



The effect of probiotic therapy on quality of life and depressive symptoms in patients with diarrhea-predominant irritable bowel syndrome

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Abstract

Aim: The aim of this study was to analyze the effect of probiotics on quality of life and depressive symptoms in patients with diarrhea-predominant irritable bowel syndrome (IBS) and moderate or severe depressive mood.

Materials and Methods: Patients diagnosed with diarrhea-predominant IBS using the Rome IV criteria and Bristol Stool Form Scale and with moderate or severe depressive symptoms according to the Beck Depression Inventory comprised the study participants. The patients were randomized and divided into two groups as the medication only group and the medication + probiotic group. The IBS 36 questionnaire and Beck's Depression Inventory were administered to all patients in the first and second groups and the scores were recorded.

Results: The change in IBS-36 scores from the beginning to the 10th week was significant in both groups ($p < 0.001$). According to the IBS-36, the median change from the beginning to the 10th week was 32 for the medication group and 48 for the medication + probiotic group. The change in the Beck's Depression Inventory scores from the beginning to the 10th week was significant in both the medication group and the medication + probiotic group ($p < 0.001$). According to the Beck's Depression Inventory, the median change from the beginning to the 10th week was 7 for the medication group and 9.5 for the medication + probiotic group.

Conclusion: In the treatment of diarrhea-predominant IBS patients, the use of probiotics together with traditional drugs will improve quality of life by reducing both gastrointestinal symptoms and psychological symptoms.



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Introduction

Irritable bowel syndrome (IBS) is a functional bowel disease characterized by abdominal pain, gas, bloating, and changes in bowel movements. It is extremely prevalent worldwide and has a significant impact on quality of life. IBS is divided into 4 types according to the Bristol stool scale: diarrhea-predominant IBS, constipation-predominant IBS, mixed type IBS, and unsub typed IBS [1]. Many factors have been blamed for the etiology including atrophy of the gut microbiota, impaired mucosal immune activation, visceral hypersensitivity, infections, and stress [2]. Due to its beneficial effects on microbiota, the usage of probiotics is now more prevalent than ever [3]. The World Health Organization defines probiotics as living bacteria that promote host health when consumed in sufficient quantities [4]. Probiotics reduce abdominal bloating

and abdominal pain, inhibit proinflammatory cytokine release and stimulate anti-inflammatory cytokine release [5]. Furthermore, they prevent harmful germs from adhering to the intestinal surface, enable their elimination with feces, and have a beneficial effect on intestinal flora by tightening the tight junction channels that regulate intestinal permeability [6,7]. In recent years, a second probiotic effect that may be useful in the treatment of IBS has come to the fore. Studies examining the brain-gut axis indicate that bacteria in the gastrointestinal tract are related to the central nervous system and imply that microbiota exchange through probiotics would be efficient at producing psychologically positive benefits [8-10]. Psychobiotics are probiotics that have mentally positive benefits by affecting the central nervous system [11,12]. Lactobacillus and Bifidobacterium are the primary psychobiotic probiotics. Thus far, the majority of studies on the topic have been undertaken on animals and healthy people while studies on

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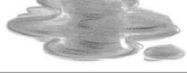
Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces ENTIRELY LIQUID

Figure 1. Bristol Stool Form Scale.

individuals with psychological illnesses are scarce. Given that IBS is frequently associated with psychological disorders such as depression and anxiety and that certain probiotics are effective for both gastrointestinal symptoms and psychological disorders, it was presumed that their use would be particularly advantageous in this patient group. Studies have shown that the most common type of IBS is diarrhea-predominant type and psychological disorders such as depression and anxiety are most common in diarrhea-predominant IBS patients. Therefore, the aim of the present study was to analyze the effect of probiotics on quality of life and depressive symptoms in patients with diarrhea-predominant irritable bowel syndrome and moderate or severe depressive mood.

Materials and Methods

This study was a single-centered, cross-sectional study. For the power analysis, Bülent Baran's thesis was used as reference [13]. According to the results of this study, the IBS-36 score decreased from 84 to 32 in the treatment group and from 85 to 69 in the control group. The difference in decline between the treatment and control groups was approximately 36 units (treatment group SD:35, control group SD:40). In the study, the number of samples per group was calculated as 19 with a Type 1 error $\alpha=0.05$ and the power of the study $(1-\beta) = 80\%$. At least 23 people per group should be included in the study with the missing data supplement. Sample calculation was performed using the MedCalc® Statistical Software version 20.027 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2022). Male and female patients between the ages of 18 and 65 who were admitted to the Istanbul Medipol University Internal Medicine outpa-

tient clinic and diagnosed with diarrhea-predominant IBS using the Rome IV criteria and Bristol Stool Form Scale (BSFS) and with moderate or severe depressive symptoms according to the Beck Depression Inventory comprised the study participants. Patients were informed about the study and written informed consent was obtained.

According to the Rome IV criteria, IBS is defined as recurrent abdominal pain on average at least 1 day/week in the last 3 months, and is associated with two or more of the following criteria: related to defecation, associated with a change in the frequency of stool, and associated with a change in form (appearance) of stool. These criteria should have occurred over the last 3 months with symptom onset at least 6 months prior to diagnosis [14].

The BSFS defines IBS-D as having more than 25% loose stool (Type 6 or 7) and less than 25% hard stool (Type 1 or 2) (Figure 1) [15].

Inclusion criteria

- Age 18-65
- Diarrhea-predominant IBS diagnosis according to the Rome IV diagnostic criteria and the Bristol Stool Scale
- Moderate or severe depressed mood in accordance with the Beck Depression Inventory (score of 17-63).

Exclusion criteria

- Thyroid dysfunction
- Liver dysfunction
- Renal dysfunction Acute / Chronic Infection
- Malignancy
- Inflammatory Bowel Disease
- Lactose Intolerance
- Use of medication that affects bowel movements
- Pregnancy
- Suicidal thoughts
- Smoking
- Use of medication / herbal agents (St. John's wort, lavender, etc.) that affect mood
- Receiving therapy for depression at present / within the last 6 months.

Examinations

A detailed medical history of patients was obtained, and physical examination was performed. Tests including complete blood count, kidney function tests, liver function tests, serum electrolytes, C-reactive protein, erythrocyte sedimentation rate, thyroid function tests, fecal occult blood tests, and stool microscopy tests were performed on all patients participating in the study. Moreover, anti-endomysium and anti-gliadin antibodies were tested for

celiac disease. Blood samples of the patients were taken between 8:00 a.m. and 10:00 a.m. on an empty stomach. Endoscopic screening was performed on patients over 50 years of age who had concerning symptoms. As a result of these examinations, 3 patients were diagnosed with sub-clinical hyperthyroidism, 1 patient with rectal cancer, 2 patients with inflammatory bowel disease, 6 patients with infectious gastroenteritis, and were all excluded from the study. The study was completed with a total of 53 patients (26 males, and 27 females) after 9 patients dropped out.

Randomization

The patients were randomized to form two parallel groups according to the order of arrival, with the first patient in the medication group, and the second patient in the medication + probiotic group.

Intervention

After randomization, the IBS 36 questionnaire and Beck's Depression Inventory were administered to all patients in the first and second groups and the scores were recorded. The first group received the antispasmodic pinaverium bromide 50 mg 3x1 posology and the second group received pinaverium bromide 50 mg 3x1 posology + one probiotic capsule containing *Lactobacillus helveticus* R0052- 3.596x10⁹ cfu + *Bifidobacterium longum* R0175- 0.4x10⁹ cfu + *Lactobacillus rhamnosus* R0011- 1.332x10⁹ cfu, in total 5,326x10⁹ cfu microorganisms. Patients were instructed to take the 50 mg pill of pinaverium with meals and the probiotic capsule before sleeping. The patients were informed about not using any medication that could affect the gastrointestinal system and depressive symptoms throughout the study period. The patients were followed up and treated for 10 weeks. At the end of 10 weeks, the IBS-36 questionnaire and Beck's Depression Inventory were repeated in both groups. Both groups were evaluated in terms of whether there was a significant difference in baseline and post-treatment scores. Subsequently, the groups were compared, and it was determined whether there was a greater improvement in scores in the probiotics group. The association between baseline and post-treatment IBS-36 scores and Beck's Depression Inventory scores was also examined.

IBS-36

Each participant was asked thirty-six questions specific to IBS, which they were instructed to answer considering the last 2 months. Each question was given an answer ranging from 0 (never) to 6 (always), expressing how often the problem in the question was encountered. The level of quality of life for the pre-treatment period was measured by summing the scores of the answers (a maximum of 216 points can be obtained on the IBS-36 with higher scores indicating worsening quality of life) [16].

Ethical considerations

Approval for this research was obtained by the local ethics committee (Istanbul Medipol University, Clinical Research Ethics Committee, Date: 27/09/2022, Decision No: 810) and the study was conducted in accordance with the Helsinki Declaration principles.

Beck's depression inventory

The Beck's Depression Inventory consists of 21 questions. Each question has four possible responses which are scored between 0 and 3 points. A score of 0 to 9 indicates minor depression, 10 to 16 mild depressions, 17 to 29 moderate depression, and 30 to 63 indicates severe depression [17].

Statistical analysis

Descriptive statistics were used for the continuous variables (mean + standard deviation, median [minimum, maximum]). Using the Shapiro-Wilks test, the adherence of the data to a normal distribution was evaluated. The Mann-Whitney U test was used to assess the connection between two non-normally distributed continuous variables. The Wilcoxon Signed Rank test was used to examine the change between two continuous dependent variables that did not conform to a normal distribution. Statistical significance was accepted at 0.05. Analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013).

Results

No statistically significant differences in age and gender distributions were found in the study groups (Table 1).

The Beck's Depression Inventory ratings changed significantly between baseline and after therapy in the medication-only group. The change in Beck's Depression Inventory ratings between baseline and post-treatment was statistically significant in the medication + probiotic group. While the median change from baseline to post-treatment in the medication group was 7, this difference was 9.5 in the medicine + probiotic group. The difference was statistically significant (Mann Whitney U $p=0.001$) (Table 2).

The change in IBS 36 scores at baseline and post-treatment was statistically significant in the medication-only group. The change in IBS 36 scores at baseline and post-treatment periods in the medicine + probiotic group was statistically significant. The median change from baseline to post-treatment in the medication group was 32, while this difference was 48 in the medication + probiotic group. The difference was statistically significant (Mann-Whitney U $p<0.001$) (Table 3).

At baseline, there was a good, positive, statistically significant correlation between the Beck Depression Inventory Score and IBS 36 Score. At 6 months, there was a weak, positive, statistically significant correlation between the two scores (Table 4).

Discussion

Within the scope of the present study, as a result of the 10-week treatment period, it was determined that depression symptoms decreased and quality of life increased, with this improvement being considerably greater in the medication + probiotics group than in the medication-only group. Considering that IBS is a chronic disease characterized by symptoms such as abdominal pain, gas, bloating, constipation, and diarrhea, which have a significant

Table 1. Demographic data.

Distribution of Sex				
n (%)	Medication	Medicine + Probiotic	All patients	p*
Sex				
Male	13(48.1)	13(50)	26(49.1)	1.00
Female	14(51.9)	13(50)	27(50.9)	
*Yates Continuity Correction.				
Distribution of Age				
	Medication	Medicine + Probiotic	All patients	p*
Mean \pm SD, n	39.3 \pm 16.3	39.8 \pm 14.2	39.6 \pm 15.2	0.918
Med (min-max)	36 (18-65)	36(19-62)	36 (18-65)	

*Mann Whitney u test.

Table 2. Assessment of Beck's depression inventory.

	Medication			Medicine + Probiotic		
	Beginning n=27	Week 10 n=27	Difference	Beginning n=26	Week 10 n=26	Difference
Mean \pm SD, n	32.8 \pm 11.6	25.1 \pm 8.9	-7.7 \pm 6.7	30.9 \pm 11.8	19.8 \pm 8	-11.2 \pm 6.5
Med (min-max)	31(17-59)	24(12-48)	-7(-29-0)	29(17-56)	19(10-44)	-9.5(-26-(-1))
p		<0.001 ²			<0.001 ¹	

¹Wilcoxon Signed Rank test, ²Paired Sample test.**Table 3.** Assessment of IBS 36.

	Medication			Medicine + Probiotic		
	Beginning n=27	Week 10 n=27	Difference	Beginning n=26	Week 10 n=26	Difference
Mean \pm SD, n	168.9 \pm 22.1	132.6 \pm 18.7	-36.2 \pm 16.3	165.5 \pm 16.8	119 \pm 16.5	-46.5 \pm 16.8
Med (min-max)	161 (131-198)	133(102-169)	-32(-70-(-10))	167.5(130-198)	120(93-154)	-48(-85-(-9))
p		<0.001 ¹			<0.001 ²	

¹Wilcoxon Signed Rank test, ²Paired Sample test.**Table 4.** Examination of Correlation between BECK and IBS-36.

	r	p
Beginning Beck x IBS-36	0.721	<0.001
6 th Month Beck x IBS-36	0.303	0.027

Spearman's Rho Correlation Coefficient.

impact on the quality of life and functionality of the patient, it is not surprising that quality of life and mood improved as these symptoms subsided in the group using only medication. On the other hand, the disease is closely linked to psychological disorders such as anxiety and depression, and it is anticipated that the use of an agent that will affect both the gastrointestinal system and the central nervous system will produce more positive results in this complex and difficult disease. Bidirectional neuronal, hormonal, and immunologic connections between the central nervous system and the gastrointestinal tract coordinate digestion [18]. Among IBS patients, 40% are in the diarrhea predominant group. Diet and intestinal microbiota

play a significant role in the pathogenesis of IBS with diarrhea as the primary symptom [19,20]. The reason for this is the fact that alterations in the gut microbiota result in increased intestinal wall permeability, colonization by pathogenic microorganisms, and proinflammatory response. Visceral hypersensitivity and disturbances in the brain-gut axis result from the release of proinflammatory cytokines, which interfere with the signaling of serotonin-containing chromaffin cells in the enteric crypt epithelium [21,22]. Further evidence of the effect of microbiota on IBS is the frequency with which diarrhea-predominant IBS develops following illness due to flora disruption [23]. Post-acute infectious gastroenteritis IBS (Post-infectious-IBS) occurs due to the deterioration of the microbiota and is characterized by frequent recurrent diarrhea [24]. In the United States, 1 in 6 adults develops foodborne gastroenteritis each year [25]. Therefore, many people are at risk of developing PI-IBS. Estimates suggest that the prevalence of PI-IBS in the population may be around 9% [26]. In the treatment of diarrhea-predominant IBS, the FODMAP diet (a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) is used. Opioid receptor agonists, serotonin receptor antagonists, and an-

tidepressants can also be used, but these treatments frequently do not work alone [27-30]. According to the UK National Institute for Health and Clinical Excellence, probiotics are safe and highly effective for IBS [31]. Probiotic agents should be used for a minimum of four weeks and contain at least 10^6 cfu [32,33]. In the present study, probiotics containing 10^9 cfu were used for 10 weeks. *Lactobacillus helveticus* and *Bifidobacterium longum* are the agents with the best documented psychobiotic effect in the scientific literature, but the majority of investigations have been conducted on animals and healthy people [12,34]. Tillisch et al. established via functional magnetic resonance imaging that probiotics impact brain activity in healthy subjects [35]. The usage of *Lactobacillus helveticus* and *Bifidobacterium longum* for 30 days reduced depressive symptoms and anxiety in a different study involving 55 healthy participants and evaluating mood using questionnaires identical to those used in the present study [36]. A study conducted in Japan in 2019 evaluated the efficacy of long-term use of a tablet containing the *Lactobacillus gasseri* CP2305 strain in healthy young adults. Sixty Japanese medical students were randomized to receive a tablet containing *Lactobacillus gasseri* CP2305 strain once daily for 24 weeks in one group and a placebo in the other group. At the end of the study, the anxiety level of the students was measured with the Spielberger State Trait Anxiety scale and their sleep quality was measured with the Pittsburgh Sleep Quality Index. The results showed that the use of probiotics both reduced anxiety and significantly reduced sleep disturbance compared to placebo [37]. The 2016 study by Akkasheh et al. is the first investigation into the effect of probiotics on major depressive disorder patients. In this study, the Beck Depression Inventory was utilized, and one group was administered citalopram + placebo while the other group was administered citalopram + probiotic for 8 weeks. At the conclusion of the study, the regression of depression symptoms was considerably greater in the probiotics group [38]. In a double-blind, placebo-controlled, randomized study of 79 depressive patients in New Zealand, one group received a placebo and the other group received probiotics comprising *Lactobacillus helveticus* and *Bifidobacterium longum* for 8 weeks. In terms of depressed symptoms, this study discovered no significant differences between the two groups [39]. However, the probiotic agent was the sole medicine anticipated to have mentally positive benefits in this study, and it was directly compared to a placebo. Therefore, 8 weeks may not have been long enough for the effect to manifest. In addition, the majority of participants in this study exhibited significant depressive symptoms which they had had for a long time. A milder and shorter depression may perhaps have had a positive result. The Royal Australian and New Zealand College of Psychiatrists recently issued clinical practice guidelines for stress-related mood disorders given the tremendous burden of mood disorders in western countries, emphasizing that the therapeutic potential of probiotics for low mood should not be overlooked [40]. In a meta-analysis examining the link of IBS subtypes with anxiety and depression, a total of 10 studies, 885 patients, and 1,384 healthy controls were analyzed. It was found that anxiety and depression were significantly higher in

IBS patients than in healthy controls, and that anxiety was particularly associated with IBS-C and IBS-D, while depression was particularly associated with IBS-D [41]. In accordance with this information, it was found that the IBS-D patients who participated in the current study had a poorer quality of life and severe depression symptoms at baseline.

Limitations

This was a single-center study with 53 patients. Multicenter studies with more patients are needed. Furthermore, the use of pinaverium bromide alone was compared to the use of pinaverium bromide with probiotics in the present study. It is necessary to conduct studies that directly compare placebo and probiotics in order to determine the state of gastrointestinal symptoms and psychiatric issues in IBS patients.

Conclusion

In the present study, it was found that the addition of probiotics to standard treatment significantly reduced both gastrointestinal and psychological symptoms as well as improved quality of life in patients with IBS-D, the most common type of IBS and the type most frequently associated with psychological disorders. No side effects related to probiotic use were reported during the study. IBS is a challenging disease that can progress with various symptoms in each patient. There is no single successful treatment for each patient, and tailored treatment should be conducted according to the symptoms. However, a combination of several medications can often control the symptoms. Probiotics, which are safe and effective medicines, may be used alone or in combination therapy to treat irritable bowel syndrome.

Conflict of interest statement

We have declared that we do not have any conflict of interest.

Ethical approval

Approval was obtained by Clinical Research Ethics Committee of Istanbul Medipol University (Date: 27/09/2022, Decision No: 810) and it was carried out in accordance with the Helsinki Declaration principles.

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