Dietary Triggers of Abdominal Symptoms in Patients With Irritable Bowel Syndrome: Randomized Placebo-Controlled Evidence

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See Alonso C et al on page 163 for companion article in the July 2008 issue of *Gastroenterology*.

Background & Aims: **Observational studies suggest dietary fructose restriction might lead to sustained symptomatic response in patients with irritable bowel syndrome (IBS) and fructose malabsorption. The aims of this study were first to determine whether the efficacy of this dietary change is due to dietary fructose restriction and second to define whether symptom relief was specific to free fructose or to poorly absorbed short-chain carbohydrates in general.**

Methods: **The double-blinded, randomized, quadruple arm, placebo-controlled rechallenge trial took place in the general community. The 25 patients who had responded to dietary change were provided all food, low in free fructose and fructans, for the duration of the study. Patients were randomly challenged by graded dose introduction of fructose, fructans, alone or in combination, or glucose taken as drinks with meals for maximum test period of 2 weeks, with at least 10-day washout period between. For the main outcome measures, symptoms were monitored by daily diary entries and responses to a global symptom question.**

Results: **Seventy percent of patients receiving fructose, 77% receiving fructans, and 79% receiving a mixture reported symptoms were not adequately controlled, compared with 14% receiving glucose ($P \leq 0.002$, McNemar test). Similarly, the severity of overall and individual symptoms was significantly and markedly less for glucose than other substances. Symptoms were induced in a dose-dependent manner and mimicked previous IBS symptoms.**

Conclusions: **In patients with IBS and fructose malabsorption, dietary restriction of fructose and/or fructans is likely to be responsible for symptomatic improvement, suggesting efficacy is due to restriction of poorly absorbed short-chain carbohydrates in general.**

Irritable bowel syndrome (IBS) is a common gastrointestinal condition contributing to considerable financial burden and impact on quality of life.[1–3] Current therapeutic strategies, however, have disappointing efficacy, and new approaches are needed. Because many abdominal symptoms might originate from bowel distention,[4] altering factors that contribute to luminal distention, particularly the osmotic load within the lumen,[5] and the fermentative gas content might offer symptomatic benefit. Candidate substrates that are highly fermentable exerting an osmotic effect are dietary, poorly absorbed, short-chain carbohydrates,[5] collectively termed FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols).[6] FODMAPs can include fructose and lactose in patients in whom these are malabsorbed (found in about 40% and 15%–100% of the population, respectively),[7,8] polyols (such as sorbitol) because they are generally poorly absorbed by humans,[9] and fructo-oligosaccharides (fructans) and galacto-oligosaccharides (such as raffinose), for which humans do not express suitable hydrolases and are always poorly absorbed.[10]

Major dietary FODMAPs include fructose and fructans. Common dietary sources of fructose are fruits, honey, and high fructose corn syrup, and of fructans they are wheat and onions.[11] Estimated daily intake of fructose in the USA was 15–54 g,[12] but it is likely to be considerably higher now with increased consumption of high fructose corn syrups.[13] U.S. intake of fructans has been estimated to be 1–20 g/day,[14,15] but it might be higher now because of the addition of inulins for putative health benefits.[16–18]

We have hypothesized that restriction of all dietary FODMAPs will optimize symptom control in patients with IBS. This contrasts with previous dietary approaches specifically restricting lactose alone[19] or fructose with or without sorbitol.[20,21] We have developed a low FODMAP diet that restricts quantities of all FODMAPs and in particular fructans, fructose, and foods in which free fructose greatly exceeds free glucose.[22,23] This diet led to marked and sustained improvement in all gut symptoms in 74% of 62 patients with IBS and fructose malabsorption (FM).[22] Likewise, previous reports of restricting free fructose alone have also led to sustained benefit in functional gut symptoms in a proportion of patients with FM.[20,21] Unfortunately, such data could be explained by strong placebo effect.[24] If the benefit were due to dietary change, it is uncertain whether reduction of fructose specifically was the mechanism by which the diet exerted its effect, or whether the restriction of fructans played any role in efficacy. If indeed fructans were an important trigger of symptoms, then the dietary principles of the low FODMAP diet might be equally applicable to patients with functional gut disorders without FM, as suggested in a preliminary report.[25]

This study aimed first to determine whether the dietary restriction is the likely mechanism for symptomatic benefit and second to define whether the efficacy resided in the restriction of free fructose specifically, or whether it reflected restriction of

Abbreviations used in this paper: FM, fructose malabsorption; FODMAPs, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols; IBS, irritable bowel syndrome; ITT, intention to treat; PP, per protocol; VAS, visual analogue scale.

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poorly absorbed short-chain carbohydrates in general by comparing the effects of free fructose and fructans reintroduction to the diet. To do this, the effects on gastrointestinal symptoms of these substances alone or in combination were evaluated in a randomized, double-blinded, quadruple-arm, crossover, placebo-controlled, rechallenge trial in patients with IBS and FM who had previously responded to a low FODMAP diet.

Methods

Patient Selection

Twenty-six patients with IBS and FM were recruited during a 5-month period from a hospital-based dietetic practice serving the community. Inclusion criteria comprised diagnosis of IBS fulfilling Rome II criteria,[26] positive fructose breath hydrogen test following a 35-g load of fructose, instruction at least 3 months before recruitment in the low FODMAP diet (as outlined in detail elsewere[22,23]), and marked and sustained global improvement in gastrointestinal symptoms on the diet. Patients were excluded if they had celiac disease (by serology and/or duodenal biopsy), inflammatory bowel disease, or other concomitant serious morbidity; or if taking medication potentially influencing gastrointestinal symptoms.

Baseline Diet

Patients were provided all food, low in FODMAPs[6,23,27] (therefore, the intake of free fructose, fructans, polyols, and galactans was minimized), for the entire study duration (up to 22 weeks). The diet was designed and prepared by an Accredited Practicing Dietitian (S.J.S.) and consisted of a 4-week rotation of a diet with the energy content of 8, 10, or 12 MJ per day, according to the needs of the individual. The menu provided was formed from ingredients that are low in FODMAPs.[22,23] Thus, foods omitted included fruits containing fructose in excess of glucose (including apples, pears, watermelon), fructan-containing vegetables (including onion, leeks, asparagus, artichokes), wheat-based products (including bread, pasta, breakfast cereals, cakes, biscuits), sorbitol-containing foods (including stone fruits), raffinose-containing foods (including legumes, lentils, cabbage, and brussels sprouts), and lactose-containing foods (if lactose malabsorption was present on breath hydrogen testing following a load of 50 g). Alternative foods were provided to ensure nutritional adequacy. The baseline diet was nutritionally adequate, meeting the Australian Recommended Daily Intakes for macronutrients and micronutrients. For example, the 10 MJ day diet provided (without study treatment drinks) an average of 9.5 MJ, 104 g protein, 68 g fat, 277 g carbohydrate, and 26 g fiber (analysis of 7 days' menu with Foodworks food analysis software; Xyris Software, Qld, Australia). Patients were provided with a list of suitable alternative foods to follow when eating out. Consumption of approved foods was considered adherence to the diet.

The dietary content of fructose and fructans was measured in aliquots of 4 thoroughly mixed and homogenized 7-day menus by using commercially based assay kits (Megazyme International Ireland Ltd, Wicklow, Ireland) as per manufacturer's instructions. The range in daily quantities was fructans (1.1–2.7 g), fructose (11.3–20.6 g), and fructose in excess of monomeric glucose (0.6–5.3 g).

Test Substances

Patients were challenged with 1 of 4 test substances, given in the form of powders and reconstituted in water before consumption. They comprised fructans (Raftilose P-95; Orafti, Belgium), fructose (Fructofin C; Danisco, Kantvik, Finland), fructose and fructan mix, or glucose (Staleydex 333; Tate & Lyle, Staley, London, UK). The drinks were formulated and prepared by an industrial chemist as powders identical in appearance and color. The drinks were orange-flavored and rated similarly in prestudy taste testing in healthy volunteers. The powders were provided in otherwise empty 500-mL bottles containing 19 g fructans, 50 g fructose, alone or combination, or 20 g glucose. Final doses were low dose g/day (fructan 7, fructose 14, glucose 7), medium dose g/day (fructan 14, fructose 28, glucose 14), and high dose g/day (fructan 19, fructose 50, glucose 20). The amounts for high dose were chosen on the basis of estimated usual daily intake consumed.[28]

Preliminary Testing in Healthy Subjects

Preliminary testing of fructose/fructan drink was performed on 7 healthy subjects without IBS. All had prior breath hydrogen testing, and two had FM. The drinks were well-tolerated by all. No subject reported that symptoms were not adequately controlled during the 2-week test phase. Four subjects described very mild symptoms; 3 had bloating (visual analogue scale [VAS] score of 27, 35, and 43 mm, as defined below), and 4 had increased wind (VAS scores 27, 28, 33, and 43 mm).

Study Protocol

Patients' symptoms were evaluated by daily diary entries, comprising a global symptom question, "Were your symptoms adequately controlled in this phase?", answered at the end of each dose phase and weekly during washout periods; a score on a 100-mm VAS regarding severity of overall abdominal symptoms, wind, bloating, abdominal pain, tiredness, and nausea, and any medication taken, other symptoms, or adverse events.

Patients were provided with the low FODMAP diet for a run-in period of $\geq$10 days. The order of study treatments was allocated consecutively according to a randomly constructed table. The study treatments were prepared and allocated by a person independent of the recruitment and evaluation of patients. Thus, the patients, evaluating dietitian, and physician were blinded to the drinks being taken. Patients were instructed to take the drinks with food 3 times a day, initially at 50 mL/meal for 3 days (low dose), then 100 mL for 3 days (medium dose), and then 170 mL (high dose) for the remainder of the 2-week test. Patients experiencing intolerable symptoms could withdraw from a test phase early. A washout period of at least 10 days was implemented between test phases, while patients continued the low FODMAP diet. The next test drink challenge was not permitted until the patient had reached baseline symptom level for at least 7 days.

Adherence to diet was evaluated by patient entries into a tick-box diary each week. Diary entries of timing and volume of ingested test drinks and the numbers of used and unused bottles were counted to assess adherence to the intervention.

The conduct of this study complied with ethical guidelines of the National Health & Medical Research Council of Australia and was approved by Eastern Health Research and Ethics Com-

mittee and by Monash University Standing Committee on Ethics in Research Involving Humans.

End Points

The primary end point was the answer to the question, "Were your symptoms adequately controlled in this phase?", which was asked at the end of the test phase with the highest dose consumed for each test drink. Secondary end points were mean VAS scores for individual symptoms at the highest dose consumed for that test phase and for the different doses taken.

Statistical Analysis

The number of patients for this study was chosen after a sample size estimate, on the basis of 23 required in each group to detect a 30% difference in the primary end point, in a one-sided test with a *P* value of .05 and power of 80%, in an independent sample study that is known to provide a conservative approximation for a matched study design. Analysis was performed per-protocol (PP) but was also evaluated on an intention-to-treat (ITT) basis. Treatment arms where no evaluable data were collected (withdrawal from or failure to start the treatment arm, or failure to complete diary cards), or where serious adverse event unrelated to the study treatment but influencing symptom evaluation occurred, were excluded from analysis. Violations in test drink protocol, nonadherence to diet, or premature commencement of test drink (patient not asymptomatic) excluded data pertaining to that test arm from PP analysis, but they were included in the ITT analysis. Decisions regarding admissibility of data for analysis were made before data locking and subsequent breaking of the blind. Where the patient was unable to complete the higher dose, the VAS score from highest tolerated dose was used.

All data were collected and entered on a computer spreadsheet (Excel; Microsoft, Seattle, WA). All statistical calculations were performed with Stata version 8.2 software (Stata Corporation, College Station, TX). McNemar test was used for categorical data. The distributions of continuous data were assessed, and non-normally distributed data with repeated measures were analyzed with Friedman test and then Wilcoxon matched pairs signed rank test. Stratified analysis of dose effect was performed to eliminate confounding. The Bonferroni adjustment was made to critical *P* values to account for multiple comparisons. A possible carryover effect was examined by post hoc subgroup analysis according to the position of the placebo drink in the randomized sequence.

Results

Patients

One of the 26 patients recruited was excluded from all analyses because she withdrew before completing the first test drink arm. No data were collected for some test arms in 3 patients; one withdrew after 2 test arms because of family tragedy; one developed acute cholecystitis during the third arm, underwent cholecystectomy, and was withdrawn from the study; and one failed to complete records for 1 arm, such that end points could not be assessed. Five patients did not follow protocol in 1 test arm each, and these were all deleted from PP evaluation; 1 grossly violated the diet by consuming excluded foods, 2 incorrectly followed drink protocol, and 2 commenced the next test phase prematurely (were not asymptomatic). Thus, included in PP analysis were fructose 23, fructans 22, fructose/fructan mix 24, and glucose 21 patients; and in the ITT analysis were fructose 24, fructans 24, fructose/fructan mix 24, and glucose 23 patients. Complete data for all test arms were obtained from 18 patients for the PP analysis and from 22 patients for the ITT analysis.

The patients were aged 22–63 years (median, 38 years). Four were men. The patients were white, except for 1 male patient who had 1 Chinese parent. Symptoms of IBS had been present for 0.5–31 years (median, 9 years). Twelve patients had diarrhea-predominant IBS, 5 constipation-predominant IBS, and 8 had alternating bowel habits. All patients had followed the low FODMAP diet a median of 24 months (3–36 months) previously. Twelve were taking medications at recruitment, had been on a stable dose for at least 3 months before screening, and continued the medications at a constant dose throughout the study period.

Test Drink Ingestion, Washout Periods, and Patient Adherence

The proportion of patients able to reach the high dose of test drink was similar across the 4 drinks (Table 1). The median washout period overall was 14 days (10–40 days). There was no difference in washout duration after each of the arms; the median was 14 days after each of the test drinks.

The overall adherence to the diet as provided in test phases was >95%. Only 1 patient consumed substantial quantities of food containing FODMAPs during 1 test phase. Six patients had dietary indiscretions during washout periods, but these did not impact on the symptom records during the test phases. Adherence to the test drink regimen was >90% for all drinks. In a single test arm in 2 patients, dose escalation regimens were incorrect.

Effect of Test Drinks on Symptoms

One patient remained asymptomatic across all test arms. Proportions of patients who answered positively to global symptom question "Were your symptoms adequately controlled in this phase?" are shown in Figure 1. The proportions for fructans, fructose, and fructan-fructose mix were similar, but they were all statistically significantly greater than that for

Table 1. Proportion of Patients Reaching Their Maximum Tolerated Dose (Low, Medium, or High) in Each Treatment Group

	Test substance			
Maximum dose tolerated	Fructan	Fructose	Fructan-fructose mix	Glucose
Low	1/24 (4%)	3/24 (13%)	2/24 (8%)	1/23 (4%)
Medium	4/24 (17%)	5/24 (21%)	5/24 (21%)	1/23 (4%)
High	19/24 (79%)	16/24 (66%)	17/24 (71%)	21/23 (92%)

NOTE. There were no differences across the groups (McNemar test).

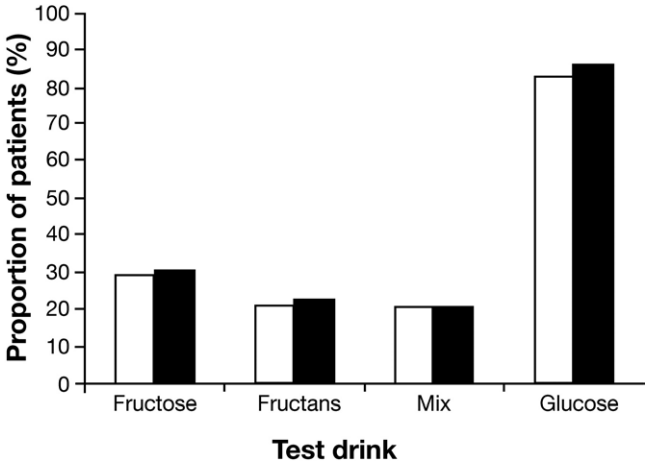

Figure 1. Proportion of patients who answered positively to the global symptom question (primary end point) at the maximal test dose they achieved. PP data are shown in *black*, and ITT data are shown in *white*. *$P < .0039$; McNemar test.

glucose (all $P \leq .002$; McNemar test). A similar result was found for an ITT analysis.

Effect of study treatments on overall and individual symptoms at the highest dose taken are shown in Figure 2. All IBS symptoms evaluated were significantly greater with ingestion of fructose, fructans, and fructose-fructan mix than with glucose. In contrast, nausea and tiredness did not significantly differ across treatment groups. Statistical comparison of treatment pairs is shown in Table 2. Fructan-fructose mix caused a greater symptom severity than did fructose alone. Although the mix induced a numerically higher symptom severity than did fructans alone, the difference was not statistically significant after adjusting for multiple comparisons. There was no difference in symptom severity with fructans or fructose alone. Analysis of the ITT data yielded similar results (not shown). No evidence of a carryover effect was observed.

As shown in Figure 3, intensity of overall symptoms increased as the doses of fructose, fructans, and fructose-fructan mix increased ($P < .01$ for all dose comparisons, Wilcoxon matched pairs signed rank test). In contrast, the severity of overall symptoms did not change for increasing doses of glucose ($P > 0.2$). Significant dose-dependent differences were also observed in specific abdominal symptoms for all test drinks ($P < .002$) except glucose (Figure 3).

Adverse Events

The only serious adverse event was acute cholecystitis, leading to cholecystectomy in one patient. This was considered unlikely to be causally related to the current test drink (glucose). Headaches, borborygmi, belching/burping, reflux/indigestion, and other symptoms were reported by a minority of patients, but no differences were noted across test drinks (data not shown).

Discussion

Providing high level evidence in support of therapeutic dietary interventions is difficult because of complexity of diet, heterogeneity of dietary intake across the community, and difficulty in successfully instituting change in dietary patterns. It is for these reasons that a placebo-controlled "rechallenge" design was used on the background of controlled dietary intake. The results of the study represent the first high-level evidence that dietary FODMAPs, in the form of fructose and fructans, are dietary triggers for symptoms in patients with IBS, and that diets that restrict their level of intake might lead to durable symptomatic improvement.

All patients had IBS diagnosed previously but had improved symptoms on the low FODMAP diet, which they had been consuming for the previous 3–36 months. About 3 of every 4 patients with IBS referred for dietary advice improved on this diet.[22,25] However, only patients who incompletely absorbed fructose on a breath hydrogen test were included. Malabsorption of a 35-g load of fructose is present in about 40% of the healthy population, and the proportion in those with IBS is similar.[21,27] Thus, malabsorption of fructose should be considered a physiologic state, but when the luminal distention that malabsorbed fructose putatively induces is poorly tolerated, as in patients with visceral hypersensitivity, its dietary restriction might reduce symptoms.[27] It was important that the patients in the present study had FM because the patients were being rechallenged with fructose in some of the treatment arms. Because induction of symptoms made up the end points of the study, patients had to be virtually symptom-free before commencing test drinks. This design, in addition to the random

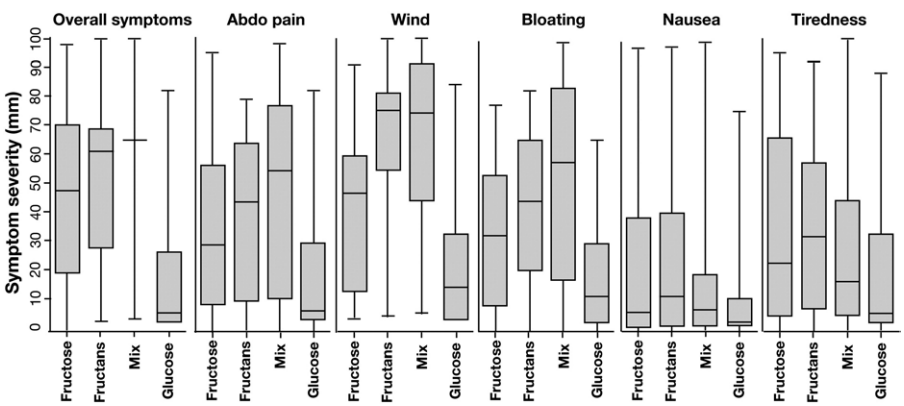

Figure 2. Scores as reported on the 100-mm VAS for symptoms at the end of the phase of the maximal dose of test drinks taken by the patients. Results are shown as median, interquartile range, and maximum and minimum scores of ITT data. For statistical analysis, see Table 2. *F*, fructose; *Fn*, fructans; *G*, glucose.

Table 2. Results of Statistical Analysis Comparing the Scores From the VAS for Overall and Individual Symptoms During the Four Treatment Arms at Maximal Dose Consumed

	Overall	Pain	Bloating	Wind	Nausea	Tiredness
Friedman test	**0.0041**	**0.0261**	**0.0109**	**0.0007**	0.7525	0.9359
Fructan versus						
Fructose	0.4589	0.1986	0.1907	0.0640	0.8476	0.8838
Mix	0.0103	0.0974	0.0405	0.0385	0.5727	0.4217
Glucose	**0.0005**	**0.0016**	**0.0005**	**0.0003**	0.2467	0.0148
Fructose versus						
Mix	**0.0020**	**0.0078**	**0.0028**	**0.0003**	0.2539	0.7651
Glucose	**0.0010**	0.0176	**0.0046**	0.0611	0.3065	0.3312
Mix versus						
Glucose	**0.0020**	**0.0002**	**0.0003**	**0.0002**	0.1265	0.3328

NOTE. Severity of symptoms across the groups was compared by the Friedman test. Paired data were compared with the Wilcoxon matched pair signed rank test, with $P < .0083$ considered statistically significant (Bonferroni adjustment). Statistically significant results are shown in bold.

order by which test drinks were administered, negated carryover effects previously noted in therapeutic crossover studies in patients with IBS.[29,30] The background diet consumed by the patients in the present study was rigorous; this was essential to minimize noise from dietary indiscretions. A further advantage of this design might be the low placebo response observed; in contrast, high placebo responses are observed when reduction of symptoms is the end point of the study. Glucose was chosen as a placebo because it is rapidly and completely absorbed[31] and is not usually implicated in inducing symptoms of IBS.[32]

The only exception would potentially be in a patient who has bacterial overgrowth in the proximal small intestine. In the current patient population, glucose breath hydrogen testing was not routinely performed. It is possible that screening patients with the glucose breath hydrogen test might further reduce the "placebo" response and should be considered in future studies in this area.

Because the test carbohydrates were given in liquid form, 2 important issues must be considered. First, blinding of the test substance might be compromised because of differences in taste and sweetness. Taste was similar across the 4 drinks (orange flavoring), and variations of sweetness were not detectable in preliminary taste testing in healthy volunteers. Second, physiologic responses to fructose or fructans delivered in liquid form might be different from their delivery within food. Because ingestion of liquids with solids slows the gastric emptying of those liquids,[33] patients were carefully instructed to consume drinks only during meals with food to most closely mimic normal eating situations. Although this might still have resulted in faster gastric emptying, faster small intestinal transit, and potentially greater malabsorption of fructose, the same cannot be said of fructans, which have virtually no absorption in the small intestine under any conditions.[10,27]

The high-dose intake for fructans was estimated by using best available evidence of fructan content formed from published data, as recently reviewed,[22,23] and was similar to amounts currently used in clinical trials investigating the physiologic responses to fructans in the diet (15–20 g/day[34–38]). The high-dose intake for fructose was comparable to estimated average ingestion in the USA in the 1970s.[12] A dose escalation regimen was used in case of severe symptomatic responses to the target amount. Indeed, there was a clear dose-dependence in symptom induction, and one fourth to one third of patients failed to reach high dose for fructose and fructans, alone or in combination. This response is likely to represent an IBS-specific one, because preliminary testing of the high dose in a group of healthy controls with and without FM resulted in induction of few trivial symptoms. Because the patients had been restricting FODMAPs for the previous 3–36 months, their colonic microbiota might have altered such that they now hyper-reacted to the delivery of a fermentable substrate. However, the patients were still consuming other fermentable carbohydrates such as resistant starch (as

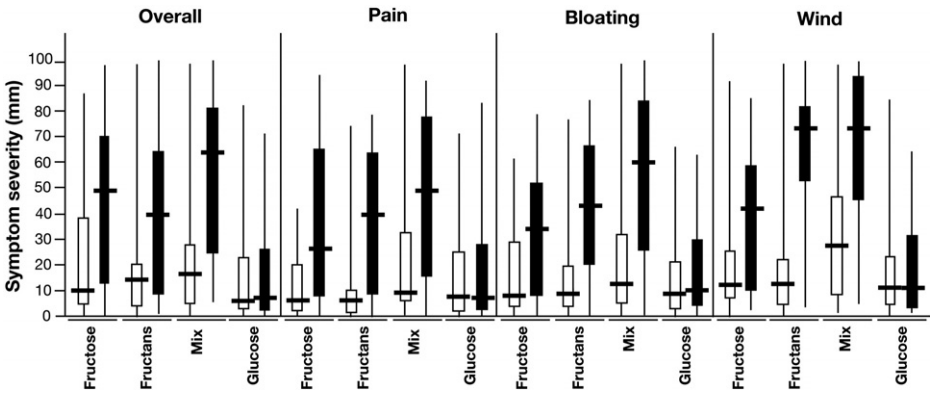

Figure 3. Comparison of abdominal symptoms scores on VAS for low dose (*white*) with those for the maximum volume tolerated (*black*) in patients able to take greater than low dose, according to the test drink. Results are shown as median, interquartile range, and maximum and minimum scores of ITT data. Dose-dependent differences were found for all test drinks except glucose ($P < .002$; Wilcoxon matched pair signed rank test).

a proportion of normal dietary starch intake) and non-starch polysaccharides. Nevertheless, further studies will need to be performed to ensure that the induction of symptoms by fructose and fructans was not purely a reflection of prolonged periods during which the intake of these was restricted.

The present findings were demonstrated in patients who were shown to incompletely absorb a load of fructose, which represents at least 40% of patients with IBS.[21,27] However, symptoms were induced in the present study by fructans alone, for which small intestinal hydrolases do not exist, and almost complete malabsorption always occurs.[10,27,39] This observation suggests that fructose itself is not the trigger for symptoms, but rather the bowel's response to the delivery of FODMAPs (here fructose and/or fructans) to distal small bowel and colon. Therefore, it might be anticipated that the 2 FODMAPs might be additive in their induction of symptoms.[19,40–42] This effect was observed for the mix over fructose alone, but not significantly over fructans. Severity of symptoms was quite high, and it is more difficult to show additive effects in such a setting. Furthermore, there were only a minority of patients who completed high dose of all arms, reducing the study's power to detect such an effect. The applicability of the findings to patients with IBS who completely absorb a fructose load needs addressing, although a preliminary report suggested similar efficacy in this group.[24]

In conclusion, the results of the present study provide strong evidence that fructose and fructans are dietary triggers for symptoms of IBS when FM is present, supporting the benefits of the low FODMAP diet being due to reduction of FODMAP intake. They discount efficacy of the diet being a placebo effect. It also shows that fructans might be as important as fructose, supporting the FODMAP concept that it is poorly absorbed short-chain carbohydrates that trigger the symptoms in IBS, rather than being a specific phenomenon restricted free fructose in patients with FM.

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Susan J. Shepherd has published three cookbooks directed toward issues of fructose malabsorption and celiac disease. The term *FODMAPs* has been registered by Susan Shepherd and Peter Gibson.

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