorus, from the greater curvature of antrum) and one corpus biopsy (midpart of the body mucosa, 4-5 cm above the corpus/antrum junction, along the greater curvature) were collected. At least four weeks after cessation of the eradication therapy, a repeat gastroscopy was performed to collect biopsies in the same positions. The biopsy samples were put in sterilized EP tubes and were snap-frozen on dry ice, then stored in a refrigerator at -80°C prior to DNA extraction. Feces samples were also collected before and after therapy.

**DNA extraction from biopsy specimens**

We extracted bacteria DNA from biopsy specimens using TIANamp Bacteria DNA kit (Tiangen, Beijing, China) according to the manufacturer’s instructions.

**DNA extraction from fecal samples**

Stool bacterial genomic DNA was extracted using QIAamp DNA Stool Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions.

**Quantitative Real-time PCR**

The reaction included 0.2 μL of forward primer (25 mMmoll/L), 0.2 μL of reverse primer (25 mMmoll/L), 1 μL of DNA template, 5 μL of SYBR Green (including 10×buffer, 4×dNTP, MgCl2 and Taq polymerase) and 3.6 μL of distilled water, for a total of 10 μL. Sequences were amplified by a GeneAmp PCR system 7500 fluorescent quantitative PCR equipment (Applied Biosystems, Inc, Foster City, CA, USA), and a melting curve was made. The reaction conditions were set as follows: 95°C 2 min denaturation, 40 amplification cycles of 95°C 10 sec, 60°C 30 sec, 70°C 45 sec, with 165 rRNA-gene-targeted group-specific primers for the these GI flora (Table I).

**Drawing standard curve and quantitative analysis**

Plasmid quantitation standards for quantitative real-time PCR (q-PCR) assays were the representative clone of each specific group, purified using QIA Miniprep columns according to the manufacturer's protocol (QIAGEN, Valencia, CA) and quantified by fluorimetry as described above. A 10-fold dilution

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series, ranging from $1 \times 10^9$ copies to $10^2$ copies, was made by serial dilution in H$_2$O. For each q-PCR assay, PCR was carried out on the plasmid dilution series to generate a standard curve. Three replicate PCRs were performed for each sample. Quantifications of template concentrations were calculated by comparison with a standard curve, plotted from a dilution series of these bacteria 16S rRNA gene carried by a plasmid.

**Statistical methods**

All data were expressed as the mean ± SD of at least three independent experiments. Paired t-test or Student’s t-test was used for statistical analysis when appropriate, a two-tailed value of $P<0.05$ was considered to indicate statistically significant differences.

**RESULTS**

The quadruple therapy was effective for *H. pylori* eradication in this developing area

In total, 30 patients were diagnosed with chronic antral gastritis: of these, 15 were *H. pylori*-positive and 15 were *H. pylori*-negative. Forty patients were diagnosed with DU, of whom 38 patients were *H. pylori*-positive. At the end, 23 DU patients completed this eradication treatment (Table II). The average eradication rate of *H. pylori* was 90.48% (19/21).

After *H. pylori* eradication, symptoms such as abdominal pain (15/21), abdominal distention (17/21), acid reflux (12/21), belching (18/21) were significantly relieved. No adverse effects were reported.

**Different parts of the stomach might affect the distribution of bacteria**

To investigate the effect of the position in the stomach on the distribution of bacteria, we compared the number of bacteria from the antrum and corpus that was collected from the same patients. There were no significant differences in patients with antral gastritis (Fig. 1A, B). As shown in Fig. 1C, before the eradication of *H. pylori* in DU patients, the number of *Prevotella* and *Clostridium leptum* subgroup were aberrantly different between the antrum and the corpus ($p<0.01$). After *H. pylori* eradication, these flora were re-colonized, *Lactobacillus* group in the antrum was more abundant than that in the corpus, suggesting that after eradicating *H. pylori*, *Lactobacillus* group tended to re-colonize the antrum rather than the corpus ($P=0.001$). This suggested that after *H. pylori* eradication the micro-ecology of stomach seemed to be much more balanced.

**The distribution of bacteria shifted dramatically after *H. pylori* eradication in DU patients**

To explore the number of these bacteria before and after the eradication of *H. pylori*, q-PCR analysis was performed in 21 pairs of *H. pylori*-positive related tissues both in the antrum and the corpus. The distribution of bacteria amounts shifted dramatically after *H. pylori* eradication. An increase in the *Lactobacillus* group ($p<0.05$), *Clostridium leptum* subgroup ($p<0.05$), *Enterobacteria* ($p<0.05$), and a decrease in the *Clostridium coccoides* subgroup ($p<0.05$) were seen in the antrum. In the corpus, the expression levels of the *Lactobacillus* group ($p<0.05$) and *Clostridium coccoides* subgroup

**Table I.** Group-specific primers based on 16S rRNA sequences

<table>
<thead>
<tr>
<th>Target bacteria</th>
<th>Primer</th>
<th>Sequence (5'-3')</th>
<th>Product size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>F</td>
<td>CTCATTGCGAAGGCCGCACCT</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>TCTAATCCCTGTTTGTGCACCCCA</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus</em> group</td>
<td>F</td>
<td>AGCAGTACGGGAACTCTCCA</td>
<td>341</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>CACCGCTACACATGGAG</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium coccoides</em> subgroup</td>
<td>F</td>
<td>AAATGACGGTGACCTGACTAA</td>
<td>440</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>CTTTGAGTTTCTACCTGCACAA</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium leptum</em> subgroup</td>
<td>F</td>
<td>GCACAAAGCGATGGAG</td>
<td>246</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>CCTCCTCCGTTTGTCAAA</td>
<td></td>
</tr>
<tr>
<td><em>Prevotella</em></td>
<td>F</td>
<td>CACCAAGCGCGAGATCA</td>
<td>283</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>GGATAACGCGCGACCT</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteria</em></td>
<td>F</td>
<td>CATTGACGTACCCGACAGAAGGC</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>CTCTACGAGACTCAAGCCTTGC</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em> group</td>
<td>F</td>
<td>ATAGCCTTTGAAAAAGAAGAT</td>
<td>495</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>CCAGTATCAAATGCAATTATA</td>
<td></td>
</tr>
</tbody>
</table>

**Table II.** Summary information on samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Biopsy</th>
<th>Stool</th>
<th>Biopsy</th>
<th>Stool</th>
<th>Biopsy</th>
<th>Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>30</td>
<td>30</td>
<td>38</td>
<td>25</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Male/Female</td>
<td>15/15</td>
<td>15/15</td>
<td>20/18</td>
<td>14/11</td>
<td>12/9</td>
<td>12/9</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>35.1±10.69</td>
<td>35.1±10.69</td>
<td>42.42±10.97</td>
<td>41.64±11.75</td>
<td>42.19±12.41</td>
<td>42.19±12.41</td>
</tr>
</tbody>
</table>

GS: antral gastritis; DU: duodenal ulcer; SD: standard deviation.
(p<0.05) were significantly up-regulated and down-regulated, respectively. However, only the number of the Lactobacillus group (P=0.023) was increased in stool samples (Fig.2C).

Re-colonization of Prevotella and Clostridium leptum subgroup seemed to recover the gastric ecology

Our results suggested that before eradicating H. pylori, the number of Prevotella and Clostridium leptum subgroup in the corpus was more abundant than that in the antrum (Fig. 1C). However, after the eradication of H. pylori, the number of the Prevotella and Clostridium leptum subgroup was not significantly different between the antrum and the corpus (Fig. 1D). We could see that the number of Clostridium leptum subgroup and Prevotella in the antrum was increased (p<0.01, p=0.055, respectively). The above results indicated that after eradicating H. pylori, Prevotella and Clostridium leptum subgroup were re-colonized in the antrum which reflected a resilience curve of gastric ecology compared to that before the eradication of H. pylori.

H. pylori infection might impact composition of GI microbiota

With the infection of H. pylori, the number of Enterobacteria in the antrum was less abundant than that in patients with antral gastritis without H. pylori infection. On the contrary, in feces samples, the expression of Enterobacteria was up-regulated in patients with antral gastritis and H. pylori infection. On the other hand, the number of Clostridium leptum subgroup in feces of patients with antral gastritis without H. pylori infection was greater than in those with H. pylori infection (Fig. 3). This suggested that the presence of H. pylori in stomach might inhibit the distribution of Enterobacteria, which was consistent with our findings in DU patients.

Gender might affect the distribution and/or recolonization of bacteria in DU patients

As shown in Fig.4, after H. pylori eradication, the bacteria in the Clostridium leptum subgroup both in the antrum and the corpus were significantly increased in female DU patients (P = 0.031 and 0.034, respectively). Moreover, the number of...
Enterobacteria in the feces samples was significantly decreased (p=0.004). The change was different in male DU patients. For example, only the expressions of Lactobacillus group (p=0.008) and Prevotella (p=0.022) in the antrum were up-regulated significantly. There was no significant difference in other bacteria in male DU patients. Consequently, we concluded that the gender might affect the distribution and/or recolonization of bacteria in DU patients.

DISCUSSION

Infection with H. pylori continues to be a cause of concern, and the search for an optimal therapy continues due to the changing in antibiotic sensitivity patterns in different geographic areas. In our study, the effect of the quadruple therapy with rabeprazole, colloidal bismuth pectin, amoxicillin and clarithromycin showed a slightly higher rate than that reported by the World Gastroenterology Organisation (WGO) guidelines, which mentioned 90% [16]. Antibiotic resistance patterns are due most likely to the abuse of drugs such as antibiotics, and failure to eradicate H. pylori in clinical trials is approximately 20% after first-line eradication therapy as reported [17]. As the present study was performed in a rural town, the majority of residents were firstly infected with H. pylori or might never have regularly eradicated this microorganism, thus the rate of eradication was considerable. The results suggested that this quadruple therapy could be available in the relatively poor towns.

In the stomach, the pH of the gastric juice significantly modifies the composition of the bacteria [18]. Decreased gastric acid output may lead to progressive atrophic gastritis and then to an increase in microbial diversity [19]. Obviously, acid inhibition with either PPIs or histamine 2-receptor antagonists could change intragastric pH. Sanduleanu et al. [20] demonstrated that the non-H. pylori flora seems to be largely influenced by the infection with H. pylori and the duration of antisecretory therapy. On the other hand, antibiotics might also affect the GI micro-ecology. However, the ecological impact of antibiotics on GI flora might be lower than we expected. For example, Kim et al. [21] found that a 10-day course of rifaximin had a modest but significant effect on stool Coliforms and Staphylococcal spp. However, these counts quickly recovered within 3 days after cessation of therapy. Levofloxacin was associated with a mild effect on the normal GI microflora, reaching a maximum at 4 days of therapy and complete recovery was achieved by 7 days post-therapy [22]. Thus, in order to exclude the influence of PPIs or antibiotics on the GI microbiota, in our present study, we selected samples at least 4 weeks after cessation of this eradication therapy to analyze the quantity of microbiota in gastric mucosa samples and stool samples.

Human microbiota studies reported similar bacterial profiles in the antrum and the corpus [23, 24]. Our results suggested that these bacteria kept balance in the antrum and the corpus in patients with antral gastritis, no matter whether they were infected with H. pylori or not. However, the numbers in the Prevotella and Clostridium leptum subgroup were aberrantly different between the antrum and the corpus in the DU patients with H. pylori infection. Above all, the discrepancy might be the outcome of the disease itself, i.e. of DU.

However, after H. pylori eradication, regardless of the effects of antibiotics and antacids, Prevotella and Clostridium leptum subgroup were re-colonized in the antrum. It indicated that after H. pylori eradication, the micro-ecology homeostasis in stomach tended to be balanced, which suggests a resilience curve of gastric ecology.

Several studies have indicated that H. pylori competitively inhibited other microbiota such as Lactobacillus acidophilus and Bifidobacterium bifidum in vivo and in vitro [13, 14]. However, the effect of H. pylori on other GI microbiota is currently not fully understood. One study indicated that H. pylori virulence factor VacA played a key role by blocking the activation of innate cytokines, such as interferon beta (IFN-β) and interleukin 12 (IL-12) induced by the probiotic Lactobacillus acidophilus in macrophages [14]. Consistent with our results, after the eradication of H. pylori, the numbers of the Lactobacillus group, Clostridium leptum subgroup and Enterobacteria were increased significantly, which indicated that the presence of H. pylori in the stomach suppressed their colonization.
On the other hand, live microorganisms serving as probiotics are of benefit to peptic ulcers. As reported, the probiotic mixture VSL#3 (including Lactobacilli, Bifidobacteria and Streptococcus species) healed acetic acid induced GU in rats by increasing the expression and production of angiogenesis promoting growth factors, primarily vascular endothelial growth factor [25]. And Lactobacillus gasseri OLL 2716 could accelerate the healing of GU, which significantly influenced gastric erosive lesions and enhanced the generation of gastric mucosal prostaglandin E2 [26]. Similar to our results, after H. pylori eradication, Lactobacillus acidophilus were re-colonized in the antrum and corpus. Thus, we hypothesized that Lactobacillus acidophilus, thought as beneficial to the host, could promote the healing of DU.

Recently, molecular technologies have reported that the Clostridium leptum subgroup is one of the predominant groups of bacteria in the gastrointestinal tract, which contains butyrate-producing and fibrolytic bacteria [27]. Another dominant part of the normal indigenous flora in the human gut is Bacteroides, which makes up more than 25% of bacteria in human fecal flora [28]. These bacteria are contributing to the metabolism, nutrition, and health of humans, having a significant influence on the health of the colon [29, 30]. A decreased fecal population level of the Clostridium leptum subgroup was observed in patients with inflammatory bowel disease [31]. Our study did not find a significant difference of Clostridium leptum subgroup in feces in H. pylori-related DU patients. However, their number was increased in the antrum after H. pylori eradication. Thus, we supposed that a decrease of the Clostridium leptum subgroup, as beneficial bacterium, might be involved in the development of DU, but the underlying mechanism is still unclear. Our results indicated that the Bacteroides fragilis group composition did not differ markedly after H. pylori eradication, either in the stomach or in the feces samples. The potential role of the Lactobacillus group, Clostridium leptum subgroup, Enterobacteria and Clostridium coccoides subgroup in the etiology of DU should be more closely evaluated in future researches.

On the other hand, Lertpiriyapong et al. [32] found that, based on H. pylori infection, compared to the female mice, the male mice co-colonised with restricted Altered Schaedler’s flora (rASF) or intestinal flora (IF) developed more severe pathology and were supposed to develop gastrointestinal intraepithelial neoplasia (GIN). The lesions were less severe in females and none developed GIN. These results suggested that the gender has an influence on GIN development. Consistent with our results, after H. pylori eradication, the number in Clostridium leptum subgroup in both the antrum and the corpus increased significantly and the number of Enterobacteria in the feces sample decreased significantly in female DU patients. However,
H. pylori infection.

We concluded that the gender was an influencing factor that could have an effect on the bacteria distribution and/or recolonization in DU patients.

To better interpret the results, some limitations of our study should be acknowledged. Firstly, subjects were off any PPI, NSAIDS for four weeks prior to obtaining specimens for the culture, and these four weeks might be insufficient for the wash off of the effect of these agents on the microbiota composition. Secondly, only two DU subjects were H. pylori-negative, and although these two individuals completed our study, we could not explore the gastric and fecal ecology in DU patients without H. pylori infection.

CONCLUSION

The number of bacteria in the Lactobacillus group, Clostridium leptum subgroup, Enterobacteria and Clostridium coccoides subgroup was altered after H. pylori eradication. Our results suggested that these bacteria might be closely related to DU, and also that the gender is an influencing factor that could have an effect on the bacteria distribution and/or recolonization in DU patients.

Conflicts of interest: All authors declare no conflict of interest.

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Authors’ contribution: L.L. and G.Z. conceived and designed the experiments; L.L. and S.X. performed the experiments and analyzed the data; F.Y. contributed with reagents/materials/analysis tools; L.L., S.X., X.Z. wrote the manuscript; G.Z. contributed to the writing of the manuscript and proofread the manuscript.

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