

Association Between *Giardia Duodenalis* Infection and Irritable Bowel Syndrome

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Abstract- Some studies have shown that giardia infection is associated with some abdominal symptoms. The aim of this study was to determine the relationship between giardia duodenalis infection and irritable bowel syndrome (IBS). In this clinical trial study, 60 patients with non-constipation predominant IBS based on Rome III criteria were enrolled in the study. 30 patients with giardiasis who were diagnosed with stool Eliza as patients, and 30 other patients who did not have giardiasis as control enrolled to study. All patients were treated with 250 milligrams of metronidazole TDS for 5 days. Abdominal symptoms including abdominal pain, bloating, and diarrhea were determined and compared in both groups before and after treatment. The mean age and sex distribution of the two groups were similar ($P>0.5$). The pain, bloating, and diarrhea severity before treatment with metronidazole were not significantly different in the two groups. The pain and bloating and diarrhea severity in both groups significantly decreased after the treatment period, but reductions were significantly higher in the case group ($P<0.001$ and $P<0.001$ $P<0.001$, respectively). The mean score of global symptoms before treatment in both case and control groups was similar. ($P=0.88$), but after treatment it was 4.85 ± 2.18 ($P<0.001$) and 10.48 ± 2.14 ($P<0.001$) respectively and the difference between the two groups was significant ($P<0.001$). The recovery percentage was 0.61 ± 0.16 in the case group and 0.14 ± 0.17 in the control group ($P<0.001$). Giardia infection in patients with IBS seems to play a significant role in clinical manifestations of non-constipation IBS and treatment with metronidazole can improve these symptoms significantly.

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Introduction

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits. IBS can be presented with different clinical pictures: patients with diarrhea-predominant (IBS-D), patients with constipation-predominant (IBS C), and patients with pain predominant. IBS is a common gastroenterology problem in the world and also in Iran. In a systematic review reported in Iran, the prevalence of IBS was in the

range of 1.1% to 25% and was more common in women (1). There are many hypotheses about the etiology of IBS and one of the most important of those is post-infectious IBS. In many studies, the role of specific infections has been mentioned and one of these organisms is *Giardia duodenalis* (*giardia lamblia*, *giardia intestinalis*). This protozoan of the duodenum is very common in the world and causes symptomatic and asymptomatic infection in 500 million people annually (2). In a systematic review and meta-analysis reported in Iran, the overall pooled prevalence of intestinal parasites

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Giardia infection and IBS

in food handlers was 19.3% and *Giardia lamblia* (5.2%) was the most common protozoan parasite (3). *Giardia* infections can be chronic and after resolution may be terminated to IBS (2). Since these symptoms may overlap with other gastrointestinal disturbances, it is not clear when this infection should be suspected. In fact, the absence of definitive etiological factors for IBS, the constant similarity between IBS and giardiasis, and the high number of undiagnosed patients for *giardia duodenalis* infection leads to a causal relationship investigation between these two diseases.

This study aimed to investigate relationship between *giardia duodenalis* infection and IBS symptoms in an Iranian small group.

Materials and Methods

A prospective and case-control study was conducted in three tertiary big hospitals in Mashhad and Isfahan, IRAN. The target population was patients with non-constipation IBS based on Rome III criteria. Inclusion criteria included the age of 18 to 60 years, the absence of diabetes and immune system disturbances, the absence of warning symptoms (significant weight loss and anorexia, recurrent vomiting, gastrointestinal bleeding, and family history of gastrointestinal malignancies), lack of antibiotics uses in the past 30 days, no use of NSAIDs or PPIs in the past 15 days, no abnormality in routine biochemical tests including thyroid tests, and negative transglutaminase and anti endomysial antibodies in serum. Patients with lactose intolerance and who did not respond accurately to the questionnaire were excluded.

The procedure was followed by obtaining consent from the Medical Ethics Committee of Mashhad University. For all patients with nonconstipation IBS based on Rome III criteria, we performed *Giardia duodenalis* detection by "Fecal *Giardia Lamblia* Antigen ELISA Kit" (Epitope Diagnostic, Inc.). A fresh fecal sample was collected from the patient and kept at 2-8 C and tested within 2 days. According to *giardia* results, there were two groups: 1-The patients group had all criteria of ROM III for non-constipation IBS diagnosis and all of these patients had *giardia* infection. 2-The control group included patients with ROM III criteria for non-constipation IBS, but they were not infected with giardiasis.

Both groups were treated with metronidazole, 250 mg, TID for 5 days. These patients were examined after 2 weeks by telephone call and referral to the clinic for

clinical evaluation and also a stool test was done to check the giardiasis parasitic infection.

The severity of pain and bloating based on the 7-point Likert system was divided (indicating not at all, hardly, somewhat, moderately, a good deal, a great deal, a very great deal), and the diarrhea score based on the 5-point Likert system was also divided (very hard, hard, formed, loose, watery). Finally, the mean score of global symptoms in the two groups were determined before and after treatment with metronidazole.

The score of each of the above symptoms was determined by adding the number of scores divided by the number of patients in each group and was presented by the mean \pm standard deviation. The above items were investigated in all patients before and after treatment and the percentage of score change in each of these symptoms was calculated.

Patient's recovery status was calculated by the percentage of score change, and changes of 70% and higher as desirable improvement, 40-70% as relative improvement, score less than 40% as poor recovery, and no difference between before and after therapy as a failure was considered.

After collecting data, all data were analyzed by SPSS software version 24. Chi-square, independent sample T-test, paired sample T-test and repeated measure ANOVA tests were used to analyze the data.

Results

In this study, 240 patients with irritable bowel syndrome were included and 33 of them (13.75%) had giardiasis infection. 30 patients with IBS and *Giardia* infection as the case group and 30 patients with IBS but without *Giardia* infection as the control group were selected and both groups were treated with metronidazole.

The mean age of the two groups was 30.94 ± 10.35 and 28.52 ± 9.59 years, respectively ($P=0.33$). In terms of sex distribution, 16 and 10 patients were males (48.5% vs. 69.7%) and other patients were female ($P=0.13$) in both groups respectively.

According to Table 1, the pain score before treatment with metronidazole was not significantly different in the two groups ($P=0.27$). However, after treatment with metronidazole, the reduction in pain score in the case group was 0.70 ± 0.23 ($P<0.001$), and in the control group was 0.11 ± 0.02 ($P=0.002$). The pain score in both groups was significantly decreased during the treatment period, but pain reduction was

significantly higher in the case group ($P<0.001$).

Table 1. The mean (SD) of Pain, Bloating, and Diarrhea before and after treatment

Symptoms	Time	Giardiasis		P*
		Yes	No	
Pain intensity	Before	3.85±0.83	3.61±0.93	0.27
	After	1.21±0.96	3.15±0.97	<0.001
	Percent of decrease P**	0.7±0.23 <0.001	0.11±0.2 0.002	<0.001***
Bloating intensity	Before	4.06±0.79	4.27±0.8	0.28
	After	1.27±1	3.51±0.91	<0.001
	Percent of decrease P**	0.7±0.24 <0.001	0.16±0.22 <0.001	<0.001***
Diarrhea intensity	Before	4.39±0.5	4.36±0.49	<0.001
	After	2.33±0.92	3.79±0.74	<0.001
	Percent of decrease P**	0.46±0.25 <0.001	0.13±0.18 <0.001	<0.001***

*Difference between the two groups based on independent sample T-test

** Difference within any group based on paired sample T-test

*** mean changes between the two groups based repeated measures ANOVA

There was no significant difference in the score of bloating before treatment in both groups ($P=0.28$). However, after treatment with metronidazole, the percentage of reduction in bloating score in the case group was 0.70 ± 0.24 ($P<0.001$), and in the control group was 0.16 ± 0.22 ($P<0.001$) but the reduction of bloating in the case group was significantly higher ($P<0.001$)

Diarrhea severity also showed that there was no significant difference between the two groups in the pre-treatment ($P=0.8$). The percentage of decrease in diarrhea score in the case group was 0.46 ± 0.25 ($P<0.001$) and in the control group was 0.13 ± 0.16 ($P<0.001$) but diarrhea severity changes were significantly more prominent in the case group.

($P<0.001$). It should be noted that according to the mentioned test, the age and sex of the patient did not have a significant effect on changes in the severity of pain, bloating, and diarrhea.

There was no significant difference between the mean score of global symptoms of the disease before treatment in both case and control groups ($P=0.88$). The mentioned mean score after treatment in the case and control groups was 4.85 ± 2.18 ($P<0.001$) and 10.48 ± 2.14 ($P<0.001$) respectively and the difference between the two groups was significant ($P<0.001$). According to the results, the recovery percentage was 0.61 ± 0.16 in the case group and 0.14 ± 0.17 in the control group and the recovery rate was significantly higher in the case group ($P<0.001$) (Table 2).

Table 2. The mean (SD) of intensity symptoms of Irritable bowel syndrome symptoms before and after treatment

Time	Giardiasis		P*
	Yes	No	
Before treatment	12.3±1.57	12.24±1.6	0.88
After treatment	4.85±2.18	10.47±2.14	<0.001
Percent of improvement P**	0.61±0.17 <0.001	0.14±0.17 <0.001	<0.001***

*Difference between the two groups based on independent sample T-test

** Difference within any group based on paired sample T-test

*** mean changes between the two groups based repeated measures ANOVA

Discussion

In this study, the prevalence of giardiasis infection among 240 patients with non-constipation irritable bowel syndrome was 13.3%.

Giardia is the most common parasite causing

chronic diarrhea. *Giardia* infection typically lasts 2-6 weeks but can become chronic and may recur after treatment. Symptoms are similar to IBS-D with diarrhea, bloating, and pain (4). Because of this, we select non-constipation IBS patients in this study.

The prevalence of giardia in IBS patients was studied

in different studies. In Italy, a consecutive series showed *G. lamblia* infection in 6.5% of 100 patients with IBS based on Rome III criteria (5). In a case-control study in Iran, 8% of IBS patients based on Rome III criteria had giardia infection and no case in the control group (6). In a case-control study in Jordan, 11% of IBS patients based on Rome III criteria had giardia infection and 1% in the control group ($P=0.0029$) (7).

On the other hand, the effect of *Giardia* infection on mitigating the symptoms of irritable bowel syndrome has been studied in many studies. In 2004, the parasite *Giardia lamblia* contaminated drinking-water reservoirs in Bergen, Norway and this event was a good opportunity to determine the relationship between giardia infection and subsequent IBS development. The first study in 2009 revealed that the giardia outbreak resulted in IBS symptoms in 80.5% of patients 12-30 months after the onset of *Giardia* infection, and at least 6 months after *Giardia* eradication (8). In another study, 817 cases of giardiasis that were attributed to the above outbreak in Bergen, Norway were matched with 1128 people randomly selected from the population of Bergen. The prevalence of IBS was 46.1% in exposed patients versus 14% in controls. The adjusted relative risk (RR) of IBS 3 years after acute giardiasis was 3.4 (9,10). In the third study about the above event, the prevalence of IBS 10 years after the outbreak was 43% among 576 exposed individuals and 14% among 685 controls (adjusted odds ratio for development of IBS in exposed individuals, 4.74; 95% CI, 3.61-6.23) (11).

In a large insurance database in the United States, the one-year incidence of IBS was higher in persons with giardiasis (3935 persons) than controls (19 663 persons) (IR=37.7/1000 person-years vs 4.4/1000 person-years). The adjusted hazard ratio was 3.9 (95% CI=2.9-5.4) (12).

Giardia is the most common parasite causing chronic diarrhea, but it is unclear if we must check giardia in any patients with IBS. One may consider pretest probability before ordering giardia tests. The highest risks are exposure to endemic areas and drinking untreated or contaminated water. In these groups, it is better to investigate giardia in IBS patients. In practice, an empiric trial of therapy may be given if the pretest probability is high, but the testing is negative (4).

What is the mechanism for post-giardia IBS? There are limited studies about the pathogenesis of IBS after *Giardia* infection. Development of post-infectious visceral hypersensitivity (13), an increase of pro inflammatory cytokines (TNF α , IFN,

Myeloperoxidase), and a decrease of EC cell, nitric oxide synthesis, and IL8 (14) are discussed in this pathogenesis.

According to our study, treatment of IBS patients with and without giardia infection with metronidazole could significantly and reliably reduce the severity of IBS symptoms and this response was significantly better in IBS patients with giardia infection. Response to treatment by metronidazole in the IBS-giardia group is clear but about IBS patients without giardia also there are important reasons for response to treatment by metronidazole. Emerging data suggest that the fecal microbiota in individuals with IBS differ from healthy controls (15,16,17). Because of potential microflora alterations in IBS, it is possible that patients with IBS would benefit from antibiotics or probiotics. On the other hand, there is greater intestinal bacterial overgrowth probability in IBS with a prevalence that varies widely (2-84%) and Rifaximin is an effective treatment for the majority of overall symptoms and abdominal bloating in IBS (18).

A systematic review of interventions for post-infectious IBS in 2015 was performed and only 1 study about the efficacy of metronidazole in IBS patients was funded. Thakur et al. recruited 17 patients with PI-IBS, 24 patients with IBS-constipation (IBS-c), and 35 patients with IBS-diarrhea (IBS-d) based on Rome II criteria and a history of acute gastroenteritis. The participants took metronidazole orally for seven days and then returned on day twenty-eight for reassessment. There was a significant improvement in pain, modified stool score (Stool frequency and consistency), and total symptom scores on days 7 and 28 compared to baseline. The authors concluded that metronidazole may be considered in therapeutic trials in PI-IBS patients (19).

In an abstract presentation, among 70 patients with IBS, 74% had improvement in symptoms after treatment with one month of metronidazole therapy (20).

Finally, according to the results of our study, the prevalence of *Giardia* infection in patients with non-constipation irritable bowel syndrome is high and treatment of these patients with metronidazole reduces abdominal symptoms such as pain, bloating, and diarrhea.

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