Efficacy, safety, and tolerability of fructooligosaccharides in the treatment of irritable bowel syndrome[1–3]

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ABSTRACT

Background: Interest in fructooligosaccharides as a health-promoting food component is increasing. Fructooligosaccharides are mainly indigestible and large amounts in the colon may provoke gastrointestinal symptoms.

Objective: The symptoms of irritable bowel syndrome (IBS) may be provoked by large quantities of carbohydrates in the colon. The objective of this study was to determine whether regular consumption of fructooligosaccharides worsens gastrointestinal symptoms in patients with IBS.

Design: A multicenter, prospective, randomized, double-blind, placebo-controlled parallel group comparison was conducted at 24 sites. The study consisted of a 2-wk, single-blind run-in phase and a 12-wk, double-blind comparative phase. Subjects were randomly assigned to receive 20 g fructooligosaccharides powder/d (n = 52) or a placebo (n = 46). Efficacy was based on the patients' overall response to treatment at completion of the study and on the severity and duration of individual symptoms (abdominal distension, abdominal rumbling, abnormal flatulence, and abdominal pain).

Results: Data from 96 patients (16 men and 80 women) were analyzed. After 4–6 wk of treatment, IBS symptoms improved more in the placebo group than in the fructooligosaccharide group. After completion of the study, there were no significant differences between the 2 groups: symptoms improved in 58% of the fructooligosaccharide group and in 65% of the placebo group and symptoms worsened in 8% of the fructooligosaccharide group and in 13% of the placebo group.

Conclusion: Although symptoms worsened in patients with IBS at the onset of treatment with 20 g fructooligosaccharides/d, continuous treatment for 12 wk resulted in no worsening of symptoms. *Am J Clin Nutr* 2000;72:1570–5.

KEY WORDS Fructooligosaccharides, irritable bowel syndrome, placebo-controlled clinical trial, efficacy

INTRODUCTION

Several new types of oligosaccharides have been developed as bulking sucrose substitutes and are claimed to have beneficial health effects. These compounds are of interest as low–glycemic index and low-energy bulk sweeteners, especially for use in patients with diabetes mellitus, and as noncariogenic sucrose substitutes (1–3). Oligosaccharides were shown to improve the bioavailability of calcium, magnesium, and iron in rats (4) and in humans (5, 6) and may affect human lipid metabolism (7). Oligosaccharides are used in processed foods such as table sugar, candies, chocolate, soft drinks, yogurt, and chewing gum. In the area of nutritional sciences, oligosaccharides are attracting interest and debate.

A prebiotic is a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth, activity, or both of one or a limited number of bacteria in the colon and thus improves the health of the host (8). Of the natural nondigestible oligosaccharides (and polysaccharides) that fulfill the criteria of a colonic food, fructooligosaccharides are the only products currently recognized and used as food ingredients that meet all criteria allowing classification as prebiotics.

Contrary to most dietary fibers, which act mainly as bulking agents, fructooligosaccharides are osmotic laxative agents. However, fructooligosaccharides exert their osmotic effect in the colon and are similar to other dietary fibers in that they enter the colon virtually unchanged. Contrary to most dietary fibers, once in the colon, fructooligosaccharides are rapidly fermented to short-chain fatty acids, especially by bifidobacteria, whose growth is consequently promoted. The breakdown of fructooligosaccharides by bacterial fermentation is followed by a pronounced increase in hydrogen concentrations, which promotes peristalsis of the colon. These effects of fructooligosaccharides are similar to the effects of lactose in people with lactose maldigestion, a condition that produces symptoms similar to those of irritable bowel syndrome (IBS): bloating, flatus, abdominal rumbling, and an irregular defecation pattern (9). Thus, although fructooligosaccharides may have health-promoting effects, they can also have adverse effects; therefore, the usefulness of fructooligosaccharides as a functional food has its limitations. IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation disorders (10). IBS is one of the most common disorders in the Western population. Symptoms consistent

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Received August 25, 1999.

Accepted for publication April 24, 2000.

with IBS are reported by 5–25% of the population (11–14). In this population, the general health condition can worsen if fructooligosaccharides are consumed unknowingly, resulting in additional health care costs.

Because the portion of the population with IBS is so large, and because the use of fructooligosaccharides will probably increase, we found it of interest to study the effect of fructooligosaccharides on patients with IBS.

SUBJECTS AND METHODS

Subjects

The study was conducted in accordance with the Helsinki Declaration II and was approved by the local ethical committee. Participants were recruited from general practice and were well known to their primary care physicians. Subjects had to be white, 18–70 y of age, and attending a general practice for treatment of IBS. Symptoms of IBS had to have been present for ≥12 wk before visit 1. Furthermore, the results of a physical examination had to be normal and the following laboratory variables had to be within normal ranges: blood hemoglobin, C-reactive protein, serum alkaline phosphatase, serum acetylornithine transaminase, and serum creatinine.

Exclusion criteria included a history of severe chronic medical disease, including colorectal disease or surgery, anal disease, and other gastrointestinal diseases; severe abdominal discomfort; severe obstipation (<2 defecations/wk); abnormal dietary habits; regular use of strong analgesics or strong laxatives; use of medication that might influence bowel function; foreseen introduction of the regular use of new medication during the trial period; alcohol abuse; known or suspected lack of compliance with the study protocol; and abnormal results of a physical examination.

IBS is defined according to the Manning criteria (15) as *1*) mild-to-moderate abdominal discomfort relieved by defecation, accompanied by ≥2 of the following symptoms: abdominal distension, abdominal rumbling, abnormal flatulence, or abdominal pain; and *2*) a defecation pattern that is irregular >25% of the time, accompanied by ≥2 of the following symptoms: a change in defecation frequency, a change in the consistency of the feces, or discharge of mucus. The subjects discontinued the study under the following conditions: voluntary withdrawal, unacceptable treatment response, medical deterioration, adverse events, and exclusion criteria becoming apparent during the study. All participating patients signed informed consent forms after receiving written and oral information of the aim, course, and potential hazards of the trial.

Trial medication

A white, crystalline fructooligosaccharide powder (Idolax; Orafti, Tienen, Belgium) certified by Ferrosan A/S (Soeborg, Denmark) and provided in 10-g sachets was used. The product was a semisynthetic carbohydrate produced by the hydrolysis of inulin and extracted from chicory root. The hydrolysis of inulin produces linear oligomers of the Gf_n type, in which one glucose moiety is bound to (β2–1) fructooligosaccharides by a (1–2)-type linkage, and of the F_m type, in which the homopolymers of fructose are bound by a (2–1) linkage. The placebo was a powdered, dry, glucose syrup (Ferrosan A/S, Soeborg, Denmark) and was provided in 10-g sachets identical in appearance to those of the fructooligosaccharide.

Study design

The study was designed as a prospective, randomized, placebo-controlled, parallel group comparison. The study was divided into 2 phases.

2-wk Single-blind run-in phase

A total of 114 patients received 10 g placebo powder. The main purpose of this phase was to wash out any effect of medication or dietary supplements that the patients had received for IBS before their participation in the study. Medication that might influence the outcome of the study was stopped at the screening visit (eg, psyllium, wheat bran, and laxatives). During this phase, the patients were offered optional treatment with 5 mg bisacodyl (Toilax; Ercopharm, Kvistgaard, Denmark). The tablets were returned at the second visit and if >2 were used over 2 wk, the patient was considered to have severe obstipation and was excluded from the study. Sixteen patients withdrew from the study during or at the completion of this phase.

12-wk Double-blind comparative phase

Ninety-eight patients were randomly assigned to receive either fructooligosaccharide (n = 52) or a placebo (n = 46), 10 g/d for the first 2 wk and 20 g/d for the following 10 wk. Efficacy, safety, tolerability, and compliance were recorded at 2, 4, 6, 8, and 12 wk. The patients were advised to take the powder with their morning meal, dissolved in either milk or juice. The primary efficacy endpoint was the patient's overall response to treatment at completion of the comparative phase. Secondary efficacy endpoints were the investigator's overall assessment of the patients' response to treatment, changes in individual symptom scores, changes in total symptom scores, and changes in defecation frequency. All changes are changes from baseline (the end of the 2-wk run-in period). At each visit, any adverse event that occurred since the previous visit was recorded. The adverse events were graded by the investigator as mild, moderate, or severe and as probably, possibly, or unlikely related to the trial medication. Patients were asked to return any unused sachets at each visit, which were counted by the investigator and by the trial monitor.

Randomization procedure

Only patients who complied with the protocol of the run-in phase were eligible for the comparative phase. Patients were admitted in consecutive order at each trial site and were assigned a code number in that order. Randomization was in balanced blocks according to a computer-generated list of random numbers. The randomization list was generated by Unikem, Copenhagen, and was retained until the study code was broken.

Two study populations were analyzed: the intention-to-treat (ITT) population and the per protocol (PP) population. The ITT population consisted of all patients (n = 98) randomly assigned to the study who received at least one treatment dose. The PP study population consisted of all patients who were randomly assigned to the study and who did not violate the protocol inclusion or exclusion criteria and who received treatment for ≥2 wk, taking ≥70% of the prescribed powder while participating in the study. Two patients, both belonging to the fructooligosaccharide group, failed to comply with the protocol requirement to take ≥70% of the prescribed powder during the first 2 wk of the double-blind phase of the study. Both left the study within 4 wk because of adverse events and were excluded from the PP analysis.

TABLE 1
Reasons for study discontinuation during the run-in phase[1]

Reason	No. of patients
Voluntary withdrawal	5
Unacceptable treatment response	0
Medical deterioration	0
Adverse events	3
Exclusion criteria became apparent	9
Other	2

[1] A total of 16 patients discontinued the study during this phase; some patients discontinued the study for more than one reason.

Statistical analysis

For all baseline patient characteristics, the between-group difference and the SE of this difference were calculated. For categorical data, all tests were performed by using chi-square tests or Fisher's exact test. The exact test was used when one cell had an expected count <5. For continuous data, tests were performed by using two-sample *t* tests. Before tests were carried out, the assumptions underlying the tests (normality and homogeneity of variance) were examined. If the assumptions were not met, Wilcoxon's rank-sum test was used. The significance level for all tests was 5%.

The statistical analysis of efficacy endpoints was conducted in the PP population. If efficacy data were missing at completion of treatment, the last observed values were used. The 2 treatment groups were compared by using the two-sample Wilcoxon's rank-sum test. Changes in individual symptom scores were categorized on a 5-point scale: 1, major improvement; 2, minor improvement; 3, no change; 4, minor deterioration; and 5, major deterioration. Changes in feces consistency and in discharge of mucus from visit 2 to end of treatment were analyzed by using Fisher's exact test. All changes are individual changes from baseline to the end of the study.

Reported adverse events were tabulated and the 2 treatment groups were compared by using Fisher's exact test and the chi-square test. Changes in serum lipids and lipoproteins from baseline to the end of the study were analyzed by using Student's *t* test.

RESULTS

Study discontinuation

2-wk Run-in phase

The reasons subjects discontinued the study during the run-in phase are listed in **Table 1**. The exclusion criteria that became apparent were a lack of compliance with the study protocol ($n = 3$), abnormal results of a blood test that required further examinations ($n = 3$), regular use of H_2-receptor antagonists ($n = 2$), and severe constipation (<2 bowel movements/wk; $n = 1$).

12-wk Comparative phase

During the comparative phase, 23 patients ($n = 14$ in the fructooligosaccharide group and 9 in the placebo group) discontinued the study. The reasons for discontinuation are listed in **Table 2**. Seventy-five patients ($n = 38$ in the fructooligosaccharide group and 37 in the placebo group) completed the 12-wk comparative phase. Ninety-six patients ($n = 50$ in the fructooligosaccharide group and 46 in the placebo group) were eligible for the PP analysis.

TABLE 2
Reasons for study discontinuation during the comparative phase[1]

Reason	FOS group ($n = 52$)	Placebo group ($n = 46$)
Voluntary withdrawal	2	2
Unacceptable treatment response	5	4
Medical deterioration	0	1
Adverse events	9	2
Exclusion criteria became apparent	1	1
Other	1	1

[1] A total of 14 patients in the fructooligosaccharide (FOS) group and 9 in the placebo group discontinued the study during this phase.

TABLE 3
Comparability of treatment groups at entry to the study[1]

	FOS group[2] ($n = 50$)	Placebo group[2] ($n = 46$)	Difference[3]
Sex distribution (% men)	22.0	10.9	11.1 ± 7.1
Age (y)	45.1 ± 13.1	45.1 ± 13.1	0.0 ± 2.7
Body weight (kg)	74.1 ± 14.4	71.5 ± 13.3	2.7 ± 2.8
Duration of IBS (mo)	159 ± 141	175 ± 143	−15.8 ± 29.3
Average no. of defecations over the preceding 12 wk	5.4 ± 3.9	4.5 ± 3.5	0.9 ± 0.8
Currently receiving drug treatment for IBS (%)	66.0	69.6	−3.6 ± 9.5

[1] There were no significant differences between the groups. IBS, irritable bowel syndrome.
[2] $\bar{x}$ ± SD.
[3] $\bar{x}$ ± SE. Difference between the fructooligosaccharide (FOS) and placebo groups.

Comparability of subjects at baseline

A comparison of the 2 treatment groups at entry to the study is shown in **Table 3**. The 2 study groups were compatible except for sex (11 men in the fructooligosaccharide group compared with only 5 in the placebo group), although this difference was not significant.

Symptoms of IBS

2-wk Run-in phase

Of the 96 patients eligible for the PP analysis, 1 patient reported marked improvement, 14 reported moderate improvement, 25 reported slight improvement, 54 reported no changes, and 2 reported worsened symptoms. Thus, 41% of the patients

TABLE 4
Patients' overall assessment of treatment response at completion of the comparative phase

Assessment	FOS group ($n = 50$)	Placebo group ($n = 46$)
Clearance of symptoms	0	2
Marked improvement	15	6
Moderate improvement	6	13
Slight improvement	8	9
Condition unchanged	17	10
Condition worse	4	6

[1] There were no significant differences between groups by Wilcoxon's rank-sum test. FOS, fructooligosaccharide.

TABLE 5
Overall assessment of treatment response at completion of the comparative phase in the male participants[1]

Assessment	FOS group (n = 11)	Placebo group (n = 5)
Clearance of symptoms	0	0
Marked improvement	2	0
Moderate improvement	2	4
Slight improvement	2	0
Condition unchanged	4	1
Condition worse	1	0

[1]There were no significant differences between groups by Wilcoxon's rank-sum test. FOS, fructooligosaccharide.

reported an improvement of their symptoms after completion of the 2-wk period of placebo treatment.

12-wk Comparative phase

The patients' overall assessment of their response to treatment at completion of the comparative phase—the primary efficacy endpoint—is delineated in **Table 4**. Fifty-eight percent of the patients in the fructooligosaccharide group and 65.2% of the patients in the placebo group experienced some improvement in their symptoms. Because the results might be influenced by sex and because the study was unbalanced in this respect, we assessed the response in men only (**Table 5**).

The investigators' overall assessment of treatment response was not significantly different from the patients' overall assessment of treatment response. The patients' assessment of their response to treatment at the different time points is shown in **Table 6**. The placebo group had fewer symptoms at weeks 4 and 6 than did the fructooligosaccharide group; the differences were nearly significant. At weeks 8 and 12, there were no significant differences between the groups. The effect of fructooligosaccharides on the different symptoms of IBS (abdominal distension, abdominal rumbling, abnormal flatulence, and abdominal pain) is shown in **Table 7**. The patients in the fructooligosaccharide group complained more of abnormal flatulence than did the patients in the placebo group; however, the difference was not significant. There were no significant differences in the effect on IBS symptoms between the fructooligosaccharide and placebo groups. Changes from baseline in defecation frequency are presented in **Table 8**. The defecation frequency was significantly greater in the fructooligosaccharide group than in the placebo group at weeks 4 and 6, but there was no significant difference between the groups at the end of the study.

Serum lipids

Serum lipids and lipoproteins were measured at baseline and again at the completion of the comparative phase. There were no significant within-group or between-group changes or differences observed.

Safety and tolerability of fructooligosaccharide treatment

Twenty-one patients in the fructooligosaccharide group experienced a total of 32 adverse events and 22 patients in the placebo group experienced a total of 29 adverse events. Seven patients in the fructooligosaccharide group and 1 patient in the placebo group complained of abdominal pain (P = 0.063; Fisher's exact test). Ten patients in the placebo group and 3 patients in the fructooligosaccharide group reported some type of infection (P = 0.020; chi-square test). Otherwise, adverse events reported in the study were few and not significantly different between the fructooligosaccharide and placebo groups.

TABLE 6
Mean changes from baseline in total symptom scores during the comparative phase of the study

	FOS group[1]	Placebo group[1]	Difference[2]
Week 2	−0.39 ± 2.48 [44]	−0.95 ± 2.27 [43]	0.57 ± 0.51
Week 4	−0.30 ± 3.28 [33]	−1.55 ± 2.59[3] [38]	1.25 ± 0.7
Week 6	−0.51 ± 3.93 [35]	−1.97 ± 2.76[4] [36]	1.46 ± 0.8
Week 8	−1.29 ± 3.67 [35]	−1.55 ± 2.58 [33]	0.26 ± 0.77
Week 12	−1.82 ± 3.94 [33]	−2.35 ± 3.34 [34]	0.53 ± 0.89
End of treatment	−1.09 ± 3.94 [46]	−1.84 ± 3.44 [43]	0.75 ± 0.89

[1]$\bar{x}$ ± SD; number of patients eligible for evaluation in brackets.
[2]$\bar{x}$ ± SE. Difference between the fructooligosaccharide (FOS) and placebo groups.
[3,4]Nearly significantly different from the FOS group: [3]P = 0.071, [4]P = 0.067.

DISCUSSION

The use of low-energy bulk sweeteners has become increasingly popular. In the area of nutritional sciences, fructooligosaccharides are currently attracting interest as a functional food with beneficial health effects. It might be anticipated that an increased use of fructooligosaccharides would enhance symptoms

TABLE 7
Effect of placebo and fructooligosaccharide (FOS) treatment on the irritable bowel syndrome

	FOS group (n = 50)	Placebo group (n = 46)
	% of patients	
Abdominal distension		
Major improvement	13.0	16.3
Minor improvement	28.3	34.9
No change	37.0	25.6
Minor deterioration	13.0	16.3
Major deterioration	8.7	7.0
Abdominal rumbling		
Major improvement	15.3	14.0
Minor improvement	28.3	32.6
No change	43.5	27.9
Minor deterioration	6.6	23.3
Major deterioration	6.5	2.3
Abnormal flatulence		
Major improvement	15.2	11.6
Minor improvement	15.2	39.5
No change	41.3	34.9
Minor deterioration	17.4	9.3
Major deterioration	10.9	4.7
Abdominal pain		
Major improvement	13.0	20.9
Minor improvement	34.8	34.9
No change	37.0	30.2
Minor deterioration	6.5	11.5
Major deterioration	8.7	2.3

TABLE 8
Mean changes from baseline in weekly defecation frequency

	FOS group[1]	Placebo group[1]	Difference[2]
Week 2	1.5 ± 2.94 [43]	0.6 ± 2.38 [43]	0.89 ± 0.58
Week 4	2.1 ± 3.51 [33]	0.5 ± 2.53[3] [37]	1.56 ± 0.73
Week 6	2.6 ± 3.39 [34]	0.9 ± 2.87[3] [36]	1.64 ± 0.75
Week 8	2.4 ± 3.13 [35]	1.8 ± 3.45 [33]	0.64 ± 0.8
Week 12	1.3 ± 2.78 [30]	1.0 ± 2.76 [32]	0.28 ± 0.7
End of treatment	1.9 ± 3.18 [45]	0.7 ± 2.97 [43]	1.15 ± 0.66

[1] $\bar{x}$ ± SD; number of patients eligible for evaluation in brackets.
[2] $\bar{x}$ ± SE. Difference between the fructooligosaccharide (FOS) and placebo groups.
[3] Significantly different from the FOS group, $P = 0.04$.

similar to those associated with IBS in the general population. The clinical tolerance to regular consumption of fructooligosaccharides was studied in healthy volunteers (16, 17). Both of these studies found that tolerance did not improve during 12 or 15 d of regular fructooligosaccharide use. The main complaint related to all doses of fructooligosaccharide was excessive flatulence, but daily doses of <20 g resulted in only minor complaints. Doses >40 g/d resulted in abdominal rumbling and bloating; doses >50 g/d resulted in abdominal cramps and diarrhea (17). Pronounced gastrointestinal distress may be provoked in IBS patients because of the malabsorption of small amounts of fructose, sorbitol, and mixtures of fructose and sorbitol (18) and by lactulose and fructooligosaccharides in people with lactose maldigestion (19). The treatment most widely recommended for IBS patients is an increased intake of dietary fibers (9). This recommendation has been modified in recent years (20). Although dietary fiber consumption has been proven to increase stool volume and reduce colonic transit time (21), there are serious doubts about the effect of a high-fiber diet on IBS symptoms. According to Klein's (22) literature review of placebo-controlled clinical trials, the only beneficial effect of bulking agents on IBS symptoms was the alleviation of constipation; abdominal pain and bloating did not improve. Francis and Whorwell (23) found that 55% of patients who answered a questionnaire about the effects of bran consumption reported that their IBS symptoms worsened, specifically bowel disturbance, abdominal distension, and abdominal pain.

In the present study, we found that the symptoms of IBS patients did not worsen significantly after daily ingestion of 20 g fructooligosaccharides for 12 wk; however, 7 fructooligosaccharide-treated patients reported abdominal pain compared with only 1 placebo-treated patient. These patients were all included in the final statistical analyses (Tables 4, 6, and 7). At weeks 4 and 6, the total symptom score improved in the placebo and fructooligosaccharide groups, more so in the placebo group (NS), but at weeks 8 and 12, this difference in symptom score reduction leveled out.

Prolonged ingestion of lactulose or lactose in lactose-intolerant persons may result in colonic adaptation and a reduction in symptoms indicating intolerance (24, 25). This same phenomenon may have occurred in the present study. For example, the laxative effect of fructooligosaccharide changed during the study because the defecation frequency was significantly greater in the fructooligosaccharide group than in the placebo group at visits 4 and 5, whereas the difference was not significant at visit 7 or at the end of the study (Table 8).

Men constituted only 16.6% of the participants in the present study. This reflects well the proportion of men among IBS patients seeking medical advice for their problems (10, 22). The mens' responses were not significantly different from those of the population as a whole in both the placebo and fructooligosaccharide group. Whether fructooligosaccharides have a beneficial effect on IBS symptoms is impossible to evaluate from the present study. Both the placebo and fructooligosaccharide groups improved significantly during the 12-wk study, which was expected. In a comparative analysis, Klein (22) found that >50% of IBS patients responded positively to placebo in 15 of 28 placebo-controlled studies. Whether fructooligosaccharide consumption has an effect on IBS symptoms different from traditionally recommended dietary fibers could not be deduced from the present study. The results obtained may simply indicate that the symptoms of IBS fluctuate and whether they fluctuate due to or despite a given diet is unknown.

In conclusion, in most patients with IBS, symptoms are not constant but return intermittently for years and may worsen transiently at the onset of fructooligosaccharide ingestion. The disappearance of this effect after continuous ingestion of 20 g fructooligosaccharide/d for 12 wk may be a result of the adaptation.

We acknowledge Bente Brünner for motivating and encouraging the primary care physicians to participate in the study and UNI-C (Aarhus, Denmark) for providing statistical support.

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