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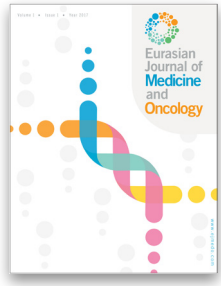

Research Article

Eradication of *Helicobacter pylori* in Patients with Inflammatory Bowel Disease for Prevention of Recurrences - Impact on the Natural History of the Disease

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Abstract

Objectives: Although, currently, it turns to speculate on infectious etiology of Crohn's disease (CD), many studies have attributed a lower prevalence of *Helicobacter pylori* infection in patients with inflammatory bowel disease (IBD). The aim of this retrospective study was determining the benefit of detection and eradication of *H. pylori* in patients with IBD and its potential impact on the natural history of the disease.

Methods: Retrospective study of 125 patients: 20 of the control group and 105 with gastrointestinal disorders. The ^{13}C-urea breath test was required as a routine procedure for all patients before receiving any dose of sulfasalazine.

Results: Case group had an average of infection with *H. pylori* (42%), similar to the control group (40%). IBD showed a similar positivity to ^{13}C-urea breath test (OR=0.99; 95% CI: 0.32–3.05). Higher incidence was found in microscopic colitis (46%) and CD (52%), than in ulcerative colitis (40%), without substantial differences. Patients treated for *H. pylori*, reduced the number of recurrences.

Conclusion: The eradication of *H. pylori* in patients with IBD may have a positive impact on the natural history of the disease, although more prospective studies are needed.

Keywords: Inflammatory bowel disease, Crohn's disease, ^{13}C breath test, *Helicobacter pylori* sulfasalazine

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Eighteen years ago, Puspok et al.[1] published that over 38% of patients with Crohn's disease (CD) had *Helicobacter pylori* in the gastric biopsies taken along their study. Mantzaris' group, at the American DDW in Orlando (Florida), reported that all patients with CD and *H. pylori* eradicated remained in remission. These latest data have not been reproduced so far.[2]

Since then, many papers about the frequency and prevalence of *H. pylori* in patients with inflammatory bowel disease (IBD) have been published. The diagnostic methods have been through serology,[3–8] biopsies,[2, 9–18] ^{13}C-urea breath test (^{13}C-UBT),[19–28] and the combination of the above. In a meta-analysis, the conclusion was the lower prevalence of *H. pylori* infection in IBD in children 27.1% and adults 40.9% as well,[28] and a high frequency of endoscopic and histological injuries (above all and focal).[13, 14, 17, 18] These findings were attributed to the maintenance treatment with sulfasalazine, structurally composed of a sulfonamide (sulfapyridine) and 5-aminosalacyclic acid (5-ASA)

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joined by an azo bond, and its antibactericidal effect,[3, 6, 19] but not related to the treatment with mesalazine.[19] In spite of there are some studies on the protective effect of 5-ASA and the antibiotic therapy,[9, 20] this still remains controversial,[8, 21, 22] inviting to speculate again about the infectious etiopathogeny of CD. Only some Italian authors,[20, 27] using the ^{13}C-UBT for *H. pylori* detection, their results showed no statistically significant differences between the prevalence of *H. pylori* infection in patients with IBD and controls.

In our service, as a routine procedure, ^{13}C-UBT (Otsuka method) has been required to all patients with gastrointestinal (GI) disorders to detect the presence of *H. pylori* and avoiding leaving affected patients without treatment (previously, none of them received any doses of sulfasalazine). In our clinical experience, we have found that many patients with IBD have positive ^{13}C-UBT tests for the presence of *H. pylori-pos*, similar to healthy patients.

This fact led us to perform a prospective and longitudinal study to analyze our results with the aim of determining, through the results of the ^{13}C-UBT, the frequency of *H. pylori* active infection in patients with GI disorders compared with a control group. Furthermore, determine if the *H. pylori* eradication in *H. pylori-pos* patients showed some relation with the number of recurrences and some effect over the natural history of the disease.

Methods

For the selection of the patients, a retrospective, multicenter observational analysis was carried out of a database of a center with local CEIC. The purpose of the study was to analyze the breath test ^{13}C-UBT (Otsuka method) results of 125 patients including 20 control and 105 patients.

Control Group

A total of 20 asymptomatic patients without gastric pathology recruited in the outpatient gastroenterology service, 12 women and 8 men (aged 20–83 years, average 50.6).

Case Group

A total of 105 patients were selected with GI disorders: Celiac disease: n=10, seven women and three men (aged 10–79 years, average 39); microscopic colitis: n=15, 10 women and 5 men (aged 20–72 years, average 50); ulcerative colitis: n=40, 23 women and 17 men (aged 26–74 years, average 37.3); and CD: n=40, 20 women and 20 men (aged 17–60 years, average 36.6).

Inclusion Criteria

Patients with consistent anatomopathological diagnosis of GI disorders (endoscopy, biopsy and laboratory tests), patients with celiac disease that did not take any gluten-free diet before ^{13}C-UBT, and patients with microscopic colitis, ulcerative colitis, and CD, in remission, receiving maintenance therapy with probiotics, 5-ASA or azathioprine, after taking them in a staggered dose were included in this study.

Exclusion Criteria

Patients in treatment with sulfasalazine as chronic maintenance therapy or having previously received antibiotic treatment, and patients with indeterminate colitis (10% of our entire series), were discarded. This condition was included for avoiding the potential protective effect against *H. pylori* infection, mentioned in the literature reviewed.

A granulocyte apheresis was carried out in some patients with UC 4/40 (10%) and CD 4/40 (10%).

The 40% (42/105) of cases undergone gastroscopy and biopsy and the data were consistent with the positivity or negativity of ^{13}C-UBT that was considered negative when the result was less or equal to 2.5% (therefore, absence of *H. pylori-neg*) and positive when this was >2.5%. The specialist who performed the ^{13}C-UBT was blind for the diagnosis of patients included in this study.

Patients with *H. pylori-pos* were treated for 10 days with one of these triple therapies:

- OCA: Omeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1 g every 12 h.
- OFA: Omeprazole-20 mg, 500 mg metronidazole, and amoxicillin 1 g every 12 h.

None of the 80 patients with IBD: Ulcerative colitis (40 cases) and CD (40 cases) received previously any doses of sulfasalazine.

All were followed up for 48 months. The number of recurrences was assessed.

Statistical Analysis

Proof of the Student's t-test for quantitative variables or Fisher's exact test for qualitative variables was used. Odds ratio (OR) for comparing the results obtained with the ^{13}C-UBT in subgroups of patients with IBD and celiac disease or microscopic colitis compared to those observed in the control group and adjusting for age and sex distributions were estimated by logistic regression (STATA 10.1).

Results

^{13}C-UBT

In the control group (n=20), the positivity of *H. pylori* was 40% (8/20). In the case group (n=105), the average of positivity was 42% (47/105). In detail: Patients with microscopic colitis 46% (7/15) and celiac disease 30% (3/10), in the ulcerative colitis group 40% (16/40), and CD group 52% (21/40).

In overall, in the IBD group, the positivity was 46% (37/80).

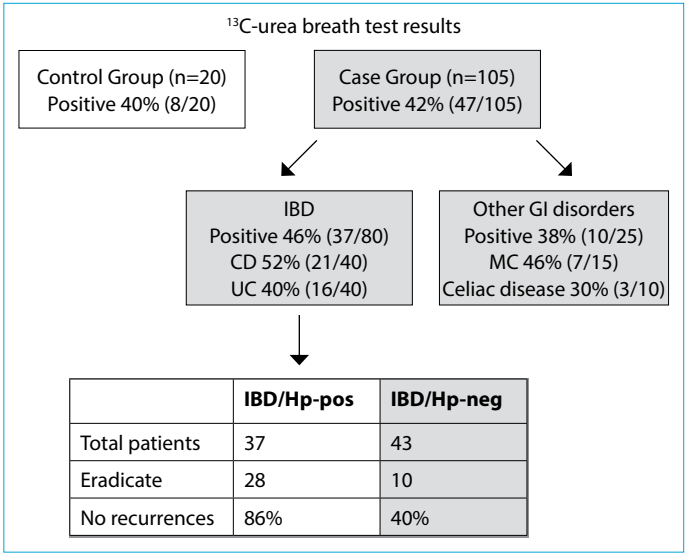
Comparing the results with the control group, after controlling for age and sex: Patients with IBD showed a similar positivity to ^{13}C-UBT (OR=0.99; 95% CI: 0.32–3.05). Patients with celiac disease or microscopic colitis, compared to controls, gave similar results (OR=0.93; 95% CI: 0.25–3.44).

Treatments

In the IDB group, 76% (28/37) of patients with *H. pylori -pos* (14 with UC and 14 with EC) had an effective eradication with one of the triple therapies (OCA or OFA) for 10 days and a follow-up of 48 months. Only in 9 patients (24%), H. pylori was not eradicated. The clinical follow-up of recurrences was carried out every 3 months, for an average of 48 months (4 years) (range 2–7 years).

The 28 patients with effective *H. pylori* eradication, were compared with the 10 patients of the IBD group with a negative result of ^{13}C-UBT (*H. pylori-neg*) 23% (10/43) of patients with *H. pylori-neg*, which, therefore, they did not receive any treatment doses for *H. pylori* eradication.

Along the follow-up period, 48 months (median: 36 months), of patients in clinical remission (effective treatment eradication), 78.6% with UC (11/14) and 93% with CD (13/14), and 86% with IBD (24/28) (95% CI 73–99%), did not show any clinical recurrences of the disease, while patients with no treatment effective eradication, showed recurrences. Only 40% of patients with *H. pylori* - (4/10) (95% CI 9.6–70%), p<0.05, no outbreak was observed (Fig. 1).



	IBD/Hp-pos	IBD/Hp-neg
Total patients	37	43
Eradicate	28	10
No recurrences	86%	40%

Figure 1. Study outline. Positive results of *Helicobacter pylori* by groups, number of eradication and percentage of recurrences. IDB: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; GI: Gastrointestinal; C: microscopic colitis; *Helicobacter pylori-pos*: Presence of *H. pylori*; *H. pylori*-neg: Absence of *H. pylori*.

Discussion

Although, currently, it turns to speculate on infectious etiology of CD,[7] reviewed in this study, many studies have attributed the low prevalence of *H. pylori* in patients with IBD to the effect of chronic maintenance therapy with sulfasalazine (bactericidal) instead of mesalazine. Moreover, some authors also believe in the protective effect of 5-ASA,[20] unlikely, because it is released beyond the stomach.

The eradication of *H. pylori* in patients with IBD appears to have a beneficial effect on the natural history of the disease, although studies with more cases would be needed.

Numerous studies have studied the frequency and prevalence of *H. pylori* infection in patients with IBD using different diagnostic methodologies.

Serology in Peripheral Blood (IgG and IgA Antibodies)

A lower prevalence of *H. pylori-pos* in IBD compared to the control group, with statistically significant results in most comparative studies is shown.[8] The largest prospective comparative study, 100 cases included per group,[3] shows statistically significant differences not attributable to treatment with sulfasalazine (*H. pylori* diagnostic by IgA antibody). In another study, in which the diagnosis was performed by IgG determining,[4] results were not statistically significant.

GI biopsies with or without *H. pylori* determination:[1, 9–17, 29] The largest prospective comparative study[12] demonstrated a 63% of endoscopic lesions on CD and chronic gastroduodenitis not associated with *H. pylori-pos*. Another controlled study,[13] but with differences in age, shows statistically significant differences attributable to antibiotic treatment and endoscopic lesions in 92.2% of CD patients.

^{13}C-UBT in the expired breath:[18–27] The largest prospective and controlled study did not demonstrate statistically significant differences,[19] while Asian studies did (Table 1).[21, 24, 27, 30, 31]

Combination of Several Methods

Serology and biopsies,[3] serology and ^{13}C-UBT,[18] biopsies and ^{13}C-UBT.[21, 22] A large, controlled study showed a statistically significant difference.[21]

When most sensitive and specific methods are utilized, less convincing results are obtained. Few written reports have reported the substantial difference. Our results suggest that the frequency is similar when compared to asymptomatic subjects and even, tends to be higher in patients with CD than with UC and controls. In comparison with asymptomatic patients, after controlling for the different age and sex, regarding the distribution among groups, we did not

Table 1. Bibliographic review of studies with 13C-UBT as the diagnostic test, alone or combined with biopsy or serology

Author	Diagnostic test	Cases and controls	Results	Study design
Pearce et al.[18]	^{13}C-UBT serology	42 CD/51 UC	11.9% and 21.6%	P
		40 IBD	25% (NS)	
Piodi et al.[19]	^{13}C-UBT	72 IBD	47%	P and C
		72 controls	61% (NS)	
			65% treated with sulfasalazin 34% con 5-ASA	
			P=0.017	
Prónai et al.[20]	^{13}C-UBT	133 IBD versus COPD	12.78%	
			66.7%	
			No controls	
Hwang et al.[21]	^{13}C-UBT biopsy	97 IBD 270 controls	29%	C
			54% (P<0.001)	
Ando et al.[22]	^{13}C-UBT biopsy	38 CD 20 controls	8%	
			42% (P<0.05)	
			C53% versus 8% duodenal wounds	
Oliveira et al.[36]	^{13}C-UBT biopsy	43 CD 74 controls	51.2%	P and C
			70.3% (NS)	
			14% versus 1.4%	
Song et al.[24]	^{13}C-UBT	316 IBD 316 controls	25%	C and Multicentric
			52.5% (P<0.001)	
Lorenzo et al.[25]	^{13}C-UBT biopsy	30 CD	50%	P and C
		20 controls	40%	
		30 UC	37% versus 40%	
		60 IBD	43% versus 40% (NS)	
Pellicano et al.[26]	^{13}C-UBT	20 IBD	60%	P and C
		29 controls	41% (NS)	
Zhang et al.[27]	^{13}C-UBT	208 IBD	19.7%	
		416 controls	48.8% (S)	
Xiang et al.[30]		229 IBD		
		248 controls	27.1%	
			47.9% (S)	
Jin et al.[31]		153 UC	30.5%	
		121 controls	57% (S)	

CD: Crohn's disease, IBD: Inflammatory bowel disease, UC: Ulcerative colitis, COPD: Chronic obstructive pulmonary disease, P: Prospective, C: Controlled and matched by age and gender, NS: Not significant, S: Significant.

find any difference. In fact, in our study patients with IDB and *H. pylori* eradicated, showed clinical improvement and reduced the number of recurrences over 4 years follow-up. Hence, it seems that *H. pylori* could play a role in the pathogenesis of IBD and the natural history of the disease.

However, our results are limited by the number of patients studied (similar sample size to previously published works (Table 1)) as is reflected in the confidence intervals (contain the null value but is broad).

Some studies have identified other species of *H. pylori* in the digestive tract of patients with IBD, CD, or UC.[32–37] Recently, it has been speculated again on the infectious etiology of IBD,[38, 39] attributing potential pathogenesis to some Helicobacter species or Mycobacterium avium paratuberculosis.[40–42]

Some sources do not assign any role to the effect of antibiotic treatment. The implication of the *H. pylori* presence still remains controversial.[7, 20] Other researchers attribute the low prevalence of *H. pylori* infection in patients with IBD, to previous antibiotic treatment.[14, 35, 43, 44] Triantafillidis et al. match with these results, because patients who had not taken antibiotics had a prevalence of 55% versus 55.1% of controls.[43]

Taking into account that *H. pylori* causes granulomatous gastritis in the antrum;[45] however, patients with CD disease are not often infected by this microorganism.[13] Only one patient with CD of our study (1/40, 2.5%) showed the presence of the disease located at the stomach, and regarding *H. pylori*, the macroscopic vision, biopsy, and ^{13}C-UBT were negative. In addition, frequent endoscopic lesions,[10, 13, 14] focal gastritis,[10, 16] focal cryptitis,[17] and CD8 focal gastritis[46] have recently been described in patients with IBD.

Most of our patients with IBD and *H. pylori* -pos eradicated, remained asymptomatic for an average of 48 months of follow-up. Only 4 patients (14%) had clinical recurrences in monitoring, confirmed by endoscopy.

It is worth noting that an oligosymptomatic patient, with UC and *H. pylori* -pos, had a major outbreak of diarrhea caused by *Clostridium botulinum* and after eradication, developed IBD; as recently it has published in other studies.[47, 48, 49]

A recent review,[49] has arrived at the same conclusion, pointing that the relationship between *H. pylori* infection and IBD still remains controversial. In spite of other groups do not support our thesis,[30, 31, 50] the results obtained provide enough data to take them into consideration and might guide new studies to clarify this possible relationship (Table 1).

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Disclosures

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.V.L.; Design – M.V.L.; Supervision – M.V.L.; Materials – M.V.L., F.M.A.; Data collection &/or processing – M.V.L., F.M.A.; Analysis and/or interpretation – M.V.L.; Literature search – M.V.L., E.S.V.M.; Writing – M.V.L., E.S.V.M.; Critical review – M.V.L., E.S.V.M.

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