Review Article

Intestinal microbiota and gastrointestinal diseases: Irritable Bowel Syndrome

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ABSTRACT

Gastrointestinal microbiota, also known as "microflora," is a collection of microorganisms that inhabit the gastrointestinal tract. Under normal circumstances, the microbiota helps maintain intestinal homeostasis. However, some resident bacteria can transition from symbionts to pathobionts, leading to the development and progression of gastrointestinal diseases such as functional dyspepsia, severe diarrhea, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS). IBS is a chronic gastrointestinal disorder characterized by abdominal pain and altered bowel habits, including cramping, gas, and constipation. This mini-review will briefly describe microbiota, IBS, the interrelationship between IBS and microbiota, and the therapeutic use of microbiota in treating IBS..

Keywords: Gut microbiota, Gastrointestinal disorders, Dysbiosis, IBS.

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Microbiota

The collection of microorganisms inhabiting the digestive tract, known as the human gastrointestinal microbiota or "microflora," forms a metabolically active and intricate ecosystem. This community is composed of numerous microorganisms, including bacteria, viruses, and some eukaryotes, and takes root in the digestive tract shortly after birth (1, 2). Through a dynamic symbiotic relationship, the microbiota establishes mutual benefits with the human organism, contributing to the upkeep of essential immunological, metabolic, and motor functions, as well as the proper digestion and absorption of nutrients (1-4).

Approximately 100 trillion microorganisms, spanning diverse species, populate the human gastrointestinal tract (5). This complex and varied community, known as the gastrointestinal microbiota, resides in the gut, engaging in a mutual symbiotic relationship with the host (6). The host provides a nourishing and welcoming environment for the microbes, and in return, the microbiota plays a crucial role in numerous physiological and metabolic processes. These processes include maintaining immune homeostasis, fortifying the intestinal epithelial barrier, fermenting undigested carbohydrates, and offering protection against pathogen colonization (7, 8). The cecum and proximal colon harbor the highest microbiota density, while both the large and small intestines exhibit

similar microbiota biomass. The microbial composition undergoes considerable variations with aging, typically featuring a predominance of strict anaerobes like Bacteroidetes and Firmicutes in a healthy colon, which tends to remain stable over time (5, 8). Overall, the gut microbiota contributes significantly to the host's well-being and the maintenance of a healthy ecosystem (9).

Functioning as a formidable barrier, the microbiota comprises over 10^14 microorganisms covering the entire surface of the digestive tract, especially in the intestine. This microbial population competes with pathogens for nutrients and binding sites, produces inhibitory substances, and prevents the penetration of pathogens into the intestinal mucosa (3, 10, 11). Encoding 3 to 4 million genes, approximately 150 times more than the human genome, the microbial genome allows the microbiota to perform metabolic activities not encoded by the human genome, offering potential benefits to the host (2, 10).

Individual patterns of microbiota distribution and composition in humans are influenced by factors such as host genotype and initial colonization occurring shortly after birth (11). Various elements, including delivery type, breastfeeding, lifestyle, diet, hygiene, environmental conditions, antibiotic usage, and vaccination status, can induce definitive changes in microbiota patterns (11-13). The intestinal microbiota comprises over 1500 species distributed across more than 50 different phyla, with Firmicutes and Bacteroidetes being the most abundant. Other phyla, including Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia, are present in minor proportions (4).

An extensive European study, the "MetaHit project," examined the intestinal microbiota of 700 healthy volunteers, revealing that participants' microbiota composition fell into three major groups or enterotypes, identified by the abundance of bacteria related to Bacteroides (enterotype 1), Prevotella (enterotype 2), and Ruminococcus (enterotype 3). The factors influencing the aggregation of bacterial communities into enterotypes remain unclear, with the belief that species variation in the digestive tract may be constant (10, 15).

The distribution of the intestinal microbiota varies along the digestive tube, with low bacterial density in the stomach and duodenum due to acidic gastric juice and pancreatic enzymes. The bacterial concentration gradually increases in the distal small intestine, reaching its peak in the colon predominantly with anaerobes (1, 2).

Under normal conditions, the microbiota receives nutritional support from the host, reciprocated by providing symbiotic assistance in maintaining intestinal homeostasis. However, some resident bacteria may transition from symbionts to pathobionts, contributing to the development and progression of gastrointestinal diseases. Studies indicate a strong correlation between disturbances in intestinal microbiota and the onset and advancement of gastrointestinal conditions, including functional dyspepsia, severe diarrhea, inflammatory bowel disease (IBD), colorectal cancer (CRC), celiac disease, and irritable bowel syndrome (IBS) (16, 17). Disturbances, referred to as dysbiosis, can be triggered by external factors like diet, appendectomy, and antibiotic use, as well as intrinsic factors such as genetics, stress, and aging (18). In this context, we will delve into the pathogenic role of gut microbiota in irritable bowel syndrome (IBS).

The consistency of gut microbiota largely depends on factors such as diet, ingested drugs, intestinal mucosa, and the microbiota's composition. Microbial dysbiosis occurs when there is an imbalance or alteration in the microorganism ratio due to oxidative stress, bacteriophage induction, and the secretion of bacterial toxins. Dysbiosis has been implicated as a cause of various inflammatory, autoimmune, metabolic, and neurological disorders, including its association with gastrointestinal pathologies such as IBS. Moreover, it is linked to the promotion of colorectal cancer and stands as a hallmark of ulcerative colitis and Crohn's disease (19). Recent advancements in microbiome research, utilizing sophisticated microbiological technologies, have provided insights into dysbiosis and its connection to the pathophysiology of IBS.

Pathophysiology of Irritable Bowel Syndrome (IBS)

IBS is acknowledged as a chronic gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits, including diarrhea, cramping, gas, and constipation (20). Multiple factors contribute to its pathophysiology, encompassing host and environmental factors, intestinal dysmotility, increased intestinal permeability, mucosal immune dysfunction, alterations in brain-gut interaction, enteric infections, visceral hypersensitivity, and psychological disorders (21, 22). Based on symptoms, IBS is categorized into four subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed IBS (IBS-M), and unclassified IBS (9, 23). IBS-M is reported as the most common subtype in the United States, constituting 44% of total cases, with IBS-D and IBS-C diagnosed in approximately 26% and 28% of patients, respectively (23). Globally, IBS prevalence is around 10%-15%, making it one of the most common gastrointestinal disorders. IBS accounts for approximately 12%-14% of primary care visits and 28% of gastrointestinal referrals (21). Typically diagnosed in individuals under 50, IBS exhibits a female-to-male ratio of 2:1 (24). Health-related quality of life is negatively impacted in IBS patients, often accompanied by comorbidities such as anxiety, depression, fibromyalgia, migraine, headache, interstitial cystitis, and temporomandibular joint syndrome (6, 23). Although the precise pathophysiological mechanisms of IBS

remain unclear, factors such as genetics, psychosocial elements, environment, visceral hypersensitivity, low-grade inflammation, changes in gastrointestinal motility, food components, and intestinal microbiota are believed to play roles in the disease process (21, 24, 25).

Given the heterogeneous nature of IBS and the varied disease progression, managing IBS patients poses a challenge to physicians. No specific biomarkers or laboratory tests are available for IBS evaluation, and treatment primarily addresses patients' primary symptoms, involving various pharmacotherapies, lifestyle modifications, and dietary changes (9, 24, 26). The role of gut dysbiosis in IBS is gaining attention, particularly in relation to gut motility dysfunction, intestinal permeability, and visceral pain responses (27, 28).

Trillions of microorganisms inhabit the gastrointestinal tract, and disruptions in these microbiomes can contribute to various gastrointestinal pathologies, including IBS (25). Recent advancements in technologies such as metagenomics and metatranscriptomics have facilitated the study of gut microbiota, revealing alterations in microbiota and changes in the intestinal mucosa (dysbiosis) in some IBS patients (23, 29-31). A one-year population-based prospective study identified a bidirectional relationship between IBS and psychiatric conditions like anxiety and depression, signifying IBS as a disorder of the brain-gut interaction (32, 33).

Key evidence supporting the potential involvement of microbiota in IBS pathophysiology includes alterations in intestinal microbiota, post-infection IBS following acute gastroenteritis, and a higher prevalence of intestinal bacterial overgrowth. Symptoms are often alleviated by restricting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in the diet and may be modulated with antibiotics, probiotics, and prebiotics (34-36). Patients with IBS exhibit variations in microbial composition, with higher numbers of Ruminococcaceae and Clostridium cluster XIVa and lower numbers of Bacteroides compared to healthy individuals (37). The causal relationship between intestinal dysbiosis and IBS remains unclear, but animal-based studies support the idea that gut dysbiosis contributes to disease pathogenesis (38).

IBS patients also display defects in luminal metabolic function associated with dysbiosis, as evidenced by increased methane production correlated with constipation incidence. Methanogenic bacteria, particularly Methanobrevibacter smithii, are more abundant in patients with constipation-predominant IBS, suggesting their role in IBS pathogenesis (39). Factors such as intestinal infections with pathogenic bacteria and antibiotic use during childhood have also been associated with an increased risk of IBS (41, 44, 45). While the effects of physical and psychological stressors and dietary factors on IBS have been extensively studied, the precise mechanisms by which these factors influence the gut microbial profile and contribute to IBS development and progression remain unknown, warranting further research (18).

Microbiota and IBS

Around 10% of reported IBS cases stem from episodes of gastroenteritis, resulting in post-infectious IBS. The severity of IBS symptoms has been inversely associated with microbiome density (25). While study findings vary, most agree that IBS patients exhibit reduced bacterial diversity and increased temporal instability of the microbiota (6). Comparing IBS patients with healthy controls, one study revealed fewer Bacteroidetes and more Firmicutes in IBS patients, along with higher abundances of Verrucomicrobia, Proteobacteria, Actinobacteria, and Ruminococcus (46).

Initial investigations into the intestinal microbiota of IBS patients showed decreased proportions of Bifidobacterium and Lactobacillus, coupled with an increase in Enterobacter (47). Lactobacillus reduction was more pronounced in IBS patients with diarrhea (IBS-D) than in those with constipation (IBS-C) (30). Furthermore, IBS-D patients had fewer Bifidobacteria, while IBS-C patients had more Veillonella than control groups (48). Evidence also indicates higher levels of Enterobacteriaceae and lower levels of Faecalibacterium prausnitzii in IBS-D patients than in healthy controls (49).

In a study using DNA sequencing techniques, IBS patients exhibited decreased proportions of Lactobacillus and Bifidobacteria (50). Another study reported a twofold increase in the Firmicutes/Bacteroidetes ratio in IBS patients, coupled with an association between abdominal pain and low Bifidobacteria levels during a 7-week follow-up (51). Conversely, another report showed lower Bacteroidetes levels in IBS patients, along with lower concentrations of aerobic bacteria in IBS-D patients compared to healthy controls (52).

A meta-analysis found that IBS patients had higher levels of fecal Escherichia coli and Enterobacter and lower levels of fecal Lactobacillus and Bifidobacterium (9). Several pathogenic bacteria and viruses have been implicated in IBS, leading to cell death, increased gut permeability, and immune-related cell activation, influencing vascular permeability, gastrointestinal motility, secretion, and pain signaling (53).

The onset of chronic IBS-compatible symptoms after acute gastroenteritis emphasizes the role of microbiota and low-grade inflammation in IBS etiology (29). Post-infection IBS has been linked to various microorganisms, including Campylobacter jejuni, Yersinia, Salmonella, Shigella, rotavirus, adenovirus, calicivirus, Giardia lamblia, and Blastocystis hominis (31).

The pathogenesis of IBS involves the interaction between gut microbiota and the host, leading to the production of

metabolic substances like bile acids, neurotransmitters, short-chain fatty acids, and other signaling factors. Microorganisms such as Listeria monocytogenes, B. vulgatus, Lactobacillus, Clostridium perfringens, Bifidobacterium, and Bacteroides fragilis contribute to secondary bile acid production, which, when altered, can cause cytotoxicity, leading to apoptosis, necrosis, DNA damage, and functional gastrointestinal disorders (52). Research on IBS-D patients revealed an increase in primary bile acids and a decrease in secondary bile acids in feces, correlated with a reduction in the Ruminococcaceae family (55). Behavioral changes, such as stress, can alter the composition of the intestinal microbiota in experimental animals, making it more susceptible to inflammatory and immunological stimuli in the gastrointestinal tract (29, 30).

Heterogeneous results in studies may be attributed, in part, to diverse methods of microbiota determination and different inclusion criteria for IBS patients (Roma II/III). Meta-analyses demonstrated a higher risk of developing IBS after acute intestinal infections, such as gastroenteritis and traveler's diarrhea (56, 57, 58).

Evidence suggests that alterations in the intestinal microbiota and mucosal microinflammation characterize post-infection IBS. Bacterial overgrowth in the small intestine (BOSI) is frequently associated with post-infection IBS, and there's a significant overlap in symptoms between the two conditions, prompting questions about underlying BOSI in IBS patients. Studies have shown an association between bacterial overgrowth and a reduction in interstitial cells of Cajal, potentially explaining the development of post-infectious IBS (59). The prevalence of overgrowth is significantly higher in IBS patients than in healthy controls (60).

Therapeutic Use of Microbiota-Directed Therapies in IBS

The involvement of bacterial fermentation products is believed to play a role in the etiopathogenesis of IBS (29, 31). Increased fermentation can lead to elevated gas production, triggering typical symptoms such as flatulence, abdominal pain, and distension. Reports indicate that concentrations of short-chain fatty acids (SCFAs) are increased in IBS-D, stimulating serotonin release from the intestinal mucosa, and subsequently increasing intestinal motility and transit (61).

Recent studies have explored the potential of dietary manipulation of the gut microbiota and the use of probiotics, prebiotics, and synbiotics in treating IBS, showing promising results (62). Probiotics are known to modulate immune functions, enhance the intestinal mucosal barrier, and reduce inflammation in IBS patients. They can increase SCFAs, facilitating the colonization of beneficial strains like Lactobacillus, Bifidobacterium, and certain probiotic bacteria that decrease colonic hypersensitivity by elevating μ-opioid and cannabinoid receptor expression (63). A combination of Lactobacillus acidophilus Rosell-52 and Bifidobacterium longum-175 as a prebiotic has been successful in relieving stress-related gastrointestinal symptoms (33). In a double-blinded randomized control trial with 50 IBS-D patients, probiotic supplementation using microorganisms such as Lactobacillus acidophilus, L. plantarum, L. rhamnosus, Bifidobacterium breve, B. lactis, B. longum, and Streptococcus thermophilus resulted in a significant improvement in depressive symptoms, likely modulated by the gut-brain axis (53).

Dietary modifications, such as low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diets, are recommended for IBS treatment. FODMAPs are poorly absorbed in the small intestine, used as a substrate for bacterial fermentation in the colon, and have an osmotic effect, causing water displacement to the intestinal lumen. The effect of a FODMAP-rich diet on IBS symptoms is associated with the composition of the intestinal microbiota, suggesting that its manipulation could be an effective therapeutic approach for IBS treatment. Recent studies have shown that a low FODMAP diet effectively relieves IBS symptoms, especially flatulence and diarrhea, providing an effective approach for patients with functional intestinal symptoms (29, 61). Patients with IBS have reported a significant reduction in pain and bloating with a low FODMAP diet. Several studies in IBS patients on a low FODMAP diet have reported decreases in Actinobacteria, Bifidobacterium, Faecalibacterium, total SCFAs, and n-butyric acid, along with lower levels of serum proinflammatory IL-6 and IL-8 (64).

Probiotics are living microorganisms that, when consumed in adequate amounts, contribute to good health (65). Although many questions regarding the optimal doses, duration of treatment, physiological and immunological effects, and safety in debilitated patients remain unanswered, studies on the role of probiotics in different gastrointestinal disorders show promising trends. Significant improvement in abdominal distension and pain has been reported with the use of probiotics containing Bifidobacterium infantis 35624 (66). Lactobacillus supplementation has been associated with decreased gas-production-related symptoms in patients with IBS (67).

The use of probiotics in IBS has demonstrated efficacy in relieving symptoms, with a systematic review of 19 randomized controlled trials concluding that probiotics are superior to placebo in relieving IBS symptoms (67). The mechanism of action of probiotics appears to extend beyond modulating the intestinal microbiota, potentially inhibiting the colonization and adherence of pathogenic bacteria to enterocytes, increasing the secretion of defensins, and decreasing the synthesis of pro-inflammatory cytokines such as IL-10 and IL-12 (60).

Prebiotics are foods resistant to enzymatic and chemical

digestion that promote the proliferation of a healthy gut microbiota. IBS patients treated with four weeks of prebiotics have shown improvement in symptoms such as bloating, flatulence, and stool consistency. In a study of IBS patients, Bifidobacterium colonization increased after the intake of a prebiotic transgalactooligosaccharide mixture (62, 63).

Fecal microbiota transplantation (FMT) has also been considered for restoring a healthy gut microbiome and treating IBS. A randomized controlled trial in IBS-D and IBS-M showed symptom relief at three months with active FMT treatment, but not at 12 months. However, more extensive clinical trials are needed for a conclusive assessment of FMT efficacy in IBS (32, 62).

Conclusion

Taken together, microbiota alteration occurs in different types of IBS. However, the bacterial alteration in different studies is inconsistent, and the exact underlying mechanism behind the role of dysbiosis in IBS is not clear. Dietary modification and the use of probiotics, prebiotics, and symbiotics in treating IBS through gut microbiota manipulation have indicated promising results.

Conflict of Interest

The authors have nothing to declare.

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