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MINIREVIEWS

Probiotics and irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is common gastrointestinal problems. It is characterized by abdominal pain or discomfort, and is associated with changes in stool frequency and/or consistency. The etiopathogenesis of IBS may be multifactorial, as is the pathophysiology, which is attributed to alterations in gastrointestinal motility, visceral hypersensitivity, intestinal microbiota, gut epithelium and immune function, dysfunction of the brain-gut axis or certain psychosocial factors. Current therapeutic strategies are often unsatisfactory. There is now increasing evidence linking alterations in the gastrointestinal microbiota and IBS. Probiotics are living organisms which, when ingested in certain numbers, exert health benefits beyond inherent basic nutrition. Probiotics have numerous positive effects in the gastrointestinal tract. Recently, many studies have suggested that probiotics are effective in the treatment of IBS. The mechanisms of probiotics in IBS are very complex. The purpose of this review is to summarize the evidence and mechanisms for the use of probiotics in the treatment of IBS.

Key words: Probiotics; Irritable bowel syndrome; Visceral hypersensitivity; Brain-gut axis; Immune function

Core tip: Irritable bowel syndrome (IBS) is a common gastrointestinal problem and its etiopathogenesis is not fully understood. So the treatments of IBS are based on the predominant symptom. But these treatments are often unsatisfactory. Probiotics have numerous positive effects in the gastrointestinal tract. Many studies have shown that probiotics are effective in the treatment of IBS. In this review, we have summarized the efficacy, the safety and the mechanisms of probiotics in IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most frequent gastrointestinal problems. IBS has a prevalence of 12%-20% of the population worldwide and 18%-23% in China, and it is 2-3 times more common in women than men[1]. About 20%-38% of IBS patients will consult their doctor, accounting for 12% of visits to general practitioners, 28% of visits to specialists, and a significant percentage of visits to outpatient departments of tertiary level hospitals[2].

IBS is characterized by abdominal pain or discomfort, which is relieved by defecation or the passage of gas,

and is associated with changes in stool frequency and/or consistency, without physical, radiological or endoscopic abnormalities or laboratory findings indicating organic disease[3]. Abdominal bloating or distension affects 15%-30% of the general population, but is increased to 75%-90% in female IBS patients and constipation-predominant IBS[4]. In all, 28% of IBS patients suffer from abdominal bloating all the time, which is slightly less than abdominal pain (33%)[5,6]. Many IBS patients state that abdominal discomfort is greater than abdominal pain. It is worse in the afternoon and evening, but better at night; it becomes worse when standing and is relieved when in a supine position. There is no correlation with defecation or retaining flatus, although it is worsened by eating and menstruation. Other gastrointestinal symptoms are also common: incomplete defecation, burning pain on defecation, urgency to defecate, rectal tenesmus, esophageal balloon, heartburn, chest pain, early satiety, abdominal bloating or distension, flatulence; and extragastrointestinal symptoms: asthenia, adynamia, headache, dizziness, sleep disorders, pollakiuria, neck pain, back pain, dysmenorrhea, dyspareunia, fibromyalgia. IBS patients have more psychosocial or mental complaints, and they are absent from work due to acute common diseases. This comorbidity has a significant influence on the patient's clinical and diagnostic management, and therapeutic plan. Although the symptoms of IBS are used to establish the suspected diagnosis, individually they are not sufficiently sensitive or specific. Predictive value increases when patients are aged < 50 years and an absence of warning symptoms or signs are considered, which is not the case with another common functional digestive disorder, functional dyspepsia.

Diagnosis is fundamentally through clinical symptoms, and is based on the Rome Ⅲ criteria of 2006, with the isolated exclusion of metabolic or organic diseases (benign or malignant) according to the patient's personal or family history. If there is abdominal bloating or distension, it is advisable to rule out lactose, fructose or trehalose intolerance, an excessive intake of insoluble fiber, and small intestinal bacterial overgrowth. According to Rome Ⅲ there are several types of IBS: (1) diarrhea-predominant IBS; (2) constipation-predominant IBS; (3) alternating IBS (sometimes diarrhea, sometimes constipation); and (4) undefined IBS. In any of these types there may be psychological, psychosocial or psychiatric alterations, or an exaggerated intestinal response to everyday stress. It seriously affects the quality of life of those who suffer from it, and accounts for the use of large amounts of healthcare resources.

IBS patients are known to self-medicate very often. A review of the use of OTC drugs and medicines shows that they take antacids, proton pump inhibitors, fiber and laxatives, antidiarrhea agents, antispasmodics, antidepressants, sedative-hypnotics, and analgesics more frequently[7]. Treatment of IBS has been based on the predominant symptom. It must be individualized, emphasizing the absence of a serious or worrying condition, and straightforwardly explaining the nature and cause of the symptoms. But the therapies available at present (spasmolytics or antidepressants at low doses for the pain, anti-diarrhea agents or 5HT3 antagonists for diarrhea, lubiprostone, linaclotide, bulk-forming laxatives or 5HT4 agonists for constipation) have only proven slightly more effective in comparison with placebo, and none have been capable of altering its natural course, as the effect disappears as soon as treatment is stopped[8-11]. At the same time IBS patients often resort to alternatives such as medicinal herbs, homeopathy, acupuncture, antibiotics, hypnosis or psychotherapy, but randomized controlled studies with these types of therapy are compromised by their low methodological quality, and in general these treatments are not recommended[12,13].

Now there is a tendency to return to an etiopathogenesis-based or pathophysiology-based therapeutic approach, attempting to influence the possible existence of intestinal dysbacteriosis, altered intestinal fermentation and intestinal microbiota, excess production or alteration in the management of intestinal gas, but also subclinical mucosal inflammation, especially in patients in whom the onset of IBS followed an episode of acute bacterial gastroenteritis, antibiotics or immunosuppressants, because these can affect the normal balance of intestinal microflora[14,15]. Thus, one therapeutic approach in IBS patients could be to modulate intestinal microflora to correct an imbalance such as probiotics.

MECHANISMS OF IBS

The etiopathogenesis, which is not fully understood, may be multifactorial, as is the pathophysiology, which is attributed to alterations in gastrointestinal motility, visceral hypersensitivity, intestinal microbiota, gut epithelium and immune function, dysfunction of the brain-gut axis or certain psychosocial factors. Some studies have demonstrated that there may be some autonomic dysfunction with an increased or sustained response to normal psychophysical stress in IBS patients; and further studies have found that salivary chromogranin, a derivative of catecholamines that is released in response to acute stress, is high in IBS patients and may be reduced using muscle relaxation techniques[16]. At the same time the management of intestinal gas is different in IBS patients and control subjects; whilst the latter expel the gas infused into the jejunum rapidly, the former retain it, causing them symptoms, regardless of whether or not intestinal gas production is increased[17]. Although genetic factors play a minor role compared to learned behavior, they do influence symptomatic expression and especially therapeutic response[18,19]. The specific mechanisms have been reported as follows.

Visceral hypersensitivity

There is visceral hypersensitivity in IBS patients, expressed by: (1) increased ileocolonic response to bile acid perfusion; (2) reduced rectal adaptation to distension; and

(3) reduced pain threshold to rectal distension. Hypervigilance to digestive events would contribute to visceral hypersensitivity, perhaps due to inadequate processing of afferent information in certain areas of the central nervous system, such as the anterior cingulate cortex, the amygdala, and the dorsomedial frontal cortex, as shown by dynamic magnetic resonance imaging studies, which indicate an increase in the vascularization of these areas in response to colon stimulation that does not occur in controls[20,21]. IBS patients are more prone to take surgical interventions such as appendicectomy, cholecystectomy and hysterectomy to relieve symptoms; this is because these symptoms can be mistaken for other diseases. Now It was pointed out that patients who have undergone cholecystectomy with follow-up as a cohort for 10-15 years have twice as high a risk of suffering from IBS[22]. It is assumed that the continued presence of bile salts in the colon may give rise to symptoms of IBS, as these patients are known to have a hyper response to these substances.

Immune activation

Despite being considered a non-organic disease, it has certain organic components problems, especially in post-infectious IBS (PI-IBS)[23]. Although PI-IBS explains only 23%-35% of IBS cases, it shows the relationship between exposure to the infectious agent → mucosal and systemic inflammation → clinical expression of IBS. Increased levels of peripheral cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, intraepithelial lymphocytes and CD3 and CD25 cells in the lamina propria, were found in IBS patients[24,25]. At the same time, a nonspecific microscopic inflammation with increased mast cells and neutrophils were found in mucosal biopsies. There is speculation that IBS symptoms may result from cytokine or mediator secretion by these inflammatory cells. Increased production of proinflammatory and decreased production of anti-inflammatory cytokines was in fact demonstrated[26]. In addition, a low-grade inflammatory infiltration and activation of mast cells in proximity to nerves in the colonic mucosa were found and may be involved in the pathogenesis of pain episodes. These results suggested that immune activation plays an important role in IBS patients.

Intestinal hormone secretion

Although little is known about intestinal hormone secretion in IBS patients, high levels of cholecystokinin and vasoactive intestinal polypeptide were found in the plasma and rectosigmoid mucosa, whilst substance P (SP) and somatostatin were normal[27]. However, neuropeptide Y levels in the plasma and rectosigmoid mucosa are lower in diarrhea-predominant IBS, but not in constipation-predominant IBS.

Intestinal microflora

Host intestinal microflora interactions lead to immune tolerance, sustain the function and integrity of the epithelial barrier and its vascularization, promote the development and maintenance of gut-associated lymphoid tissue (GALT), and are essential for the development of jejuno-colonic motility under physiological conditions. Some studies have found that a dysregulated interaction between the intestinal bacteria, the gut barrier, the intestinal immune system and GALT play a fundamental role in IBS. Patients have a different composition of intestinal bacteria such as *Bacteriodes* spp., *Bifidobacterium* spp., *Lactobacilli* spp. and others compared to healthy controls. When ribosomal RNA-based microbiological technologies were used with cloning and sequencing of genes, these differences were even more significant. These new views in the pathogenesis of IBS changed the treatment approach to influence the composition of the gut microbiota and to stop the inflammatory process and to interfere in the dysregulated intestinal immune system. Among several treatment options, the use of probiotics seemed to be promising.

PROBIOTICS

Since Elie Metchnikoff first published "The prolongation of life: optimistic studies" in 1907, the concept of probiotics is 100-year-old now. In 1998 Guarner *et al* defined probiotics as living microorganisms that have benefits for the gastrointestinal tract and its immune function after being ingested. In 2003 the concept of "immune function of probiotics" was introduced, including the fact that probiotics modulate the immune response throughout the mucosa associated lymphoid tissue system; this idea maintains the concept that intestinal mucosa and intestinal microflora constitute an anatomical-functional unit that regulates both the cell-mediated and humoral immune responses and the local production of cytokines. In 2008, a review defined probiotics as living microorganisms, which when ingested in certain numbers, exerted health benefits beyond inherent basic nutrition.

Now probiotics are becoming an increasingly important part in the diet of everyday life, as their general and gastrointestinal beneficial effects are being gradually proven. It has become necessary to harmonize marketing criteria, evaluate the efficacy of probiotics, and correctly define what is a probiotic, what the effective doses are, and whether they are completely safe. Probiotics are defined at three levels: genus, species and strain; it is essential to understand that their properties depend on all three and cannot be assigned to other similar ones, even if they share the same genus and species. The therapeutic benefits of a strain of probiotics cannot be extended to other strains, and their efficacy has to have been proven individually. Therefore, we shall now examine evidence available to date. Usually probiotics are certain types of Streptococcus, Lactobacilli, and Bifidobacteria, but also other non-pathogenic bacilli such as *E. coli*-Nisle1917 and yeasts such as *Saccharomyces boulardii*. The best known and most widely used probiotics are *Lactobacillus plantarum* 299v, *Lactobacillus rhamnosus* LGG, *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium*

infantis, *lactis* or *brevis*. Probiotics can be administered not only as functional foods, but also in pharmaceutical forms similar to medicines. For a probiotic to be effective, five conditions must be fulfilled: (1) it must not be toxic or pathogenic; (2) it must have a proven beneficial effect on the host; (3) it must contain a sufficiently large number of viable microorganisms per unit; (4) it must be capable of surviving in the intestine, reproducing, maintaining itself, and having intraluminal metabolic activity; and (5) it must remain viable during storage and use.

EFFICACY AND SAFETY OF PROBIOTICS IN IBS

The evidence about probiotics in the treatment of IBS is type Ⅱ (grade B). It is because not all probiotics have been shown to be equally effective, and there are still relatively few studies, some of which are not randomized controlled trials (RCTs), some with a single probiotic, others with multiple species, and even some combined with prebiotics. The Clinical Practice Guideline about IBS in the Treatment section concluded that probiotics could improve the global symptoms of IBS patients based on some RCTs. In recent years there have been numerous publications, which have confirmed the effect[28-32]. Many good clinical studies using mainly lactobacilli and bifidobacteria alone or in combination have been published[33-37]. In general, it appears that probiotics are effective in IBS patients. However, looking at single trials, it seems that probiotics are more effective on single symptoms than on the entire IBS. It is difficult to compare because of variations in the study design, probiotics strains used, doses administrated and formulation. There is still a need for further studies to determine the most effective species and strain, the right doses and to clarify whether a combination is better than a single strain.

The safe use of probiotics is an absolutely crucial matter. Conventional toxicology and safety evaluation has limitations for the safety assessment of probiotics. Vigorous debate continues on what constitutes appropriate safety testing for novel probiotic strains proposed for human use. In recent years several organizations have formulated approaches to assess the safety of probiotics. The Joint FAO/WHO working group on drafting guidelines for the Evaluation of Probiotics in Food proposed a framework consisting of strain identification and functional characterization, followed by safety assessment and Phase 1, 2 and 3 human trials. These studies have shown that the use of probiotics in IBS patients and healthy subjects involves a very low risk of bacterial complications, although over 80 cases of bacteremia have been reported in Finland, associated with severe prior comorbidities or surgery, and always with *Lactobacillus*[38]. Lactobacilli, Bifidobacteria and other commensal microorganisms are generally regarded as safe, although certain doubts have been raised regarding their use at massive doses in immunodepressed patients or in those who undergo intestinal resection due to benign or malignant disease[39]. Other microorganisms such as *Enterococcus* may be opportunistic pathogens depending on host conditions.

In conclusion, the concept of using probiotics in IBS patients is interesting and it appears that certain probiotics strains are efficacious on several symptoms and very safe.

MECHANISMS OF PROBIOTICS IN IBS

It is well known that probiotic strains have numerous positive effects in the gastrointestinal tract. The beneficial effects of probiotics in IBS could be explained by increasing the mass of beneficial bacteria in the digestive tract, decreasing bacterial overgrowth in the small bowel and reversing the imbalance between the pro- and anti-inflammatory cytokines. Probiotics can also reinforce the intestinal mucosal barrier and normalize the motility of the digestive tract and its visceral sensitivity. Recently it was also demonstrated that some lactobacilli strains may modulate intestinal pain attacks by inducing the expression of μ-opioid and cannabinoid receptors in the intestinal epithelial cells. In conclusion, probiotics have various actions: (1) physical barrier effect; (2) competition for nutrients; (3) metabolic interactions; (4) bacteriocin production; (5) reinforcement of the intestinal mucosal barrier; (6) reduction of intestinal permeability and bacterial translocation; and (7) regulation of the intestinal inflammatory response by modulating the secretion of cytokines and the immune response. The specific mechanisms of probiotics have been reported as follows.

Inhibition of pathogen binding

Bacteria in the gut compete for nutrients and space. Probiotics have been demonstrated to adhere to a range of human intestinal cell lines and commonly found in mucosal biopsies of healthy individuals[40]. Probiotics reduce the adherence of pathogenic bacteria on the epithelial cells and thus the ability of pathogenic bacterial translocations. Probiotics can control the growth of pathogenic bacteria and regulate intraluminal fermentation by stimulating the secretion of bacteriocins and defensins, modulate signal transduction (*e.g.*, NF-κB) and influence the innate/adaptive immune system (*e.g.*, IgA secretion).

Enhanced barrier function

Probiotics have been demonstrated to enhance barrier function. The probiotic VSL#3 can protect cultured T84 monolayers from invasion by *Salmonella* by enhancing barrier function[41,42]. Our studies have also found that VSL#3 protected the epithelial barrier and increased the tight junction protein expression in vivo and in vitro by activating the p38 and extracellular regulated protein kinases (ERK) signaling pathways[43].

Immune function

Some studies have demonstrated that probiotics have an anti-inflammatory effect. In a study from Cork, assessing individual bacterial species, improvement in symptoms

with Bifidobacteria was associated with changes in the relative production of anti-inflammatory (IL-10) to pro-inflammatory (IL-12) cytokines[44]. Animal model and human studies have evaluated immunologic modulation with specific probiotics. The potential anti-inflammatory effect of *Lactobacillus reuteri* in an experimental rodent study demonstrated an inhibition of TNF-α-induced production of IL-8[45]. *Lactobacillus casei* can also significantly decreased TNF-α release in ileal tissues from an experimental rodent study[46]. Other studies also evaluated the anti-inflammatory effects of probiotics and demonstrated activity against cytokines, including interferons.

The main action on the immune function of probiotics is carried out by dendritic cells (DCs), antigen presenting cells for T lymphocytes that are found in mucosas, lymphoid tissues, lymph, lymph nodes, spleen and peripheral blood. DC phenotype and cytokine production is modulated by the intestinal microflora; furthermore, these cells are involved in the local immune response to B lymphocyte activation and IgA synthesis by plasmacytes.

Colonic transit and motility

Effects of probiotics on colonic transit have been reported in IBS patients with predominant bloating. In IBS patients with predominant bloating, the colonic transit was significantly retarded with probiotic VSL#3 relative to placebo. The effect on transit was not associated with the worsening of bowel function. Bazzocchi *et al* showed that the colon's reflex motor responses to balloon distension were reduced during an open-label study with VSL#3. Further studies are indicated to explore the mechanism of the retarded transit of stools and potential effects on colonic sensation and fermentation of nutrients reaching the colon.

Effect on intraluminal milieu

Effects of probiotics on intraluminal milieu have been reported as follows: (1) reduction of intracolonic gas of bacterial origin due to an increase in Lactobacilli and Bifidobacteria, and a consequent decrease in the proportion of Clostridia and Veillonella; (2) normally metabolize nutrient substrates reaching the colon with the formation of gas and increase in the production of intracolonic short chain fatty acids (SCFA) and a consequent improvement in colonic propulsion. The SCFA may induce propulsive contractions and accelerate transit or enhance fluid and sodium absorption in the colon[47]. Thus, alteration in the resident colonic flora with administration of probiotics may modify the colonic metabolism of nutrient substrates to alter colonic transit and fluid fluxes; and (3) reduced malabsorption of bile acids in diarrhea predominant IBS, because Lactobacilli and Bifidobacteria are capable of deconjugation and absorbing bile acids, thus reducing luminal bile salt load to the colon, which reduces colonic secretion and mucosal permeability changes.

Alterations in visceral hypersensitivity

Some studies have shown that *E. coli* Nissle 1917 inhibits the visceral hypersensitivity associated with trinitrobenzene sulphonic acid (TNBS) colitis and *L. paracasei* inhibits the visceral hypersensitivity associated with inflammation in healthy mice in whom the bacterial microbiota have been disturbed by antibiotics[48]. This latter study showed a clear anti-inflammatory effect and also an inhibition of SP staining, a marker of afferent pain pathways, which was increased after the antibiotic treatment[49]. This effect on neuropeptides is of particular interest given the key role visceral hypersensitivity is believed to play in IBS and the recent demonstration of increased SP and transient receptor potential vanilloid 1 receptor (TRPV1) positive fibres in IBS mucosal biopsies[50]. Probiotics can regulate the action of mastocytes in the vicinity of nerve endings within the intestinal lamina propria. An entirely novel mode of action of probiotics has recently been demonstrated in which *L. acidophilus* increased the expression of l-opioid and cannabinoid receptors in normal animals, a phenomenon which was associated with an inhibition of visceral sensitivity equivalent to that of morphine 0.1 mg/kg[51].

FECAL MICROBIOTA TRANSPLANTATION AND IBS

Fecal microbiota transplantation (FMT), or infusion of a fecal suspension from a healthy individual into the gastrointestinal tract of another person to cure a specific disease, is best known as a treatment for recurrent *Clostridium difficile* infection. The earliest and most frequently quoted report of FMT is that by Eiseman *et al*[52], who successfully treated patients using fecal enemas in the 1950s.

FMT also has been used successfully for IBS. Recent studies have shown that the intestinal microbiota play an important role in immunity and energy metabolism and that an imbalance in our commensal intestinal bacteria can predispose to disease development[53-56]. Re-establishment of the wide diversity of intestinal microbiota *via* infusion of donor feces into the colon is the proposed mechanism by which FMT results in clinical improvement in patients with IBS.

FMT is by no means a new therapeutic modality, however, it did not receive public attention until recently, after several studies were published showing that stool is a biologically active, complex mixture of living organisms with great therapeutic potential for *Clostridium difficile* infection[57-59] and other gastrointestinal diseases[60-63].

Unlike the concept of probiotics, which alter the metabolic or immunological activity of the native gut microbiota, the premise of FMT has always been to introduce a complete, stable community of gut microorganisms, which are aimed at repairing or replacing the disrupted native microbiota. Engraftment of donor micro-biota was accompanied by normalization of the patient's bowel function. In addition, other mechanisms could be involved that might explain how FMT works. The metabolic activities of gut bacterial species can have

consequences both locally, on the gut mucosa, and systemically. Disruption of these bacterial species can result in potentially harmful metabolic alterations, leading to the partitioning of toxic substances across the gastrointestinal mucosa where these substances are absorbed into systemic circulation. Gustafsson *et al*[64] analyzed gut microbiota metabolism pre-FMT and post-FMT in patients with antibiotic-associated diarrhea and found marked disturbances in the majority of microflora-associated characteristics in patients with antibiotic-associated diarrhea. Administration of a human fecal enema corrected these alterations and relieved diarrhea.

CONCLUSION

Probiotics are used regularly in most populations regardless of medical indications. There is reasonable evidence of a modest benefit in IBS patients. Selection of those who will respond requires a better understanding of exactly what the mode of action is in IBS. Like most therapies in IBS probiotics are unlikely to be beneficial for all patients. However, given their impressive safety profile, a trial of probiotics is certainly worth considering. Care must be taken to recommend the exact strain or species that has shown benefit in treating IBS, and not to extrapolate success of one probiotic species to another. In addition, further large good quality trials are needed to predict which patient groups are most likely to respond to probiotics, perhaps through fecal microbial profiling.

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