



Helicobacter pylori infection and inflammatory bowel disease: is there a link?

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Abstract:

Inflammatory bowel disease (IBD) that include Crohn's Disease (CD) and Ulcerative colitis (UC) are types of digestive system disease that still have not been properly identified as their original causes. Our goal was to evaluate lower infection with *H.pylori* in patients who suffer from IBD in comparison with the normal population.

Method: IN this case-control study 146 patients with IBD (32 with CD and 114 with UC) and 146 volunteers who donated blood as control group were tested for IgG and IgA antibody against *H.pylori* since Dec 2017 to May 2018 in Shiraz that were randomly selected from IBD registry software in Motahari clinic. **Result:** The presence of *H.pylori* IgG was confirmed in 10 (31.2%) of CD, 37 (32.4%) of patients with ulcerative colitis and 105 (71.9%) of the control group that it was significant ($P < 0.001$). The presence of *H.pylori* IgA was confirmed in 25% of CD, 31.6% of patients with UC and 40.4% of the control group that it was not significant. In order to relation between IBD treatment regimens and presence of *H.pylori* IgG, there were significant differences between patients who received immune-modulator and immune-suppressive drugs and those who were not using these drugs ($p < 0.001$). **Conclusion:** Our results show that the prevalence of serum IgG antibody against *H.pylori* was significantly lower in patients with IBD than in controls. The use of immune-modulator and immune-suppressive drugs may reduce the involvement of IBD patients with *Helicobacter pylori* infection.

Keyword: Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, *H.pylori*, Immuno-suppressive



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Introduction

Intestinal inflammation (IBD), which includes Crohn's disease (CD) and Ulcerative colitis(UC), is a chronic, recurrent and prolonged illness that has caused many problems for global health(1, 2). Over time, the disease may lead to dyspepsia, surgery, or digestive discomfort(3, 4).IBD seems to be the result of unknown interactions between environmental factors (eg, infections, drugs, smoking, food) and host genetic factors resulting from inappropriate or anomalous immunological reactions to intestinal microorganisms. The current hypothesis due to the etiology of IBD is that gastrointestinal microbes or their bio-products, in association with a disruption in the gastrointestinal epithelium and / or environmental trigger, distribute a deregulated immune response leading to chronic inflammation in genetically susceptible one(5, 6).For example, Gerald et al. (7) showed that infection with *Campylobacteria* or *Salmonella* species predisposes patients to the spread of IBD.

The *Helicobacter* species are colonized in the gastrointestinal tract due to its micro-aerophilic metabolism, spiral shape and amazing mobility(8). The digestive tract growth site is divided into two major groups. The first group grows in the stomach, such as *Helicobacter Pylori*, and the second group, such as enterohepatic *Helicobacter*, which grows in the biliary system of the liver and is associated with chronic intestinal and gastrointestinal diseases(9). *Helicobacter pylori* usually resides at the epithelium of the stomach, but it can also be found in the colon and stool samples of patients(10). This fact raised the possibility that they may well play a role in the development or perpetuation of IBD(11).The inflammatory response of the stomach mucus to *Helicobacter pylori* is likely to signal the combined effects of cellular immune responses that are caused by bacteria through persistent stimulation of the host immune system(12). Local immune response products may go to other places of the body, and in turn, it can relate *Helicobacter pylori* infection to the pathophysiology of various types of gastrointestinal disorders, including autoimmune disorders (13).

However, it is interesting to note that *Helicobacter Pylori* plays a protective role in the development of autoimmune disorders(14), such as asthma (15) and type I diabetes (16). The main role of the protective effects of *Helicobacter Pylori* infection in the treatment of acute or chronic localized mucosal is that it may be due to systemic cytokine secretion, which in turn leads to negative regulation of systemic immune responses and autoimmune suppression. An increase in the binding of gastrointestinal bacteria to intestinal epithelial cells has been reported in IBD. Intestinal inflammation (IBD), an intolerance to host immune responses to cumulative bacteria, has created a major pathogenic mechanism. The immune response to lymphocyte (Th1) cells and the secretion of pre-inflammatory cytokines in IBD, particularly Crohn's disease (CD), is involved. Positive cellular signaling molecules, such as macrophage inflammatory protein 3a (MIP-3a), have also been confirmed in IBD(17).

H.pylori infection is an infectious disease that occurs in deprived societies and, in fact, improves the health of the environment, reducing its prevalence. On the contrary, an increase in the



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prevalence of IBD is seen in Western-style populations (18). Therefore, it is clear that there is an inverse relationship between the outbreak of IBD and Helicobacter pylori infection. The prevalence of IBD in the United States is enormous, while the rate of infection with Helicobacter pylori is low. While in the area where treatment with Helicobacter Pylori is widely used, the constant increase in IBD is seen as endemic(17). Although environmental changes may corroborate this inverse relationship, many epidemiological studies have shown a lower incidence of Helicobacter Pylori infection in IBD patients(19).

On the other hand, the drugs used in the treatment of IBD are those that enhance the Helicobacter Pylori, or IBD-associated mucosal changes prevent colonization of Helicobacter Pylori in the stomach(20, 21). Protective role in Helicobacter pylori infection with the mechanism of possible changes in host immune response to escape the inflammatory response of lymphocyte cells 1 and 17 (Th1, Th17) to increase the activity of lymphocyte T cells can prevent the progression of IBD(22, 23). Additionally, Helicobacter Pylori may stimulate the production of antibacterial proteins that fight against bacteria that are potentially effective in treating IBD (24), or with which bacteria compete for growth in the upper gastrointestinal tract (25).

Material and method

146 patients with IBD (32 Crohn's and 114 Ulcerative Colitis) that was selected in the registry of inflammatory bowel disease patients in Motahari Clinic affiliated to Shiraz University of Medical Sciences, Iran, and 146 volunteers donated blood from Shiraz Blood Transfusion Organization as the control group (healthy non-IBD) since Dec 2017 from May 2018 in Shiraz were included in the case-control study. The group of patients with IBD was randomly selected using randomized software(STATA ver 14.0). Their disease was confirmed by clinical diagnosis of two gastrointestinal specialists, laboratory and colonoscopy results. Demographic and disease information were extracted from the IBD registry software. In order to select normal group, any kind of clinical and/or histo-pathological diagnosis of IBD were excluded. All patients signed the form upon complete knowledge and understanding of the study conditions. This study was approved by the ethics committee of Shiraz University of Medical Sciences in May 2017 (code: 6024).

then the blood collection was done. Subsequently, the samples were transferred to the gastrointestinal lab, and the sera were divided into two parts and were kept in the -20°C freezer until beginning of the experiments. *H.Pylori*IgG and *H.Pylori* IgA assay were performed on sera with enzyme-linked immune-absorbent assay(ELISA) method(Monobind, UK).A total of 146 control blood donors from the Blood Donor who were matched for age and sex with inflammatory bowel disease were selected and the above tests were performed on them.



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Statistical methods:

The data are analyzed using SPSS19 software. To evaluate the normality, the Kolmogorov smirnov test is used. Also, t-test, χ^2 -tests are used to compare the qualitative and quantitative variables between the groups as needed. To investigate the effect of confounding variables, are used.

Results:

The groupe of IBD patients consisted of 73 women, 13 (17.8%) had CD, 60 (82.2%) of them were UC. There were also 73 men in which 19 (26%) of them had CD, 54 (74%) had UC disease. The age range of the participants was 21 to 68 years old. A total of 146 healthy volunteers blood donors were selected as control group(none IBD). The age and sex were similar to those in the patients. The presence of *H.pylori* IgG in 152 participants (52.0%) was confirmed in both case and control groups, and 10 (31.2%) of Crohn's patients, 37 (32.4%) of patients with ulcerative colitis and 105 (71.9%) of the control group were positive in this regard($P < 0.001$)(Table1).

Table1: *H.Pylori* IgG ELIZA results

		<i>H.Pylori</i> IgG			Total
			POSITIV E	NEGATIV E	
DISEASE	Count	35	0	0	35
	% within DISEASE	100.0%	0.0%	0.0%	100.0%
UC	Count	0	37	77	114
	% within DISEASE	0.0%	32.5%	67.5%	100.0%
CD	Count	0	10	22	32
	% within DISEASE	0.0%	31.3%	68.8%	100.0%
NORMA L	Count	0	105	41	146
	% within DISEASE	0.0%	71.9%	28.1%	100.0%

The presence of *H.pylori* IgA in 103 participants (35.3%) was confirmed in both case and control groups, and 8 (25%) of Crohn's patients, 36 (31.6%) of patients with ulcerative colitis and 59 (40.4%) of the control group were positive in this regard that it was not significant($P = 0.146$) (Table2).



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Table 2: *H. Pylori* IgA ELIZA results

			DISEASE			Total
			UC	CD	NORMA L	
<i>H.pylori</i> IgA	POSITI VE	Count	36	8	59	103
		% within <i>H.pylori</i> IgA	35.0%	7.8%	57.3%	100.0%
		% within Disease	31.6%	25.0%	40.4%	35.3%
	NEGAT IVE	Count	78	24	87	189
		% within <i>H.pylori</i> IgA	41.3%	12.7%	46.0%	100.0%
		% within Disease	68.4%	75.0%	59.6%	64.7%

In order to relation between IBD treatment regimens and presence of *H.pylori* IgG as shown in below table, there was significant differences between *H.pylori* positive and negative groups. Although 2 cases(50.0%) who consume “Pentasa” were positive for *H.pylori* IgG that was not significant, but 13 cases(33.3%) who are undergone “Glucocorticoid” treatment with *H.pylori* IgG Positive results, 18 cases (30.5%) undergone “Immunosuppressive” treatment, any cases(0.0%) of whom consumes “Asacol Enema”, 17 patients(32.0%) who are undergone ‘Asacol Suppository’, and 4 cases who were undergone “Mesalasin” treatment were positive also in this regard (p <0.001).



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Drugs			<i>H.pylori</i> IgG		Total
			POSITIVE	NEGATIVE	
Glucocorticoid	YES	Count	13	28	39
		% within GLUCOCORTICOID	33.3%	66.7%	100.0%
		% within <i>H.pylori</i> IgG	8.6%	18.6%	11.9%
	NO	Count	139	114	253
		% within GLUCOCORTICOID	54.9%	45.1%	100.0%
		% within <i>H.pylori</i> IgG	91.4%	81.4%	77.4%
IMMUNOSUPPRESSIVES	YES	Count	18	41	59
		% within IMMUNOSUPPRESSIVES	30.5%	69.5%	100.0%
		% within <i>H.pylori</i> IgG	11.8%	29.3%	18.0%
	NO	Count	134	99	233
		% within IMMUNOSUPPRESSIVE	57.5%	42.5%	100.0%
		% within <i>H.pylori</i> IgG	88.2%	70.7%	71.3%
ASACOL ENEMA	YES	Count	0	2	2
		% within ASACOL ENEMA	0.0%	100.0%	100.0%
		% within <i>H.pylori</i> IgG	0.0%	1.4%	0.6%
	NO	Count	152	138	290
		% within ASACOL ENEMA	52.4%	47.6%	100.0%
		% within <i>H.pylori</i> IgG	100.0%	98.6%	88.7%
ASACOL SUPP	YES	Count	8	17	25
		% within ASACOL SUPP	32.0%	68.0%	100.0%
		% within <i>H.pylori</i> IgG	5.3%	12.1%	7.6%
	NO	Count	144	123	267
		% within ASACOL SUPP	53.9%	46.1%	100.0%
		% within <i>H.pylori</i> IgG	94.7%	87.9%	81.7%
PENTASA	YES	Count	2	2	4
		% within PENTASA	50.0%	50.0%	100.0%
		% within <i>H.pylori</i> IgG	1.3%	1.4%	1.2%
	NO	Count	150	138	288
		% within PENTASA	52.1%	47.9%	100.0%
		% within <i>H.pylori</i> IgG	98.7%	98.6%	88.1%
MESALAZINEENEMA	YES	Count	4	9	13
		% within MESALAZINEENEMA	30.8%	69.2%	100.0%
		% within <i>H.pylori</i> IgG	2.6%	6.4%	4.0%
	NO	Count	148	131	279
		% within MESALAZINEENEMA	53.0%	47.0%	100.0%
		% within <i>H.pylori</i> IgG	97.4%	93.6%	85.3%

Discussion:

In this study the presence of *H.pylori* IgG was confirmed in 10 (31.2%) of CD, 37 (32.4%) of patients with ulcerative colitis and 105 (71.9%) of the control group that indicated the prevalence of serum IgG antibody against *H.pylori* was significantly lower in patients with IBD than in age and sex matched controls that was similar to recent study in other countries.(25-28)

In order to relation between IBD treatment regimens and presence of *H.pylori* IgG, there was significant differences between patients who received immune-modulator and immune-suppressive drugs (Glucocorticoid, Asacol Enema, Asacol Suppository, Mesalasin) and whom were not used these drugs. Although Some researchers reported that this was not related to any drugs used for IBD(34) but Some studies have represented that the rate of *H. pylori* is lower in the



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IBD patients prescribed Immunosuppressive drugs(25, 26, 29, 30). Also El-Omar et al(27) suggested that the low prevalence of H pylori antibodies in patients with IBD was a result of long term treatment with sulphasalazine. (34).. Immunosuppressive drugs probably blocked the adhesion of *H. pylori* to the gastric mucosa directly over

receptors or indirectly by its anti-inflammatory effects(32, 33).. There was some limitation in this study due to heterogeneity among studies regarding the method of *H. pylori* diagnosis differences in study population, ethnicity and age across study, and the possibility of publication bias may limit the certainty of the above findings. As environmental hygiene and intestinal microbiota may be strong confounders, further mechanistic studies in *H. pylori* infection for instance using mouse models are necessary to define the mechanism.

Conclusion:

In this study we confirm that the presence of *H.pylori* IgG, was significantly lower in patients who received immune-modulator and immune-suppressive drugs than whom were not received these medication. More studies investigating the effect of *H. pylori* infection eradication on the risk of development of IBD and the natural history of IBD are needed.

Conflict of interest: The authors have no conflicts of interest in this study.

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