NUTRITION™

Nutrition 22 (2006) 334–342

www.elsevier.com/locate/nut

Review article

Role of partially hydrolyzed guar gum in the treatment of irritable bowel syndrome

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Manuscript received July 5, 2005; accepted October 7, 2005.

Abstract

Irritable bowel syndrome (IBS) is the world's most common gastrointestinal functional disorder and is associated with several social and economic costs. Health-related quality of life is often impaired in patients with IBS. The pathophysiologic mechanisms underlying IBS remain poorly defined. The therapeutic approach to patients with IBS is based on symptoms, and fibers may play an important role in treatment. Among the various types of fiber, water-soluble, non-gelling fibers seem to be a promising option for treatment of IBS. Partially hydrolyzed guar gum (PHGG) is a water-soluble, non-gelling fiber that has provided therapeutic benefits. In clinical trials, PHGG decreased symptoms in constipation-predominant and diarrhea-predominant forms of IBS and decreased abdominal pain. Further, an improvement in quality of life was observed in patients with IBS during and after treatment with PHGG. Moreover, PHGG seems to have prebiotic properties because it increases the colonic contents of short-chain fatty acids, Lactobacilli, and Bifidobacteria. © 2006 Elsevier Inc. All rights reserved.

Keywords: Irritable bowel syndrome; Fibers; Treatment

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder defined as "a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation" [1]. Although the definition of IBS stems from the results of a working team of experts, many clinicians feel that in clinical practice it is restrictive and should include people without pain, pending the presence of other criteria. From a practical point of view, IBS is diagnosed on the basis of these criteria and in the absence of alarm symptoms such as bleeding, weight loss, and fever [2]. In particular situations, diagnosis of IBS is corroborated by a negative first-line biochemical and instrumental workup [3,4]. The pathophysiologic basis underlying IBS remains largely unknown, although putative mechanisms may include abnormalities in gut motor function and/or visceral sensitivity, altered encephalic representation of peripheral stimuli, and non-specific psychological disturbances [5]. Recently, subclinical inflammation of the enteric nervous system was postulated to explain some of the manifestations of IBS [6].

The prevalence of IBS ranges from 10% to 20% in the general adult population in the United States and Europe, with female preponderance in all study populations [7,8]. These prevalence data likely underestimate the true prevalence of IBS because up to 70% of adults with symptoms do not present for medical evaluation in the United States [9]. IBS is not only highly prevalent but also has a high medical and social effect. It is the most common diagnosis in gastroenterologic practices, accounting for 19% of referrals to specialists [10]. From a financial point of view, some recent studies performed in the United States found that the total costs for health care were 50% higher in patients with IBS than in control subjects without IBS [11,12], and the yearly financial burden of IBS has been estimated at approximately €28 billion in Europe and $1.6 to $10 billion in direct costs and $19.2 billion in indirect costs in the United States [13,14].

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0899-9007/06/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.nut.2005.10.003

Although IBS does not cause life-threatening complications, it negatively affects patients' health-related quality of life (QOL) [15,16]. QOL was reportedly lower in patients with IBS than in patients with other chronic gastrointestinal or non-gastrointestinal illnesses, such as gastroesophageal reflux disease or diabetes mellitus [17]. Due to the importance of these findings, guidelines from the American College of Gastroenterology have suggested that QOL should be routinely assessed in patients with IBS and that treatment should be started when IBS symptoms decrease functional status and QOL [18].

With respect to therapy for IBS, despite advances in understanding the pathophysiology of IBS, we are still far from a pathophysiologic approach to treatment [19]. Current treatment of IBS attempts to decrease the severity and frequency of symptoms and improve patients' QOL. Thus, therapy is aimed at relieving the predominant symptoms (constipation, diarrhea, and pain), improving patients' well-being, and decreasing negative social features correlated with this disease [1,19]. Due to the peculiarity of the syndrome and the lack of a specific biochemical marker or instrumental result that correlates with therapeutic response, symptomatic response often correlates to an increase in QOL. Further, it has recently been suggested that therapeutic trials for IBS should take into account global outcome measurements including medical, social, and financial items. All in all, according to evidence-based medicine, none of the traditional or "alternative" therapies is supported by the highest grade of recommendation [20]. Nevertheless, despite the placebo-response rate observed in therapeutic trials for IBS [21], non-pharmacologic therapies alone are adequate for many patients with this disorder, especially those under primary and secondary care, and it has been shown that non-pharmacologic therapies may improve response rate to pharmacologic treatment [22,23].

Role of fiber in treatment of IBS

In the United States and the European Union, adult dietary fiber intake falls well below the recommended range of 20 to 35 g/d [24,25]. Many patients with IBS spontaneously modify their dietary habits and/or use fiber supplementation before consulting a physician due to the belief that life-style and alimentary habits play a significant role in the genesis of their symptoms [26,27]. Oral fiber supplementation is widely recommended to patients with constipation-predominant IBS, and 20% to 36% of these patients seen in primary care are told to increase the fiber content in their diets, and "pharmacologic" fibers are prescribed to 16% of patients with IBS who are under primary care [28,29].

Currently, fiber supplementation is recommended to patients with IBS and constipation because greater fiber intake results in softer and bulkier stools, thus promoting colonic peristalsis and easing defecation. There is clear evidence that fiber decreases whole-gut transit time [30]. Accelerated oral-to-anal transit alleviates constipation and decreases intracolonic pressure, which may alleviate pain. Fiber represents a mainstay in the IBS therapeutic algorithm [31]. In a prospective, randomized, double-blind, controlled trial, fiber was shown to improve symptoms in children with idiopathic, chronic abdominal pain [32], although there is no such evidence in adult patients with IBS, and the long-term effects of fiber supplementation in patients with IBS were assessed in only small groups [33]. However, the results of studies that evaluated fiber supplementation in patients with IBS has sometimes produced contrasting results, with one of the main reasons for this inconsistency being poor knowledge of the mechanism of the action of fiber. Fibers are generally grouped under an umbrella term, although important physical and chemical characteristics are peculiar to different types of fiber. Early studies analyzed the results of fiber supplementation in IBS without taking into consideration the type of fiber that had been administered to patients, and this likely led to misinterpretation of the inconsistency among study outcomes.

A better understanding of the various properties of fibers has important clinical consequences. Fibers are widely recommended as a first step in IBS treatment, and different types of fiber reportedly modify IBS-related symptoms in different fashions. In this setting, the main distinction is between soluble and insoluble fibers (Fig. 1). On the one hand, soluble fiber dissolves in water and is widely metabolized in the large bowel, thus producing short-chain fatty acids and leading to selective stimulation of microbial growth, which eventually increases the water-holding capacity of the colonic content and fecal moisture. On the other hand, insoluble fiber is minimally modified during intestinal transit and mechanically increases fecal mass by retaining water alone, thus decreasing transit time and improving defecation. Stephen and Cummings [34] demonstrated that the actions of soluble and insoluble fibers in the colon depend on the extent to which they are digested. In an elegant study they showed that insoluble fiber alters colonic function by retaining water and increasing fecal bulk, whereas soluble fiber not only increases hydration of stool output but also influences colonic function by stimulating bacterial growth. The clinical importance of this physiochemical distinction was recently outlined by the results of a meta-analysis that evaluated randomized controlled trials of fiber supplementation in IBS carried out between 1966 and 2002 [35]. This meta-analysis clearly showed that different types of fiber have different clinical implications in the treatment of IBS. Briefly, Bijkerk et al. [35] observed that, although general fiber supplementation globally alleviates IBS symptoms (relative risk 1.33, 95% confidence interval 1.19 to 1.50), the beneficial effect is mainly associated with the use of soluble fiber (relative risk 1.55, 95% confidence interval 1.35 to 1.78) rather than insoluble fiber (relative risk 0.89, 95% confidence interval 0.72 to 1.11). When decreased abdominal pain alone was considered as

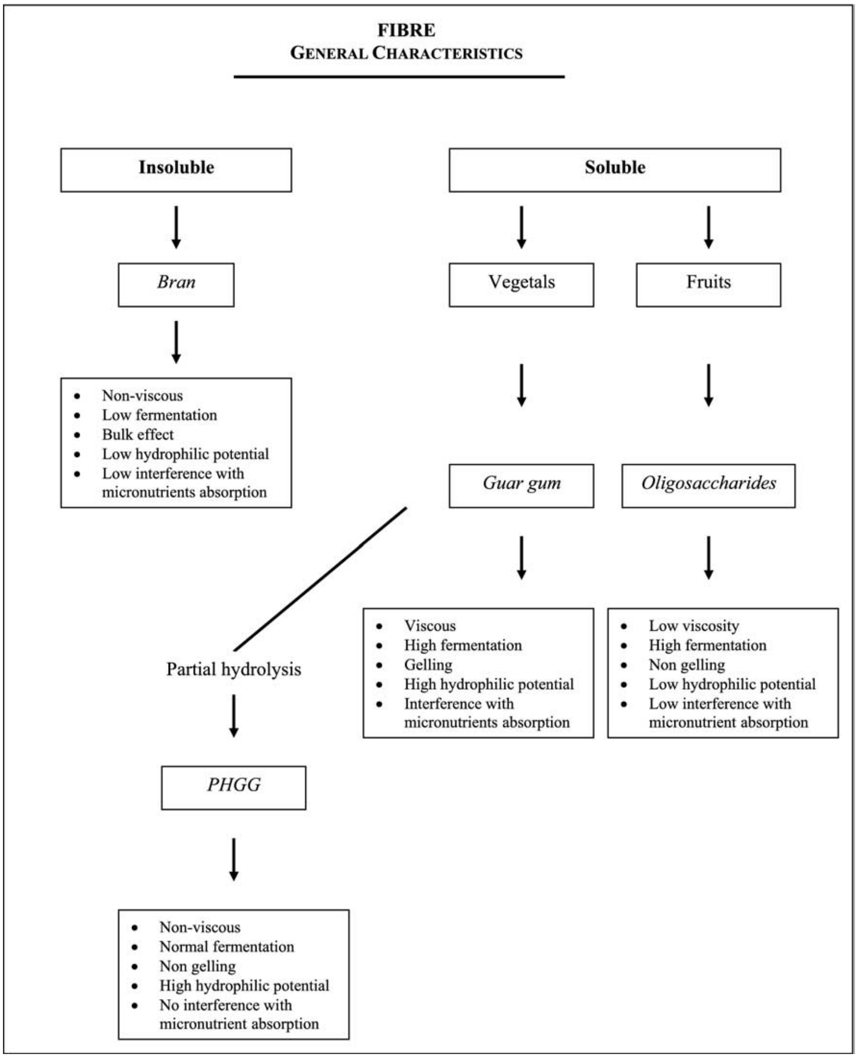


Fig. 1. Characterization of various types of fiber according to their main properties. PHGG, partially hydrolyzed guar gum.

the therapeutic endpoint, the results of the studies that were analyzed in the meta-analysis showed conflicting results between patients who were treated with soluble fiber and those who were treated with insoluble fiber. Decreased constipation was observed in patients who were treated with soluble fiber (relative risk, 1.60; 95% confidence interval, 1.06 to 2.42) and those who were treated with insoluble fiber (relative risk 1.54, 95% confidence interval 1.02 to 2.14). All in all, this meta-analysis demonstrated that soluble fiber is effective in decreasing global IBS symptoms and constipation. It also underscored the fact that insoluble fiber was no better than placebo and that a large amount of insoluble fiber may actually worsen IBS-related symptoms [35,36].

Nonetheless, some of the studies on the use of fiber in patients with IBS were biased by methodologic flaws. The placebo response in IBS patients ranged from 20% to greater than 50% [37], and some of the therapeutic trials were not controlled and randomized. Further, because IBS symptoms characteristically wax and wane, parallel group studies are preferable to crossover studies that may be flawed because they assume a constancy of symptoms and are subject to a "period effect" [20]. Moreover, because IBS is a chronic, relapsing condition, therapeutic trials need to be of appropriate duration (e.g., ≥8 to 12 wk) and patients should be adequately followed after treatment discontinuation to observe whether the effect of treatment is maintained.

Effects of partially hydrolyzed guar gum on constipation, diarrhea, and IBS

In addition to the main distinction between soluble and insoluble fibers, recent clinical trials have evaluated the particular properties of the available soluble fibers, thus allowing for better characterization of their actions in IBS. Water-soluble fibers can be subdivided on the basis of their physical and chemical characteristics: viscosity, degree of fermentation by colonic flora, gelling, and water-binding properties (Fig. 1). The studies were carried out with viscous, largely fermented, gelling fibers. Conversely, a non-viscous, non-gelling fiber such as partially hydrolyzed guar gum (PHGG) is fermented in the colon, thus abating gas overproduction. This is most likely due to partial depolymerization of PHGG and decreased gas retention (non-gelling properties). PHGG is a vegetal, water-soluble, non-viscous, non-gelling dietary fiber that is derived from guar gum, a water-soluble, viscous, gelling polysaccharide found in the seeds of *Cyamopsis tetragonolobus* (guar plant). The saccharide component of guar gum is galactomannan. Guar gum supplementation has positive physiologic benefits such as improving glycemic control in patients with diabetes and decreasing blood lipid levels in patients with hypercholesterolemia [38,39]. However, due to its high viscosity, it is difficult to incorporate adequate amounts of guar gum into foods or enteral solutions. PHGG is produced by controlled partial enzymatic hydrolysis of guar gum. Thus, PHGG is less viscous than the original guar gum because of its lower molecular weight (~20 000 Da) and therefore does not form a gel. Because of these peculiar characteristics and the fact that it retains the beneficial properties of guar gum [40], PHGG can be added to enteral solutions or administered as a dietary supplement per se [41].

Safety is a primary concern when evaluating drugs or dietary supplements. In laboratory animals, a PHGG dietary content of up to 10% showed no signs of toxicity [42]. Further, a panel of experts commissioned by the Life Sciences Research Organization of the Federation of American Societies for Experimental Biology concluded that daily consumption of up to 20 g/d of PHGG is safe [43]. In addition, PHGG did not influence absorption of iron, ions, or micronutrients in healthy volunteers or patients with IBS [44,45]. This solid evidence emphasizes the safety profile of PHGG.

The effects of PHGG on fecal output in healthy volunteers and patients with constipation were also evaluated. PHGG supplementation as a beverage at a dosage of 36 g/d in healthy volunteers led to 38.4% and 37.3% increases in fecal bulk and solids, respectively [44]. In women with constipation, administering 11 g/d of PHGG resulted in increased defecation frequency (from 0.46 to 0.63 per day) and fecal moisture (from 69% to 74%) [46]. Two different PHGG dosages (5 versus 15 g/d) produced similar results in healthy volunteers, i.e., both PHGG schedules resulted in an increase in defecation frequency and improvement in fecal consistence [47]. In particular subgroups of patients, such as elderly patients who resided in a nursing home, PHGG supplementation proved to be useful in decreasing laxative intake from 2.0 to 0.2 doses per day [48]. It is important to point out that PHGG was well tolerated in all studies and that no adverse events occurred. It is noteworthy that in 134 patients with IBS that was diagnosed according to Rome II criteria and with a wide range of alterations in bowel movements (from 2 to 35 weekly evacuations), administering PHGG (5 g/d) resulted in normalization of bowel movements (Fig. 2) and alleviation of IBS symptoms such as abdominal tension and spasms [45].

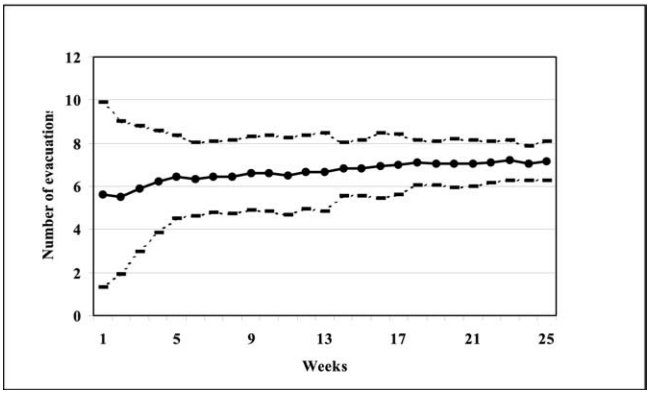


Fig. 2. Number of weekly evacuations in 134 patients who had irritable bowel syndrome and were treated with partially hydrolyzed guar gum supplementation (5 g/d) for 24 wk. There was a tendency toward normalization of bowel movements, which is highlighted by the progressive decrease in standard deviation (solid line, mean number of weekly evacuations; dashed lines, standard deviation of the mean). Adapted from Giaccari et al. [45].

Water-soluble fiber has been shown to decrease IBS global symptoms and constipation. However, a discrete proportion of patients with IBS have diarrhea. In a clinical situation with a high incidence of diarrhea, as is the case with total enteral nutrition, Homann et al. [49] found that patients who received total enteral nutrition and 20 g/d of PHGG had a significant decrease in diarrhea, whereas some patients who received the non-supplemented enteral diet had to stop enteral feeding due to severe diarrhea. However, this positive effect was no longer observed when patients were subdivided according to type of enteral feeding. When added to the World Health Organization's Oral Rehydration Solution, PHGG proved to be effective in decreasing the duration of non-cholera diarrhea and stool output in children [50]. In a double-blind, randomized trial carried out in patients with sepsis, the group that was administered PHGG and the standard enteral nutrition had a smaller number of days with diarrhea compared with patients on enteral feeding alone [51]. These studies laid the basis for a multicenter, randomized, open trial that compared the effects of PHGG with those of wheat bran supplementation in a large number of patients with IBS that included diarrhea-predominant and constipation-predominant subgroups [52]. In this study, a significantly larger number of patients who were administered PHGG supplementation (5 g/d) reported normalization of bowel movements compared with those who received wheat bran supplementation (65% versus 48% of randomized patients, $P = 0.001$, intention-to-treat analysis). Further, according to an intention-to-treat analysis, improvement in an important therapeutic endpoint of IBS, namely abdominal pain, was achieved by more patients in the PHGG-supplemented group than in the wheat bran–supplemented group (65% versus 42%, $P = 0.001$) [52]. Figure 3

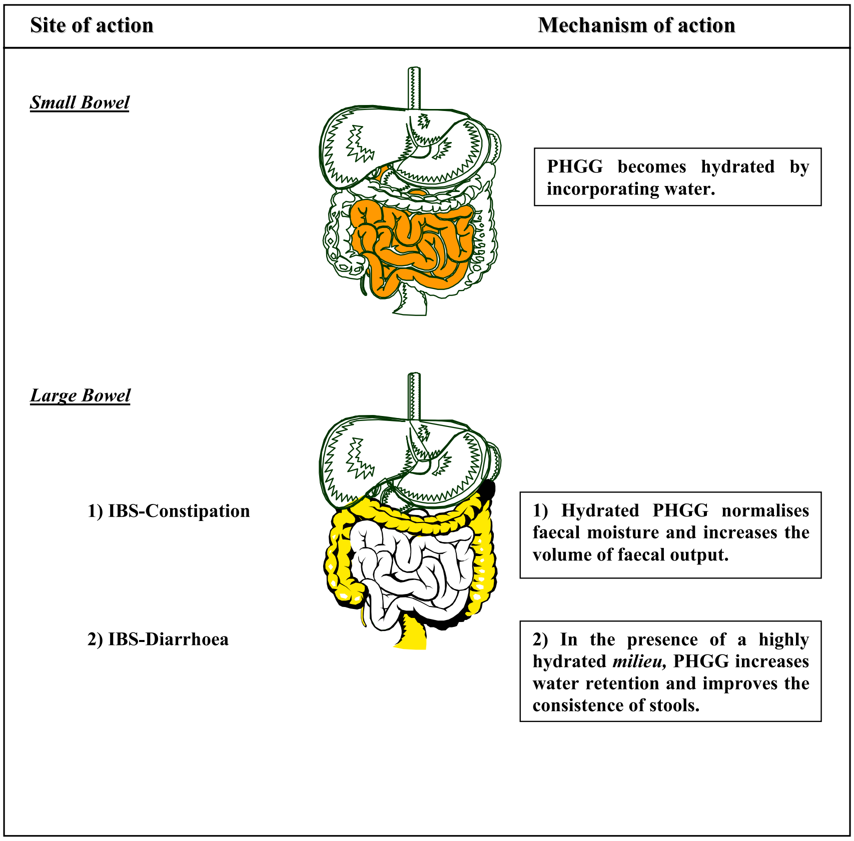
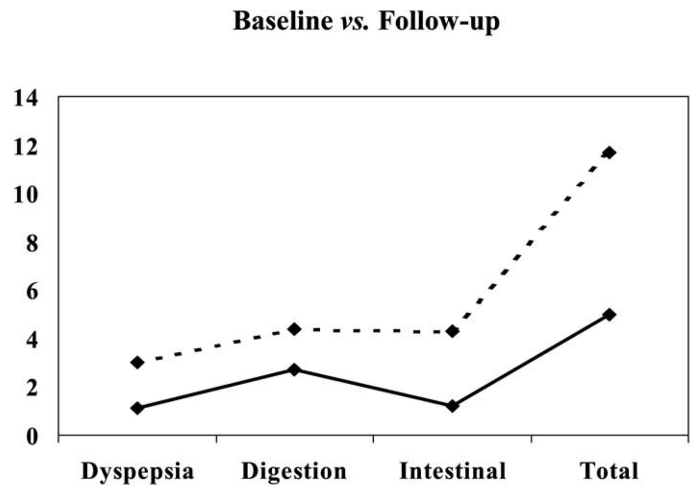


Fig. 3. Schematic representation of the mechanisms of action of PHGG in constipation and diarrhea. IBS, irritable bowel syndrome; PHGG, partially hydrolyzed guar gum.

summarizes the mechanisms of action of PHGG in constipation and diarrhea related to IBS.

Treatment aimed at relieving IBS-related constipation, diarrhea, and abdominal pain should also focus on improving patients' QOL. Health-related QOL is often impaired in patients with IBS, and well-being and improvement in psychosocial functions are important aspects of the IBS treatment strategy [53]. Decreased productivity and functioning seem to be more important than abdominal symptoms for some patients [54]. To our knowledge, only one study has evaluated the effect of fiber supplementation on important outcomes such as improvement of QOL in patients with IBS [55]. A recent study by Parisi et al. [55] evaluated the effects of two PHGG dosages (10 versus 5 g/d) on symptoms and QOL of patients with IBS in a multicenter, randomized trial [55] (Fig. 4). In addition to assessing the pre- and post-treatment Gastrointestinal Symptom Rating Scale [56], this study took into account modifications in QOL as assessed by the standardized Short Form 36 [57] and the Hospital Anxiety and Depression Scale [58,59]. In this study, treatment with PHGG supplementation proved to be effective in improving the Gastrointestinal Symptom Rating Scale, most of the Short Form 36 items, and Hospital Anxiety and Depression Scale in both treatment arms (Fig. 3). In particular, PHGG was effective at maintaining positive results even after 6 mo of follow-up, a feature that is seldom evaluated in IBS therapeutic trials [21]. Table 1 summarizes the results of the clinical trials that evaluated the use of PHGG in healthy volunteers, in patients with functional gastrointestinal disorders, and in patients with IBS.

Studies that evaluated the effects of PHGG in patients with functional gastrointestinal disorders or IBS were not free of methodologic drawbacks. The initial studies that evaluated the effects of PHGG were flawed by the lack of randomization and the absence of a control group [44,46,47]. These characteristics are especially important for a condition such as IBS in which there is high placebo response [37]. Only more recent studies were randomized and included a control arm [52,55], but these studies were open because it was not possible to blind the examiner and/or patient due to the peculiar physical nature of PHGG. Further, only two studies were of adequate duration (i.e., 12 and 24 wk), although they lacked follow-up of patients [45,55]. The study that actually did follow patients showed that the positive effects of PHGG on IBS were more often observed at the end of treatment (3 mo) rather than at 6 mo of follow-up [55]. This further underscores the need for appropriate follow-up evaluation of patients who have a disease such as IBS, which is characterized by spontaneous fluctuation of symptoms [20,37].



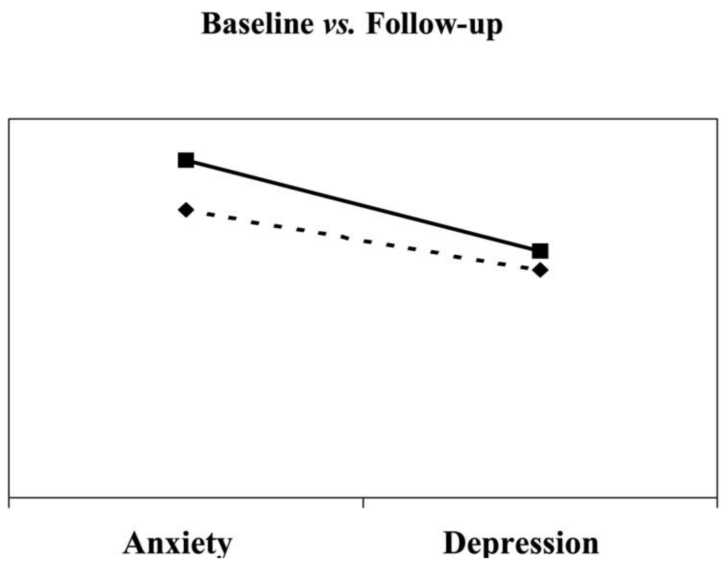


Fig. 4. Effects of partially hydrolyzed guar gum supplementation on the Gastrointestinal Symptom Rating Scale (top; all differences $P < 0.05$) and the Hospital Anxiety and Depression Scale (bottom; both $P < 0.05$). Adapted from Parisi et al. [55].

Table 1
Results of clinical trials of PHGG

Study	Year	Patients (*n*)	Study subjects	Study design	PHGG dose (per day)	Duration (wk)	Outcome measurement
Takahashi et al. [46]	1994	15	Constipated women	O	22 g	3	Constipation, fecal components
Giaccari et al. [45]	2001	134	IBS patients	O	5 g	24	Global IBS symptoms, micronutrient and electrolyte absorption
Parisi et al. [52]	2002	188	IBS patients	ROC	5 g	12	Global IBS symptoms, abdominal pain, constipation
Parisi et al. [55]	2005	86	IBS patients	ROC	5 g/10 g	12 + 12 follow-up	Global IBS symptoms, quality of life, psychological distress

IBS, irritable bowel syndrome; O, open trial; PHGG, partially hydrolyzed guar gum; ROC, randomized, open, controlled trial.

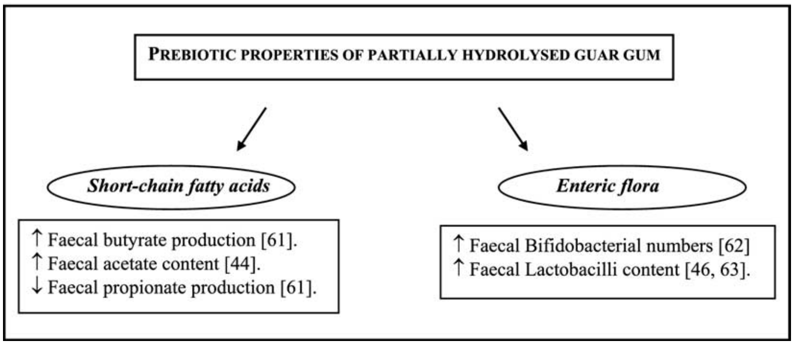


Fig. 5. Summary of prebiotic properties of partially hydrolyzed guar gum.

Is there a role for PHGG as a prebiotic?

Fibers may be useful in ways other than as a supplement to improve symptoms in patients with IBS. Recently, other potential beneficial effects have been ascribed to the use of fibers. Fiber may also act as a prebiotic, thus positively modulating intestinal microflora. Prebiotics are defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or the activity of one bacterium or a limited number of bacteria in the colon that can improve host health. This process should occur by stimulating benign or potentially health-promoting indigenous bacterial genera but not harmful organisms [60]. The prebiotic effect of PHGG is strongly supported by a line of evidence that stems from experimental studies in animals to clinical studies in humans (Fig. 5). Experimental studies have shown that azoxymethane-treated rats that were administered PHGG had increased butyrate concentrations of colonic contents [61]. This finding suggests that, once given the proper substrate, colonic microbiota adapt and produce more butyrate. Further, PHGG reportedly increased fecal acetate content in healthy volunteers [44]. Butyrate, acetate, and propionate are the main stool water short-chain fatty acids and one of the most important energy sources for colonocytes. Short-chain fatty acids affect colonic epithelial cell proliferation, and intraluminal deficiency of short-chain fatty acids likely contributes to the development of colonic disease [62].

In humans, it has been repeatedly shown that PHGG supplementation increases the colonic content of Lactobacilli and Bifidobacteria in healthy volunteers and women with constipation, further underscoring the role of PHGG as a prebiotic [46,63]. In healthy volunteers, PHGG supplementation caused a significant increase in the percentage of Bifidobacteria and an increase in the occurrence and frequency of Lactobacilli [64]. Because PHGG was not used by Bifidobacteria and Lactobacilli in vitro, Okubo et al. [64] speculated that the effect of PHGG in vivo can be attributed to the fact that, in human colon, PHGG is degraded by certain bacteria, and that the degraded products favor the growth of Bifidobacteria and Lactobacilli. In this setting, the selective increase in Bifidobacteria and Lactobacilli that was observed during PHGG administration supports the concept of beneficial modulation of intestinal microflora through dietary supplementation with fiber. Altering the gut flora by selectively increasing Lactobacilli and Bifidobacteria has been reported to ameliorate IBS symptoms and, in particular, decrease pain and flatulence [65,66].

Conclusions

Fiber supplementation has always been considered an important option for patients with IBS. Knowledge of the various properties of fiber has proved to be fundamental in improving patient management. Results of a meta-analysis showed that administering water-soluble fiber is preferable in patients with IBS. Recent studies have shown that supplementation with a water-soluble, non-gelling fiber (5 g/d of PHGG) can lessen symptoms in patients with diarrhea and with constipation-predominant IBS. It is noteworthy that PHGG improved the health-related QOL in patients with IBS, which is an important therapeutic goal. Moreover, initial studies have shown that fiber may act as a prebiotic, thus increasing the therapeutic benefits of PHGG supplementation in IBS. Well-designed studies with composite endpoints are needed to confirm the role of PHGG and to disclose their more subtle mechanisms of action in IBS.

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