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Title: Symbiotics in IBS – Better than Probiotics Alone?

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ABSTRACT

Purpose of review: Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder associated with significant physical and psychological co-morbidity. The aetiology of the condition is uncertain but recent research suggests the gut bacterial flora may play a role in its development. Therefore, manipulation of the intestinal microbiome by using probiotics and symbiotics has the potential to improve patient outcomes in IBS.

Recent findings: Numerous randomised controlled trials (RCTs) suggest a benefit of probiotics in the management of IBS, with a significant reduction in the likelihood of symptoms persisting after therapy, and improvements in abdominal pain, bloating, and flatulence when probiotics are compared with placebo. Evidence for the effect of probiotics on quality of life is conflicting. Relatively few RCTs have examined the effect of symbiotics on outcomes in IBS, but results thus far are promising.

Summary: Probiotics appear to be beneficial in IBS. Data supporting the use of symbiotics is sparse. Whether symbiotics are superior to probiotics is unclear.

Keywords: irritable bowel syndrome; symptoms; quality of life; microbiota

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder associated with a combination of symptoms including abdominal pain, altered stool frequency, and altered stool form. The population prevalence of the condition is estimated to be between 10% and 20%,[1] and it is more common in females. [2] To date, the aetiology of IBS remains uncertain but alterations of the intestinal microbiome leading to disordered intestinal immunity, chronic low-grade mucosal inflammation, visceral hypersensitivity and activation of the brain-gut axis have all been implicated. [3*,4*,5*,6*,7*,8*] As a result of the proposed role of perturbations of the intestinal microbiota, manipulation of the gut flora is an attractive target when considering the development of novel therapeutic interventions, including faecal microbial transfer, antibiotics or the use of probiotics, prebiotics, or symbiotics. Whilst faecal transplantation remains experimental,[9,10*] the use of probiotics in IBS is thought to be beneficial.[11*] What is unclear is whether the favourable effect of probiotics can be augmented by their combination with prebiotics, in preparations known as symbiotics.

TEXT OF THE REVIEW

The microbiome in the pathogenesis of IBS - is there a role for probiotics?

Although consensus regarding a microbiome that induces IBS is lacking, evidence suggests there is a relative abundance of pro-inflammatory bacterial species including Enterobacteraceae species, with a corresponding reduction in Lactobacillus and Bifidobacterium, and a reduced Bacteroidetes to Fermicutes ratio at the phylum level. [12,13] This pro-inflammatory dysbiosis seen in some individuals with IBS is thought to lead to activation of the enteric nervous system, decreased expression of epithelial tight junction proteins, and an increase in intestinal permeability, resulting in visceral hypersensitivity, dysregulation of the brain-gut axis, and generation of IBS symptoms. [4*,14*] The pathogenic role of the microbiome in the condition is supported by findings from animal studies, where the transfer of an IBS-related microbiome has been shown to be associated with the development of colonic hypersensitivity in germ-free rats. [15*]

It is suggested that the beneficial effects of probiotics result from the modulation of the microbiome, thereby minimising the effects of this pro-inflammatory cascade. Indeed, changes in the intestinal microbiome observed with probiotic use are associated with the maintenance of epithelial barrier integrity in vitro and in animal models of disease, [16*] a reduction in pro-inflammatory cytokine levels in the peripheral blood of IBS patients, and an improvement in global IBS symptoms, supporting the role of low-grade inflammation in the pathogenesis of IBS. [17*]

Probiotics and physical symptoms in IBS

Probiotics are live or attenuated organisms which may have beneficial effects in humans. [11*] Their use has been studied in the treatment of several GI disorders including, inflammatory bowel disease, [18*,19] radiation enteritis, pouchitis, [19] and Clostridium difficile infection. [20] The efficacy of combinations of probiotics, and individual strains of Lactobacillus, Bifidobacterium, Escherischia, Bifidobacterium, Saccharomyces and Streptococcus, have been assessed in IBS. A

recent systematic review and meta-analysis of 35 randomised controlled trials (RCTs) investigating the use of probiotics in patients with IBS reported an overall relative risk (RR) of IBS symptoms persisting in those treated with probiotics versus placebo of 0.79 (95% confidence interval (CI) 0.70 - 0.89) and a number needed to treat (NNT) of 7. [21**] In total, 12 RCTs assessed combinations of probiotics on the persistence of IBS symptoms, with a RR for the persistence of IBS symptoms of 0.81 (95% CI 0.67 to 0.98). There were six trials of Lactobacillus (RR of persistence of symptoms = 0.75; 95% CI 0.54 to 1.04), two RCTs of Bifidobacterium (RR of persistence of symptoms = 0.71; 95% CI 0.44 to 1.16), two RCTs of Escherichia (RR of persistence of symptoms = 0.86; 95% CI 0.79 to 0.93) and one RCT of Streptococcus (RR of persistence of symptoms = 0.79; 95% CI 0.79 to 0.89).

In addition to estimating their efficacy in preventing the persistence of symptoms, the study also assessed the effect of different probiotic preparations on global IBS symptoms or abdominal pain scores, bloating scores, and flatulence scores. The pooled standardised mean difference (SMD) for the effect of all probiotic preparations on global IBS symptoms or abdominal pain scores was -0.25 (95% CI -0.36 to -0.14), the pooled SMD in bloating scores for all probiotics versus placebo was -0.15 (95% CI -0.27 to -0.03), and the pooled SMD in flatulence scores for all probiotics versus placebo was -0.23 (95% CI –0.38 to –0.07). When data from studies reporting adverse events data were pooled, the RR of any adverse event in patients taking probiotics versus placebo was 1.21 (95 % CI 1.02 – 1.44), with a number needed to harm of 35.

A further three RCTs have examined this issue since the publication of this systematic review and meta-analysis. The first assessed the effects of a combined probiotic containing Bifidobacterium, Lactobacillus, and Streptococcus, and suggested a significant improvement in overall IBS symptom scores, compared with placebo, in 108 Iranian outpatients with IBS diagnosed according to the Rome III criteria. [22*] There was also a significant improvement in bloating and abdominal pain scores using a visual analogue scale after the 4-week treatment period in the active probiotic versus the placebo group ($P = 0.02$ and $P < 0.01$ respectively). In this study, the magnitude of the improvement diminished, but was still statistically significant, after 4 weeks of follow up ($P < 0.01$ and $P = 0.03$ for

abdominal pain and bloating respectively). Adverse event rates were similar with the active probiotic preparation to those in the placebo group.

Urgesi et al. [23*] utilised a single strain probiotic containing Bacillus coagulans in combination with simethicone in the treatment of bloating, discomfort, and pain in 52 Italian patients fulfilling Rome II criteria for IBS over 12 weeks of treatment. Overall, the effects of the probiotic/simethicone combination were reported as beneficial for boating ($P < 0.01$) and discomfort ($P < 0.01$), but not for pain, after 12 weeks when compared with placebo. However, there was no treatment arm containing only simethicone and, given that simethicone may have therapeutic effects in IBS, the benefit observed in this trial may not be attributable solely to the probiotic.

The effect of probiotics on visceral hypersensitivity was examined by Ludidi et al. [24*] in an RCT of a combination probiotic versus placebo, taken over a 6-week period. In this study, barostat measurements, and IBS symptom scores were assessed before and after treatment, with no beneficial effect of probiotics demonstrated for any of the study outcomes.

Probiotics, psychological wellbeing and quality of life in IBS

Activation of the brain-gut axis has been implicated in the development of IBS. [8*] This introduces the possibility of psychological co-morbidity, including anxiety and depression, arising either as a consequence of, or as a contributor toward, the development of symptoms. The potential for a bi-directional relationship between IBS and psychological disease has been suggested [14*,25] and, given that the microbiome is implicated in the activation of the brain-gut axis, [8*,14*] the use of probiotics may improve co-existent anxiety and depression and improve quality life, in addition to any effect on physical symptoms.

Shavakhi et al.[26*] studied the effects of a multi-strain probiotic containing Lactobacillus, Bifidobacterium and Streptococcus on abdominal pain, bloating, stool frequency, and quality of life scores in 132 IBS patients randomised to active product or placebo. After 14 days of treatment there

was no effect on IBS symptom parameters or quality of life scores, findings which were corroborated by Stevenson et al. [27*], who suggested that an 8 week course of the probiotic Lactobacillus plantarum 299 did not improve abdominal pain severity scores or IBS related quality of life scores when compared to placebo, and Sisson et al. [28*] who reported a beneficial effect of a combination probiotic containing Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus acidophilus and Enterococcus faecium in terms of IBS symptom severity, but not quality of life.

In contrast to these findings, Lorenzo- Zúñiga et al. [29*] suggested the use of a combined probiotic containing two Lactobacillus plantarum (CECT7484 and CECT7485) and one Pediococcus acidilactici (CECT7483), had beneficial effects on IBS-related quality of life, visceral hypersensitivity, and associated anxiety scores in 84 patients fulfilling Rome III criteria, who were randomised to high dose probiotic, low dose probiotic or a placebo over a 6-week treatment period. Interestingly, although the higher dose group received a five-fold higher concentration of probiotic, no additional benefit in outcomes was observed. When data from the high and low dose probiotic groups were pooled, the NNT to achieve a good response in IBS-related quality of life was 2.6.

Symbiotics in IBS

Symbiotics are combined probiotic and prebiotic preparations, with the latter being indigestible material that either activates or potentiates the action of probiotic bacteria. Examples of prebiotics include inulin and fructo-oligosaccharides. Given the potential synergistic effects of the two components, symbiotics may provide further benefit over probiotics in GI diseases including IBS.

Four RCTs have assessed the effects of symbiotics in IBS. [17*,30,31,32*] Min et al. [30] assessed the effects of a symbiotic preparation of Bifidobacterium lactis and acacia fibre on IBS symptoms in 130 patients randomised to either active treatment or a placebo yoghurt drink. Overall, there was a benefit in IBS symptoms and bowel habit satisfaction when the treatment and control groups were compared ($P < 0.001$ for both), and when IBS patients were sub-divided into those with diarrhoea-predominant or constipation-predominant symptoms ($P < 0.001$ and $P = 0.006$

respectively). Tsuchiya et al. [31] used a combination of Lactobacillus acidophilus, L. helveticus and Bifidobacterium species in a vitamin and phyloextract-enriched medium for 12 weeks, and compared its effect on IBS symptoms versus a heat-inactivated symbiotic. 80% of IBS patients reported the preparation as effective when compared with baseline, and control IBS severity scores after 6 weeks ($P < 0.01$). A further RCT by Rogha et al. [32*] compared the effect of a symbiotic preparation containing Bacillus coagulans and fructo-oligosaccharides with placebo in a 12-week follow-up study designed to assess the effect of the preparation on abdominal pain and stool frequency. The results demonstrated an improvement in abdominal pain scores in the treatment versus the placebo group, but the placebo response rate was high. In addition, dropout rates were 41% in treatment group, mainly due to adverse events.

In contrast to the positive findings noted above, the relationship between systemic and mucosal inflammation in IBS, symptom severity, and quality of life was investigated by Abbas et al. [17*] in 72 individuals with diarrhoea-predominant IBS randomised to 6 weeks of treatment with a probiotic preparation containing Saccharomyces boulardii or placebo in combination with ispaghula husk. In this study, intestinal and peripheral blood pro-and anti-inflammatory cytokine levels before and after treatment were compared, along with IBS related quality of life, and overall symptom severity. The authors demonstrated a significant reduction in pro-inflammatory cytokines interleukin (IL)-8 and tumour necrosis factor-α, and an increase in the anti-inflammatory cytokine IL-10, but no difference in overall symptom severity scores or quality of life.

CONCLUSIONS

Probiotics have beneficial effects in IBS, with improvements in global IBS symptom scores, abdominal pain, flatulence, and bloating. However, despite their apparent benefits, which particular strain or species is beneficial remains unclear, and evidence for a sustained response to these preparations is lacking. To date, evidence to support the use of symbiotics in IBS is sparse. No RCT has made a direct comparison between symbiotics and probiotics in IBS. Without head-to-head comparative trials, the use of symbiotics in preference to probiotics for the treatment of IBS cannot be recommended at the present time.

Word count: 1,898

Key points:

- Intestinal dysbiosis may contribute to the development of IBS via complex interactions with the enteric nervous system, leading to increased intestinal permeability, visceral hypersensitivity and activation of the brain-gut axis.
- Modification of the microbiome is an attractive therapeutic target for clinical trials in IBS.
- Probiotics improve global IBS symptoms, as well as abdominal pain, bloating, and flatulence.
- Evidence for the use of symbiotics is limited.

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CONFLICT OF INTEREST

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