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Research article

Association between ulcerative colitis and *Helicobacter pylori* infection: A case-control study

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ABSTRACT

Introduction: Ulcerative Colitis (UC), a type of inflammatory bowel disease (IBD), is defined as chronic inflammation of the superficial mucosal layer of the large intestine. In this study, we aimed to investigate the association between *Helicobacter pylori (H. pylori)* colonization, and UC in Palestine.

Methods: A total of 35 Palestinian patients of UC and 105 age-matched and gender-matched controls were retrospectively studied for a period of one year. Diagnosis of ulcerative colitis was based on both colonoscopy and biopsy. The presence of *H. pylori* in the stomach was evaluated by the *H. pylori* stool antigen test (HpSA). An interview-based data collection form was filled for all patients with UC before starting the test.

Results: The overall positivity of *H. pylori* infection in patients with UC was 14.3%, significantly lower than the control group, 41.9% (odds ratios (OR) = 0.23, 95% confidence intervals (CI): 0.083–0.643, *P*-value = 0.003). Interestingly, the presence of *H. pylori* showed no correlation with the extension of UC (*P*-value = 0.44). Moreover, there were no relationships between the presence of *H. pylori* and age (*P*-value = 0.97), gender (*P*-value = 0.26), smoking (*P*-value = 0.08), and medication regimen (*P*-value = 0.80).

Conclusion: The rate of *H. pylori* infection was significantly lower in patients with UC compared with the control group suggesting a protective role of *H. pylori* against the occurrence of UC.

1. Introduction

Inflammatory bowel disease (IBD) is defined as chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors; it involves alternating active and remission phases leading to an increased health burden worldwide [1]. Ulcerative colitis (UC) and Crohn's disease (CD) are the primary subtypes of IBD [2]. In recent decades, several studies, suggest a continuous increase in the incidence of IBD in developing countries [3, 4]. The estimated annual direct medical costs per patient for UC ranged from US$6,217 to US$11,477 in the US and from €8,949 to €10,395 in Europe. Hospitalization accounted for 41–55% of direct medical costs. Indirect costs accounted for about a third of total costs in the United States and 54–68% in Europe [5]. The total economic burden of UC has been estimated at US$8.1–14.9 billion annually in the United States and €12.5–29.1 billion in Europe; Total direct costs ranged from $3.4 billion to $8.6 billion in the United States and from €5.4 billion to €12.6 billion in Europe. No available date regarding the estimated annual medical cost for UC in Palestine.

UC, a chronic disease, is characterized by diffuse inflammation of the mucosa of the colon and rectum [3]. The hallmark clinical symptom of UC is the presence of diarrhea and bloody mucoid stool [6]. The clinical course of UC ranges from a dormant course with longer remission to a fulminant disease that requires intensive medical treatment or surgery [7]. UC is most commonly diagnosed in late adolescence or early adulthood, though it can occur at any age [3]. The precise etiology of UC remains unclear, but it involves a complex combination of host genetic, microbial and environmental factors. In particular, chronic inflammation seems to arise from an abnormal immune response against the microorganisms of the microbiota in genetically susceptible individuals, resulting in the breakdown of intestinal homeostasis [8, 9, 10]. Many studies have demonstrated the role of infection in extra gastric diseases. *Helicobacter pylori (H. pylori)* is a gram-negative bacterium that causes chronic gastritis and may play important role in peptic ulcer, gastric carcinoma, and gastric lymphoma [11]. It has been reported in the human stomachs in all parts of the world [12]. Recent studies have

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shown a still high prevalence of infection (more than 50%) in most countries worldwide [13].

In recent years, several studies have shown that patients with UC tend to be less frequently infected with *H. pylori* than the general population [14, 15, 16]. The best detection method of *H. pylori* is based on testing stool antigen that is used to determine active infection [17]. However, several aspects remain underestimated, including the effects of eradication therapy on the UC risk [18]. The purpose of this study was to investigate the association between *H. pylori* infection and an increased risk of developing a UC.

2. Methods

2.1. Ethics statement

The study design was based on guidelines of the World Health Organization (WHO). Ethical approval was obtained from the institutional review board (IRB) at An-Najah National University, Nablus, Palestine. A prior informed consent form was signed by all patients and the control group who agreed to participate in the study. The control group consisted of participants who were chosen randomly, and closely resembled the participants in the experimental group.

2.2. Patients and settings

This retrospective, case-control study was carried over one year. Patients attending the gastroenterology center at An-Najah National University Hospital, a major gastroenterology center that covers the North West Bank of Palestine, were requested to participate in the study. The diagnosis of UC was based on colonoscopy and pathological results in colonic biopsy as adopted by the Mayo Score [19].

All patients who were diagnosed with UC, based on both colonoscopy and biopsy, and who signed the consent form were included in the study. Patients who were diagnosed with gastrointestinal diseases other than UC or those using proton pump inhibitors, antibiotics, H_2 receptor antagonists, Nonsteroidal anti-inflammatory drugs (NSAIDs) or sulphasalazine drugs were excluded from the study. The control group included healthy volunteers randomly selected from the same area. They were matched with age, gender, and smoking status, and this matching was confirmed statistically.

2.3. Analysis of demographic and serologic data

Patients' demographic data, including their age, gender, smoking status, hypertension, and diabetes mellitus were retrieved from their medical records. All data of colonoscopy and biopsy reports were collected by reviewing pre-existing records from the hospital's database. A self-constructed interviewer-administered data collection form was completed, while patients' privacy was ensured. The data collection form had three sections and contained closed-ended questions. The first section covered the patients' socio-demographic characteristics such as age, gender, marital status, and residency. The second section covered the patients' history and status of the disease, diagnosis, and treatment. The third section covered the *H. pylori* test results.

Different methods are employed for the detection of *H. pylori*, such as stool antigen test (SAT), urea breath test, and serum *H. pylori*-IgG test [20]. In this study, the detection of *H. pylori* was based on SAT (HpSA). It is cost-effective with high specificity and sensitivity [21]. The SAT device detects *H. pylori* by visual interpretation of the color development in the inner strip. If there were enough *H. pylori* antigens in specimens, a colored band will form at the test region of the membrane that indicates a positive result. The appearance of a colored band at the control region serves as procedural control. This indicates that a reasonable sample volume has been added and a membrane wicking effect has occurred. Stool specimens obtained from 35 patients with UC and 105 controls were investigated for *H. pylori*. Specimens were stored at 2–8 °C and were analyzed within 72 h of sample collection.

Several indirect tests have been developed to diagnose *H. pylori* infection, including antibody-based tests such as serology and urine test, stool antigen test (SAT), and urea breath test (UBT) [17]. We used SAT for the diagnosis of *H. pylori* as it is one of the best methods to determine active infection.

2.4. Statistical analysis

Statistical analyses were done by using statistical software, SPSS v20.0. Pearson's chi-square test and Fisher's exact test were used to determine the relationship among nominal values. All calculations were 2-tailed, and P-value < 0.05 was considered to be significant.

3. Results

Through careful review of the An-Najah National University Hospital database, 2560 patients complaining of abdominal pain, bloody diarrhea, weight loss, recurrent vomiting or combinations between them were admitted to the gastroenterology outpatient clinic between October 2017 and May 2018. Of these patients, 42 were diagnosed with UC, 63 with Crohn's disease, nine with celiac disease, based on colonoscopy and pathological findings in the biopsy. The rest were diagnosed with other minor illnesses. In the current study, patients with UC who had earlier visited the clinic were contacted and requested to participate in the study. Thirty-five patients agreed to participate in the study and signed the consent form.

The mean age of patients was 35 ± 13 years. Thirty-seven percent of patients were within the age group (20–30) years, while 25.7% were within the age group (30–40) years (Figure 1). The age of patients at diagnosis time was variable, 45.7% of patients were between the age group 15–25 years and the rest of the patients were between 25-65 years. About 45% of the patients were malesand22% of patients were smokers (cigarettes or shisha).

The distribution of age (P-value = 0.97) and gender (OR = 0.463, 95% CI: 0.297–1.404, P-value = 0.26) were balanced between patients and controls, as shown in Table 1, which is not statistically significant. Smoking was matched between patients and controls (OR = 0.463, 95% CI: 0.192–1.116, P-value = 0.08). All patients and controls did not have appendectomy. The overall positivity of *H. pylori* infection in patients with UC was 14.3%, significantly lower than that of control group, 41.9% (OR = 0.231, 95% CI: 0.083–0.643, P-value = 0.003) and this was statistically significant.

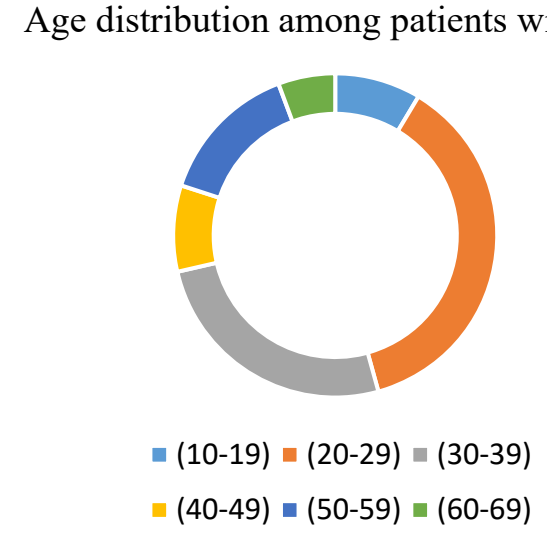

Figure 1. Age distribution among patients with ulcerative colitis.

Table 1. Comparison between patients with UC and controls.

Characteristics	UC (35)	Control (105)	*P*-value*
Age	35 ± 13	34 ± 12	0.974
Gender, M/F	16/19	37/68	0.268
Smoking History (%)	8 (22.8%)	41 (39%)	0.082
H. pylori + ve (%)	5 (14.3%)	44 (41.9%)	0.003

* The cut-off value of statistical significance was considered to be < 0.05 by using the chi-square test.

Presenting symptoms of UC were variable among patients; 65.7% of patients presented with recurrent bloody diarrhea, 31.4% of them presented with bleeding per rectum, and 2.86% with recurrent abdominal pain (Table 2). Seasonal variation in the relapse and remission course of UC was noticed in our study. The flare of UC frequently occurred during winter (57%). About 40% were not seasonally affected. Forty percent of patients complained of recurrent aphthous ulcers, 77% suffered from the effect of UC on their daily works, 8.5% had a colonoscopy done annually since the diagnosis of UC, and 80% of the patients were compliant with their medication.

In the UC group, patients were categorized according to the extent of the disease (Table 3). Eight patients had UC restricted to the rectum, 10 patients had UC involving both rectum and sigmoid, four had the disease extending to the left colon, and 13 patients had pancolitis. The *H. pylori* positivity rate in all of the patients with UC was significantly lower than that in the control group. None of the patients with UC restricted to the rectum were positive. Ten percent of patients who had UC involving both rectum and sigmoid, 25% of patients with UC extending to the left colon, and 23.1% of patients with pancolitis, were *H. pylori*-positive. The *P*-value for extension of UC and the positivity of *H. pylori* is 0.444, suggesting that the positivity of *H. pylori* is not affected by the extension of UC. Additionally, age, gender, and smoking do not affect the extension of the disease. The *P*-values were 0.307, 0.556, and 0.683 for age, gender, and smoking, respectively.

Most patients with UC (42.8%) were treated with a combination of Mesalamine and Azathioprine. The rest of the patients were using a different combination of Mesalamine, Infliximab, Adalimumab, Azathioprine or Prednisolone, as illustrated in Table 4. No effect of the drugs was observed in the treatment of UC on the positivity of *H. pylori* (*P*-value = 0.808). In addition, 80% of patients were compliant with their drug regimens.

4. Discussion

UC is a type of IBD characterized by chronic inflammation that affects the superficial mucosal layer of the colon. Different methods are used for diagnosis and confirmation of the disease, such as stool tests, colonoscopy, and biopsy. The gold standard for the diagnosis of UC is based on colonoscopy and pathological findings on biopsy [22]. All our patients with UC were diagnosed at An-Najah National University Hospital by colonoscopy and biopsy.

In Western countries, a bimodal distribution, with UC onset peaks in youth and middle age, is observed [23]. In our study, most of our patients were in the age group (20-30), whereas the peak age for onset of UC was between 15 and 25 years. Males and females were equally affected, which agrees with the previous literature [24]. An age-matched and gender-matched case-control study prospectively studied in China revealed that smoking and appendectomy are protective factors for UC [25]. In this study, nearly three-quarters of the patients were non-smokers, and none of them had an appendectomy. The key is probably the nicotine in cigarette smoke. According to Crohn's and Colitis UK, nicotine can suppress your immune system, reduce inflammation from ulcerative colitis and boost production of mucus in the colon, which acts as a protective barrier. Also, nitric oxide, a chemical released by nicotine, may help calm intestinal spasms that trigger the urge to defecate by reducing muscle activity in the colon. Nicotine has shown differential efficacy in inducing remission in UC compared to placebo and conventional drugs. Nevertheless, the high frequency of adverse events limits their clinical significance [26]. The relationships between UC and appendectomy could not be established since none of our patients with UC group nor the control group included anyone with appendectomy, in agreement with the previous studies [25].

Table 2. The presenting symptoms of patients with UC.

Presenting symptoms	Yes/No	Number (%)
Recurrent bloody diarrhea	Yes	23 (65.7)
	No	12 (34.5)
Bleeding per rectum	Yes	11 (31.4)
	No	24 (68.6)
Recurrent abdominal pain	Yes	1 (2.9)
	No	34 (97.1)
Seasonal variation	Winter	20 (57)
	Not affected	14 (40)
Recurrent aphthous ulcer	Yes	14 (40)
	No	21 (60)
Affects daily works	Yes	27 (77)
	No	8 (23)
Colonoscopy annually	Yes	3 (8.5)
	No	32 (91.5)
Compliance to medications	Yes	32 (80)
	No	3 (20)

Table 3. The comparison of data based on the extension of Ulcerative Colitis.

Characteristics	Rectum only	Rectum and sigmoid	Left colon	Pancolitis	*P*-value*
Age, mean + SD	37 ± 16	38.5 ± 10	38 ± 14	30 ± 12	0.307
Male/Female, n	4/4	6/4	2/2	4/9	0.556
Smoking	2 (25%)	3 (30%)	0	3 (23.1%)	0.683
H. pylori (+ve)	0	1 (10%)	1 (25%)	3 (23.1%)	0.444

* The cut-off value of statistical significance was considered to be < 0.05 by using the chi-square test.

Table 4. The comparison of results based on the medications used for patients with UC.

Medication	Patients, n (%)	Male/female, Number	Smokers Number	*H. pylori* (+ve), n
Mesalamine	6 (17.1)	3/3	2	0
Adalimumab	1 (2.9)	1/0	1	0
Azathioprine	1 (2.9)	0/1	0	0
Mesalamine + Azathioprine	15 (42.9)	10/5	4	3
Mesalamine + Adalimumab	1 (2.9)	0/1	0	0
Mesalamine + Prednisolone	2 (5.7)	0/2	0	0
Mesalamine + Infliximab	1 (2.9)	0/1	0	0
Mesalamine + Adalimumab + Azathioprine	6 (17.1)	2/4	1	2
Mesalamine + Prednisolone + Azathioprine	2 (5.7)	0/2	0	0
P-value*	—	0.255	0.639	0.808

* The cut-off value of statistical significance was considered to be < 0.05 by using the chi-square test.

There are many theories about its pathogenesis including genetic, immunological, and microbiological aspects. Many studies suggested a protective role of intestinal microbiota in the pathogenesis and management of the disease. Therefore, probiotics and fecal microbiota transplantation (FMT) are being increasingly used to treat UC [27]. One of the organisms suggested as pathogens for UC is *H. pylori* [28]. This is not restricted to UC, but *H. pylori* infection had a protective effect with different IBDs [29]. Our results showed that the prevalence of *H. pylori* was significantly lower in patients with UC than in the matched control group. This suggests a protective role of *H. pylori* in the development of UC. A meta-analysis of 33 observational studies showed the same results (RR estimation was 0.62) [30], which was corroborated again by an Asian meta-analysis of 10 observational studies with the same method [1].

A Systematic Review and Meta-Analysis study conducted among 58 studies in 2021 supported the theory that *H. pylori* has a protective role in IBD (pooled OR: 0.45, 95% confidence interval 0.39–0.53, $P \leq 0.001$) [31]. The mechanism by which *H. pylori* protects against celiac disease is not known, but it has been suggested that *H. pylori* induces FoxP3+ regulatory T cell development and impairs dendritic cell maturation, which may contribute to reduced inflammation [32].

Gastrointestinal pathogens have been implicated as an environmental trigger in new-onset IBD, as well as in a flare of existing IBD [33]. Environmental factors may be responsible for triggering the flare of UC. Our results confirmed that most patients had their flares during the winter season. The exact reason for this seasonal variation remains poorly understood. Similarly, a study conducted in Japan revealed that spring and winter seasonality play important role in triggering the flare of UC [34]. Moreover, Mitsuro Chiba et al. reported a case of UC that developed immediately after *H. pylori* eradication therapy [18]. However, none of the cases in the current study were tested for *H. pylori* or took eradication therapy in their life. Caner et al suggested that the extension of UC is important for the positivity rate of *H. pylori* infection [35]. The extension of the UC is important for the *H. pylori* positivity rate. The low positivity of *H. pylori* in extended UC cases could be due to immunosuppressive drugs or to the UC itself [35]. In this study, however, the presence of *H. pylori* infection was not affected by the extension of UC.

Management of UC involves both treating acute symptoms and maintaining remission. Multiple combinations of immunosuppressant and anti-inflammatory drugs could be used. Among different regimens, most of our patients (43%) were on Mesalamine and Azathioprine, which is considered a good combination choice for the treatment of UC [36]. The effect of different UC medications on the presence of *H. pylori* was evaluated and no significant relationship was found between the drug used and the presence of *H. pylori* (all *P*-values were above 0.05). This result is consistent with the finding of Caner et al. in their study on Turkish patients with UC [35].

Several new mechanisms for the treatment of IBD are currently being developed and many of them show promising results both in patients with ulcerative colitis and in Crohn's disease. In addition to efficacy, some of these treatments may provide better safety benefits over existing therapies [37]. In conclusion, our results revealed a significantly low *H. pylori* infection rate in patients with UC. This confirmed the protective effect of *H. pylori* against the development of UC, and further prospective studies are needed to evaluate a protective result. The presence of *H. pylori* had no relation with the severity of UC and the prescribed medications.

Declarations

Author contribution statement

Iyad Ali: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Qusay Abdo: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Shayma'a M. Al-Hihi and Ansam Shawabkeh: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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