

***Helicobacter pylori* and Crohn's disease: A retrospective single-center study from China**

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Abstract

AIM: To investigate the association between *Helicobacter pylori* (*H. pylori*) infection and the prevalence of Crohn's disease (CD).

METHODS: Subjects were selected from patients admitted the gastrointestinal (GI) department at The First Affiliated Hospital School of Medicine (Zhejiang University)

for abdominal pain, hematochezia, diarrhea and other GI symptoms between January 2008 and September 2012. CD was diagnosed by endoscopy and biopsy. *H. pylori* infection was detected by a ^{14}C -urea breath test and culturing of the biopsy sample. Demographic, anthropometric and serologic data were collected for each patient. *H. pylori* infection rate was compared between CD and control groups, followed by a subgroup analysis based on extent and severity of CD. Student's *t*, Mann-Whitney *U*, and χ^2 tests were used to analyze the data.

RESULTS: A total of 447 patients were analyzed, including 229 in the CD group and 248 in the control group. There were no significant differences in age, sex, and rates of hypertension or diabetes. However, the CD group showed significantly higher rates of smoking history (34.9% vs 18.1%), alcohol intake (17.4% vs 8.1%), white blood cell count ($9.7 \pm 2.9 \times 10^9/\text{L}$ vs $4.3 \pm 0.9 \times 10^9/\text{L}$), and C-reactive protein ($36.3 \pm 20.8 \text{ mg/L}$ vs $5.5 \pm 2.3 \text{ mg/L}$) but lower body mass index ($24.5 \pm 2.0 \text{ kg/m}^2$ vs $26.0 \pm 2.2 \text{ kg/m}^2$) than the control group. The *H. pylori* infection rate in the CD group was 27.1%, significantly lower than that of 47.9% in the control group. Furthermore, the *H. pylori* infection rates in patients with colonic, small intestine, ileocolonic and extensive CD were 31.1%, 28.9%, 26.8% and 25.9% respectively, all of which were significantly lower than in the control group. Finally, the *H. pylori* infection rates in patients with remission, moderate and severe CD were 34.3%, 30.7% and 22.0% respectively, which were also significantly lower than in the control group.

CONCLUSION: Lower *H. pylori* infection in CD patients suggests a correlation between bacterial infection and CD, suggesting caution when considering *H. pylori* eradication in CD patients.

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Key words: Crohn's disease; *Helicobacter pylori*; Urea breath test; Biopsy; Pathogenesis; Inflammatory bowel disease; Bacteria

Core tip: The association between *Helicobacter pylori* (*H. pylori*) infection and Crohn's disease (CD) prevalence is still unclear. In this retrospective study, we collected 229 CD patients and 248 control subjects to investigate the risk factors for prevalence, extent and severity of CD. Through extensive analysis, we found significantly lower *H. pylori* infection rates in CD patients having different disease extent and severity, providing evidence for bacteria involvement in CD pathogenesis and serving as a reminder for clinicians to remain cautious when considering *H. pylori* eradication in CD patients.

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INTRODUCTION

Crohn's disease (CD) is a chronic and relapsing inflammatory disease affecting any part of the intestine, most commonly involving the distal ileal, ileocecal and colonic sections^[1]. CD is more common in northern Europe and America than in southern Europe and developing countries, and its prevalence has increased since the mid-1970s^[2,3]. The pathogenesis of CD is unclear and increasing evidence supports the hypothesis of combinatorial involvement of genetic predisposition, immune response, and the environment, especially the gut bacteria and antigens^[4]. Though several pathogens have been considered as infectious agents in CD, conclusive data is still lacking^[5]. Therefore, identifying the correlation between a potential bacteria and CD pathogenesis is of clinical importance.

Helicobacter pylori (*H. pylori*) belongs to the family of curved or spiral flagellated, Gram-negative microaerophilic bacterium that is thought to have co-existed with humans for over 5000 years^[6,7]. Since its discovery in 1984^[8], *H. pylori* has been characterized as the causative agent for peptic ulceration and has been implicated in various autoimmune diseases^[9]. *Helicobacter* are also excellent colonizers of the gastrointestinal surface for their microaerophilic metabolism, spiral shape, and peculiar motility. Considering the immune regulation, the capacity for colonization, and the nature of autoimmune-related damage in CD, it is theoretically plausible that *H. pylori* infection may take part in the pathogenesis of CD.

In immunodeficient rodents, *Helicobacter hepaticus* and *Helicobacter bilis* induce a persistent inflammation of the colon and cecum^[10,11]. Nevertheless, the observations from human studies were confusing. *Helicobacter* was absent or only detected in the intestinal mucosa of a small subgroup of patients in both an English and an Australian study^[12,13]. In contrast, Bohr *et al.*^[14] identified entero-

hepatic *Helicobacter* species in patients with inflammatory bowel disease (IBD). Furthermore, a meta-analysis suggested a protective role of *H. pylori* infection in CD pathogenesis but the heterogeneity among enrolled studies and the possibilities of publication bias limited the confidence of these results^[15]. Therefore, we conducted a large-scale case control study to investigate the association between *H. pylori* infection and different severity and types of CD.

MATERIALS AND METHODS

Ethics statement

The protocol was approved by the institutional review board at Zhejiang University and conducted in accordance with the Declaration of Helsinki. We followed guidelines from the STROBE statement when designing the study and preparing the manuscript^[16]. Written informed consent was collected from all patients.

Patients

Study subjects were selected from patients who were admitted for abdominal pain, hematochezia, diarrhea, and other GI symptoms between January 2008 and September 2012. Patients either underwent both a *H. pylori* test and endoscopy (gastroscopy, colonoscopy, or capsule) screen during admission or had recorded evidence of current *H. pylori* infection and CD. For the CD group, diagnosis was based on endoscopy manifestation and biopsy, as adopted by the Asia-Pacific consensus^[17]. Exclusion criteria included previous acid inhibition or *H. pylori* eradication, 5-aminosalicylic acid administration and differential diagnosis with intestinal tuberculosis, ulcerative colitis (UC), Behçet's disease, or ischemic colitis. The control group was comprised of patients who underwent the initial screening but were subsequently excluded by negative results for CD and other known GI diseases.

CD patients were further categorized into subgroups according to the severity and extent of disease following the Chinese IBD guidelines^[18]. For convenience, we adopted the Harvey-Bradshaw index (HBI)^[19], a simplified version of the Crohn's disease activity index (CDAI), to evaluate CD severity. This index comprises general conditions, degree of abdominal pain, frequency of diarrhea, existence of abdominal mass, and complications such as arthritis, nodular erythema, gangrenous pyoderma, aphthous stomatitis, fistula, and abscess. Scores of 0-4 were appointed to each parameter according to disease severity. The HBI score was the summary of scores from each parameter, where ≤ 4 was remission, 5-8 was moderate, and ≥ 9 was severe. In addition, according to the extent revealed from radiology and endoscopy, CD was further divided into small intestinal CD, colonic CD, ileocolonic CD, and extensive CD, where the involved scale was over 100 cm.

Analysis of demographic, anthropometric and serologic data

Demographic and anthropometric data were retrieved

from the medical records of enrolled patients and included age, sex, smoking history, alcohol intake history (with positive designation made according to the Chinese guideline of alcoholic liver disease^[20]), hypertension (defined as a patient on antihypertensive drug for blood pressure over 140/90 mmHg), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and diabetes mellitus (DM; defined as fasting glucose ≥ 7.0 mmol/L or with past history of diagnosed DM). Patient blood samples were routinely gathered and tested for general condition and inflammation, including C-reactive protein (CRP) and complete blood cell counts. The main complications of CD were also recorded, including fistula and obstruction.

¹⁴C-urea blood test and biopsy sample culture

H. pylori infection was detected by a ¹⁴C-urea blood test (UBT) and biopsy sample culture. Serum *H. pylori*-IgG was not accepted as a diagnostic tool, as it does not reflect the current infection status. First described in 1989^[21], ¹⁴C-UBT is considered a rapid diagnostic procedure for *H. pylori* detection for its ability to convert urea to ammonia and carbon dioxide. UBT is also recommended in leading society guidelines as a preferred non-invasive choice for *H. pylori* detection^[22]. According to the manufacturer's instruction (Headway, Shenzhen, China), patients were given a tablet of urea labeled with an uncommon isotope of radioactive carbon-14. In the following 30 min, the amount of isotope labeled carbon dioxide was measured in exhaled breath by scintillation. A positive result indicated the existence of *H. pylori*. For biopsy sample culture, samples from the gastric antrum obtained by gastroscopy were cultured for *H. pylori* as previously described^[23].

Statistical analysis

Data were assessed for normality, and log-transformed as needed. Quantitative variants were expressed as mean \pm SD, and analyzed by Student's *t* test or Mann-Whitney *U* test. For qualitative variants, percentages or frequencies were calculated and a χ^2 test was used for comparison. SPSS 17.0 software (Chicago, IL, United States) was used for all statistical analyses, and a *P* value < 0.05 was considered statistically significant.

RESULTS

Characteristics of study subjects

Following careful review of medical records, we identified 1563 patients that had been admitted to our ward for abdominal pain, hematochezia, diarrhea, and other GI symptoms over the past five years. Among these patients, 1231 were selected according to their having undergone both endoscopy and *H. pylori* test. The endoscopic diagnosis of CD was given to 921 patients by colonoscopy, 603 by gastroscopy, and 105 by capsule endoscopy. Furthermore, many of the patients had received more than one type of endoscopy. For the *H.*

pylori infection test, 603 patients were investigated by biopsy sample culturing and 628 patients were investigated by ¹⁴C-UBT. Among these 1231 subjects, 287 were diagnosed as CD by endoscopy and/or biopsy confirmation, with 18 of these patients having already received 5-aminosalicylic therapy, 11 being under proton pump inhibitor (PPI) therapy for reflux symptoms, and 21 having achieved *H. pylori* eradication. Among the remaining patients, 8 were further excluded due to positive serum *H. pylori*-IgG but negative ¹⁴C-UBT or biopsy sample culture results. Finally, a total of 229 patients were enrolled into the CD group. Among them, 132 and 97 patients had ¹⁴C-UBT and biopsy sample culture, respectively.

Among 1231 subjects, 251 were diagnosed with UC, 279 with different degrees of hemorrhoids, 41 with ischemic colitis, 7 with antibiotic-associated colitis, 5 with radiation enterocolitis, 11 with intestinal tuberculosis, 71 with sigmoiditis and proctitis, and 2 with Behçet's disease. The remaining 277 patients had GI symptoms but normal endoscopy and biopsy results. Nevertheless, there were still 14 patients under anti-acid therapy (10 with PPI and 4 with H₂ receptor antagonist) and 15 patients in which *H. pylori* had been eradicated. Finally, there were 248 patients enrolled into control group. Among them, 147 and 101 patients had ¹⁴C-UBT and biopsy sample cultures, respectively.

Demographic, anthropometric and serologic data of enrolled patients

The average age and sex distribution of patients were balanced between two groups (Table 1). Differences in the rates of hypertension and DM between the two groups were not significant. However, BMI was significantly lower in the CD group than that in the control group, while the rate of smoking history was approximately twice that of the CD group (*P* < 0.01), reinforcing a correlation between smoking history and CD pathogenesis. In addition, percentage of alcohol intake was also significantly higher in the CD group. Finally, the two inflammation-associated markers, CRP and white blood cell (WBC) count, were significantly higher in the CD group, supporting the potential involvement of inflammation in CD.

Association between CD and *H. pylori* infection

Total *H. pylori* infection rate in the CD group was 27.1%, significantly lower than that of 47.9% in the control group. In the CD group, there were 45 patients with colonic CD, 28 with small intestine CD, 112 with ileocolonic CD, and 34 with extensive CD. In a subgroup analysis, all of the above-mentioned CD subgroups had significantly lower *H. pylori* infection rate than that in the control group, but the differences among these subgroups did not reach statistical significance (Table 2). We further divided the CD group into three subgroups according to severity determined by endoscopic appearance. Briefly, there were 32, 88 and 109 patients

Table 1 Demographic, anthropometric and serologic data of enrolled patients

Group	CD (n = 229)	Control (n = 248)	P value
Age (yr)	46.2 ± 10.2	46.8 ± 9.4	0.79
Sex (male/female)	133/96	141/107	0.07
Smoking history	34.90%	18.10%	< 0.01
Alcohol intake	17.40%	8.10%	< 0.01
BMI (kg/m ²)	24.5 ± 2.0	26.0 ± 2.2	< 0.01
Hypertension	14.80%	16.10%	0.09
Diabetes	7.90%	6.90%	0.13
CRP (mg/L)	36.3 ± 20.8	5.5 ± 2.3	< 0.01
WBC (× 10 ⁹ /L)	9.7 ± 2.9	4.3 ± 0.9	< 0.01

BMI: Body mass index; CRP: C-reactive protein; WBC: White blood cell.

Table 2 *Helicobacter pylori* infection rate between different Crohn's disease types n (%)

Group	<i>H. pylori</i> -positive	<i>H. pylori</i> -negative	P value
CD	62 (27.1)	167 (72.9)	< 0.01
Colonic CD	14 (31.1)	31 (68.9)	< 0.01
Small intestine CD	11 (28.9)	27 (71.1)	< 0.01
Ileocolonic CD	30 (26.8)	82 (73.2)	< 0.01
Extensive CD	7 (25.9)	27 (74.1)	< 0.01
Control	119 (47.9)	129 (52.1)	

H. pylori: *Helicobacter pylori*; CD: Crohn's disease.

in the CD subgroups of remission, moderate CD, and severe CD, with corresponding *H. pylori*-positive rates of 34.3%, 30.7% and 22.0% respectively (Table 3). All three subgroups had significantly lower *H. pylori* infection rates than the control group. Nevertheless, though there was a decrease trend in *H. pylori* infection rate from the CD remission group to the severe CD group, there was no significant difference among these three groups.

DISCUSSION

Crohn's disease can affect the entire digestive system from mouth to anus, but it is most commonly seen in the final segment of the small bowel and the first part of the colon. The frequency of CD has significantly increased in the last century, becoming a heavy economic burden^[24]. The etiology of CD is still not completely understood^[25], although *NOD2/CARD15* was the first CD susceptibility gene to be discovered^[26]. Oxidative stress, autophagy, endoplasmic reticulum stress and other molecular pathways have been correlated with CD prevalence^[27,28]. Moreover, an infectious organism might be the initiating factor for CD pathogenesis. This hypothesis was supported by evidence from animal models showing that spontaneous colitis did not develop in a germ-free environment^[29]. Nevertheless, none of suggested bacterial causes have been conclusively proven^[5].

The role of *H. pylori* in IBD pathogenesis has been enticing. Generally, *H. pylori* had two main subgroups: gastric *Helicobacter* that preferentially colonize the stomach, and enterohepatic *Helicobacter* that infect the intes-

tinal or hepatobiliary system^[30]. Accumulating evidence from gene knockout rodents indicate that the presence of enterohepatic helicobacter worsens the severity or hastens the development of colitis^[31,32]. A more causative role was suggested by the observation that *Helicobacter muridarum* can provoke CD in severe combined immunodeficiency mice upon receipt of T cells^[33]. In addition, lower *H. pylori* infection rate in CD patients was not influenced by antibiotic use^[34]. However, the results from human studies are confusing. The largest study examining the association between *H. pylori* infection and CD was conducted in the Netherlands by Wagtmans *et al.*^[35], which enrolled 386 CD patients and 277 controls. Though their results supported the positive association between *H. pylori* infection and CD prevalence, the credibility of these findings was weakened by the use of serum *H. pylori*-IgG as the diagnostic tool. A meta-analysis was conducted that supported the involvement of *H. pylori* infection in CD, but study heterogeneity and publication bias decreased its credibility^[15]. In contrast, two independent studies found higher *H. pylori* infection in CD patients than in controls (12% *vs* 4% and 14.0% *vs* 1.4%, respectively)^[14,36]. Furthermore, other studies investigating *Helicobacter* species in human colon also failed to find any correlation with CD^[37,38].

To tackle this discordancy, we retrospectively investigated the association between *H. pylori* infection and CD in a large case control study of Chinese patients. The initial results showed a significantly lower *H. pylori* infection rate in the CD group, which is in accordance with the previous meta-analysis^[15]. The ¹⁴C-UBT and biopsy sample culture had higher sensitivity and specificity than the serum *H. pylori*-IgG test, increasing the credibility of these findings. The significantly lower BMI in CD patients may be due to malnutrition caused by diarrhea and other GI symptoms. Based on subgroup analysis (Tables 2 and 3), we found significantly lower *H. pylori* infection in each CD subgroup and a trend of decreased *H. pylori* infection paralleling with increased CD severity, increasing the correlation between *H. pylori* infection and CD. Theoretically, it is possible for a protective role of *H. pylori* infection in CD^[39]. In detail, *H. pylori* is able to decrease immune-mediated intestinal injury by triggering Th1 dominated cell defense^[40] and inhibit other bacterially-induced mucosal damage by inducing antibacterial peptide production^[41].

Several limitations of this study should be acknowledged. First, *H. pylori* infection in colon biopsy was not detected, which may decrease disease occurrence rate. Furthermore, other members of the *Helicobacter* family are associated with the development of gut inflammation and some are found more commonly in people with IBD when compared to healthy controls. However, these members colonize the lower gut, rather than having a location limited to the stomach. Therefore, while these data are convincing, it would be helpful to detect them in another independent experiment. Second, it is better to use ¹³C-UBT instead of ¹⁴C-UBT, since the for-

Table 3 *Helicobacter pylori* infection between different severity of Crohn's disease and control *n* (%)

Group	<i>H. pylori</i> -positive	<i>H. pylori</i> -negative	<i>P</i> value
CD	11 (34.3)	21 (65.7)	< 0.01 ¹
Colonic CD	27 (30.7)	61 (69.3)	< 0.01 ¹
Small intestine CD	24 (22.0)	85 (88.0)	< 0.01 ¹
Control	119	129	

¹vs control group. *H. pylori*: *Helicobacter pylori*; CD: Crohn's disease.

mer has no radiation and is safer for patients^[42]. We have plans to implement this technique in our laboratory in the future. Third, wireless capsule endoscopy was used to detect small intestine CD. Though the effect of capsule endoscopy in small intestine CD diagnosis has been recognized^[43], the lack of biopsy results may decrease its credibility. It would be helpful to include double balloon small bowel endoscopy. Fourth, the trend of decreased *H. pylori* infection paralleling with increased CD severity should be repeated in a larger clinical trial for statistical significance. Fifth, it is better to report *H. pylori* infection rate in IBD, where *H. pylori* in UC should be reported. We found a 30.5% *H. pylori* infection rate in UC patients and are currently preparing these data for submission. Finally, the causative effect of *H. pylori* infection in CD cannot be established through case control studies and further prospective clinical trial data are necessary.

In conclusion, our results provide evidence for the involvement of *H. pylori* in CD prevalence. These findings should serve as an important reminder to clinicians when considering *H. pylori* eradication in CD patients.

COMMENTS

Background

Crohn's disease (CD) is a chronic and relapsing inflammatory disease affecting any part of the intestine, with distal ileal, ileocecal and colonic regions most commonly involved. CD is more common in Northern Europe and America than in Southern Europe and developing countries, with increased incidence since the mid-1970s and unknown etiologies.

Research frontiers

Increasing evidence supports the combinational involvement of genetic predisposition, immune response, and environment, especially gut bacteria and antigens. Though some pathogens have been considered as infectious agents in CD, conclusive data is still lacking. Considering the immune regulation and colonization capacity of *Helicobacter pylori* (*H. pylori*) and the nature of autoimmune-related damage in CD, it is plausible that *H. pylori* infection may take part in the etiology of CD. However, results in humans remain unclear and contradictory. While *Helicobacter* was absent or only detected in the intestinal mucosa of a few patients in English and Australian studies, another study identified enterohepatic *Helicobacter* species in patients with inflammatory bowel disease. Furthermore, a meta-analysis suggested a protective role of *H. pylori* infection in CD pathogenesis. However, the heterogeneity among enrolled studies and the possibilities of publication bias limited the confidence of those results.

Innovations and breakthroughs

The authors conducted a large-scale case control study to investigate the association between *H. pylori* infection and different severity and type of CD. These findings are the first example of a significant correlation between *H. pylori* infection rate in CD patients and different subtypes.

Applications

Lower *H. pylori* infection in CD patients provides evidence for bacterial involvement in the pathogenesis of CD and reminds clinicians remain cautious when considering *H. pylori* eradication in CD patients.

Peer review

Their results supported the potential involvement of *H. pylori* infection in CD pathogenesis and raised concern for the necessity of *H. pylori* eradication in CD patients. This manuscript provides some key information, and builds on the published literature. The authors should be able to enhance this by extensive revisions.

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