# Intestinal Microbiota Modulation in Patients with IBS-C

Subjects: Others

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Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain associated with defecation or a change in bowel habits. The pathogenesis of IBS is not completely clear, but it is known to be multifactorial and complex.

irritable bowel syndrome and diet | irritable bowel syndrome with constipation | IBS and diet

## 1. Prebiotics in the Treatment of IBS-C

Prebiotics were firstly defined as “nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health”. This definition was later refined to include other areas that may benefit from selective targeting of particular microorganisms: a selectively, generally, fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confer benefits [1].

Although all prebiotics are fibers, not all fibers are prebiotics. Classification of a food ingredient as a prebiotic requires that the ingredient (1) resists gastric acidity, hydrolysis by enzymes, and absorption in the upper gastrointestinal tract; (2) is fermented by the gut microbiota, and (3) selectively stimulates the growth and/or activity of gut bacteria potentially associated with health and well-being [1].

As has already been stated, dietary fiber has soluble and insoluble fractions. Though the insoluble fiber is less utilized by the gut microbiota, the soluble ones, such as inulin and fructans, are mostly used by the gut microbiota as an energy source promoting the development of some beneficial bacteria such as *Lactobacillus* and *Bifidobacteria* [2]. In the literature, the enrichment of the genus *Prevotella* in individuals with higher fiber diets has also been shown [3].

*Prevotella* is an abundant genus in healthy people. Intestinal *Prevotella* spp. are commonly associated with diets and nutritional patterns rich in carbohydrates, resistant starch and fibers. In Western-style diets, Ruminococcaceae and Lachnospiraceae often degrade dietary fiber, although nutritional interventions with fiber-rich foods usually result in a *Prevotella* abundance increase. Indeed, having a *Prevotella*-rich gut microbiota improves weight loss, decreases cholesterol levels and limits the bifidogenic effect in individuals consuming a fiber-rich diet [4]. It is interesting to note that patients with IBS appeared colonized by different strains of *P. copri,* and a correlation between isolates and disease grading was observed [5].

The compounds identified as having the most prebiotic effects are the inulin-type fructans (FOS, inulin, oligofructose) and GOS, many of which are widely present in grains, vegetables and legumes [6].

GOS play a role in modulating immune function, and they also have anti-inflammatory effects. This could be linked also to the possible beneficial effects of these prebiotics on IBS patients, in which a microscopic inflammation of intestinal mucosa has been found. In general, it is well recognized that GOS have important effects on global IBS symptoms, but not on abdominal pain [7].

Prebiotics such as inulin or FOS are characterized as 'functional fibers' [8]. Inulin is a nondigestible oligosaccharide which behaves as a soluble fiber that is naturally found in more than thirty thousand of plants, including vegetables such as wheat, garlic, onion, chicory, artichoke, and asparagus. Thanks to its chemical configuration, inulin is resistant to hydrolysis by digestive enzymes, so it reaches the colon undigested and is further selectively fermented by colonic microbiota [9]. Inulin intake has been linked to the regulation of bowel peristalsis and transit, of stool consistency and frequency, as it produces changes in the composition and activity of the gut microbiota to the modulation of immune response, mineral absorption, satiety and bone weight [10].

Interestingly, a pilot study conducted in 2013 by Isakov et al. [11] on IBS-C patients who received inulin enriched-yogurt demonstrated an improvement in bowel habits and transit time in patients when compared with the consumption of a traditional yogurt [11]. Even the regular consumption of inulin-enriched fermented milk beverages showed a significant improvement in the consistency of stools in patients with IBS-C.

Moreover, Pilipenko et al., conducted an RCT on 49 patients which showed that the consumption of a functional drink containing 4 g of inulin, 4 mg of menthol, and 2 mg of pyridoxine is associated with improvements in stool parameters, abdominal pain, Bristol stool scale index and an increase in QoL in patients with IBS-C, but produces noticeable heartburn. A modification of the functional drink's composition is necessary to reduce side effects [12].

Furthermore, Pilipenko et al., conducted another RCT on 50 patients fulfilling the Rome III criteria for IBS-C that were randomized into two groups: one received a standard diet plus two jelly drinks (containing 3 g of inulin, 10 mg of curcumin and 1.8 mg of pyridoxine) daily for 2 weeks, and a control group received only a standard diet. Likert scales were used daily to record abdominal pain, bloating, a feeling of incomplete bowel emptying, frequency of bowel movements and the Bristol stool scale. The jelly drinks' consumption was associated with a significant beneficial effect on the stool parameters, a reduction in abdominal pain severity, bloating and in the sense of incomplete bowel emptying, as well as an increase in QoL. Patients in the control group showed improvements in abdominal pain and bloating only. During the treatment period, no significant adverse events were found [13].

## 2. Probiotics in Patients with IBS-C

Probiotics are defined by Dr. Roy Fuller as “live microbial feed supplements which beneficially affect the host, improving its intestinal microbial balance” [14]. Probiotics are live microorganisms that when administered in adequate amounts, confer a health benefit to the host [15].

Probiotic bacteria can replace a ‘missing part’ of the commensal microbiota, either in the small and/or large intestine, or stimulate a component of the existing commensal population [16]. Thanks to this action, the functionality of the microbiota might be restored, at least in part, leading to a symptom’s improvement. This might occur through several different pathways, such as competitive exclusion of other bacteria, the production of bacteriocins or an alteration in the fermentation capacity of the microbiota. Moreover, other studies in the literature have also demonstrated that probiotics may alter motility [17], reduce intestinal permeability [18], normalize the inflammatory profile (IL-10:IL-12) [19], reduce visceral hypersensitivity, attenuate anxiety behaviors and modulate brain activity in IBS subjects [20]. A recent systematic review and meta-analysis evaluating RCTs, conducted to assess the effects of probiotics in IBS patients, demonstrated a beneficial effect of these organisms in the treatment of this disorder [21].

Spiller et al., conducted a randomized, double blind, placebo-controlled study on 379 IBS subjects (IBS-C N = 180). Subjects were randomly supplemented with probiotics (*S. cerevisiae I-3856* at the dose of 1000 mg per day) or placebo for 12 weeks. *S. cerevisiae I-3856* did not improve intestinal pain and discomfort in IBS patients, except for the constipation subgroup; in fact, the number of complete spontaneous evacuations was higher in the intervention group, and the stools tended to be softer compared to placebo, suggesting that transit may have been accelerated. Moreover, also abdominal pain/discomfort and bloating improved in the IBS-C subtype throughout the study and at the end of the supplementation compared to placebo [22].

Mezzasalma et al., conducted a randomized, double-blind, three-arm parallel group trial on 150 IBS-C subjects divided into three groups (F_1, F_2, and F_3). Researchers aim to evaluate the efficacy of two probiotic formulations on IBS-C symptoms [23]. Each group received a daily oral administration of probiotic mixtures for 60 days: F_1 (containing *L. acidophilus* and *L. reuteri*), F_2 (containing *L. plantarum, L. rhamnosus,* and *B. animalis* subsp. *lactis*) or placebo F_3, respectively. Fecal microbiological analyses were performed by species-specific qPCR to measure the amount of probiotics. The responders rate for each symptom was higher in the probiotic groups than to placebo both during the treatment and in the follow up (30 days after the end of the study). Probiotics increased during the times of treatment only in subjects treated with F_1 and F_2 but not with F_3, and the same level was maintained during the follow-up period In conclusion, the different species of probiotics administered to the IBS-C subjects constituted an important contribution to treating IBS-C symptoms [23].

Bahrudin et al., conducted an RCT to investigate whether the addition of polydextrose to sterilized probiotic containing *Lactobacillus helveticus* conferred benefits to IBS-C patients. A total of 163 patients were randomized in two groups: Group A consumed 350 mL of sterilized probiotic with 5.85 g polydextrose daily for 1 week, and Group B without polydextrose. The intestinal transit time, fecal pH, fecal weight, and pre- and post-consumption questionnaires were assessed. The addition of polydextrose to sterilized probiotic containing *L. helveticus* did not show significant benefits to IBS-C patients. However, the daily consumption of sterilized probiotic containing *L.*

*helveticus* with or without polydextrose for a week alleviated constipation-related symptoms and reduced both fecal pH and intestinal transit time [24]. In an interesting randomized cross-over case–control study, Bărboi et al., included 51 IBS-C patients, of which 47 completed the trial. Patients were randomized into two groups receiving a diet specific for constipation with or without a food supplement containing inulin, choline and silymarin. Patients were evaluated at baseline, after 4 and 8 weeks, using a questionnaire to assess IBS symptoms. In the supplemented group, abdominal pain and abdominal bloating severity improved by 68.3% and 34.8%, respectively. Even if both the evacuation frequency per week and the stool consistency according to the BSS improved in both groups, no significant differences were observed between the two groups. In conclusion, the combination of inulin, choline and silymarin associated with a diet specific for constipation showed clinical beneficial effects on IBS-C patients in terms of bowel movement, abdominal pain and bloating [25].

## 3. Symbiotic in Patients with IBS-C

In 1995, Gibson and Roberfroid introduced the term “symbiotic” to describe a combination probiotics and prebiotics that act synergistically. A symbiotic should exert a synergistic benefit, enhancing the probiotic organisms by the selective, co-administered prebiotic substrate. Therefore, a correct combination of both components in a single product should ensure a superior effect compared to the activity of the probiotic or prebiotic alone [1]. In 2013, Cappello et al., conducted a double-blinded, randomized placebo-controlled study to evaluate the effects of a commercially available multi-strain symbiotic mixture (Probinul, 5 g over 4 weeks) on symptoms, colonic transit and QoL in IBS patients who met the Rome IV criteria [26]. A total of 64 patients were randomized to either placebo ($n$ = 32) or symbiotic ($n$ = 32), and the symbiotic mixture contained lyophilized bacteria ($5 \times 10^9$ *Lactobacillus plantarum*, $2 \times 10^9$ *Lactobacillus casei* subp. *rhamnosus* and $2 \times 10^9$ *Lactobacillus gasseri*, $1 \times 10^9$ *Bifidobacterium infantis* and $1 \times 10^9$ *Bifidobacterium longum*, $1 \times 10^9$ *Lactobacillus acidophilus*, $1 \times 10^9$ *Lactobacillus salivarus* and $1 \times 10^9$ *Lactobacillus sporogenes* and $5 \times 10^9$ *Streptococcus termophilus*), prebiotic inulin (2.2 g) and 1.3 g of tapioca-resistant starch. The study preparation was administered in a powder form (5 g sachets) containing the symbiotic mixture or the matching placebo. The two sachets were comparable in color, texture and taste. The patients were instructed to ingest the preparation twice daily, far from meals, dissolved in water. Global satisfactory relief of abdominal flatulence and bloating were the primary endpoints, while changes in abdominal bloating, flatulence, pain and urgency, stool frequency and bowel functions on BSS and sense of incomplete evacuation were the secondary endpoints. Additionally, pre- and post-treatment colonic transit time and QoL were evaluated. After 4 weeks, the symbiotic group showed a reduced flatulence, a longer rectosigmoid transit time and an improved QoL [26]. In conclusion, the symbiotic mixture failed to satisfy the primary endpoints, but it demonstrated a beneficial effect on flatulence in IBS patients. The mixture, however, showed a lack of any adverse events and a good side-effect profile. In the current literature, few studies have evaluated the relationship among symbiotics, microbiota and IBS symptoms, but without specifying the IBS subtype. Further studies on a larger number of patients are needed to confirm whether a symbiotic mixture might be an effective treatment option in IBS.

## 4. Fecal Microbiota Transplantation in Patients with IBS-C

Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy or fecal infusion, consists of administration of a liquid filtrate of feces from a healthy donor into the GI tract of a recipient person. Increasing evidence supports the role of the gut microbiota in the etiology of irritable bowel syndrome (IBS). Fecal microbiota transplantation seems to be a highly effective treatment against the recurrent infection of *Clostridioides difficile,* as shown in RCTs in the literature, and may be beneficial also in case of ulcerative colitis. However, its efficacy in IBS is not well defined. In the single-center, retrospective study conducted by Cui et al., in 2021, the long-term efficacy of fecal microbiota transplantation (FMT) in patients with moderate to severe IBS was investigated [27]. They evaluated treatment efficacy rates, changes in IBS-SSS, IBS-specific quality of life and fatigue, effect on stool frequency, Bristol Stool Scale for IBS-C and IBS-D, and the side effects. Overall, 100 g of stool suspension was administered through a naso-intestinal tube or colonoscopy within 6 min/daily for six consecutive days. The stool frequency of IBS-C patients increased from 1.5 ± 1.38 times per week to 2.68 ± 1.15 times per week one month after FMT treatment and increased to 4.33 ± 1.56 times per week at the end of the fifth year of follow-up. The BSS score of IBS-C patients significantly increased ($p < 0.05$) from 2.13 ± 0.88 before treatment to 2.94 ± 1.3 one month after FMT treatment, and further increased to 3.71 ± 1.21 by the 5th year after FMT (compared with that before FMT, $p < 0.01$) [27].

Fecal microbiota transplantation (FMT) seems to be a promising treatment for IBS patients. Although in Western countries, females present a higher prevalence of IBS, El-Salhy et al. did not find a sex difference in the response to FMT either in the placebo group or the actively treated group in their study in 2021. They included 164 IBS patients with moderate-to-severe IBS symptoms belonging to the IBS-D, IBS-C and IBS m subtypes, and who had not showed improvement in symptoms after the NICE-modified diet. Patients were divided into three groups: the placebo (own feces) and two actively treated groups (30 g or 60 g superdonor feces). The results appear to be more effective in IBS-D patients compared to IBS-C ones [28].

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