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Research Paper

Association between *Helicobacter Pylori* Infection and Ulcerative Colitis-A Case Control Study from China

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Abstract

Aims To investigate the association between *H. pylori* infection and UC prevalence in China. **Materials and Methods** Subjects were selected from patients admitted in Department of Gastroenterology for abdominal pain, hematochezia, diarrhea and other GI symptoms during 2009-2012. UC diagnosis was based on both colonoscopy and biopsy. *H. pylori* detection was based on ^{14}C urea breath test (UBT) and biopsy sample culture. Patients' demographic, anthropometric and serologic data were selected. *H. pylori* infection rate was compared between UC and control groups, followed by a subgroup analysis on the association between *H. pylori* infection and extent and severity degree of UC. **Results** Totally, 153 and 121 patients were selected and divided into UC and control groups. There were no significant differences in age, gender, BMI, hypertension and diabetes. However, smoking history was significantly lower while WBC and CRP levels were significantly higher in UC group. The *H. pylori* infection rate in UC group was 30.5%, significantly lower than that of 57.0% in control group. The *H. pylori* infection rate in UC of left colon and whole colon were 33,9% and 24.2% ($p<0.05$ between them), both significantly lower than that in control group. In addition, the *H. pylori* infection rates in mild, moderate and severe UC subgroups were 37.8%, 32.3% and 22.2% ($p>0.05$ among them), all of which were significantly lower than that in control group. **Conclusion** We reported a significantly lower *H. pylori* infection rate in UC patients with different extent and severity degree, which provides evidence for bacteria involvement in UC pathogenesis and reminder clinicians to keep cautious in considering *H. pylori* eradication in UC patients.

Key words: ulcerative colitis, helicobacter pylori, urea breath test.

Introduction

Ulcerative colitis (UC) belongs to a subgroup of inflammatory bowel disease (IBD) and is characterized as chronic inflammation affecting the entire colon (1). Although genetic, immunologic and environmental factors play important roles in UC, the precise etiology is still unclear. Currently, UC has become a global health threat, which is usually common in developed countries such as northern Europe and the USA (2) and with increasing prevalence in many developing countries since 1990 (3, 4). In china, the hospital based UC prevalence has been rising by three times over a 10-year period in Hong Kong (5). In addition, a steady increase of UC has also been observed from 1990 to 2003 in Wuhan city (6). The reason for this apparent increase may be due to increased awareness and diagnosis of UC. Besides, improved access to a cleaner environment and the resulting decreased bacterial infection in children may also contribute to this change (7, 8). Therefore, the microbial in human gut may play a pivotal role in the pathogene-

sis of UC.

Helicobacter pylori (*H. pylori*) is a type of curved or spiral flagellated, Gram- negative microaerophilic bacterium and has been co-existing with human for over 5000 years (9, 10). Since discovered in 1984 (11), *H. pylori* has been recognized as the main risk factor for gastritis, peptic ulcer, gastric carcinoma and gastric mucosa- associated lymphoma (12, 13). Nowadays, accumulating evidences indicate that *H. pylori* protects human from various diseases with an auto-immune component (14). This effect may be through skewing the host immunologic tone away from inflammatory Th1/Th17 response (15) and increasing T-regulatory cell level (16). Considering the immune regulation capacity of *H. pylori* and the nature of autoimmune related damage in UC, it is theoretically reasonable that *H. pylori* may be involved in the pathogenesis of UC.

Such speculation has been investigated in various studies. According to epidemiology data, UC is more prevalent in developed countries with lower rates of *H. pylori* colonization than in developing countries with higher *H. pylori* infection (17). For instance, a small scale study showed a low *H. pylori* infection rate in UC patients in China (18). Besides, a steady rise in UC incidence was reported in *H. pylori* endemic regions after successful *H. pylori* eradication (19). In addition, a meta-analysis of 23 studies suggested a protective role of *H. pylori* infection against IBD development (20). Nevertheless, the heterogeneity among studies and the possibility of publication bias impaired the reliability of this meta-analysis while several studies also reported negative association between *H. pylori* and UC (21, 22). We previously reported the inverse relationship between *H. pylori* infection and Crohn's disease, another subtype of IBD (23). In this study, we further conducted a large scale case control study to investigate the association between *H. pylori* and UC, especially between different extent and severity degree of UC that is rarely reported.

Methods

Ethics statement

The protocol was approved by the institutional review board at Zhejiang University and conducted in accordance with the Declaration of Helsinki. The study design and manuscript preparation were based on guideline from the STROBE statement (24). Written informed consent was collected from all patients.

Patients

Study subjects were selected from patients who were admitted in Department of Gastroenterology for abdominal pain, hematochezia, diarrhea and other GI symptoms during 2009-2012. Only those who had both *H. pylori* test and colonoscopy were further considered. The *H. pylori* test was based on ^{14}C urea breath test (UBT) and biopsy sample culture in patients taking esophageal gastroscopy. As serum *H. pylori*- IgG test cannot reflect current *H. pylori* infection status, *H. pylori*-IgG positive patients were reconfirmed with above mentioned methods. The diagnosis of UC was based on colonoscopy manifestation and biopsy, as adopted by the Asia-Pacific consensus (3). Exclusion criteria included previous acid inhibition (proton pump inhibitor or H_2 receptor antagonist) or *H. pylori* eradication and 5-aminosalicylic administration. The control group was comprised of patients who underwent the initial screening but were subsequently excluded by negative results for UC and other known GI diseases.

To further investigate the association between UC and *H. pylori*, we categorized UC patients into different subgroups according to disease severity and extent. In detail, based on ESGE recommendation for image documentation in colonoscopy (25) that includes vascular pattern, erythema, edema, granularity, blood in lumen, erosion, ulcerations and friability, we divided UC into mild, moderate and severe degrees. Generally, mild degree represents reduced vascular pattern, some vulnerability; moderate degree represents absent vascular pattern, vulnerable mucosa, erosions; severe degree represents spontaneous bleeding, ulcerations. Such categorization has a good inter-observer agreement, as reported by Dr Thomas de Lange, et al (26). In addition, the extent of UC was divided into involving the whole colon and left side colon.

Analysis of demographic, anthropometric and serologic data

Patients' demographic and anthropometric data were retrieved from the medical records on enrollment, including age, gender, smoking history, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), hypertension (defined as a patient on antihypertensive drug for blood pressure over 140/90 mmHg) and diabetes mellitus (DM, defined as fasting glucose ≥ 7.0 mmol/L or with past history of diagnosed DM). Patients' blood samples were routinely collected and tested for general condition and inflammation, including complete blood cell, C reaction protein (CRP) and so on.

^{14}C UBT and biopsy sample culture

^{14}C UBT was first described in 1989 (27) as a rapid diagnostic procedure for *H. pylori* detection,

mainly based on the ability of *H. pylori* to convert urea to ammonia and carbon dioxide. Nowadays, UBT is recommended in leading society guidelines as a preferred non-invasive choice for *H. pylori* detection before and after treatment (28). Briefly, patients take a tablet of urea labeled with an uncommon isotope of radioactive carbon-14. The isotope labeled carbon dioxide in exhaled breath is measured by scintillation in 30 min. A positive result indicates the existence of *H. pylori* in the stomach. Gastric samples biopsied from gastroscopy were routinely cultured for *H. pylori* detection, according to previously developed method (29).

Statistics

Data were assessed for normality and log-transformed where appropriate. Quantitative variant were expressed as mean ± standard deviation (SD) or median with range once nonnormal distribution was found. Student t test or Mann-Whiney U-test was further applied. For qualitative variant, percentages or frequencies were calculated and a chi-square test was used for comparison. SPSS 17.0 (Chicago, IL, USA) was used for statistical analysis and $p<0.05$ was considered statistically significant.

Results

Characteristic of Study Subjects

Through careful medical record review, we identified 1031 patients that had been admitted in Department of Gastroenterology for abdominal pain, hematochezia, diarrhea and other GI symptoms over the past three years. Among these patients, 832 received both colonoscopy and *H. pylori* test and were selected for further analysis. Among them, 189 patients were diagnosed as UC by colonoscopy and biopsy confirmation, 152 patients as Crohn's disease, 251 patients as different degrees of haemorrhoids, 34 patients as ischemic colitis, 5 patients as antibiotic associated colitis, 3 patients as radiation enterocolitis and 54 patients as sigmoiditis and proctitis. The remaining 144 patients had intestinal symptoms but with normal appearance in both colonoscopy and biopsy. Among them, 23 patients were further excluded as 11 cases were under anti-acid therapy (8 with proton pump inhibitor and 3 with H_2 receptor antagonist) and 12 had previous *H. pylori* eradication therapy.

Among 189 UC patients, 12 were under 5-aminosalicylic drug therapy, 7 were under proton pumper inhibitor therapy for reflux symptom and 13 had *H. pylori* eradication therapy. Among the rest patients, 4 were further excluded for positive in serum *H. pylori* -IgG but negative in ^{14}C UBT or biopsy sample culture. Finally, there were 153 and 121 patients selected and divided into UC and control groups. In UC group, 81 and 72 patients had ^{14}C UBT and biopsy sample culture, respectively. In control group, 57 and 64 patients had ^{14}C UBT and biopsy sample culture, respectively. There was no significant difference in *H. pylori* detection method between two groups.

Demographic, anthropometric and serologic data of enrolled patients

As shown in Table 1, the age and gender distribution were balanced between patients from two groups. BMI in UC group was lower than that in control group but not reached statistical significance. The differences in the rates of hypertension and diabetes between two groups were also not significant. However, compared with UC group, rate of smoking history was approximately twice time higher in control group ($p<0.01$), reinforcing the previous hypothesis that smoking was protective for UC. In addition, two inflammation and infection associated markers (CRP and WBC) were significantly higher in UC group, reconfirming the involvement of inflammation in disease pathogenesis.

Table 1. Demographic, anthropometric and serologic data of enrolled patients

Group	UC (n=153)	Control (n=121)	p value
Age(y)	44.6 ± 10.7	49.1 ± 7.5	0.12
Gender(M/F)	79/74	57/64	0.07
Smoking history(%)	17.6	33.9	<0.01
BMI	24.4 ± 2.2	25.5 ± 1.8	0.09
Hypertension(%)	15.0	17.4	0.11
Diabetes	7.2	6.6	0.19
CRP(mg/L)	45.3 ± 14.5	6.9 ± 2.0	<0.01
WBC(*10E9/L)	10.8 ± 2.2	5.4 ± 1.6	<0.01

WBC, white blood cell,

Association between UC and *H. pylori* infection

Total *H. pylori* infection rate in UC group was 30.5%, significantly lower than that of 57.0% in control group. In UC group, the extent of UC was restricted in left colon in 112 patients, mainly involving rectum and sigmoid. The other 41 patients had entire colon injury but there were no toxic megacolon and intrusion ileitis. In subgroup analysis, the *H. pylori* infection rate in both UC of left colon and entire colon groups were significantly lower than that in control group. Intriguingly, *H. pylori* infection rate in UC of entire colon group was also significantly lower than that in UC of left colon group (Table 2).

To further investigate the association between *H. pylori* infection and UC, we divided UC group into three subgroups according severity under colonoscopy appearance as indicated in Methods. Briefly, there were 37, 62 and 54 patients in mild, moderate and severe UC subgroups with *H. pylori* positive rate of 37.8%, 32.3%, 22.2%, respectively (Table 3). All three subgroups had significantly lower *H. pylori* infection rate than that in control group. However, though there was a declination tendency of *H. pylori* infection rate from mild to severe UC group, the differences among these three groups were not significant.

Table 2. *H. pylori* infection between different extent of UC and control

Group	*H. pylori* positive(n)	*H. pylori* negative(n)	*H. pylori* positive(%)	p*
UC	46	107	30.5	<0.01
UC of left colon	38	74	33.9	<0.01
UC of whole colon	8	33	24.2#	<0.01
Control	69	52	57.0	

*, compared with control group; #, compared with UC of left colon, p<0.05

Table 3. *H. pylori* infection between different severity of UC and control

Group	*H. pylori* positive(n)	*H. pylori* negative(n)	*H. pylori* positive(%)	p*
Mild UC	14	23	37.8	<0.05
Moderate UC	20	42	32.3	<0.01
Severe UC	12	42	22.2	<0.01
Control	69	52	57.0	

*, compared with control group

Discussion

UC has been considered as a chronic condition affecting the entire human colon with superficial mucosal layer injury. The pathogenesis of UC is still vague while progress in genetics has improved our understandings (30). For instance, Parkes M reported the involvement of major histocompatibility complex and epithelial barrier related genes for UC through GWAS study (31) while Louis E reinforced the importance of interleukin-10 in UC development (32). Furthermore, the interplay between genetic predisposition, host immunology and bacteria at the mucosal surface becomes a hot research spot while a meta-analysis on GWAS studies revealed the considerable overlap between susceptibility loci for UC and mycobacterial infection (33). Nevertheless, though various organisms were suggested as pathogens for UC, none of them have been conclusively proved (34). One possible explanation is that gastrointestinal infection may facilitate the change in bacterial populations to the detriment of the host, which further contributes to UC occurrence. Therefore, finding specific bacteria in UC is of vital importance, not only for disease mechanism exploration, but also for potential antibiotic therapy.

It is well known that *H. pylori* is the causative agent in gastric and duodenal ulceration and its potential role in UC has been intensively investigated. Generally, *H. pylori* had two main subgroups: gastric helicobacter that preferentially colonized the stomach and enterohepatic helicobacter that mainly infected intestinal or hepatobiliary system (35). Previous studies in immune deficient rodents showed that *H. pylori* was capable to cause IBD like disease by initiating "auto-immune" type reaction (36, 37). Moreover, Ram M, et al reported the association between *H. pylori* and IBD (38). Nevertheless, clinical trials investigating the association between *H. pylori* and UC showed confusing results. On one hand, Oliveira AG, et al(21) and Parlak E, et al (22) failed to find any association between *H. pylori* infection and UC prevalence. Besides, *H. pylori* was not identified in colonic biopsies from UC patients by helicobacter genus-specific PCR assay (39) and nested PCR assay (40). On the other hand, He jin-de, et al found a significantly lower *H. pylori* infection in UC patents than that in patients with chronic gastritis by *H. pylori*-IgG detection (41), which was further reconfirmed by Halme, et al with the same method (42). However, Pearce et al further indicated that such positive association was irrelevant with antibiotic therapy (43).

To tackle this discordance, we retrospectively investigated the association between *H. pylori* infection and UC in a large case control study of Chinese patients. The initial results showed that *H. pylori* infection was significantly lower than that in control group, providing solid supplementary for previous meta-analysis(20). More importantly, the ^{14}C UBT and biopsy sample culture had higher sensitivity and specificity than serum *H. pylori*-IgG test in several studies, increasing the credibility of these findings. The BMI and hypertension rates were relatively lower in enrolled UC patients, which may be due to malnutrition caused by diarrhea and other GI symptoms. Differing from previous studies, we added subgroup analysis on *H. pylori* infection and UC. As shown in Table 2 and 3, we found significantly lower *H. pylori* infection in each subgroup of UC patients. More importantly, there seemed a trend that the extent and severity of UC increased with *H. pylori* infection decreasing. This finding further put weight on the positive association between *H. pylori* and UC.

It is theoretically plausible for the protective role

of *H. pylori* infection in UC. First, *H. pylori* was found to be involved in various autoimmune diseases, including giant cell arteritis, systemic sclerosis and primary biliary cirrhosis (38). Other studies also reported the association between *H. pylori* and autoimmune bollous diseases (44) and pernicious anemia (45). Since autoimmune reaction is involved in UC pathogenesis, *H. pylori* may take effect through influencing this process. Second, previous research showed that *H. pylori* was able to influence intestinal immune reaction through triggering TH1 dominated cell defense, which may further decrease immunity related intestinal injury (46). Finally, *H. pylori* may induce production of antibacterial peptide to inhibit other bacteria caused inflammatory bowel disease (47).

Several limitations of this study should be acknowledged. First, we did not test *H. pylori* in colon biopsy, which may decrease the disease prevalence rate. Second, it is better to use ^{13}C UBT instead of ^{14}C UBT, since the former has no radiation and much safer for patients (48). Third, the trend of decreased *H. pylori* infection paralleling with increased extent and severity degree of UC should be investigated in a larger clinical trial for statistical significance. Finally, the causative role of *H. pylori* infection in UC pathogenesis cannot be established through case control study and further prospective clinical trial is needed. In summary, we reported a significantly lower *H. pylori* infection in UC patients in a large scale case control study. More meaningfully, subgroup analysis showed the trend of association between decreased *H. pylori* infection and increased extent and severity degree of UC. These results provide evidence for bacteria involvement in UC pathogenesis and reminder clinicians to keep cautious in deciding *H. pylori* eradication in UC patients.

Competing Interests

The authors have declared that no competing interest exists.

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