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The fecal microbiota transplantation response differs between patients with severe and moderate irritable bowel symptoms

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ABSTRACT

Objectives: Fecal microbiota transplantation (FMT) is a promising intervention for patients with irritable bowel syndrome (IBS). The present study aimed to identify any differences in FMT response between patients with severe and moderate IBS symptoms.

Materials and method: The study included the 164 patients who participated in our previous study, of which 96 (58.5%) and 68 (41.5%) had severe (S-IBS-S) and moderate (Mo-IBS-S) IBS, respectively. The patients were randomly divided into a placebo group (own feces) and 30-g and 60-g (donor feces) FMT groups. Patients completed three questionnaires that assessed their symptoms and quality of life at baseline and at 2 weeks, 1 month, and 3 months after FMT, and provided fecal samples before and 1 month after FMT. The fecal bacteria were analyzed using the 16S rRNA gene in PCR DNA amplification covering the V3–V9 variable genes.

Results: Response rates of the placebo group did not differ between S-IBS-S and Mo-IBS-S patients at 2 weeks, 1 month and 3 months after FMT. The response rates in the active treatment group were higher in S-IBS-S patients than in Mo-IBS-S patients at each observation time. FMT reduced abdominal symptoms and fatigue and improved the quality of life in patients with both severe and moderate IBS. Patients with S-IBS-S had higher levels of *Eubacterium siraeum*, and lower levels of *Eubacterium rectale* than Mo-IBS-S, after FMT.

Conclusion: Patients with S-IBS-S have a higher response rate to FMT and a marked improvement in fatigue and in quality of life compared with those with Mo-IBS-S.

The clinical trial registration number is NCT03822299 and is available at www.clinicaltrials.gov.

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that considerably reduces the quality of life [1,2]. Clinical IBS treatment is directed merely at symptom relief [3]. The gut microbiota and bacterial diversity significantly affect IBS pathophysiology [4]. The outcomes of fecal microbiota transplantation (FMT) in treating IBS differ considerably in different studies from highly beneficial to no effect at all [5]. These mixed results are caused by differences in the selection criteria of the donor and the FMT protocol used as well as the cohort of patients included [5]. These differences explain why pooling all randomized clinical trials showed that FMT is not superior to placebo [6]. However, with careful donor selection and using the appropriate protocol, FMT reduces abdominal symptoms and fatigue and improves the quality of life of IBS patients [5,7].

FMT for IBS has been investigated in seven randomized controlled trials (RCTs) mostly involving patients with moderate-to-severe IBS symptoms [5]. In a recent study with a successful outcome, the patients included were those with

refractory IBS patients with severe bloating who had failed to respond to at least three conventional therapies for IBS [8]. This study raised the question as to which category of IBS patients should FMT used as an intervention [8].

The present study aimed to determine the differences between patients with severe IBS symptoms (S-IBS-S) and moderate IBS symptoms (Mo-IBS-S) regarding FMT response, symptom reduction, quality-of-life improvement, dysbiosis and bacteria profile for the same patient cohort included in our previous RCT [9].

Materials and methods

Study design and patient randomization

The study design has been described in detail elsewhere [9]. To summarize, patients completed three questionnaires that assessed their symptoms and quality of life at baseline and at 2 weeks, 1 month and 3 months after FMT. They also provided fecal samples for bacterial analysis both before and 1 month after FMT. The patients were randomly divided at a

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Table 1. Characteristics of the patients in the placebo and active treated groups.

	Overall	Placebo	Active treated group
Number	164	55	109
Age, years	39.9 ± 9.0	41.2 ± 13.7	39.3 ± 12.4
Sex, female/male	133/32	47/8	86/23
IBS duration, years	15.5 ± 7.9	15.6 ± 8.0	17.3 ± 8.9
Severe symptoms*	96 (58.5%)	32 (58%)	64 (59%)
Moderate symptoms**	68 (41.5%)	23 (42%)	45 (41%)
IBS-D	63	21	42
IBS-C	62	22	40
IBS-M	39	12	27

Data are *n*, *n* (%) or mean ± SD values.

*IBS-SSS total score of ≥300; **IBS-SSS total score between 175 and 300.

1:1:1 ratio into a placebo (30-g own feces) group and 30-g and 60-g (donor feces) FMT groups.[9] The patients who received 30 g or 60 g of donor feces were combined and described as the active treatment group in order to increase the sample size and thereby reduce the probability of type-II statistical errors.

Patients

The present study included 164 patients who had participated in our previous RCT [9]. Table 1 lists the characteristics of these patients. The details of these patients have previously been described in detail [9]. To summarize, outpatients from Stord Hospital who fulfilled the Rome IV criteria for an IBS diagnosis were included. The inclusion criteria were being older than 18 years and experiencing moderate-to-severe IBS symptoms, as indicated by an IBS Severity Scoring System (IBS-SSS) score of ≥175. The exclusion criteria were pregnancy or planning pregnancy, lactating, the presence of a systemic disease, immune deficiency or having received immune-modulating medication, psychiatric illness, excessive alcohol consumption, or drug abuse. Patients who took probiotics, antibiotics, or IBS medications within 8 weeks before the study were also excluded [9].

Donor

The donor used in this study has previously been described in detail [9]. To summarize, he was screened according to the European guidelines for FMT donors [10]. He was a healthy young nonsmoking male, was not taking any medication, and had a normal BMI. He had been born via vaginal delivery, breastfed and had undertaken only a few courses of antibiotics during his life. He regularly exercised and took sport-specific dietary supplements, meaning his diet was richer in protein, fiber, minerals and vitamins than average. Bacterial analysis of his feces revealed normal bacteria diversity (normobiosis) [9].

Collection, preparation and administration of fecal samples

Fecal samples from the donor and patients were immediately frozen and stored at −20 °C until delivery to the laboratory, where they were stored at −80 °C. The FMT process has previously been described in detail [9]. To summarize, fecal samples were thawed for two days at 4 °C, mixed manually (i.e.,

without using a mechanical device) with 40 ml of sterile saline, and filtered before being administered. The transplant was administered to the distal duodenum via the working channel of a gastroscop [9].

Symptom and quality-of-life assessments

IBS symptoms were assessed using the IBS-SSS questionnaire. This questionnaire contains five questions, each with a maximum score of 100 using a visual analog scale. Total scores between 75 and 175 were considered indicative of mild IBS severity (Mi-IBS-S), 175–300 were Mo-IBS-S, and >300 were S-IBS-S [11]. The response was defined as a decrease in the total IBS-SSS score after FMT of ≥50 points.

Fatigue was assessed using the Fatigue Assessment Scale (FAS) questionnaire [12]. The questionnaire comprises 10 questions with 5-point-scale answers varying from never to always. Five of these questions measured physical fatigue and the other five measured mental fatigue.

Quality of life was measured using the IBS Quality of Life Scale (IBS-QoL) questionnaire [13–15]. This questionnaire contains 34 items concerning the physical and psychological functioning of IBS patients in 8 domains: dysphoria, activity interference, body image, health concerns, food avoidance, social reactions, sexual function and impact on relationships.

Microbiome analysis and dysbiosis index

The fecal bacteria profile and dysbiosis were determined using a method utilizing a pre-determined targets (PDT) approach [16]. The test uses the 16S rRNA gene in PCR DNA amplification covering V3–V9 variable genes, and probe labeling with single nucleotide extension and signal detection using the BioCode 1000A 128-plex Analyzer (Applied BioCode, Santa Fe Springs, CA, USA) [16]. The 48 bacterial markers used covered different taxonomic levels of >300 bacteria [17]. A dysbiosis index (DI) was measured on a 5-point scale from 1 to 5, where DI values of 1 and 2 indicate normobiosis, while those of 3–5 indicate dysbiosis [16].

Statistical analysis

Differences in response and dysbiosis proportion between S-IBS-S and Mo-IBS-S patients in the placebo and active treatment groups were analyzed using Fisher's exact test. The nonparametric Kruskal–Wallis's test with Dunn's multiple comparisons test as a post-test was used in analyzing the difference between S-IBS-S and Mo-IBS-S patients in their scores for the IBS-SSS, FAS and IBS-QoL. The Mann–Whitney *U*-test was used to analyze the differences between in fecal bacteria fluorescent signals. A nonparametric Spearman's test was used for correlation between bacterial fluorescent signals and IBS-SSS total score. These analyses were performed using GraphPad Prism 8 (La Jolla, CA, USA).

Ethics

The West Regional Committee for Medical and Health Research Ethics, Bergen, Norway approved the present study (approval no. 2017/1197/REK vest). All subjects provided both oral and written consent before participation. The study was registered at www.clinicaltrials.gov (NCT03822299) and www.cristin.no (ID657402).

Results

Response to FMT

The response rates of the placebo group did not significantly differ between S-IBS-S and Mo-IBS-S patients at 2 weeks, 1 month and 3 months after FMT. The response rates in the active treatment group were significantly higher in S-IBS-S patients than in Mo-IBS-S patients at each observation time

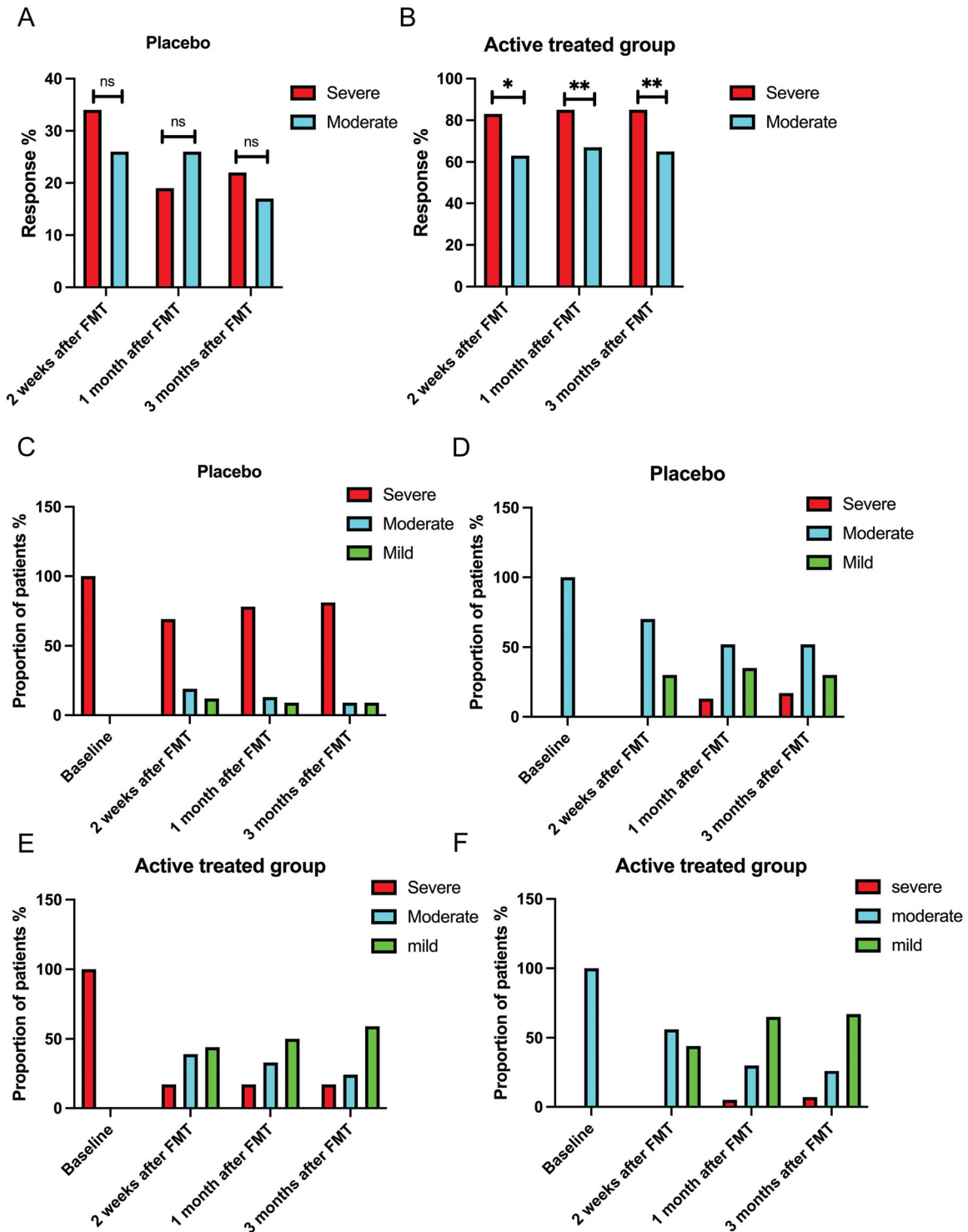


Figure 1. Fecal microbiota transplantation (FMT) response rates in patients with severe and moderate irritable bowel syndrome (IBS) symptoms at 2 weeks, 1 month and 3 months after FMT in the placebo (A) and active treatment (B) groups. Changes in IBS symptom severity over time in the placebo (C, D) and active treatment group (E, F). ns, not significant; *adjusted $p < .05$; **adjusted $p < .01$.

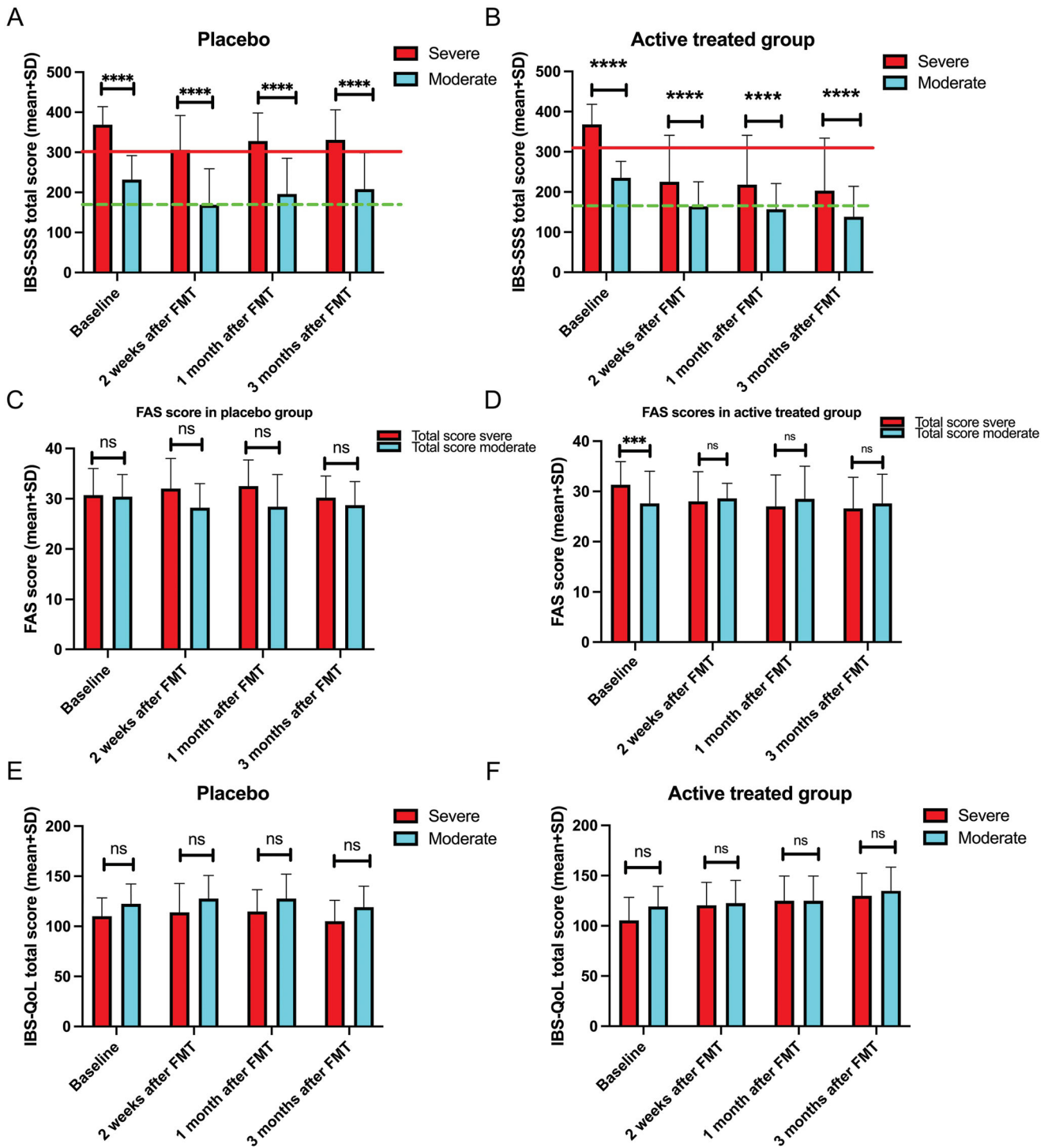


Figure 2. Total scores of IBS-SSS (A, B), of FAS (C, D), of IBS-QoL (E, F), at baseline and at 2 weeks, 1 month and 3 months after FMT. In (A) and (B), values above and below the red line indicate severe and moderate IBS symptoms, respectively. Values above and below the green line indicate moderate and mild IBS symptoms, respectively. ns, not significant; ****adjusted $p < .001$; ****adjusted $p < .0001$.

(Figure 1). In the placebo group, a small proportion of the S-IBS-S patients converted to Mo-IBS-S or Mi-IBS-S at 2 weeks, 1 month and 3 months after FMT. Similarly, a small proportion of patients with Mo-IBS-S converted to S-IBS-S or Mi-IBS-S (Figure 1). Conversely, a large proportion of either S-IBS-S or Mo-IBS-S patients experienced lower degrees of symptom severity at 2 weeks, 1 month and 3 months after FMT (Figure 1).

Symptoms and quality of life

The total IBS-SSS scores of the active treatment group decreased significantly after FMT at each observation interval, whereas those of the placebo group did not. The placebo and active treatment groups had higher total IBS-SSS scores among the S-IBS-S than the Mo-IBS-S patients at each observation interval (Figure 2). However, the difference in

Table 2. IBS-SSS total scores and scores for the four items of the scale in patients with severe and moderate IBS symptoms in placebo and active-treated groups at different intervals following FMT.

Time	Group		Total score	1	2	3	4
0	Placebo	Overall	315.2 ± 77.1	107.5 ± 46.1	55.5 ± 24.7	76.1 ± 20.7	75.4 ± 19.8
		Severe	368.9 ± 44.8	128.9 ± 40.3	70.3 ± 19.4	83.9 ± 18.0	84.2 ± 12.9
		Moderate	240.5 ± 41.5	77.8 ± 36.6	34.8 ± 14.3	65.2 ± 19.7	63.0 ± 21.4
	Active treated group	Overall	314.9 ± 83.2	108.6 ± 44.0	52.8 ± 25.6	77.1 ± 18.3	75.4 ± 19.5
		Severe	368.7 ± 51.7	124.0 ± 37.1	61.5 ± 24.0	81.8 ± 15.4	78.0 ± 18.9
		Moderate	241.5 ± 57.9	87.4 ± 44.3	41.0 ± 23.2	70.6 ± 20.1	71.8 ± 20.0
2 weeks	Placebo	Overall	278.7 ± 124.7	88.1 ± 57.0	51.2 ± 30.5	62.6 ± 28.5	64.5 ± 27.5
		Severe	383.9 ± 55.0	133.3 ± 40.0	77.0 ± 16.7	84.8 ± 19.4	85.0 ± 10.9
		Moderate	177.2 ± 80.4	44.5 ± 30.5	26.3 ± 16.5	51.1 ± 26.1	44.6 ± 23.7
	Active treated group	Overall	204.3 ± 98.9****	71.5 ± 47.3****	33.8 ± 25.3****	48.4 ± 26.2****	51.7 ± 25.6****
		Severe	214.3 ± 109.8****	75.8 ± 51.0****	36.6 ± 27.1****	50.7 ± 27.2****	54.6 ± 27.1****
		Moderate	188.3 ± 77.2****	64.8 ± 40.3**	29.3 ± 21.8**	44.8 ± 24.4****	46.9 ± 22.5****
1 month	Placebo	Overall	299.5 ± 106.1	102.0 ± 51.2	53.5 ± 27.4	70.3 ± 25.1	69.1 ± 26.3
		Severe	369.4 ± 48.3	132.8 ± 36.5	70.9 ± 20.0	80.8 ± 19.0	83.0 ± 13.5
		Moderate	202.4 ± 86.0	60.9 ± 34.4	29.1 ± 15.3	55.7 ± 25.5	49.8 ± 27.7
	Active treated group	Overall	200.0 ± 104.0****	73.2 ± 49.6****	35.3 ± 23.7****	44.8 ± 28.9****	48.6 ± 27.9****
		Severe	212.6 ± 108.9****	79.1 ± 50.6****	39.2 ± 24.5****	45.7 ± 30.0****	51.9 ± 28.8****
		Moderate	180.7 ± 94.0****	64.2 ± 47.0**	29.2 ± 21.2****	43.5 ± 27.4****	43.6 ± 26.0****
3 months	Placebo	Overall	307.0 ± 87.1	112 ± 69.7	56.8 ± 31.8	73.1 ± 22.3	71.7 ± 22.0
		Severe	363.8 ± 49.3	136.4 ± 41.6	70.5 ± 19.6	80.9 ± 18.2	82.7 ± 11.8
		Moderate	228.1 ± 63.3	71.1 ± 36.1	32.8 ± 17.0	62.0 ± 22.9	56.5 ± 24.0
	Active treated group	Overall	175.5 ± 113.6****	62.9 ± 48.4****	30.4 ± 24.2****	39.5 ± 27.3****	42.2 ± 28.6****
		Severe	190.4 ± 118.8****	69.2 ± 49.1****	32.9 ± 25.8****	42.0 ± 28.5****	45.5 ± 29.5****
		Moderate	152.9 ± 102.4****	53.5 ± 46.4****	26.5 ± 21.4****	35.8 ± 25.3****	37.2 ± 26.9****

Severe, patients with severe IBS symptoms; Moderate, patients with moderate IBS symptoms. IBS-SSS items: 1, abdominal pain; 2, abdominal distension; 3, dissatisfaction with bowel habits; 4, interference with quality of life. Data are mean ± SD values.

Adjusted $p < .01$; *adjusted $p < .001$; ****adjusted $p < .0001$ compared to baseline values.

the total IBS-SSS score between S-IBS-S and Mo-IBS-S was smaller in the active treatment group at 2 weeks, 1 month and 3 months after FMT (Figure 2). Notably, this suggests that the means of the total IBS-SSS scores of the S-IBS-S in the active treatment group were in the region of Mo-IBS-S after FMT at all of the observation intervals. Similarly, the means of the total IBS-SSS scores for Mo-IBS-S patients in the active treatment group were lower than those for Mi-IBS-S patients (Figure 2, Table 2).

The total FAS scores in both S-IBS-S and Mo-IBS patients decreased significantly compared to the baseline in the active treatment group at 2 weeks, 1 month and 3 months after FMT (Figure 2, Table 3).

The total IBS-QoL scores increased in both S-IBS-S and Mo-IBS-S patients in the active treatment group 2 weeks after FMT (Table 4). The total IBS-QoL scores increased in S-IBS-S patients, but not in Mo-IBS-S patients in the active treatment group 1 month after FMT. The total IBS-QoL scores increased in both S-IBS-S and Mo-IBS-S patients at 3 months after FMT (Table 4). There were no changes in the total IBS-QoL scores in the placebo group at any observation interval. Mo-IBS-S patients had higher total IBS-QoL scores than S-IBS-S patients at all observation intervals in the placebo group (Figure 2). In the actively treated group, the total IBS-QoL scores were higher in Mo-IBS-S patients than in S-IBS-S patients at the baseline, but there were no differences after FMT at any observation interval (Figure 2).

Bacterial analysis

DIs in the active treatment group in both S-IBS-S and Mo-IBS-S patients decreased 1 month after FMT, whereas they did not in the placebo group (Figure 3). DIs did not differ between patients with S-IBS-S and Mo-IBS-S at either the

baseline or 1 month after FMT in both the placebo and active treatment groups (Figure 3). The fluorescence signals for all investigated bacteria did not differ between S-IBS-S and Mo-IBS-S patients in the placebo group at either the baseline or 1 month after FMT. In the active treatment group, Mo-IBS-S patients had higher fluorescence signals of *Clostridia* species than did S-IBS-S patients at the baseline. The fluorescence signals of *Eubacterium siraeum*, and *Shigella* spp., were significantly higher in S-IBS-S than Mo-IBS-S patients, and that of was lower in S-IBS-S than Mo-IBS-S patients 1 month after FMT (Figure 3). In Mo-IBS-S the fluorescence signals of *Eubacterium rectale*, *E. siraeum* and *Shigella* spp. at 1 month after FMT did not differ from those at the baseline (Table 5). The fluorescence signals of *E. siraeum* significantly decreased 1 month after FMT, but not those of *E. rectale*, and *Shigella* spp. (Table 5). Whereas *E. rectale* correlated negatively with IBS-SSS total scores, *E. siraeum*, correlated positively with IBS-SSS total scores. *Shigella* spp. did not correlate with IBS-SSS total scores (Figure 4).

Discussion

FMT as a treatment for IBS patients was investigated in seven randomized controlled trials (RCTs) [8,9,18–22]. four of which showed a positive effect [8,9,18,22] while the other three showed no effect [19–21]. It is challenging to compare these RCTs as they differed considerably in the criteria used to select the donors and patients, in the dose of the fecal transplant used and in the FMT protocols [5].

There are some safety concerns when using FMT as an IBS treatment. These concerns emerged when two patients had serious adverse events in the form of infectious complications (with one fatality) after FMT for indications other than IBS [23,24]. However, long-term follow-ups of patients

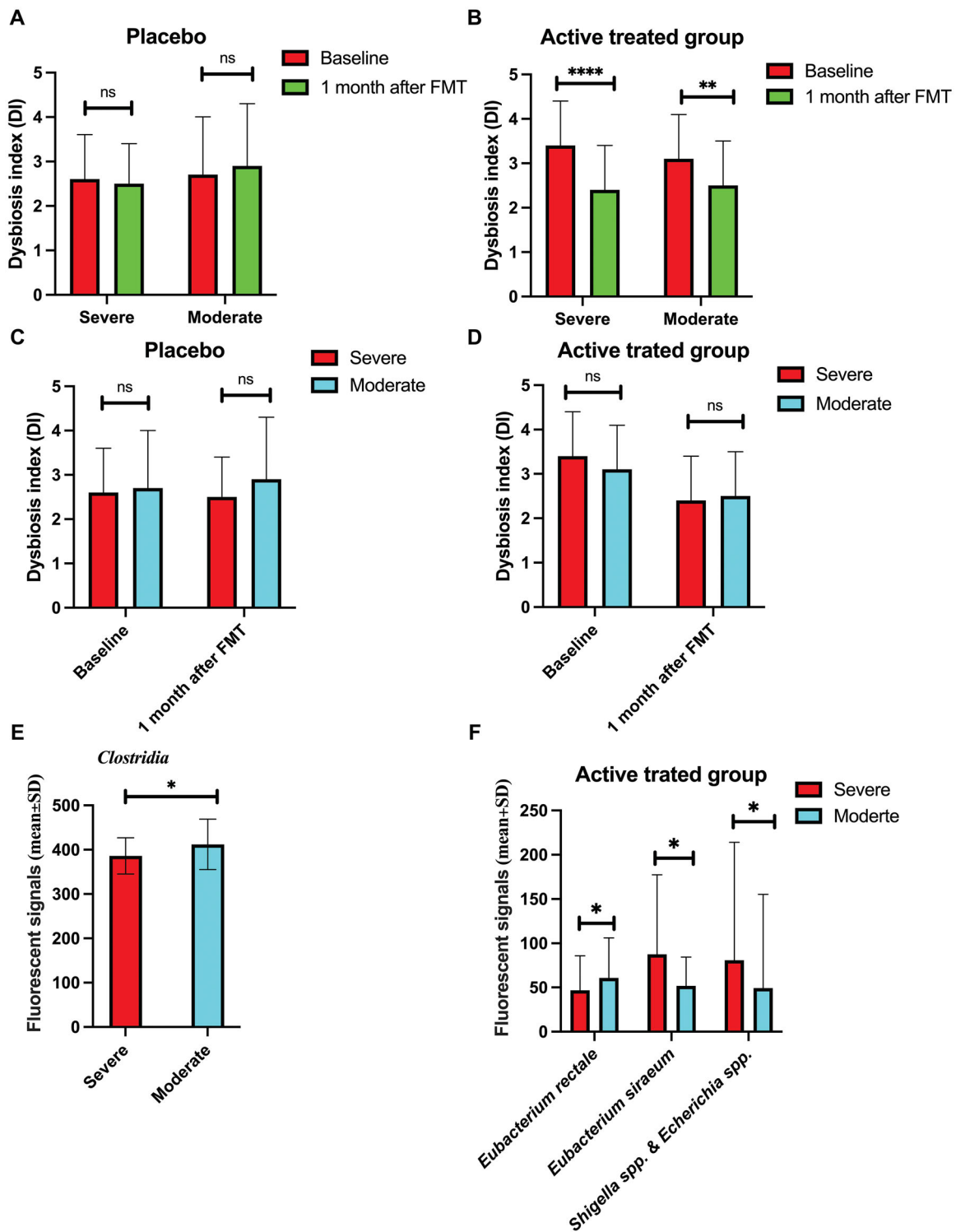


Figure 3. The Dysbiosis index (DI) of patients with severe and moderate IBS symptoms at the baseline and 1 month after FMT in the placebo (A) and active treatment (B) groups. Comparison between DIs in patients with severe and moderate IBS symptoms at the baseline and 1 month after FMT in the placebo (C) and active treatment (D) groups. The bacteria whose fluorescence signals differed between patients with severe and moderate IBS symptoms belonging to the active treatment group at the baseline (E) and 1 month after FMT (F). ns, not significant; *adjusted $p < .05$; **adjusted $p < .01$; ****adjusted $p < .0001$.

receiving FMT because of a *Clostridium difficile* infection concluded despite the development of a number of new conditions post-FMT, no clustering of diseases was associated with FMT [25]. Furthermore, recently published studies showed that FMT is safe when the international rigorous guidelines for selecting and testing the donor were applied [26–28]. IBS

has been considered a benign gastrointestinal condition that is not life-threatening and using FMT as an intervention for this condition is not justified due to possible complications [29–31]. The adverse events of FMT in IBS patients are mild and self-limited, in the form of mild abdominal pain, diarrhea, or constipation [5]. To minimize risks from FMT for IBS, it

Table 3. FAS total scores and scores for physical fatigue and mental fatigue in patients with severe and moderate IBS symptoms in placebo and active-treated groups at baseline, 2 weeks, 1 month and 3 months after FMT.

Time	Group		Total score	Physical fatigue	Mental fatigue
0	Placebo	Overall	30.6 ± 4.9	15.8 ± 2.7	14.8 ± 2.6
		Severe	30.7 ± 5.3	15.8 ± 2.8	14.9 ± 2.7
		Moderate	30.4 ± 4.4	15.8 ± 2.5	14.6 ± 2.6
	Active treated group	Overall	31.3 ± 5.0	15.9 ± 2.9	15.5 ± 2.7
		Severe	31.3 ± 4.6	16.1 ± 2.8	15.3 ± 2.5
		Moderate	27.6 ± 6.4	14.4 ± 3.6	13.3 ± 3.1
2 weeks	Placebo	Overall	24.7 ± 9.9	15.5 ± 3.3	15.2 ± 3.1
		Severe	32.0 ± 6.0	16.8 ± 3.2	15.2 ± 3.1
		Moderate	28.2 ± 4.8	14.6 ± 2.6	13.7 ± 2.4
	Active treated group	Overall	28.2 ± 5.7****	14.5 ± 3.1**	13.9 ± 3.1****
		Severe	28.0 ± 5.9**	14.4 ± 3.1**	13.7 ± 3.3**
		Moderate	28.6 ± 3.0*	14.7 ± 3.0	14.2 ± 3.0*
1 month	Placebo	Overall	30.8 ± 6.0	16.2 ± 2.9	14.7 ± 3.4
		Severe	32.5 ± 5.2	17.1 ± 2.5	15.5 ± 3.0
		Moderate	28.4 ± 6.4	14.9 ± 3.0	13.5 ± 3.6
	Active treated group	Overall	27.6 ± 6.4****	14.4 ± 3.6**	13.3 ± 3.1****
		Severe	27.0 ± 6.3***	14.1 ± 3.5	13.0 ± 3.1**
		Moderate	28.5 ± 6.5*	14.8 ± 3.7*	13.8 ± 3.1***
3 months	Placebo	Overall	29.8 ± 4.6	15.2 ± 2.6	14.5 ± 2.7
		Severe	30.2 ± 4.3	15.8 ± 2.4	14.7 ± 2.6
		Moderate	28.7 ± 4.7	14.2 ± 2.5	14.3 ± 2.8
	Active treated group	Overall	27.0 ± 6.0****	13.7 ± 3.4****	13.3 ± 3.0****
		Severe	26.6 ± 6.2****	13.7 ± 3.4****	13.0 ± 3.1****
		Moderate	27.6 ± 5.8**	13.6 ± 3.5**	13.6 ± 3.0**

Data are mean ± SD values.

*Adjusted $p < .05$; **adjusted $p < .01$; ***adjusted $p < .001$; ****adjusted $p < .0001$ compared to baseline values.**Table 4.** IBS-QoL total scores and scores in the eight domains of the scale in placebo and active treated groups.

Time	Group		Total score	1	2	3	4	5	6	7	8
0	Placebo	Overall	117.8 ± 19.7	27.3 ± 5.8	23.6 ± 5.8	11.9 ± 2.7	10.6 ± 2.6	7.2 ± 2.6	15.0 ± 3.1	7.8 ± 1.7	11.2 ± 2.5
		Severe	110.0 ± 18.4	26.5 ± 6.2	22.6 ± 5.2	11.2 ± 2.5	10.8 ± 2.8	6.8 ± 2.5	14.6 ± 3.2	7.6 ± 1.8	10.8 ± 2.6
		Moderate	122.4 ± 19.9	28.4 ± 5.1	25.1 ± 6.3	13.0 ± 2.6	10.4 ± 2.5	7.8 ± 2.7	15.4 ± 3.0	8.2 ± 1.5	11.7 ± 2.3
	Active treated group	Overall	111 ± 22.6	26.8 ± 6.8	20.7 ± 5.8	11.4 ± 3.1	10.4 ± 2.7	6.3 ± 2.8	13.8 ± 3.4	7.6 ± 1.9	10.8 ± 2.7
		Severe	105.4 ± 22.6	25.7 ± 7.1	19.7 ± 5.5	10.3 ± 2.8	10.1 ± 3.1	5.7 ± 2.3	13.2 ± 3.3	7.1 ± 2.0	10.4 ± 2.7
		Moderate	119.3 ± 20.0†	28.4 ± 6.1	22.0 ± 5.9	12.9 ± 2.9	10.9 ± 2.1	7.1 ± 3.3	14.7 ± 3.5	8.2 ± 1.5	11.3 ± 2.6
2 weeks	Placebo	Overall	122.4 ± 28.1	29.1 ± 6.5	23.0 ± 4.9	12.3 ± 3.33	11.3 ± 2.7	8.0 ± 3.4	14.7 ± 4.6	7.6 ± 2.6	11.1 ± 3.5
		Severe	113.9 ± 28.9	28.4 ± 7.0	22.4 ± 5.6	13.0 ± 3.6	11.1 ± 3.3	7.7 ± 3.7	14.3 ± 4.8	7.2 ± 2.8	10.7 ± 3.8
		Moderate	127.8 ± 23.0	30.2 ± 5.9	23.7 ± 3.6	13.7 ± 3.7	11.6 ± 1.7	8.4 ± 3.0	15.7 ± 4.3	8.3 ± 2.2	12.3 ± 2.4
	Active treated group	Overall	121.2 ± 24.2***	29.9 ± 6.7***	21.9 ± 6.0*	13.1 ± 3.5***	11.6 ± 2.9**	7.7 ± 3.0***	14.9 ± 3.5*	7.9 ± 1.9	11.3 ± 2.4
		Severe	120.4 ± 25.4***	29.8 ± 6.9***	21.2 ± 6.4*	13.1 ± 3.5***	12.0 ± 2.9***	7.6 ± 2.9****	14.8 ± 3.4**	7.8 ± 2.1	11.0 ± 2.6
		Moderate	122.4 ± 22.8	29.9 ± 6.7	22.7 ± 5.3 ^o	13.2 ± 3.6	11.2 ± 2.9	7.8 ± 3.1	15.1 ± 3.7	8.1 ± 1.6	11.7 ± 2.1
1 month	Placebo	Overall	122.9 ± 25.4	29.2 ± 7.7	23.1 ± 4.8	12.7 ± 4.2	12.3 ± 2.4	8.6 ± 2.9	14.7 ± 3.4	7.0 ± 2.3	11.4 ± 2.8
		Severe	114.8 ± 21.7	28.8 ± 6.8	21.1 ± 4.2	11.7 ± 4.2	12.4 ± 2.5	8.2 ± 3.2	14.4 ± 3.5	6.8 ± 2.3	11.0 ± 2.8
		Moderate	127.7 ± 24.4	30.0 ± 7.3	24.0 ± 5.1	13.9 ± 3.9	12.2 ± 2.3	9.1 ± 2.4	15.1 ± 3.1	7.3 ± 2.2	11.8 ± 2.7
	Active treated group	Overall	124.7 ± 24.8****	30.3 ± 6.9****	22.4 ± 5.0**	13.6 ± 3.6****	11.9 ± 2.5****	7.9 ± 3.2***	15.5 ± 3.5***	8.0 ± 1.8	11.6 ± 2.6*
		Severe	124.8 ± 25.2****	30.7 ± 7.0****	22.5 ± 4.9***	13.5 ± 3.3***	12.1 ± 2.5***	7.9 ± 3.1**** ^o	15.2 ± 3.7***	8.0 ± 2.1*	11.3 ± 2.7
		Moderate	124.5 ± 24.7	29.8 ± 6.8	22.2 ± 5.0	13.7 ± 4.0	11.6 ± 2.3*	8.0 ± 3.2 ^o	15.8 ± 3.3	8.1 ± 1.5	12.0 ± 2.3
3 months	Placebo	Overall	113.0 ± 24.3	27.2 ± 6.3	21.2 ± 4.6	12.1 ± 3.0	12.8 ± 6.3	7.1 ± 3.0	13.6 ± 3.8	7.3 ± 2.3	10.4 ± 2.5
		Severe	105.1 ± 21.3	23.8 ± 6.6	19.2 ± 4.1	11.4 ± 3.1	11.3 ± 4.6	6.7 ± 3.2.7	12.7 ± 4.1	6.8 ± 2.3	10.1 ± 2.6
		Moderate	119.1 ± 21.0	28.9 ± 5.5	22.3 ± 4.3	13.0 ± 2.8	14.1 ± 6.8	7.8 ± 3.2	14.7 ± 3.1	8.0 ± 2.1	10.9 ± 2.2
	Active treated group	Overall	131.7 ± 23.2****	32.3 ± 6.8****	24.1 ± 4.9****	14.0 ± 3.2****	12.4 ± 2.6****	9.2 ± 3.4****	15.9 ± 3.1****	8.2 ± 1.6*	12.4 ± 2.2****
		Severe	129.6 ± 22.8****	31.8 ± 6.6****	23.5 ± 4.6****	13.8 ± 3.3****	12.0 ± 2.7***	9.2 ± 3.5****	15.7 ± 3.1****	8.0 ± 1.6*	12.2 ± 2.3****
		Moderate	134.7 ± 23.7****	34.0 ± 7.0****	24.8 ± 5.3**	14.9 ± 3.0****	12.8 ± 2.3****	9.2 ± 3.3**	16.4 ± 3.0*	8.6 ± 1.5	12.6 ± 2.2*

IBS-QoL domains: 1, dysphoria; 2, interference with daily activities; 3, body image; 4, health worries; 5, food avoidance; 6, social reaction; 7, sexual function; 8, impact on relations.

*Adjusted $p < .05$; **adjusted $p < .01$; ***adjusted $p < .001$; ****adjusted $p < .0001$ compared to baseline values. † $p < .05$ compared to patients with severe IBS symptoms.

has been proposed that donor screening should include testing for extended-spectrum-beta-lactase-producing *Escherichia coli* and SARS-CoV-2, and FMT for IBS patients should be restricted to those without systemic disease, immune deficiency, immune-modulating medication treatment, or severe illness [31]. A recently published RCT involving refractory IBS patients with a successful outcome indicated that not all patients will benefit from FMT treatment and that the success of FMT is dependent on the IBS subset [8].

The present study showed that FMT reduces abdominal symptoms and fatigue and improves the quality of life in both S-IBS-S and Mo-IBS-S patients. FMT is therefore beneficial for both groups of IBS patients, but its effects differed between these two groups. The response rates were higher in S-IBS-S patients than in Mo-IBS-S patients at all observation intervals. Moreover, Fatigue that was higher in S-IBS-S than that of Mo-IBS-S patients at baseline decreased to the same level of MO-IBS-S after FMT. Furthermore, the quality of

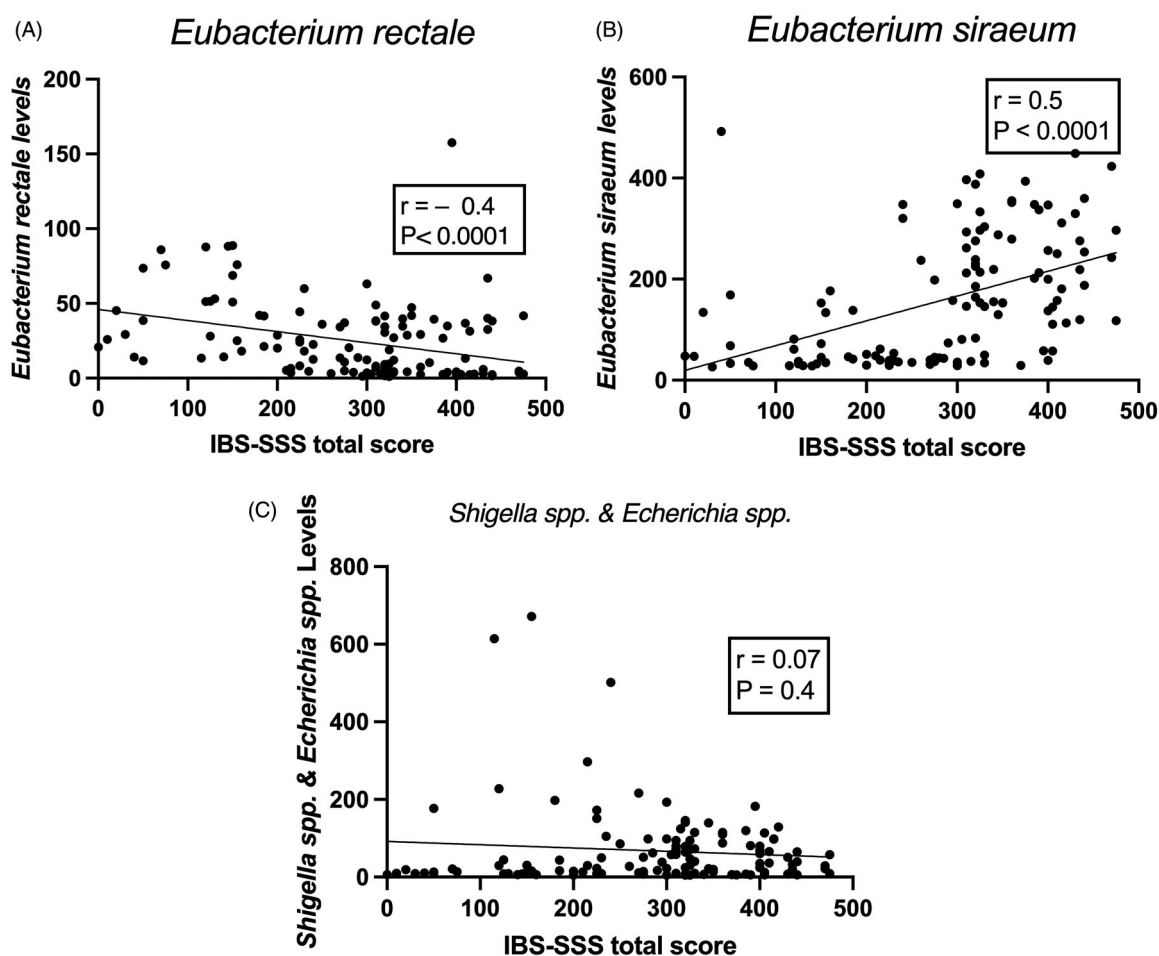


Figure 4. Correlation between IBS-SSS total score, and *Eubacterium rectale* (A), *Eubacterium siraeum* (B) and *Shigella* spp. (C).

Table 5. The fluorescence signals of *Eubacterium rectale*, *Eubacterium siraeum* and *Shigella* spp. at baseline and 1 month after FMT in IBS patients with moderate IBS symptoms (Mo-IBS-S) and patients with severe IBS Symptoms (S-IBS-S).

Bacteria	Mo-IBS-S			S-IBS-S		
	Baseline	1 month after FMT	<i>p</i> -Values	Baseline	1 month after FMT	<i>p</i> -Values
<i>Eubacterium rectale</i>	48.9 ± 40.1	76.6 ± 104.3	.6	62.7 ± 63.1	48.8 ± 39.4	.06
<i>Eubacterium siraeum</i>	56.2 ± 39.6	60.1 ± 59.9	.7	248.0 ± 92.1	83.0 ± 87.7	<.0001
<i>Shigella</i> spp.	53.7 ± 123.5	49.3 ± 108.1	.5	58.0 ± 46.0	81.1 ± 134.0	.4

Values expressed as mean ± SD.

life of S-IBS-S patients, which was lower than that of Mo-IBS-S patients, increased to the same level as that of Mo-IBS-S patients after the FMT intervention.

S-IBS-S patients had lower levels of *E. rectale*, and higher levels of *E. siraeum* than Mo-IBS-S patients at 1 month after FMT. It is worthy of note that the levels of *E. siraeum* decreased in S-IBS-S patients 1 month after FMT. *Eubacterium rectale* and *E. siraeum* are both anaerobic rod-shaped, Gram-positive bacteria belonging to the *Eubacteriaceae* family. *Eubacterium rectale* produces butyrate and *E. siraeum* produces acetic acid during carbohydrate fermentation [32,33]. Butyrate is a modulator of colonic hypersensitivity, and butyrate intake decreases abdominal pain in IBS patients [34–36]. Butyrate is also used as an energy source for epithelial cells in the colon. Furthermore, butyrate decreases intestinal cell permeability and intestinal motility, and modulates

the immune response [37,38]. Recent research has shown that butyric acid levels are inversely correlated with the total scores for both the IBS-SSS and FAS [39]. On the other hand, acetic acid has been indicated to induce visceral hypersensitivity in rodents [40]. It is therefore tempting to speculate that the lower levels of *E. rectale* and the higher levels of *E. siraeum* in S-IBS-S patients after FMT with the subsequent decrease of butyrate and increase in acetic acid production explains why the total IBS-SSS score was higher in S-IBS-S patients than in Mo-IBS-S patients in the present study. In support of this assumption are the present findings that *E. rectale* correlated negatively with IBS-SSS total score, and *E. siraeum* correlated positively with IBS-SSS total score.

The strengths of this study are that it included a relatively large cohort of IBS patients, comprising three IBS subtypes and used a single well-defined donor. Thus, allowing a

subgroup analysis. limitations of this study are that it did not include the fourth IBS subtype, IBS-U, predominated by females and it only investigated some of the intestinal bacterial contents.

In conclusion, FMT reduced abdominal symptoms and fatigue and improved the quality of life in both S-IBS-S and Mo-IBS-S patients. However, S-IBS-S patients have a higher response rate to FMT and a marked improvement in fatigue and in quality of life compared with Mo-IBS-S patients. Although FMT seems to be more beneficial for S-IBS-S patients, FMT trials should also include Mo-IBS-S patients.

Author contributions

M.E.S. designed the study, obtained the funding, administered the study, recruited the patients, performed FMT, collected, analyzed and interpreted the data, and drafted the manuscript. T.M., T.H. and J.G.H. contributed to the design of the study, to data analysis and critically revised the manuscript for important intellectual content.

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