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국내 염증성 장질환 환자들의 헬리코박터 파이로리 감염률에 관한 다기관 공동연구

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The Prevalence of *Helicobacter pylori* Infection in Korean Patients with Inflammatory Bowel Disease, a Multicenter Study

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Background/Aims: The prevalence of *Helicobacter pylori* (*H. pylori*) infection has been reported to be lower in individuals with inflammatory bowel disease (IBD) in some Western countries. We investigated *H. pylori* infection in Korean patients with IBD and any possible associations of *H. pylori* infection with drug therapy for IBD and the phenotype of Crohn's disease (CD). **Methods:** We studied 316 unselected patients with IBD, including 169 ulcerative colitis (UC) patients and 147 with CD, and the control group consisted of 316 age- and gender-matched healthy people who received a comprehensive medical examination for a regular checkup purpose. Infection rates of *H. pylori* as detected by the urea breath test were compared between the IBD patients and the controls. **Results:** A statistically significant difference in *H. pylori* infection rate was noticed between the IBD patients (25.3%) and the controls (52.5%; $p<0.001$), and between UC (32.0%) and CD patients (17.7%; p=0.04). Among the IBD patients, the age group of <60 and individuals with a history of taking metronidazole (13.0%; p=0.038) or ciprofloxacin (6.7%; p=0.001) were found to have a meaningfully lower infection rate, but those who did not take antibiotics still showed *H. pylori* infection rate significantly lower than the controls (CD 22.0% *vs.* UC 33.8% *vs.* Control 52.5%, $p<0.001$). With an exception of age, phenotypic characteristics showed no significant relations with *H. pylori* infection rate in CD patients. **Conclusions:** Korean patients with IBD, particularly CD, were found to have a significantly lower *H. pylori* infection rate than the controls. This association was more evident in those <60 years old, which suggested that *H. pylori* infection might be deemed to lower possible risks of IBD in younger adults. **(Korean J Gastroenterol 2009;53:341-347)**

Key Words: *Helicobacter pylori*; Ulcerative colitis; Crohn's disease

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Introduction

The prevalence of *Helicobacter pylori* (*H. pylori*) infection in patients with inflammatory bowel disease (IBD) is considered to be lower than that in the general population.[1-5] However, the reason for this lower prevalence of *H. pylori* infection in IBD patients is largely unknown although many potential causative factors, i.e. a history of previous antibiotic therapy, and the long term use of medications like sulfasalazine, have been investigated.[1,3,5-7]

It is interesting that published epidemiologic data shows that environmental factors, such as age and country of origin, are significantly related to the prevalence of IBD and *H. pylori* infection.[8-11] *H. pylori* infection was found to show an age-related increase in prevalence, compared to bimodal distribution pattern for age at onset in IBD.[8,11] Over the past decades, the prevalence of IBD has steadily increased in some countries while the incidence of *H. pylori* and other similar infectious agents has declined.[8,10,12] Furthermore, the prevalence of *H. pylori* infection varies from country to country, and is higher in Asia than in developed Western countries. However, IBD is relatively uncommon in Asian countries, but far more prevalent in developed Western countries.[8,10] Like other Asian countries, Korea has a high prevalence of *H. pylori* infection, and a low prevalence of IBD,[12,13] and interestingly, the prevalence of *H. pylori* in Korea has fallen while that of IBD has increased, which suggests that environmental changes associated with socioeconomic development and particularly industrialization may have modified respective disease risks.[12,14]

Thus, we decided to investigate the possibility of a relationship between *H. pylori* infection and IBD morbidity in Korea, where socioeconomic changes was dramatic in recent decades. In addition, we also analyzed the nature of the association between the prevalence of *H. pylori* infection and a history of IBD therapy although such association remained to be controversial.[1,3,5-7,15,16] Because CD was a heterogeneous disease with a relatively unpredictable clinical course, we analyzed the prevalence of *H. pylori* infection by phenotype, as defined by the Vienna classification.[17]

The aim of this study was to find out the prevalence of *H. pylori* infection in Korean IBD patients and to compare it with that of normal controls matched for age and gender. We also attempted to identify possible relations between a history of IBD treatment and the phenotypes of CD, and the prevalence of *H. pylori*.

Materials and Methods

This multicenter prospective study was conducted in IBD patients who visited an outpatient clinic at 6 centers in Korea from November 2004 to April 2006. Of the 316 patients, 147 and 169 patients had CD and UC. Based on a previous report that the *H. pylori*-positive rate in healthy individuals in Korea increases with age,[12] the control group was comprised of 316 healthy age (±2)- and gender-matched subjects without IBD who had a regular medical checkup (including gastroscopy and colonoscopy) on the same day. The *H. pylori* status was determined using the urea breath test.

Data concerning the clinical parameters of IBD patients and their treatments were obtained from patients' documents and by personal interview. The details of previous treatment with 5-aminosalicylic acid, sulfasalazine, corticosteroids, antibiotics, and immunosuppressants (like azathioprine) were obtained from medical records and verified by personal interview. A positive history of antibiotic usage was defined as an accumulated treatment time of more than 7 days. The usages of other drugs were categorized as 'no use' or 'continuous use'. Smoking habits were classified as never, previous, and current. The socioeconomic status was determined based on the education level received - 1) "less educated group" for those with an education received up to junior high school level (<9 years) and 2) "more educated group" for high school level or above (≥9 years).[18]

According to the Vienna classification, patients were classified as A1 if a diagnosis was made before the age of 40 and as A2 if made later. Location was defined according to maximum extent of disease before the first resection. L1 was defined as disease limited to the terminal ileum (the lower one-third of the small bowel) with or without any spillover into the cecum; L2 as a colonic location between the cecum and rectum with no small bowel or upper gastrointestinal involvement; L3 as disease of the terminal ileum with or without spillover into the cecum and any location between the ascending colon and rectum; and L4 was any disease location proximal to the terminal ileum (excluding the mouth) regardless of any additional involvement of the terminal ileum or colon. B1 was defined as inflammatory disease without stricturing or penetrating episodes; B2 as stricturing disease without penetrating disease at any time during the disease course; B3 as penetrating disease at any time, i.e. once a patient had been assigned B3, then he/she was regarded as B3 for the remainder of the disease course.[17] Patients who

had recently received proton pump inhibitors, antibiotics and/or bismuth compounds were excluded.

1. Statistical analysis

The data were recorded and calculations were performed using SPSS statistical software (Statistical Package for the Social Sciences, version 13.0). Prevalences were compared with using chi-square statistics. Associations between *H. pylori* status, and treatment for IBD and the CD phenotype were determined using the chi-square test. Two tailed values for significance were used in all statistical tests, and significance was accepted at the $p<0.05$ level.

Results

1. Patient characteristics

The mean age of the IBD patients was 40.1 (range 13-85). Mean age was 33.5±14.5 for the CD patients, 44.7±14.0 for the UC patients and 40.7±14.2 for the controls ($p<0.001$). Men composed 67.3% of CD patients, 63.3% of UC patients, and 65.2% of controls, respectively. Socioeconomic status as we determined upon education levels was higher in the controls (Table 1).

2. Prevalences of *H. pylori* infection in IBD patients and in controls

17.7% of CD patients, 32.0% of UC patients, and 52.5% of the controls were found to be infected by *H. pylori* ($p<0.001$) (Table 1). The prevalence of *H. pylori* infection in the IBD patients was significantly lower than in the controls (25.3% *vs.* 52.5%, respectively, $p<0.001$), and CD patients were observed to have a meaningfully lower rate than UC patients (32.0% *vs.* 17.7%, respectively, p=0.04) (Fig. 1). When classified by age, IBD patients of 15 to 59 years old were found to have a significantly lower *H. pylori* infection rate than age-matched

Table 1. Clinical Characteristics of the IBD Patients and Controls

	CD	UC	Control	p
Number	147	169	316	
Mean age (years)*	33.5±14.5	44.7±14.0	40.7±14.2	<0.001
Male/Female	99/48	107/62	206/110	N.S.
Education (years) n (%)				<0.001
≤9	46 (31.3%)	57 (33.7%)	73 (23.1%)	
>9	101 (68.7%)	112 (66.3%)	243 (76.9%)	
Prevalence of *Hp*+ (%)	17.7	32.0	52.5	<0.001

* Expressed as means±SD (95% confidence interval). Data are numbers of patients unless otherwise specified.
IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; *Hp*+, *H. pylori* positive.

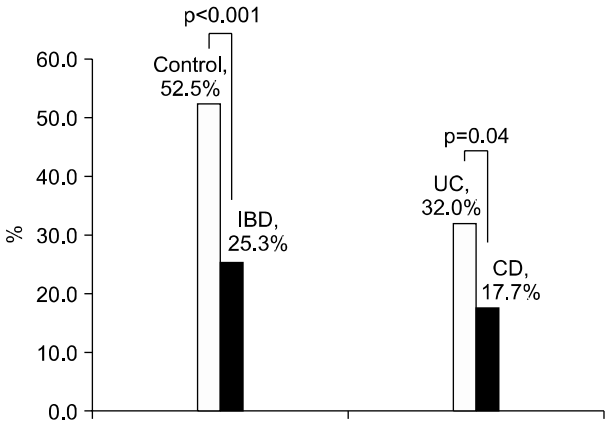

Fig. 1. The prevalence of *Helicobacter pylori* infection in the IBD patients and controls.
IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

Table 2. Prevalence of *Helicobacter pylori* Infection in the IBD Patients and Controls by Age

	Number	Prevalence of *Hp* infection (%)			
		Control (n=316)	IBD (n=316)	CD (n=147)	UC (n=169)
<30	167	31/72 (43.1%)	14/95 (14.7%)*	8/70 (11.4%)*	6/25 (24.0%)
30-44	247	77/135 (57%)	26/112 (23.2%)*	6/45 (13.3%)*	20/67 (29.9%)*
45-59	143	40/74 (54.1%)	21/69 (30.4%)*	8/22 (36.4%)	13/47 (27.7%)*
≥60	75	13/35 (51.4%)	19/40 (47.5%)	4/10 (40.0%)	15/30 (50%)

* $p<0.05$, *vs.* control.
IBD, inflammatory bowel disease; *Hp*, *Helicobacter pylori*; UC, ulcerative colitis; CD, Crohn's disease.

controls ($p<0.05$), but no meaningful difference was found between the corresponding >60 year old groups (p=0.819) (Table 2).

3. *H. pylori* infection and a history of IBD treatment

For IBD patients, the prevalence of *H. pylori* infection was significantly different for users and non-users of antibiotics (Table 3). IBD patients who had taken metronidazole (13.0%; p=0.038) or ciprofloxacin (6.7%; p=0.001) for 1 week or longer were found to have a lower infection rate than non-users. However, IBD patients who had not taken any antibiotics also showed a significantly lower rate of *H. pylori* infection than controls (CD 22.0% *vs.* UC 33.8% *vs.* Control 52.5%, $p<0.001$). Drugs other than antibiotics were found to have no influence on *H. pylori* infection rate among IBD patients (Table 3).

4. The prevalence of *H. pylori* infection in CD patients as defined by the Vienna classification

When the cases were classified according to age at diagnosis, the prevalence of *H. pylori* infection was 14.7% in the group A1 (<40 years old) and 33.3% in A2 group (≥40 years old) ($p<0.05$). The location of Crohn's disease showed no significant associations with *H. pylori* infection rate, i.e. 28% in L1 (terminal ileum), 25% in L2 (colon), 14.9% in L3 (ileocolon), and 0% in L4 (upper GI). When classified according to the disease behavior, infection rate of 20.0% was found in B1 (non-stricturing and non-penetrating), 16.7% in B2 (stricturing), and 17.6% in B3 (penetrating), which were not statistically significant (Table 4). With an exception of age, the prevalences of *H. pylori* infection among CD patients bore no relation with the other disease phenotypic characteristics examined.

Table 3. Prevalence of *H. pylori* Infection in the IBD Patients according to Drug History

	Prevalence of *Hp* infection (%)		p
	User	Non-user	
Sulfasalazine	11/59 (18.6%)	69/244 (28.3%)	N.S.
5-ASA	65/261 (24.9%)	15/55 (27.3%)	N.S.
Steroid	32/139 (23.0%)	48/177 (27.1%)	N.S.
Azathioprine	9/55 (16.4%)	71/261 (27.2%)	N.S.
Metronidazole	6/46 (13.0%)	74/270 (27.4%)	0.038
Ciprofloxacin	3/45 (6.7%)	77/271 (28.4%)	0.001

5-ASA, 5-aminosalicylic acid; *Hp*, *Helicobacter pylori*.

Discussion

Our results confirm the lower prevalence of *H. pylori* infection in IBD patients, particularly in the patients with CD, in whom its prevalence was only one-third of that in normal controls. Moreover, CD patients had a significantly lower prevalence of *H. pylori* infection than UC patients. However, we did not find any meaningful associations of *H. pylori* infection rate to smoking history or gender.

When analyzed by age, IBD patients of younger age (<60) were found to have a significantly lower prevalence of *H. pylori* infection than the age-matched controls, but no such difference was found among those older patients (>60). This result concurs with the findings of a recent study conducted on CD patients only.[6] The bimodal distribution pattern for the age of onset in IBD patients might be connected with the different pathogenetic mechanisms in the different age groups. Although age groups were not divided by age at IBD onset in the present study, a significant inverse relationship was found between *H. pylori* status and the prevalence of IBD among the younger age groups, which suggested that *H. pylori* infection mainly

Table 4. Prevalence of *H. pylori* Infection according to IBD Phenotype

	Subgroup	Number	Prevalence of *Hp* infection (%)
Crohn's disease			
	Age*		
	A1, <40 years	114	14.7%
	A2, ≥40 years	33	33.3%
	Location		
	L1, terminal ileum	27	28.0%
	L2, colon	39	25.0%
	L3, ileocolon	74	14.9%
	L4, upper GI	7	0%
	Behavior		
	B1, non-stricturing non-penetrating	95	20.0%
	B2, stricturing	33	16.7%
	B3, penetrating	19	17.6%
Ulcerative colitis			
	Proctitis	65	29.4%
	Left colitis	53	31.7%
	Pancolitis	51	35.0%

* $p<0.05$.
Hp, *Helicobacter pylori*.

influenced the incidence of IBD in early adulthood. From this result, we infer that in young adults, *H. pylori* infection may act to prevent IBD.

The mechanisms responsible for the lower prevalence of *H. pylori* infection in IBD are unknown. However, *H. pylori* infection is known to be associated with environmental factors, such as, sanitary conditions during childhood and adolescence,[9,10,19,20] and it has been proposed that IBD development may also be influenced by environmental factors, such as domestic hygiene, mode of feeding, and perinatal infections.[21-24] Thus, the lower prevalence of *H. pylori* infections in patients with IBD might be due to better hygiene and sanitation during childhood and adolescence, and this may have predisposed them to IBD. This proposition is consistent with the findings of previous studies which indicated that improved hygiene might increase the risk of IBD.[24,25] As has been previously mentioned for allergic and autoimmune disease, the "hygiene hypothesis" may explain this causal relationship between *H. pylori* infection and IBD. Improvements in living standards, including better nutrition, safer food, clean water, and improved hygienic facilities, have led to a progressive decline in the incidences of infectious diseases, and reduced levels of exposure to infectious agents has increased immune disorders, due to inappropriate immunopathologic responses to autoantigens, allergens, and/or antigens.[26] Although clinical and experimental studies on the relationships between microbial factors and the subsequent risk of IBD have yielded conflicting results,[27-29] the results from our study suggested that *H. pylori* infection might have a nonspecific preventive effect on the development of IBD.

Taking this suggestion a little further, this raises the possibility that the eradication of *H. pylori* infection contributes to IBD development. No study has been conducted on this topic, but two reports on 3 cases support the possibility. Tursi[30] and Jovanovic et al.[31] reported cases of a rapid development of CD after *H. pylori* eradication, but they were unable to explain why this had occurred. Although they suggested that it might have been a pure coincidence, or CD might have been present before the antibacterial treatment, they also pointed out the possibility that an immune response elicited by the eradication of *H. pylori* contributed to the development of CD. They also suggested that long term *H. pylori* infection might cause an unstable equilibrium between the Th (T-helper) 1 and Th2 phenotypes, and that the eradication of *H. pylori* may have induced the Th1 pattern by reducing levels of Th2 (an anti-inflammatory cytokine), and subsequently augment pro-inflammatory cytokines. Thus, the predominance of a Th1 pattern may favor the onset of Th1-related chronic inflammatory diseases, such as, CD. The above arguments raise the question as to whether *H. pylori* eradication should be recommended to patients with no clear-cut treatment indications.

Early studies have reported that the *H. pylori*-positive rate can be reduced by sulfasalazine treatment in CD. However, several *in vitro* studies failed to show that sulphasalazine has any bacteriocidal or bacteriostatic effect on *H. pylori*.[1] On the other hand, some have reported that antibiotics reduce *H. pylori*-positive rates.[6,7] Thus, we examined the impact of IBD therapy (sulfasalazine, 5-ASA, steroid, azathioprine, metronidazole and ciprofloxacin) on *H. pylori* infection rates. Our study suggests that current or past use of antibiotics (metronidazole and ciprofloxacin) for more than one week could lower *H. pylori* infection rates, but no significant impact was observed from use of the other drugs examined. However, this does not mean that use of antibiotics has entirely caused the lower *H. pylori* infection rates in IBD patients, because IBD patients that had not used any antibiotics also had a significantly lower rate of *H. pylori* infection than controls.

The present study also showed that CD patients had a significantly lower *H. pylori* infection rate than UC patients (17.7% *vs.* 32.0%, respectively, p=0.04). We presume that this lower infection rate in CD patients might be due to the frequent and prolonged use of antibiotics to treat abscesses or anal fistulas, or to their administration during the perioperative period, which supports our findings concerning the impact of IBD therapy on *H. pylori* infection rates.

Several reports have been issued on the relationship between *H. pylori* infection and the gastrointestinal lesions associated with CD.[5,6,15] In the present study, we analyzed associations between *H. pylori* prevalence and CD phenotype using the Vienna Classifications of lesions, behavior, and age. According to our findings, age was the only characteristic that was significantly related to the *H. pylori* infection rate. However, several factors should be taken into consideration when interpreting this result, as the onset of IBD is often gradual, with variable periods of remission and relapse, which makes the age at onset difficult to be determined. Furthermore, disease behavior changes during the disease course.

In summary, the inverse relationship found between *H. pylori* status and the prevalence of IBD in Korean patients, especially in patients younger than 60 years old, suggests that *H. pylori*

infection may have a nonspecific protective effect on IBD development in younger adults. Moreover, medical treatment (except for the use of antibiotics) and phenotype characteristics (besides age) are found to have no significant impact on *H. pylori* infection rates. Further studies are required to ascertain whether *H. pylori* infection affects the onset of IBD and acts as a protective factor.

요 약

목적: 국외 연구에서 염증성 장질환 환자에서 *H. pylori* 감염률은 일반인보다 낮다고 한다. 이에 국내 염증성 장질환 환자들에서 *H. pylori* 감염률을 알아보고, IBD 치료약제나 표현형과 관계가 있는지 조사하였다. **대상 및 방법**: 2004년 11월부터 2006년 4월까지 국내 6개 의료기관의 외래를 방문한 169명의 궤양성대장염 환자와 147명의 크론병 환자들을 대상으로 전향 연구를 시행하였다. 염증성 장질환 환자들과 같은 날 상부위장관 및 대장내시경을 포함한 건강검진을 받은 수진자(염증성 장질환이 없는 것으로 확인된) 중 성별과 나이가 일치한 316명을 대조군으로 선정하였다. **결과**: 염증성장질환 환자의 *H. pylori* 감염률은 25.3% (궤양성대장염 32.0%, 크론병 17.7%)로 대조군(52.5%)에 비해 통계적으로 유의하게 낮았다. 염증성 장질환 환자 중 특히 60세 미만, metronidazole이나 ciprofloxacin을 복용한 경우 *H. pylori* 감염률이 낮았지만, 항생제 복용력이 없는 경우에도 대조군에 비해 *H. pylori* 감염률이 낮았다. 크론병의 표현형에 따른 *H. pylori* 감염률의 차이는 없었다. **결론**: 국내 염증성 장질환 환자들은 대조군에 비해 *H. pylori* 감염률이 낮았고 이러한 현상은 특히 60세 미만에서 두드러졌다.

색인단어: 헬리코박터 파이로리, 궤양성대장염, 크론병

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