The role of probiotics in irritable bowel syndrome

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Irritable bowel syndrome (IBS) is a complex gastrointestinal disorder. There is increasing evidence linking changes in the gastrointestinal microbiota and IBS. Probiotics are living organisms and studies have shown that probiotic treatment may have positive effects in the gastrointestinal tract of IBS patients. The mechanism of action of probiotics in IBS is complex. The aim of this review is to summarise the mechanisms of probiotics in the treatment of IBS.

Keywords: irritable bowel syndrome, complex gastrointestinal disorder, gastrointestinal microbiota, probiotics

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that is predominantly characterised by abdominal pain or discomfort associated with changes in bowel habit such as diarrhoea and constipation.[1,2] IBS is a non-fatal disease but the symptoms experienced negatively impact the quality of life of affected patients, which may ultimately result in societal economic burdens.[1] IBS has a worldwide prevalence of approximately 12 to 20% of the population and is almost 2–3 times more common in women than in men. It is, however, one of the most difficult GI disorders to manage. Despite pharmacologic approaches, the use of probiotics has become an attractive alternative to conventional medicines for the treatment of IBS considering their favourable safety profile and relatively low costs.[3,4]

Pathophysiology of IBS

Despite several studies, the pathophysiology of IBS is not clearly understood. The condition is suggested to be multifactorial with central and peripheral mechanisms linked to inherited, psychosocial and environmental factors.[1,5,6] The gut microbiota has emerged as a significant factor contributing to the pathophysiology of IBS.[4] Refer to Table I for a summary of possible central and peripheral factors.

Symptoms of IBS[5]

- Abdominal pain or discomfort
- Change in bowel habits (diarrhoea/constipation/or combination)
- Abdominal bloating
- Flatulence
- Extra-gastrointestinal symptoms such as headache, dizziness, sleep disorders, back pain, neck pain, fibromyalgia, dysmenorrhea, etc.

Table I: Possible central and peripheral factors affecting IBS[1,5,6]

Central mechanisms	Peripheral mechanisms
• Altered brain-gut axis associated with a dysfunction of the GI autonomic nervous system • Genetic – mutation of SCN5A • Altered serotonin metabolism • Dietary influence – gluten and fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)	• Altered gastrointestinal motility • Disturbances in the epithelial barrier integrity resulting in abnormal change in intestinal permeability • Local immune response disorder • Low grade inflammation • Post-infectious changes • Disordered bile salt metabolism • Chronic infections • Alterations of gut microbiota

Diagnosis and classification

Since there are no objective tests to diagnose IBS, diagnosis is based on clinical symptoms as per the Rome IV criteria.[3,6]

IBS is classified into subtypes based on the bowel habit patterns:[3,6]

- C-IBS – IBS with predominant constipation
- D-IBS – IBS with predominant diarrhoea
- M-IBS – IBS with mixed constipation and diarrhoea
- U-IBS – unclassified IBS (These patients meet the diagnostic criteria for IBS, but bowel habits cannot be accurately classified into the above subtypes.)

Treatment options

The most common treatment options aim at treating the predominant symptoms experienced by the patient. A

recommended dietary strategy is a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs). However, diet modification or pharmacological treatment do not completely eliminate the symptoms necessitating the need for alternative approaches to improve symptoms of the patients.[5]

Clinical observation of symptoms developing after an infection has advocated that changes in the gut microbiome is a likely contributor to IBS. The bacterial overgrowth in the small intestine often causes symptoms similar to those of IBS. Studies have also compared the gut microbiota of healthy controls to IBS patients and have suggested an altered microbiota profile in IBS. It has been found that the composition and activities of *Lactobacillus* and *Bifidobacterium* are severely compromised in IBS patients. Therefore, one of the approaches to treating IBS is the use of probiotics to correct the dysbiosis and stabilise the microbiota of the host.[6]

What are probiotics?

The term 'probiotics' has Greek origins and means 'for life'. The World Health Organization/Food and Agriculture Organization (WHO/FAO) defines probiotics as living microorganisms that, when administered in adequate amounts, contribute a health benefit to the host.[6,7]

The following conditions need to be fulfilled for a probiotic to be effective:[3]

- It must have demonstrated beneficial effect on the host
- It must not be pathogenic or toxic
- It must remain sustainable during use and storage
- It must have an adequately sizeable number of viable microorganisms per unit
- It must be able to maintain itself in the intestine, reproducing and surviving and having intraluminal activity

Probiotic classification

Probiotics are classified according to genus, species and strain. The therapeutic benefits of probiotics depend on all three and cannot be extended to other similar probiotics even if they may be of the same genus or species.[3,6]

The most widely studied probiotics species in the context of IBS are *Lactobacillus* and *Bifidobacterium* because of their numerical superiority and the number of aerobes vs anaerobes.[3,6]

Lactic acid bacteria (LAB) are often present in the human gut via ingestion of fermented milk products such as cheese, yoghurt and fermented cured meat by-products. The LABs have antimicrobial action and work to:[6]

- create an unsuitable environment for the growth of undesirable microorganisms
- compete for binding sites and nutrients to the intestinal epithelium
- produce products of toxic microbes for foreign microbes
- prevent pathogens from settling and feeding in the body

Probiotic effects in IBS

The efficacy of probiotics in IBS has been evaluated in several publications.[4]

The mechanism of action of probiotics in the human body is only partly understood.[6,7]

Probiotics have been found to have a beneficial effect on the gastrointestinal tract, such as:[3]

- decreasing bacterial overgrowth in the small intestine
- increasing the mass of beneficial bacteria in the gastrointestinal tract
- reversing the imbalance between the pro and anti-inflammatory cytokines
- normalise the motility of the digestive tract and visceral hypersensitivity
- reinforce the intestinal mucosal barrier
- some strains may modulate intestinal pain attacks by inducing the expression of the μ-opioid and cannabinoid receptors in the intestinal epithelial cells

Pathogen binding inhibition

Probiotics decrease the adherence of pathogenic bacteria on the epithelial cells and thereby reducing pathogenic bacterial translocations. Probiotics can regulate intraluminal fermentation and control growth of pathogenic bacteria by stimulating the secretion of defensins and bacteriocins and influence the adaptive immune system.[3]

Enhanced barrier function

Several factors, such as a mucous layer, secretory IgA, water and chloride secretion and the epithelial junctional adhesion complex, maintain the intestinal barrier function. Evidence suggests that disturbance of the intestinal barrier may contribute to the loss of immune tolerance of microbiota in the gut resulting in decreased immune response and development of IBS symptoms. There have been several experimental studies about the role of probiotics to maintain this barrier function. However, although probiotics have been shown to enhance the barrier function, the exact mechanism by which this occurs is still not known.[1,3]

Anti-inflammatory effects

Probiotics have demonstrated anti-inflammatory effects in some studies. Human studies and animal models have evaluated anti-inflammatory effects with specific probiotics. In an experimental rodent, *Lactobacillus reuteri* demonstrated a potential anti-inflammatory effect by inhibition of TNF-α-induced production of IL-8. Another

experimental rodent study also showed that *Lactobacillus casei* can also significantly decrease TNF-α-release in ileal tissues. The anti-inflammatory effects of probiotics were also demonstrated in activity against cytokines and interferons in various other studies. In order to outline the precise role of probiotics in IBS, there needs to be additional trials to investigate the immunologic reaction of probiotics in humans and the correlation between IBS symptoms and immune cell activities.[1,3]

Colonic motility and transit

Colonic transit is significantly reduced with probiotics in IBS patients with predominant bloating. This effect on transit did not result in a worsening of bowel function.[1,3]

Effect on intestinal luminal environment

Supplements with probiotics could alter the intestinal luminal environment in IBS patients by:[1,3]

- preserving intestinal homoeostasis
- restoring the dysbiosis by the maintenance of luminal acidity
- inhibition of bacterial adherence
- producing anti-bacterial substances such as bacteriocin and defensin
- decrease in intracolonic gas from bacterial origin by increase in *Bifidobacteria* and *Lactobacilli* resulting in a decrease of *Clostridia* and *Veillonella*
- modification of the colonic metabolism of nutrient substrates to alter colonic transit and fluid fluxes
- decreased malabsorption of bile acids in diarrhoea predominant IBS. *Bifidobacteria* and *Lactobacilli* are capable of deconjugation and absorbing bile acids decreasing colonic secretion and mucosal permeability changes.

Changes in visceral hypersensitivity

A change in visceral perception and gut dysmotility are key contributors to symptoms of IBS. Visceral hypersensitivity is responsible for inducing abdominal pain in IBS patients, who generally show a lower threshold for discomfort compared with healthy controls. Studies have shown that *L. paracasei* inhibits visceral hypersensitivity association with inflammation in healthy mice in whom antibiotics have disturbed the bacterial microbiota. This study demonstrated a clear anti-inflammatory effect and also inhibition of SP staining (a marker of afferent pain pathways) which was increased after antibiotic treatment. In other experimental studies, *L. acidophilus* was shown to blunt visceral pain responses by increasing expression enterocyte opioid and cannabinoid receptors and by inhibiting sodium channels.[1,3,6]

Mono-strain probiotic vs multi-strain probiotic

A systematic review of recent randomised controlled trials by Dale et al., evaluating the effect of probiotic supplementation on symptoms in IBS patients, suggests a trend that multi-strain probiotic treatment had a tendency of a more beneficial effect in alleviating IBS symptoms compared to mono-strain probiotics or placebo.[2,5] A meta-analysis, by Ford et al., of randomised controlled trials published between 1946 and 2013, evaluated probiotics as a treatment option for IBS. The review concluded that probiotics had a beneficial effect on IBS symptoms and highlighted that the effect was more pronounced when using multi-strain probiotics. Another review and meta-analysis by Ford et al. was also cited which evaluated the efficacy of probiotics, prebiotics and antibiotics on IBS and was found to support their previous publication. They concluded that specific combinations of probiotics or specific species and strains, appeared to have beneficial effects on general IBS symptoms and abdominal pain.[2,5]

Conclusion

There is reasonable evidence that probiotics play a beneficial role in IBS patients, improving the overall symptom response and quality of life compared to placebo. Given their impressive safety profile, probiotics are certainly worth considering. Probiotic treatment seems appropriate in the context of dysbiosis as the pathogenesis of IBS, as it restores the intestinal microbiota. Clinical studies and systemic meta-analyses have also shown that some strains of probiotics have valuable outcomes in certain patients. Supplementation with multi-strain probiotics has also shown to be more beneficial than mono-strain probiotics. In order for probiotics to be an accepted treatment option, there needs to be clarity on which species are effective, on which subset of patients probiotics are effective, whether single or mixed species are indicated and dosage and duration of treatment. Collectively though, probiotics may have a favourable therapeutic role in IBS patients.

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