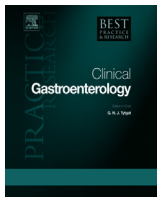
Best Practice & Research Clinical Gastroenterology 30 (2016) 89–97

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology



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Probiotics in functional bowel disorders

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Keywords:
Probiotics
Functional bowel disorders
Irritable bowel syndrome
Intestinal mocrobiota

A B S T R A C T

Functional bowel disorders (FBDs) are the most common gastrointestinal (GI) disorders seen by gastroenterologists and primary care physicians. The disorders affect patients functioning and quality of life (QOL) and are associated with significant healthcare burden. The current theory regarding the development of FBDs suggests brain-gut axis dysfunctions associated abnormal GI motility and sensation. Recent data suggest that alterations in the intestinal microbiota may have a role in the pathogenesis of FBDs; or at least have the potential to affect intestinal functions that are thought to be relevant to the development of functional GI symptoms. This has led to growing interest of healthcare providers and patients in targeting the intestinal microbiota for the treatment of FBDs. In this article we discuss the potential role probiotic interventions in the treatment of FBDs. We review the evidence from pre-clinical and clinical studies and discuss the current recommendations for the use of probiotics for FBDs in clinical practice.

Abbreviations: CIC, chronic idiopathic constipation; FAP, functional abdominal pain; FBD, functional bowel disorders; FODMAP, fermentable oligo-, di-, monosaccharides and polyols; GI, gastrointestinal; HC, healthy controls; IBS, irritable bowel syndrome; IBS-C, IBS-constipation; IBS-D, IBS-diarrhea; IBS-M, mixed IBS; NNT, number needed to treat; RCT, randomized control trials; SIBO, small-intestine bacterial overgrowth.

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http://dx.doi.org/10.1016/j.bpg.2016.01.003
1521-6918/

Functional bowel disorders

Functional bowel disorders (FBDs) are a group of functional gastrointestinal (GI) disorders characterized by symptoms attributed to the middle and lower GI tract not explained by unified structural and/or biochemical abnormalities [1,2]. FBDs include IBS, functional bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder [1]. In the absence of identifiable unified etiopathophysiology the diagnosis of FBDs relies on clinical presentation, use of symptom-based criteria and limited investigations to exclude possible other causes [2]. Important factor in the diagnosis of FBDs is the chronicity of the symptoms which helps separate these conditions from acute, transient, self-limited conditions. Accordingly, the commonly used diagnostic criteria (Rome III criteria) require the presence of the typical symptoms for at least 6 months prior to diagnosis. FBD are highly prevalent in Western countries with irritable bowel syndrome (IBS) being the most prevalent (10%–20%) and best studied condition [3]. Although FBDs have not been found to have significant impact on life expectancy, they account for significant morbidity, utilization of healthcare and socio-economic burden [4,5].

Traditionally, IBS and other FBDs have been considered disorders arising from abnormal function along the brain-gut axis associated with GI hypersensitivity (which may lead to discomfort and pain) and GI motor dysfunction (which may lead to diarrhea, constipation, or alternating bowel movements). However, despite intensive research over the years, no single ethological factor with a defined pathogenic mechanism has been identified thus the pathophysiology of these disorders is still not completely understood. Nevertheless, the research in this area has implicated new theories and suggested additional new underlying pathophysiological mechanisms including genetic predeterminants [6], peripheral GI factors [7] and extra-intestinal neurohormonal and central factors [8].

The role of the intestinal microbiota in functional bowel disorders

The intestinal microbiota, the complex community of microorganisms residing in the GI tract is believed to contain greater than 1,000 different bacterial species that can reach viable numbers of 10^{14} bacteria per gram of luminal content. The highest density of the human intestinal microbiota is in the colon and is dominated by two main bacterial genera *Firmicutes* (64%) and *Bacteroidetes* (23%) followed by *Proteobacteria* (8%) and *Actinobacteria* (3%) [9,10]. The intestinal microbiota plays an important role in maintaining the integrity and normal function of the gastrointestinal (GI) tract. There is growing evidence for bidirectional communications between the intestinal microbiota the peripheral (enteric) and central (brain) nervous systems [11]. The human host can respond to commensal and pathogenic bacteria via multiple mechanisms including epithelial receptor-mediate signaling or direct stimulation of enteric neurons and immune cells. Indeed, studies in animal models have shown that products of microbiota have the potential to affect the excitability of enteric and vagal afferents neurons [12]. Conversely, the enteric mictobiota can be influenced though the brain effects on intestinal motility, secretion and immune function [13].

Several layers of evidence suggest a role for the intestinal microbiota in IBS and possibly in other FBDs. Epidemiological observations have demonstrated the development of IBS symptoms following disruption of the individual 'normal' microbiota. Examples are development of IBS symptoms following acute gastroenteritis (i.e., post-infectious IBS) [14,15] and after the use of antibiotics; although for the latter the association is less established and based only on a few small retrospective cross-sectional studies [16]. An association between IBS and small-intestine bacterial overgrowth (SIBO) has also been suggested but the data on this association is non-conclusive and the relationship is debatable [17–19].

From a microbiological perspective, several studies have demonstrated compositional differences in the intestinal microbiota between IBS patients and healthy controls (HC) [20–22]. The current data indicate that the overall microbial diversity of the intestinal microbiota of patients with IBS is reduced compared with the microbiota of HC [20,23,24]. In addition, several studies have demonstrated alterations in specific bacterial taxa between IBS and HC, as well as between clinically relevant subtypes of IBS [22–25]. However, although the data suggest increased levels of *Firmicutes* and decreased levels of *Bacteroidetes* in the majority of patients with IBS [25], the differences in the abundance of specific