Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: Magdy El-Salhy, Odd Helge Gilja & Jan Gunnar Hatlebakk (12 Dec 2023): Increasing the transplant dose and repeating faecal microbiota transplantation results in the responses of male patients with IBS reaching those of females, Scandinavian Journal of Gastroenterology, DOI: 10.1080/00365521.2023.2292479

To link to this article: https://doi.org/10.1080/00365521.2023.2292479

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
https://doi.org/10.1080/00365521.2023.2292479

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RESEARCH ARTICLE

Increasing the transplant dose and repeating faecal microbiota transplantation results in the responses of male patients with IBS reaching those of females

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ABSTRACT

Background: Faecal microbiota transplantation (FMT) performed with a proper protocol is a safe treatment for IBS that has high efficacy and durable effects. Females have been reported to respond better than males to FMT. The present study aimed at determining whether increasing the transplant dose or repeating FMT improve the responses of males to FMT.

Methods: This study included 186 IBS patients (131 females and 55 males) who were randomized at a 1:1:1 ratio to receive 90 g of donor faeces once into the large intestine, once into the small intestine or twice into the small intestine. Patients completed five questionnaires that assessed their symptoms and quality of life, and provided faecal samples at baseline and at 3, 6 and 12 months after FMT. The faecal bacterial profile and dysbiosis index were determined using 16S rRNA gene PCR DNA amplification covering variable genes V3–V9.

Results: The response rates to FMT at all observation times did not differ significantly between females and males regardless of the transplant administration route or whether it was repeated. Faecal *Alistipes* levels were higher in females than in males at baseline and increased in both females and males after FMT. In the repeated group, the *Alistipes* levels did not differ between females and males after FMT.

Conclusions: Increasing the transplant dose and repeating FMT results in the responses of male IBS patients to FMT reaching those of females regardless of the administration route. *Alistipes* spp. levels appear to play a role in this improvement.

www.clinicaltrials.gov (NCT04236843).

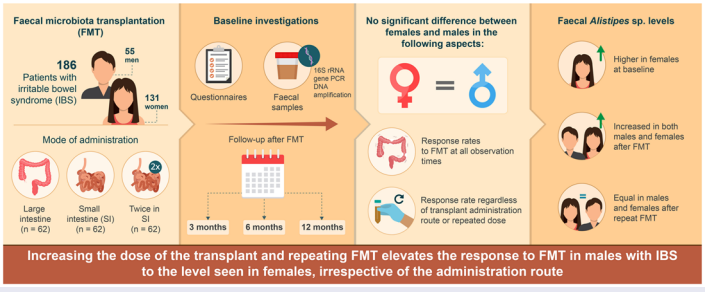
ARTICLE HISTORY

Received 3 November 2023
Revised 15 November 2023
Accepted 4 December 2023

KEYWORDS

Alistipes spp; fatigue; faecal microbiota transplantation; non-responders; responders; sex

GRAPHICAL ABSTRACT



Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder with an unknown aetiology [1]. IBS patients have an intestinal bacteria profile with a lower bacterial abundance (dysbiosis) and different bacterial profile than that of healthy subjects [2–7]. This abnormality is considered to play a key role in the pathophysiology of IBS [7]. Several clinical trials (RCTs) using Faecal microbiota transplantation (FMT) as a treatment for IBS have been done with different outcome [8]. It is challenging to compare these RCTs due to variations in the criteria used to select the donors and patients, in the dose of the faecal transplant used in the FMT, the way the transplant preserved and prepared and the route of administration [8]. Several systematic meta-analysis has been done to evaluate FMT as a treatment for IBS [9–18]. In all these systematic meta-analyses, the authors concluded that FMT is a safe intervention, but further RCTs are needed before it can be applied in everyday clinical practice. In some of these reviews, the authors concluded that FMT is beneficial to patients with IBS when the transplant administrated to either the small or the large intestine [9,10,12,14,15,17,18]. Moreover,

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/00365521.2023.2292479.

it was concluded in some meta-analyses that well-defined donors and small intestine delivery of transplant faecal administration routes proved to be effective [14,15]. Faecal microbiota transplantation (FMT) using an appropriate protocol has been found to be safe for treating IBS, and have a high efficacy and durable effects [8,19–21]. This protocol included a combination of favourable factors such as a high dose of donor faeces, careful donor selection, faeces transplant being handled in such a way that preserved both aerobic and nonaerobic bacteria, and delivering the faeces transplant *via* the small intestine [8,22–24].

IBS predominates in females in Western countries (USA and Europe), with a female:male ratio of 2:1 [25] .Females reportedly respond better than males to FMT [21,26,27]. A previous study found that patients with IBS who did not respond to FMT using a 30-g transplant did respond to a 60-g transplant [28]. However, it was not clear if the increased response was due to increasing the dose of the transplant or to repeating FMT.

The present study aimed at determining whether increasing the transplant dose or repeating FMT would improve the responses of males to FMT. It also aimed at determining whether the administration route of the transplant would affect how males respond to FMT. Moreover, correlation between the changes in bacterial levels after FMT and IBS symptoms was investigated.

Materials and methods

Study design

The design of this study has been described in detail elsewhere [22]. Briefly, patients completed five different questionnaires that assessed their IBS symptoms, fatigue and quality of life, and provided faecal samples at baseline and at 3, 6 and 12 months after FMT. The patients were randomized at a 1:1:1 ratio to receive 90 g of donor faeces once into the caecum of the colon (LI group), once into the small intestine (SI group) or twice into the small intestine at a 1-week interval (R group) [22] .Faecal samples were immediately frozen and stored at −80 °C. The FMT process has previously been described in detail [22] .In summary, 90 g of the transplant was mixed manually with 90 ml of sterile saline, and administered to the caecum of the colon or to the distal duodenum *via* the working channel of a colonoscope or gastroscope, respectively [22] .

Patients and donor

The study included the 186 patients who had participated our previous study (Table 1) [22] .The inclusion criteria were age ≥18 years and having moderate-to-severe IBS symptoms, as indicated by an IBS Severity Scoring System (IBS-SSS) score of ≥175. The exclusion criteria were being pregnant or planning pregnancy, lactating, having a systemic disease, having immune deficiency, taking an immune-modulating drug, having a psychiatric illness, excessively consuming alcohol or abusing drugs. Patients who took probiotics, antibiotics or IBS drugs within 8 weeks prior to the study were also excluded [22].

Table 1. Characteristics of patients included in the study at baseline.

	Total	Females	Males	*p*
Number	186	131	55	
Age, years	37.1 ± 12.7	36.4 ± 12.5	39.0 ± 12.9	0.2
Body mass index, kg/m^2	24.9 ± 5.2	24.7 ± 5.4	25.9 ± 4.1	0.1
IBS-diarrhoea	69	50	19	
IBS-constipation	64	45	19	0.9
IBS-mixed	53	36	17	
IBS duration, years	22.9 ± 13.5	23 ± 13	23 ± 15	0.8
Total IBS-SSS score	345.7 ± 76.8	355.4 ± 72.8	336.2 ± 80.8	0.1
Birmingham IBS Symptom Questionnaire total score	26.2 ± 6.1	26.6 ± 5.7	25.1 ± 6.3	0.1
FAS total score	34.2 ± 5.2	34.5 ± 5.0	33.5 ± 5.5	0.3
Total IBS-QoL score	97.9 ± 20.9	96.2 ± 20.7	102.3 ± 21.0	0.09
Total SF-NDI score	34.7 ± 7.2	34.4 ± 7.1	35.5 ± 7.3	0.3
DI	2.3 ± 1.0	2.2 ± 1.0	2.5 ± 1.0	0.01
Proton-pump inhibitor	23 (12.4)	12 (9.2)	11 (20)	0.05
Painkiller	20 (10.8)	15 (11.5)	5 (9.1)	0.8
Antidepressant	28 (15.1)	20 (15.3)	8 (14.5)	0.5
Birth-control drug	51 (38.9)	51 (38.9)	0 (0)	<0.0001
Asthma/allergy drug	43 (23.1)	32 (24.4)	11 (20)	0.6
Levothyroxine-containing drug	3 (1.6)	3 (2.3)	0 (0)	0.6
Heart/vascular drug	11 (5.9)	8 (6.1)	3 (5.5)	>0.999

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

The donor used in this study was the same as the person who participated in our previous study [19] .To summarize, he was a healthy male aged 40 years who was screened according to the European guidelines for FMT donors [4,8] and fulfilled the clinical criteria of a superdonor. He was vaccinated against COVID-19 and tested weekly for COVID-19 during the period in which he donated his faeces. The bacteria composition of his faecal samples was analysed every 3 months during the donation period. The donor had a dysbiosis index (DI) of 1 for all tested faecal samples and had a stable bacterial profile [19,22].

Symptoms and quality-of-life assessments

This study used the IBS-SSS, Birmingham IBS Symptom Questionnaire, Fatigue Assessment Scale (FAS), IBS Quality of Life Scale (IBS-QoL) and Short-Form Nepean Dyspepsia Index (SF-NDI) [29–35] .A response to FMT was defined as a decrease of ≥50 points in the total IBS-SSS score.

Faecal bacterial analysis and DI

The faecal bacteria composition and DI were determined using 16S rRNA gene PCR DNA amplification covering variable genes V3–V9. Probe labelling was achieved by single-nucleotide extension and signal detection using the BioCode 1000A 128-Plex analyser (Applied BioCode, Santa Fe Springs, CA, USA) [5]. The predetermined 48 bacterial markers used detected bacteria within 5 phyla (Firmicutes, Proteobacteria, Bacteroidetes, Tenericutes and Verrucomicrobia) and assessed >300 bacteria at different taxonomic levels [5,6]. DI was measured on a 5-point scale from 1 to 5, where DIs of 1 and 2 indicated normobiosis, and those of 3–5 indicated dysbiosis [5].

Statistical analysis

Differences between IBS subtypes and drugs were analysed using Fisher's exact tests. The Mann-Whitney test was used to analyse differences between females and males in age, body mass index, scores on the IBS-SSS, Birmingham IBS Symptom Questionnaire, FAS, IBS-QoL and SF-NDI, and DI. Fluorescence signals of faecal bacteria were analysed using the Kruskal-Wallis's test and a post-test of Dunn's multiple comparisons. Correlations were determined using nonparametric Spearman correlation.

These analyses were performed using GraphPad Prism software (version 9.0, La Jolla, CA, USA).

Results

Patients and responses to FMT

At 3 months after FMT, one male patient dropped out and one female was excluded because of pregnancy. Another female patient dropped out at 6 months, and at 12 months another male patient dropped out and another female patient was excluded because of pregnancy.

The response rates in females were 82%, 78% and 71% at 3, 6 and 12 months after FMT, respectively; the corresponding values for males were 72%, 67% and 67%. The response rates at 3, 6 and 12 months after FMT did not differ significantly between females and males ($p = 0.2$, 0.2 and 0.7, respectively). The response rates to FMT also did not differ significantly between females and males in the LI, SI or R group (Figure 1).

Symptoms and quality of life

The total IBS-SSS scores did not differ significantly between females and males at baseline in the LI or SI group, but they were significantly lower in males in the R group. After FMT the total IBS-SSS scores did not differ between females and males at all observation times regardless of the transplant administration route (Figure 2 and Supplementary Material Tables 1–4). However, females experienced greater abdominal distension than did males at baseline and less dissatisfaction with bowel habits at 3 months after FMT (Supplementary Material Table 1).

The Birmingham IBS Symptom Questionnaire total scores did not differ between females and males at baseline or at

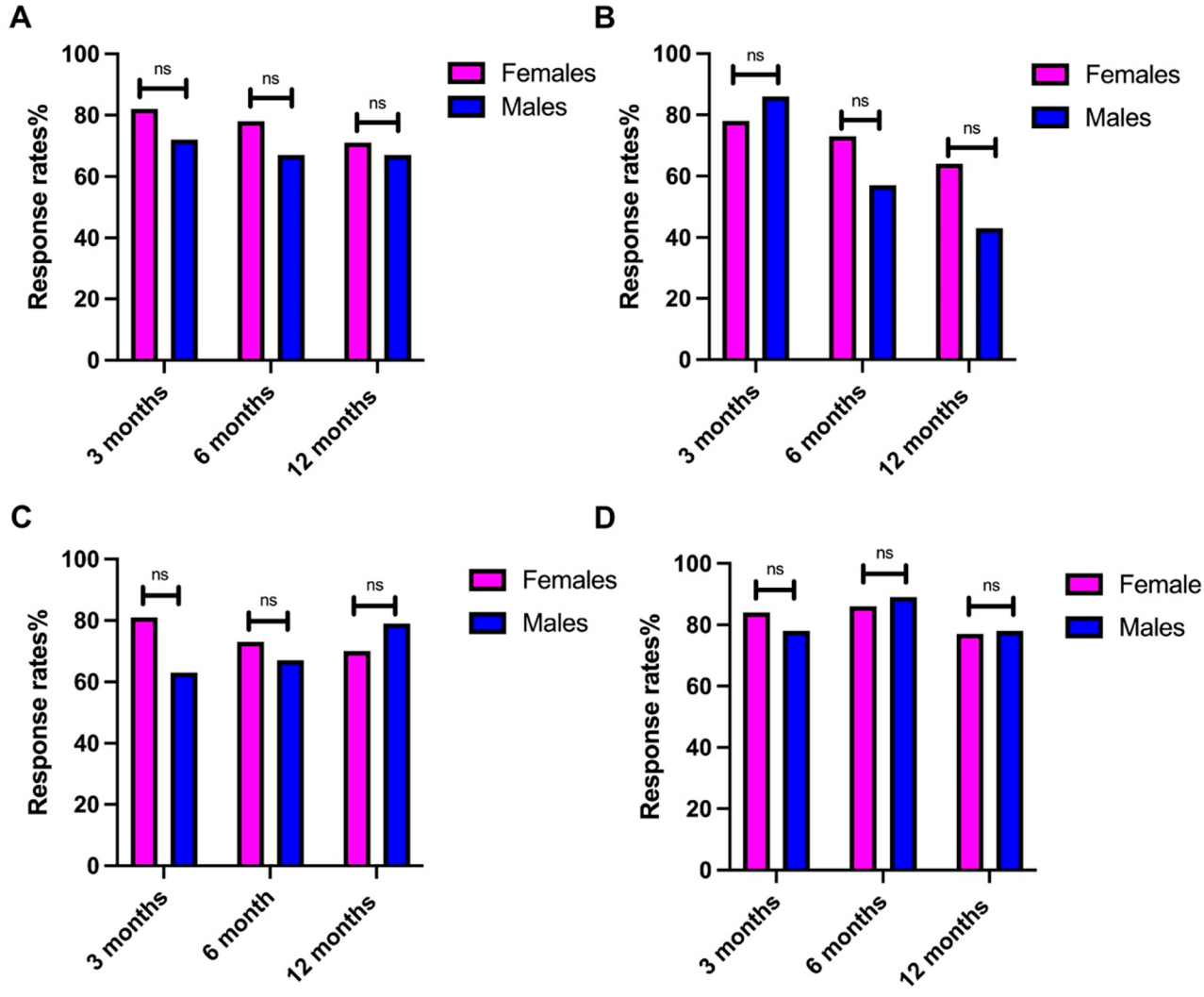

Figure 1. Response rates of females and males to FMT in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups. ns, not significant.

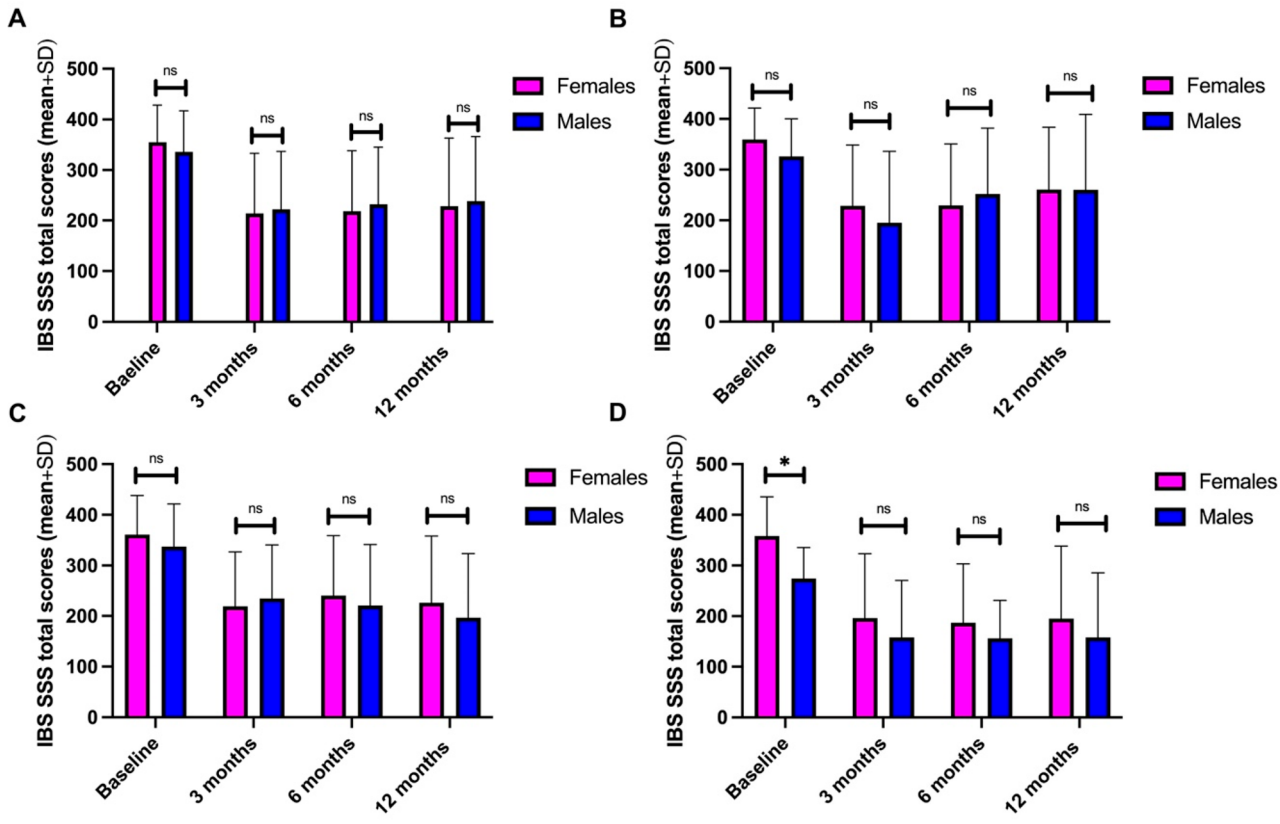

Figure 2. Total IBS-SSS scores in females and males in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups. *, $p < 0.05$.

all observation times after FMT. However, female IBS patients experienced more constipation than did male IBS patients at 12 months after FMT (Figure 3 and Supplementary Material Tables 5–8). There were no differences in the FAS total scores between females and males at baseline or at all observation times after FMT in the total patient cohort or in the LI, SI or R group (Figure 4 and Supplementary Material Tables 9–12). The total IBS-QoL scores in females in the total patient cohort did not differ from those in males at baseline or at all observation times after FMT. In the SI group the total IBS-QoL scores were higher in males than females at baseline and continued to be higher at all observation times after FMT (Figure 5 and Supplementary Material Tables 13–16). The scores for body image and sexual function were significantly higher in males than females at baseline and after FMT (Supplementary Material Table 13). The total SF-NDI scores of females did not differ from those of males in the total patient cohort or in the LI, SI or R group (Figure 6 and Supplementary Material Tables 17–20). However, males experienced significantly greater interference with daily activities and with work/study at 6 months after FMT.

Bacterial analysis

The DI was higher in males than females at baseline, especially in the R and SI groups. After FMT, the DI in females did not differ from that in males in the total patient cohort or in the LI, SI or R group (Supporting information Figure 1).

At baseline, the levels of *Alistipes* spp., *Ruminococcus albus*, *Ruminococcus bromii* and *Ruminococcus gnavus* were higher in females than in males, whereas the level of *Holdemanella biformis* was higher in males. At 3 months after FMT, the levels of *Alistipes* spp., *Parabacteroides johnsonii* and *Anaerobutyricum hallii* were higher in females than in males. The levels of *Alistipes* spp. and *Bacteroides zoogleoformans* at 6 months after FMT were higher in females than in males. The levels of *Alistipes* and Proteobacteria spp. at 12 months after FMT were higher in females than in males, whereas those of *Eubacterium rectale*, *Streptococcus agalactiae* and *Eubacterium rectale* were lower in females (Supplementary Table 21). Although the levels of *Alistipes* spp. increased significantly in both females and males at all observation times after FMT, their levels were higher in females than in males at all observation times except 12 months after FMT in the LI group (Figure 7). In contrast, in the R group there were no differences in the levels of *Alistipes* spp. at all observation times after FMT.

The levels of eight bacterial markers differed between females and males in the LI group at baseline, which reduced to four, five and two bacterial markers at 3, 6 and 12 months after FMT, respectively (Supporting information Table 22). In the SI group, the levels of five bacterial markers differed between females and males, which reduced to two bacterial markers at 3 and 6 months after FMT before increasing again after 12 months to six bacterial markers (Supplementary Material Table 23). In the R group the levels of *Alistipes* spp.

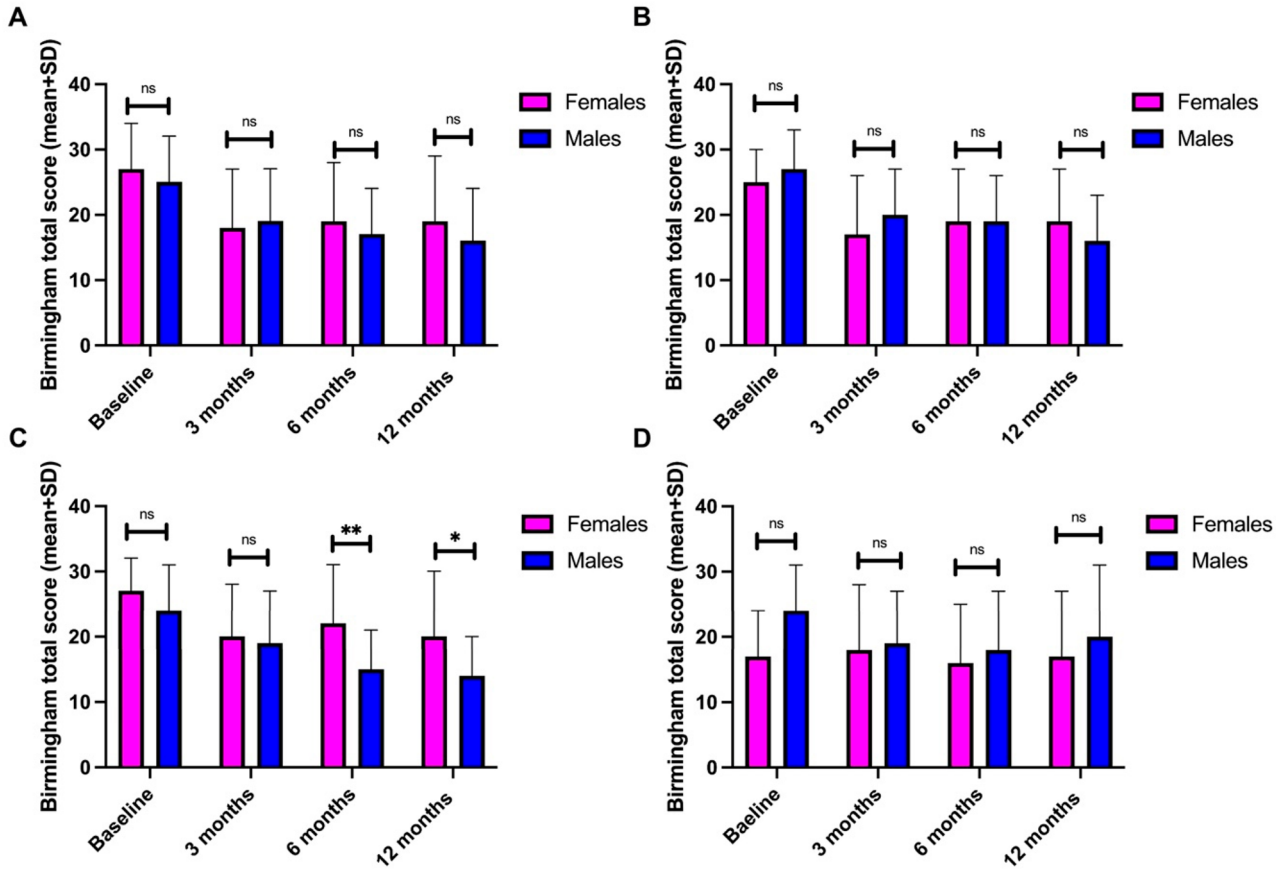

Figure 3. Birmingham IBS Symptom Questionnaire total scores for females and males in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups. *, $p < 0.05$; **, $p < 0.01$.

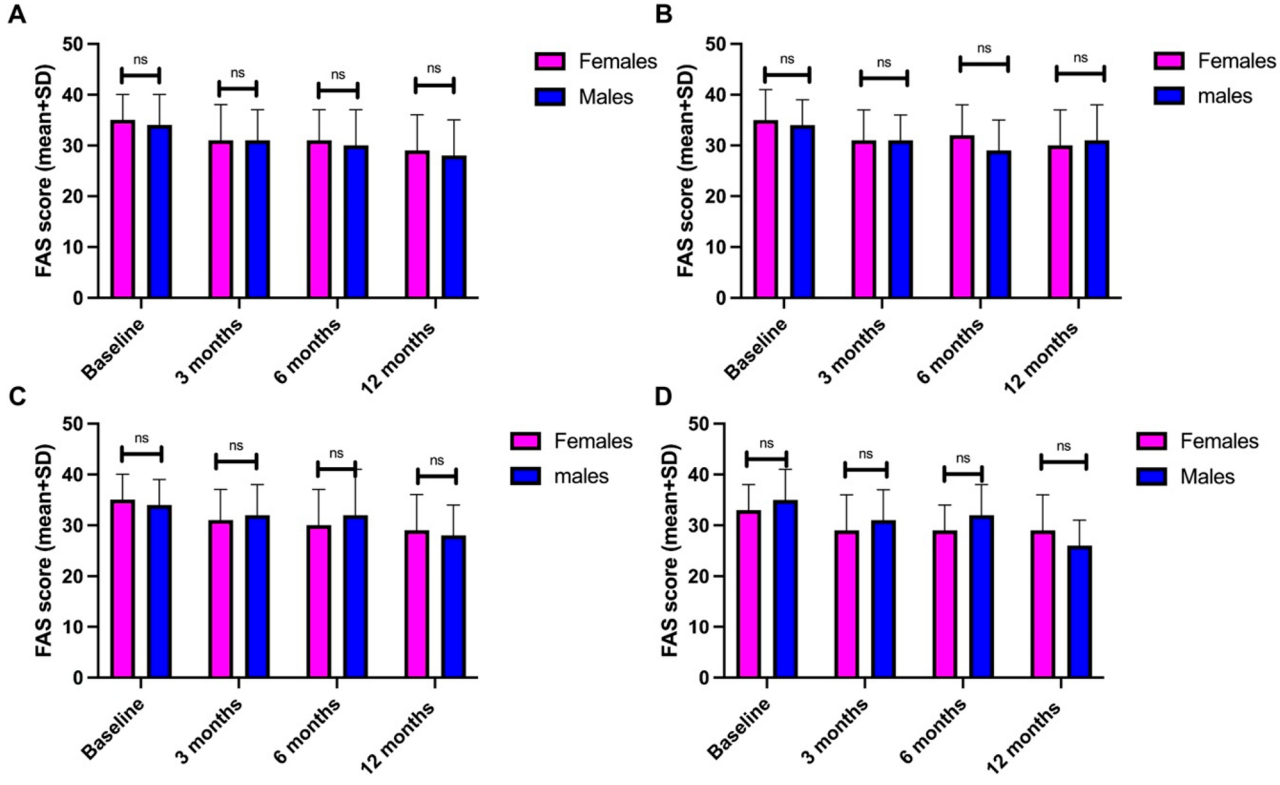

Figure 4. FAS total scores for females and males in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups.

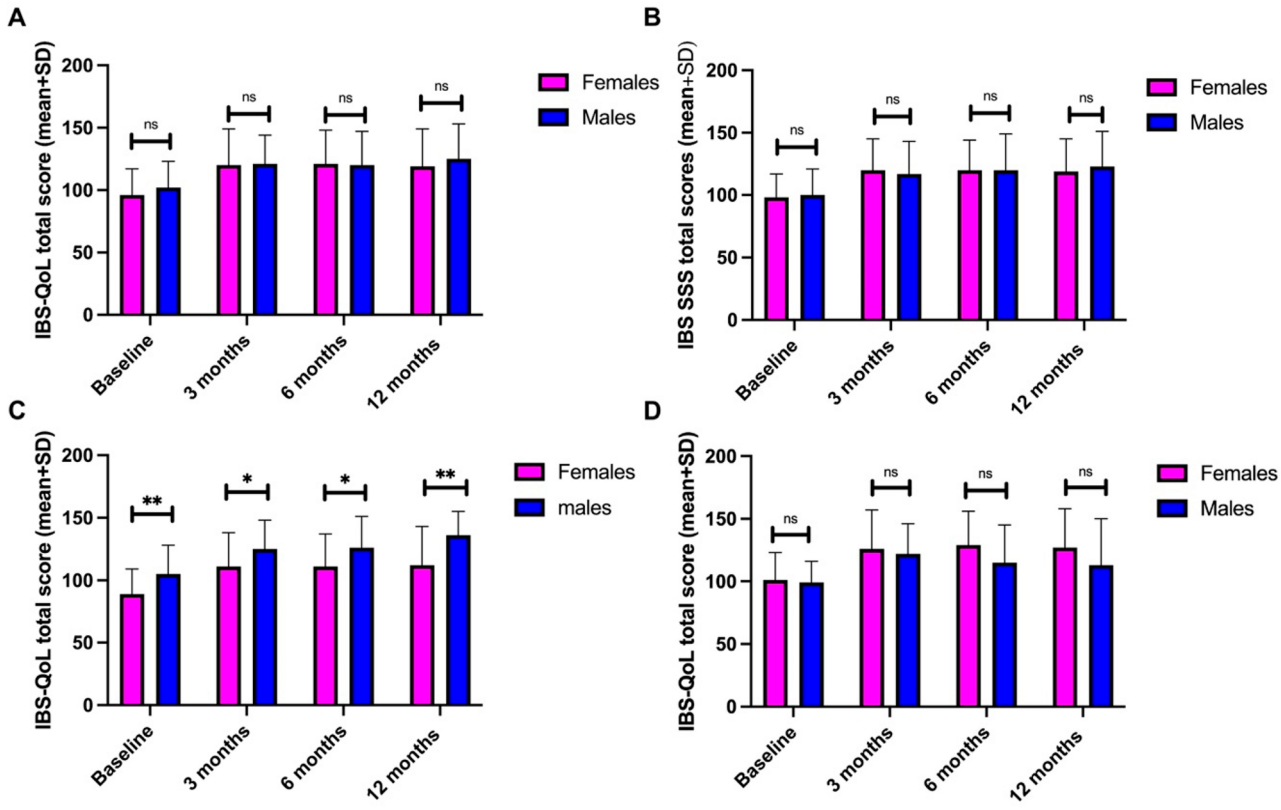

Figure 5. Total IBS-QoL scores in females and males at different times after FMT in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups. *, $p < 0.05$; **, $p < 0.01$.

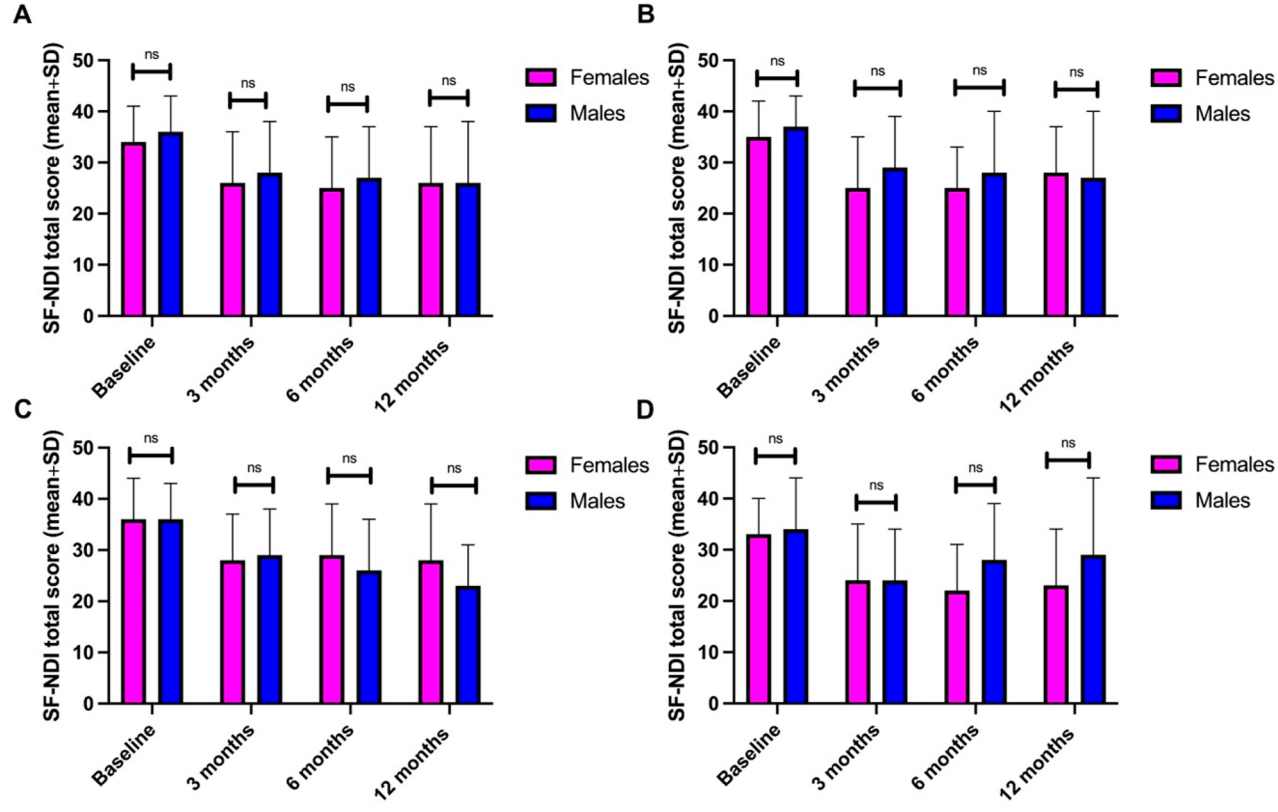

Figure 6. Total SF-NDI scores in females and males at different times after FMT in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups.

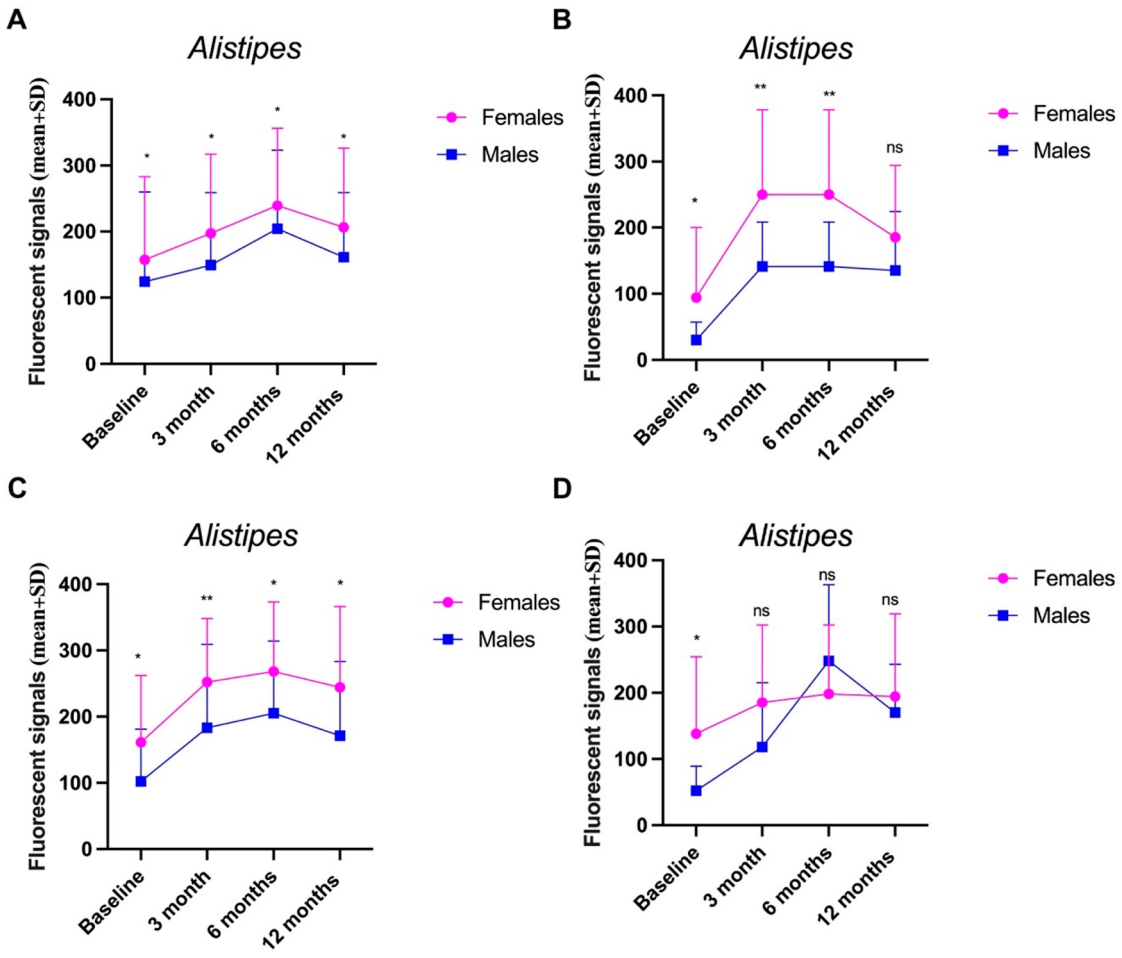

Figure 7. Levels of *Alistipes* spp. in females and males at baseline and at different times after FMT in the total patient cohort (A) and in the LI (B), SI (C) and R (D) groups. *, $p < 0.05$; **, $p < 0.01$.

were higher in females than in males at baseline, and the levels of three, two and three bacterial markers differed between females and males in this group after 3, 6 and 12 months, respectively (Supplementary Material Table 24).

Correlations

The levels of *Ruminococcus albus*, *Ruminococcus bromii* and *Ruminococcus gnavus* were not correlated with total IBS-SSS scores (r = −0.1 and $p = 0.2$, and r = −0.05 and $p = 0.5$, respectively).

Discussion

In a previous study from our group, males responded less than females when 30 g or 60 g of the faecal transplant was used [19] .In this study, the same protocol for FMT and the same donor, whose bacterial profile was stable over time, were used as well as similar IBS patient's cohort with moderate to severe IBS were included [22,26] .The present observation that increasing the transplant dose of donor faeces from 60 g to 90 g increased the response rates of males to those of females. However, a RCT comparing different doses is required to confirm this conclusion. The response rates were not affected by where the transplant was administered. However, in both the females and males the response rates were higher when the transplant was administered to the small intestine than when it was administered to the large intestine. Although the total IBS-QoL scores did not differ between females and males at baseline, the scores for body image and sexual function were higher in males. It is tempting to speculate that these differences are caused by psychosocial factors rather than by IBS itself. It is worthy of note that FMT improved sexual function in males with refractory Crohn's disease [36].

The degree of dysbiosis was greater in male than female IBS patients at baseline, but this difference vanished at all observation times after FMT. In healthy subjects the gut bacterial profile differs between females and males [37] .The present study has shown that the intestinal bacterial composition also differs between female and male patients with IBS, with females having higher levels of *Alistipes* spp., *Ruminococcus albus*, *Ruminococcus bromii* and *Ruminococcus gnavus*, and a lower level of *Holdemanella biformis*.

The *Alistipes* genus comprises 13 species [38] that in humans are mostly localized in the gastrointestinal tract [39] .*Alistipes* spp. are Gram-negative, rod-shaped, anaerobic, non-spore-forming and bile-resistant bacteria [40–42] .This bile-resistant genus is expected to be more abundant in the

terminal ileum [43] .*Alistipes* spp. seem to play a significant role in several diseases such as depression, anxiety, chronic fatigue syndrome, autism, cirrhosis and aging [38].

Alistipes spp. hydrolyse tryptophan (which is a precursor for serotonin) to indole, and consequently increases in the levels of *Alistipes* spp. would decrease serotonin availability [38] .Serotonin is a neurotransmitter acting *via* a paracrine mode of action that plays a central role in the brain–gut axis [44–46] .Changes in serotonin metabolism are reportedly a probable cause of the visceral hypersensitivity seen in IBS patients [44–46] .*Alistipes* spp. express glutamate decarboxylase, an enzyme that metabolizes glutamate into GABA (γ-aminobutyric acid) [38] .*Alistipes* spp. also produce short-chain fatty acids with anti-inflammatory effects such as acetic, succinic and propionic acids [38,47] ;for example, propionic acid exerts neurobiological effects in rats [48] .In addition, *Alistipes* spp. express methylmalonyl-CoA epimerase, and the gene for this enzyme is located on an operon with the acetyl-CoA carboxylase gene [38].

The faecal levels of *Alistipes* spp. increased significantly 1 month after patients received FMT, and remained high at 1, 2 and 3 years after FMT. These levels were inversely correlated with scores on the IBS-SSS and FAS at 1 month, 1 year, 2 years and 3 years after FMT [19–21] .A recently reported study found that IBS patients with low levels of *Alistipes* spp. were unlikely to respond to FMT [21] .It is therefore reasonable to speculate that increasing the transplant dose increased the levels of *Alistipes* spp. enough to increase the response rates of males to those of females. It is worth noting that although the levels of *Alistipes* spp. in males increased after FMT at a higher dose, they were still significantly lower than those in females who received single FMT. However, repeating FMT resulted in the levels of *Alistipes* spp. in males reaching those in females at all observation times.

Ruminococcus albus, *Ruminococcus bromii* and *Ruminococcus gnavus* are Gram-negative, coccoid-shaped, anaerobic, non-spore-forming bacteria [49–51] .These bacteria are amylolytic bacteria that ferment non-digestible carbohydrates such as cellulose, starch, xylan and pectin, which results in the production of hydrogen gas [50,51] .Hydrogen gas exerts antioxidant, antiapoptotic and anti-inflammatory effects [52] .The higher levels of these bacteria in females than in males at baseline may explain why female IBS patients experienced greater abdominal distension than did males. In the present study these bacteria were not correlated with the total IBS-SSS score and therefore they are unlikely to play a role in IBS symptoms.

Holdemanella biformis is a coccus-shaped anaerobic bacterium [53,54] .It produces the long-chain fatty acid 3-hydroxyoctadecaenoic acid (C18-3OH). This long-chain fatty acid exerts an anti-inflammatory effect on colitis and protects against the growth of intestinal tumours [53,54] .The level of *Holdemanella biformis* has been reported to be inversely correlated with scores on the IBS-SSS and FAS [21] .The lower level of *Holdemanella biformis* in females than in males found at baseline in the present study is difficult to explain.

One strength of this study is that it involved a large number of male IBS patients that almost reflects the prevalence of IBS in females and males in the Western world, included three of the IBS subtypes, and utilized a single well-defined donor. However, the study also had limitations: it investigated selected predetermined bacteria rather than the entire intestinal bacterial contents, it did not include the fourth IBS subtype (IBS-unspecified) and it did not include a placebo group. Statistical error type II due to small sample size cannot be excluded. However, the number of males in the present study was 55 patients, which exceeds the number of males in the studies that showed a difference in response to FMT between males and females (24 and 32, respectively) [26,27].

In conclusion, this study has shown that increasing the dose of the transplant and repeating FMT—independent of the administration route—results in the responses of males to FMT reaching those of females. Our observations provide support further for the role of *Alistipes* spp. in the response to FMT.

Ethical approval

The study was approved by the Western Regional Committee for Ethics, Bergen, Norway (approval no. 2019/6841/REK vest). All subjects provided both oral and written consents prior to participation. The study was registered at www.clinicaltrials.gov (no. NCT04236843).

Authors' contributions

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

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Helse Fonna (grant no. 40415).

Data availability statement

Data obtained in this study are available from the corresponding author on request.

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