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The effect of fecal microbiota transplantation on psychiatric symptoms among patients with inflammatory bowel disease: an experimental study

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Introduction. Over the past decade, evidence that supports the relationship between intestinal microbiota and the brain has been obtained. Ageing, stress, nutrition and medicines can alter the composition of bacteria in the intestinal microbiota. This condition, called dysbiosis, can be repaired through prebiotics, probiotics or fecal microbiota transplantation (FMT). FMT is effective in the treatment of inflammatory bowel diseases (IBD). Information on FMT's use with psychiatric disorders is limited. This study aims to investigate changes in the severity of depression, anxiety and obsession of patients who received FMT for the treatment of inflammatory bowel diseases.

Methods. This study was conducted with 10 patients with IBD who underwent FMT between March and September 2017. FMT was performed by an experienced gastroenterologist. The patients completed the Beck Depression Inventory (BDI), Symptom Checklist-90-Revised (SCL-90-R) and Maudsley Obsessive Compulsive Inventory (MOCI) before FMT and again at 1 month after FMT.

Results. Significant decreases were found in BDI (Z=2.49, p=0.013), SCL-90-R (Z=–2.09, p=0.037) and MOCI (Z=2.08, p=0.037) scores after 1 month of FMT. Although the SCL-90-R anxiety subscale scores decreased, this decrease was not statistically significant (Z=–1.55, p=0.121).

Conclusions. The severity of anxiety, depression and obsession in IBD patients decreased after FMT. The decrease in psychiatric symptoms may result from the direct neuropsychiatric effect of FMT (primary effect), but also the improvement of gastrointestinal symptoms (secondary effect). Another possibility is that this result is independent of these two conditions. Therefore, the results of our study are not sufficient to establish a cause-effect relationship. More randomised controlled trials with larger samples from patients with anxiety or depression but without comorbid physical illnesses are needed to generalise these results.

Keywords: Inflammatory bowel disease, Ulcerative colitis, Crohn's disease, Anxiety, Depression, Obsession, Gut microbiota, Fecal microbiota transplantation

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Efecto del trasplante de microbiota fecal sobre los síntomas psiquiátricos de los pacientes con enfermedad intestinal inflamatoria: estudio experimental

Introducción. Durante la última década, se ha obtenido evidencia que respalda la relación entre la microbiota intestinal y el cerebro. El envejecimiento, el estrés, la nutrición y los medicamentos pueden alterar la composición bacteriana de la microbiota intestinal. Esta condición, llamada disbiosis, se puede reparar con prebióticos, probióticos o con trasplante de microbiota fecal (TMF). El TMF es eficaz en el tratamiento de enfermedades inflamatorias intestinales (EII). La información sobre el uso del TMF en los trastornos psiquiátricos es limitada. Este estudio tiene como objetivo investigar los cambios en la severidad de la depresión, la ansiedad y la obsesión de los pacientes que recibieron TMF para el tratamiento de enfermedades inflamatorias intestinales.

Metodología. Este estudio se realizó con 10 pacientes con EII que se sometieron al TMF entre marzo y septiembre de 2017. El TMF fue realizado por un gastroenterólogo experimentado. Los pacientes completaron el Inventario de Depresión de Beck (IDB), el Listado de Síntomas Revisado (SCL-90-R) y el Inventario Obsesivo-Compulsivo de Maudsley (MOCI) antes del TMF y otra vez un mes después del TMF.

Resultados. Se encontraron disminuciones significativas en las puntuaciones del IDB (Z=2.49, p=0.013), SCL-90-R (Z=–2.09, p=0.037) y MOCI (Z=2.08, p=0.037) un mes después del TMF. Aunque las puntuaciones de la subescala de

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ansiedad del SCL-90-R disminuyeron, esta disminución no fue estadísticamente significativa (Z=–1.55, p=0.121).

Conclusiones. La severidad de la ansiedad, la depresión y la obsesión en los pacientes con EII disminuyó después del TMF. La disminución de los síntomas psiquiátricos puede deberse al efecto neuropsiquiátrico directo del TMF (efecto primario), pero también a la mejora de los síntomas gastrointestinales (efecto secundario). Otra posibilidad es que este resultado sea independiente de estas dos hipótesis. Por lo tanto, los resultados de nuestro estudio no son suficientes para establecer una relación de causa-efecto. Para generalizar estos resultados, se necesitan más ensayos controlados aleatorizados con muestras de más pacientes con ansiedad o depresión, pero sin enfermedades físicas concomitantes.

Palabras clave: Enfermedad intestinal inflamatoria, Colitis ulcerosa, Enfermedad de Crohn, Ansiedad, Depresión, Obsesión, Microbiota intestinal, Trasplante de microbiota fecal

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal system, with a high mortality rate, recurrent and acute attacks[1]. There are two subtypes of IBD: ulcerative colitis (UC) and Crohn's disease (CD). The clinical manifestations of UC and CD are similar. The main symptoms are abdominal pain and cramps, diarrhoea, bloody stools, rectal bleeding, decreased appetite, weight loss and fatigue[2].

There is a high comorbidity of depression and anxiety in IBD[3,4]. In IBD patients, the intensity of depression and anxiety is twice as high as in the control group, and this intensity is higher in active periods of IBD than in inactive periods[4]. Psychiatric comorbidity negatively affects the clinical course of IBD by decreasing functionality and increasing treatment costs[5].

In the treatment of IBD, medicines (systemic corticosteroids and immunosuppressants) and when necessary, surgical procedures (bowel resection, colectomy, ileostomy, ileoanal anastomosis) are administered[6]. Recently, however, fecal microbiota transplantation (FMT) has become an alternative to older methods of treatment[7,8]. When refractory to conventional treatment, UC cases with Mayo score (disease activity index) ≥6 and CD cases with Harvey-Bradshaw Index score ≥7 are eligible for FMT[8-11].

In recent years, interest in the gut-microbiota-brain axis has increased[12]. According to numerous preclinical and clinical studies, there is a bidirectional relationship between intestinal microbiota and the brain[13]. Diet affects neuronal functions[14]. For physical and psychological health, commensal microorganisms (e.g. *Bifidobacterium spp., Lactobacillus spp.*) are needed. The increase in the proportion of pathogenic bacteriain the intestinal microbiota (dysbiosis) may be involved in the etiopathogenesis of many neuropsychiatric disorders[15,16]. Prebiotics[17], probiotics[18], 'psychobiotics' (certain types of live bacteria)[19], antibiotics[20] and FMT[21] are microbiota-based therapies for repairing dysbiosis.

FMT is the transfer of stool from a healthy donor to the intestines of the patient through endoscopy or colonoscopy. FMT aims to repair the dysbiosis of the patient's intestines through the bacterial composition taken from a healthy person[21]. FMT is the strongest restorer of intestinal microbiota when compared to prebiotics, probiotics and antibiotics. FMT is indicated in IBD and treatment-resistant *Clostridium difficile* infection[7,22]. FMT may also have the potential to restore dysbiosis in neuropsychiatric disorders and, in particular, to treat treatment-resistant psychiatric disorders[21,23].

Few studies have been conducted with human participants in the literature regarding psychiatric disorders and dysbiosis. No studies have been identified that showed how psychiatric symptoms were affected in patients with IBD. Therefore, in this preliminary study, we first investigated the levels of anxiety, depression and obsessions before and after FMT in patients with IBD. Our study is the first clinical trial in the literature that examines the efficacy of FMT on psychiatric symptoms.

METHOD

Subjects

The sample of our study consisted of IBD patients followed by the Gülhane Training and Research Hospital Gastroenterology Clinic. The patients who were monitored due to IBD diagnosis and were found suitable for FMT (Mayo score ≥6, Harvey-Bradshaw Index score ≥7) by an experienced gastroenterologist were consecutively invited to our study.

The study inclusion criteria were defined as follows: being diagnosed with IBD, volunteering to participate in the study and being at least a high school graduate (to be able to complete self-report tests according to the instructions).

The exclusion criteria of our study included the following: people with a psychiatric or neurological diagnosis, receiving neurological or psychiatric pharmacotherapy, psychotherapy, history of organic mental disorder, alcohol or substance abuse and acute psychotic state, and use of prebiotics, probiotics and antibiotics in the last month.

This research conforms to the Declaration of Helsinki and has been approved by the Üsküdar University Ethics Committee. Each participant received detailed verbal information when they were referred for FMT (about 1 week be-

fore the transplantation), and their written consent was obtained.

Procedure

Our research was carried out between March 2017 and September 2017. Face-to-face interviews with the participants were performed by the psychologist (the first author). The first interview was held a week before the FMT application. During this interview, questions including sociodemographic data were asked of the participants, and psychometric questionnaires were completed. Control colonoscopies evaluating the participants' level of response to FMT were performed after a month. Therefore, the second interview with the participants was held one month after the FMT. The same questionnaires were used again during this interview. The corresponding author supervised the study.

Fecal Microbiota Transplantation

The procedure was implemented according to international standards[24]. The stool was supplied a few hours before application and was transferred freshly (not frozen). To prevent the recipient from being exposed to a new disease via FMT, donors were examined in detail. Donors were people who have regular health check-ups, did not have any neuropsychiatric or somatic (e.g. metabolic, neoplastic, infective, autoimmune, allergic) illnesses, who do not use medicines regularly (e.g. antihypertensive, antidiabetic, anti-inflammatory) who were about the same age as the patients and who are regular providers of stool to the hospital. The fresh stool was diluted with saline before transplantation, and the suspension was prepared by mixing with a spatula. The stool suspension was infused into the patient through colonoscopy.

Measurement Instruments

The Symptom Checklist-90-Revised (SCL-90-R)[25], Beck Depression Inventory[26] and Maudsley Obsessive Compulsive Inventory[27] were completed by the participants. The SCL-90-R scans general psychiatric symptoms, the Beck Depression Inventory measures the severity of depression and the Maudsley Obsessive Compulsive Inventory evaluates the severity of obsessive and compulsive symptoms. All of these tests are self-reported.

Data Analysis

Descriptive statistics are given as frequency and percentage. Pre- and post-FMT test scores were evaluated with the Wilcoxon signed rank test. Statistical analyses were performed with IBM SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). A p value of <0.05 was accepted for statistical significance.

RESULTS

In this experimental study, 43 patients who accepted our invitation were included in the study. We found that 7 participants were diagnosed with a psychiatric illness and were receiving psychiatric treatment, while 15 participants did not complete the questionnaires according to the instructions. Eleven participants did not attend the interview after FMT, so the questionnaires could not be repeated. Therefore, 33 participants were excluded from the study. The data of the remaining 10 participants were analysed.

FMT was well tolerated by all patients except for one (Patient 2), and no serious side effects were observed. One month after FMT, another colonoscopy was performed to control the severity of the gastrointestinal disease. Colonoscopy results of 4 cases (patients 7, 8, 9 and 10) did not show a significant difference compared to pre-FMT. The other 6 cases showed a decrease in the number of ulcers, polyps, fissures and fistulas in the colon.

The sociodemographic and diagnostic data of the participants are shown in Table 1. Table 2 shows the statistical analysis results of the change in the test scores. Significant improvement was observed in all scales before and after FMT. There was a statistically significant decrease in BDI ($Z=-2.49$, $p=0.013$), MOCI ($Z=-2.08$, $p=0.037$) and SCL-90-R ($Z=-2.09$, $p=0.037$) scores after FMT. The anxiety subscale of the SCL-90-R test was used to evaluate the anxiety levels of the participants. The literature includes microbiota studies on the etiopathogenesis of anxiety. However, there is not enough research background to compare the other subscales of the SCL-90-R test. Therefore, the scores of the other subscales of the SCL-90-R test were excluded from the scope of this study. Although SCL-90-R anxiety subscale scores decreased, it was not statistically significant ($Z=-1.55$, $p=0.121$). Figure 1 shows the changes in the questionnaire mean scores before and after treatment.

DISCUSSION

In our study performed on adult patients with IBD, changes in the severity of anxiety, depression and obsession were reported after FMT. The results of our study showed that FMT is effective in both gastrointestinal and the above-mentioned psychiatric symptoms. To the best of our knowledge, there has been only one other study performed to evaluate the efficacy of FMT on psychiatric symptoms[28]. In

Table 1 Subject sociodemographics, information about inpatient diagnoses and FMT

Patient	Sex	Age	Marital status	Occupation	Diagnosis	Duration of illness (years)	Number of FMT applications
Patient 1	M	24	S	Student	UC	5	1
Patient 2	F	20	S	Student	CD	9	1
Patient 3	F	35	M	Teacher	CD	19	3
Patient 4	F	38	M	Housewife	UC	4	2
Patient 5	M	40	M	Civil Servant	UC	9	4
Patient 6	M	30	S	Civil Servant	UC	12	1
Patient 7	F	35	M	Housewife	CD	12	3
Patient 8	M	49	M	Retired	UC	18	3
Patient 9	F	32	M	Housewife	UC	1	1
Patient 10	M	24	S	Student	CD	10	4
Mean (SD)		32.7 (8.7)				9.9 (5.7)	2.3 (1.3)

FMT: fecal microbiota transplantation; M: male; F: female; S: single; M: married; UC: ulcerative colitis; CD: Crohn's disease; SD: standard deviation

Table 2 Changes in mean scores of ten patients for each scale

	BDI	MOCI	SCL-90-R	SCL-90-R anxiety
Before FMT	16.80 (7.22)	14.90 (8.38)	101.60 (76.01)	9.40 (8.92)
After FMT	11.80 (7.37)	11.90 (5.72)	69.00 (44.18)	6.60 (4.67)
Statistics before and after treatment	Z(10)=-2.49** **p=0.013**	Z(10)=-2.08* **p=0.037**	Z(10)=-2.09* **p=0.037**	Z(10)=-1.55 p=0.121
Reduction rates (%)	29.8	20.1	32.1	29.8
Effect size	0.83	0.84	0.81	0.54

Values are presented as mean (standard deviation)

BDI: Back Depression Inventory; MOCI: Maudsley Obsessional-Compulsive Inventory; SCL-90-R: The Symptom Checklist-90-Revised; FMT: fecal microbiota transplantation.

Statistic: Wilcoxon signed rank test from before FMT to after FMT; *p<0.05, **p<0.025.

this study, baseline levels and levels of anxiety and depression levels of 17 patients who were treated with FMT due to irritable bowel syndrome, functional diarrhoea and functional constipation were compared. According to the results of the study, psychiatric symptoms decreased after FMT. One interesting finding of the study was the improvement in psychiatric parameters, even in patients without improvement in gastrointestinal symptoms[28]. In one of our patients (Patient 2), intestinal perforation occurred after FMT and resection of 10 cm was required from the ileum. However, all scale scores decreased (SCL-90-R scores decreased by 52%).

In two recent studies, the feces of depressed individuals were transferred to germ-free mice. Depression-like behaviours were determined in mice following FMT[29,30]. This experiments are interesting in terms of demonstrating that depression can be transported with FMT. This two studies are also promising because it shows that FMT can be used in the treatment of depression. In another experimental study, autistic symptoms regressed in 18 children with autism who underwent microbiota transfer therapy (a modification of FMT) for 8 weeks[31]. In a study comparing stool microbiota analysis of 46 patients with depression and 30 healthy subjects, *Bactericides, Proteobacteria* and *Actinobacteria* levels

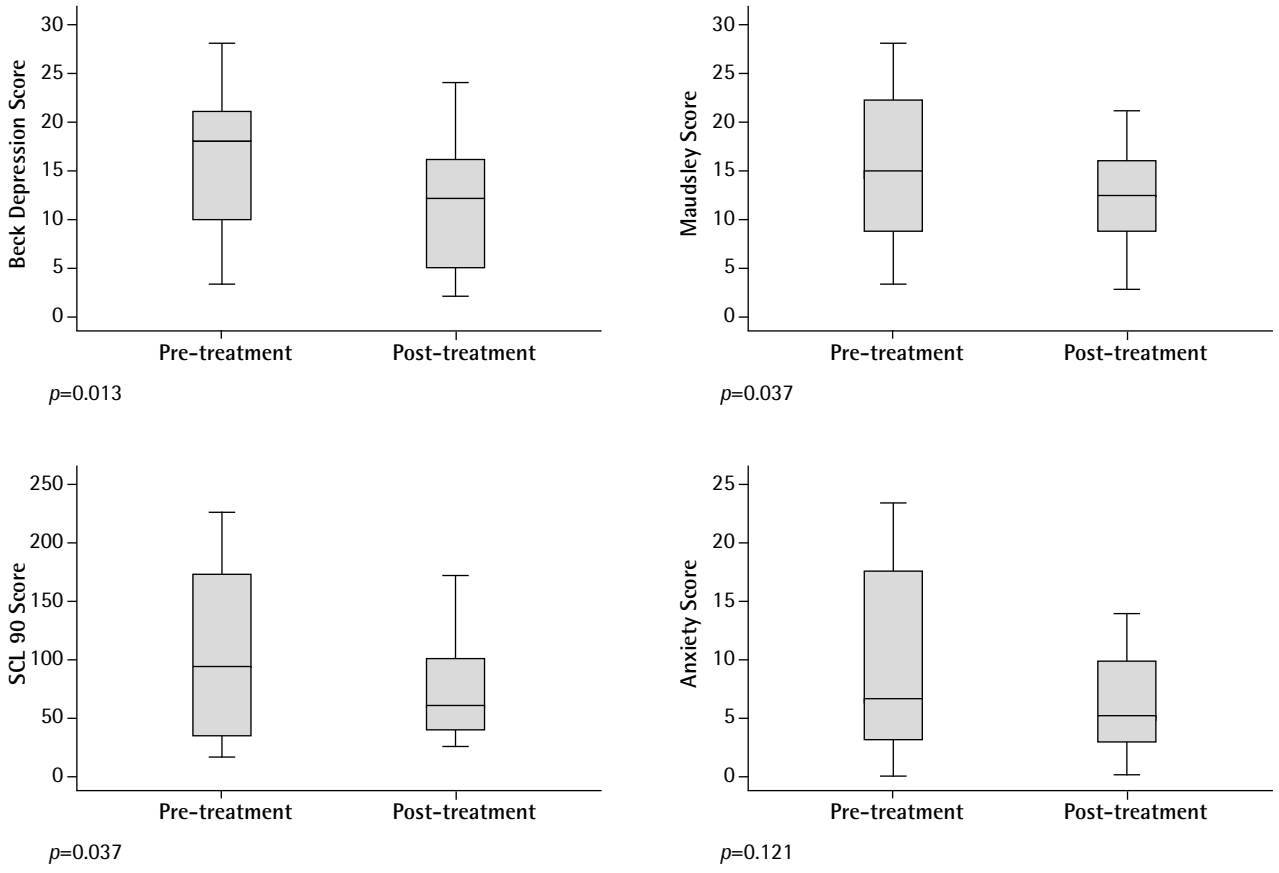

Figure 1 | *Changes in scores of each scale from pre-treatment to post-treatment*

were higher, and *Firmicutes* levels were lower in the stool of patients with depression. These results suggest that pathogenic bacterial groups increase and symbiont bacteria decrease in patients with depression[32]. In another study with a similar design, stool microbiota analyses of 28 patients with first-episode psychosis and 16 healthy subjects were compared. In this study, there was a significant difference in *Lactobacillus* levels between the two groups. This difference also correlates with symptom severity and treatment response[33]. Dysbiosis plays an important role in the etiopathogenesis of anxiety disorders by causing problems in the immune-kynurenine pathway[34].

The results of our study support previous studies. SCL-90-R, BDI and MOCI mean scores were significantly decreased after FMT administration. There could be two reasons for this decline. The first reason may be that patients with bad general medical condition due to IBD may have reduced physical complaints, particularly pain. Abdominal pain, cramps, diarrhea and fatigue are common in IBD patients[2]. Pain is one of the leading causes of reduced quality of life in IBD patients[35]. These somatic complaints regressed after FMT and may be positively reflected in the psychological parameters. The second reason may be the antidepressant and anxiolytic efficiency on the gut-brain axis as a result of decreased dysbiosis.

The patients were not homogeneous in terms of sociodemographic data. The psychological parameters of all participants, except patient 10, improved in varying proportions after FMT. The MOCI score of patient 10 did not change after FMT, but the scores of the other tests increased.

The limitations of our study are as follows:

- The results of the study cannot be generalised due to the small size of our sample.

- There is no control group in our study and therefore the placebo effect of FMT is unknown.
- The cases had different ages and illness duration, which may have had a confounding effect on the results.
- Microbiota transplantation was performed for the first time in four of the ten cases (patient 1, 2, 6 and 9) while FMT had been applied in the past to the other six cases. Repeated applications of FMT may affect treatment outcomes, as with electroconvulsive therapy (ECT) and transcranial magnetic stimulation. The results obtained after the first FMT in a group with similar characteristics in terms of disease duration and age would be more enlightening.
- General medical conditions of the cases were impaired due to IBD. As FMT affects body health positively, anxiety and depression scores might have reduced.
- Questionnaires were evaluated for only one month after FMT application. Questionnaires should be repeated at the third and sixth months after FMT to evaluate the long-term results of FMT.
- Immunological markers of cases were not analysed. Therefore, the effect of FMT on the immune system of the participants is not known.

In this study, general psychiatric symptoms, depression, obsessions and anxiety severity in IBD patients treated with FMT were investigated. After the administration of FMT, the measured parameters of the patients decreased significantly. In sum, the results of this experimental study should be seen as a preliminary suggestion to further examine the study hypothesis, ideally through controlled studies with larger samples.

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CONFLICT OF INTEREST

The authors report no potential conflicts of interest relevant to this article.

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