THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2003 by Am. Coll. of Gastroenterology
Published by Elsevier Inc.

Vol. 98, No. 6, 2003
ISSN 0002-9270/03/$30.00
doi:10.1016/S0002-9270(03)00251-X

Fructose Intolerance: An Under-Recognized Problem

Young K. Choi, M.D., Fredrick C. Johlin, Jr., M.D., Robert W. Summers, M.D., Michelle Jackson, and Satish S.C. Rao, M.D., Ph.D.

Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa

OBJECTIVES: Although the role of lactose intolerance in the pathogenesis of abdominal symptoms is well known, the role of fructose intolerance is unclear. Our aims were 1) to examine the prevalence of fructose intolerance in patients with unexplained abdominal symptoms, and 2) to explore whether fructose concentration influences fructose breath test.

METHODS: Over 2 yr, patients with unexplained symptoms answered questionnaires and underwent fructose breath tests. Patients received 50 g fructose in 150 ml water (33% solution). Breath samples were collected for hydrogen and methane. In a second study, breath test was performed after giving either 10%, 20%, or 33% fructose solution. Data were analyzed retrospectively.

RESULTS: A total of 183 patients (50 male, 133 female) had breath tests, of whom 134 (73%) were positive. Among these, 119 (89%) had elevated H_2, and 15 (11%) had elevated CH_4 or both gases. Questionnaires showed that flatus (83%), pain (80%), bloating (78%), belching (70%), and altered bowel habit (65%) were the most common symptoms. Breath test reproduced symptoms in 101 patients (75%). In the second study, 14/36 (39%) tested positive with a 10% solution, 23/33 (70%) with a 20% solution, and 16/20 (80%) with a 33% solution (10% *versus* 20% or 33%, $p < 0.01$).

CONCLUSIONS: Fructose intolerance may cause unexplained GI symptoms. The higher yield of positive tests in our initial study may be due to referral bias or testing conditions; lower test dose produced a lower yield. Nonetheless, recognition and treatment of fructose intolerance may help many patients. (Am J Gastroenterol 2003;98:1348–1353. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Fructose is a hexose sugar that is now commonly consumed in the Western diet. It is often used as a sweetener or as high fructose corn syrup in soda, fruit juices, or candy, and it is naturally present in such fruits as apples, peaches, pears, and oranges (1). Unlike glucose, which has an active transport mechanism and is completely absorbed, fructose is absorbed in the small intestine through facilitative diffusion, and its absorption capacity is limited (2). When ingested in small quantities, most dietary fructose is completely absorbed. If unabsorbed, fructose may serve as an osmotic load that draws fluid into the intestinal lumen. This may cause distention of the small intestine and lead to such symptoms as abdominal pain, bloating, and discomfort. Furthermore, after reaching the colon, unabsorbed fructose may be fermented by the anaerobic colonic flora, producing excessive amounts of hydrogen, methane, carbon dioxide, short chain fatty acids, and other gases (3). This may lead to bloating, flatus, and diarrhea. However, such symptoms are not specific for fructose intolerance but are similar to the constellation of symptoms described by patients with lactose (4) or sorbitol (5–7) intolerance.

Although lactose intolerance is well recognized as a cause of nonspecific GI complaints (4, 8), malabsorption of other carbohydrates, such as fructose, is less well known. In one study, Rumessen and Gudmand-Hoyer reported that 9 of 25 patients with a functional bowel disorder had malabsorption of fructose, and the clinical features of patients with or without fructose intolerance were indistinguishable (6). In a larger study, Mishkin *et al.* reported fructose malabsorption in 40%–55% of 520 adults with functional dyspepsia (5). These studies suggest a higher prevalence of fructose intolerance among subjects with functional GI disorders. The aims of our retrospective study were 1) to examine the prevalence of fructose intolerance in patients with otherwise unexplained chronic GI symptoms, and 2) to explore whether the results of the fructose breath test are influenced by the concentration of fructose consumed.

MATERIALS AND METHODS

Between January, 1998 and December, 1999, patients with persistent, unexplained, nonspecific GI complaints were evaluated with a fructose breath test. Before this, patients had appropriate workup for their symptoms, including barium studies, CT/ultrasound scan of abdomen, upper/lower endoscopy, hematologic/biochemical studies, and/or stool

Part of this study was presented at the 66th Annual Scientific Meeting of the American College of Gastroenterology, Las Vegas, NV, October, 2001, and published as an abstract in the American Journal of Gastroenterology 2001;96:A1001.

Table 1. A List of Coexisting Conditions in Each of the Study Groups

	Fructose Test 1998–1999		Fructose Test 2001	
	Positive (n = 134)	Negative (n = 29)	Positive (n = 49)	Negative (n = 53)
Peptic disorders	82 (61%)	25 (86%)	23 (47%)	12 (23%)
Pancreatic disorders	40 (30%)	11 (38%)	9 (18%)	3 (6%)
Unexplained/irritable bowel syndrome	40 (30%)	10 (34%)	15 (31%)	13 (25%)
Lactose intolerance	28 (21%)	10 (34%)	6 (12%)	6 (11%)
Liver disorders	14 (10%)	9 (31%)	7 (14%)	

All patients in 1998–1999 received 50 g of fructose in 150 ml of water. In 2001, patients received either 25 g in 250 ml of water, 50 g in 250 ml of water, or 50 g in 150 ml of water.

tests. Patients were excluded if they had bowel resection, malignancy, small bowel obstruction, pancreas divisum, malabsorption syndrome, pancreatic insufficiency, or other comorbid illness. Patients found to have active coexisting problems, such as bacterial overgrowth, were excluded. However, patients who were treated for such conditions as peptic disease and lactose intolerance and had unexplained symptoms were included (Table 1).

The following protocol was used for testing fructose intolerance. Patients were asked to refrain from taking high fat-, lactose-, or fructose-containing foods for 1 day before testing, and the subjects were asked to fast after midnight of the night before testing. After arrival in the motility lab, the subject was instructed to blow into a modified (Haldane-Priestley) bag (QuinTron, Milwaulkee, WI) and an end-expiratory breath sample was collected. A 50-ml sample of air was taken from the bag and injected into a gas chromatography analyzer (Microlyzer Self-Correcting Model SC, QuinTron), and baseline values for hydrogen (H_2) and methane (CH_4) were measured. These values were corrected for CO_2. Next, the subjects were asked to drink a solution containing 50 g of fructose dissolved in 150 ml of water (a 33% solution). Thereafter, breath samples were analyzed for H_2 and CH_4 at 30-min intervals for 5 h. During the test, the subjects were asked to report any symptoms. If the patient was unable to tolerate the procedure owing to severe abdominal pain, nausea, vomiting, gas, or flatus, the test was terminated early. A rise in breath H_2 and/or CH_4 of at least 3 ppm over 3 consecutive breath samples from the baseline value or a value $>$ 20 ppm above baseline was interpreted as a positive test (Fig. 1) (9).

Before the evaluation, patients were asked to fill out a symptom questionnaire that assessed the presence of and the severity of ten common bowel symptoms (Appendix 1). (Table 1a). The questionnaire data were analyzed subsequently to provide information regarding the frequency, intensity, and duration of each symptom. From this data, a mean symptom score was calculated.

To assess the possibility of a dose-related effect of fructose on the subjects' ability to digest this sugar, patients with unexplained symptoms between January, 2001 and June, 2001 randomly received either 50 g of fructose in 150 ml water (33% solution), 50 g in 250 ml water (20% solution), or 25 g in 250 ml water (10% solution). Fructose breath test was performed and interpreted as described above. The results from each group were computed and compared. The study was approved by the University of Iowa Institutional Review Board.

Statistics

The prevalence of symptoms at baseline in those who had a positive fructose test and in those who had a negative fructose test was compared with the Fisher exact test. Sim-

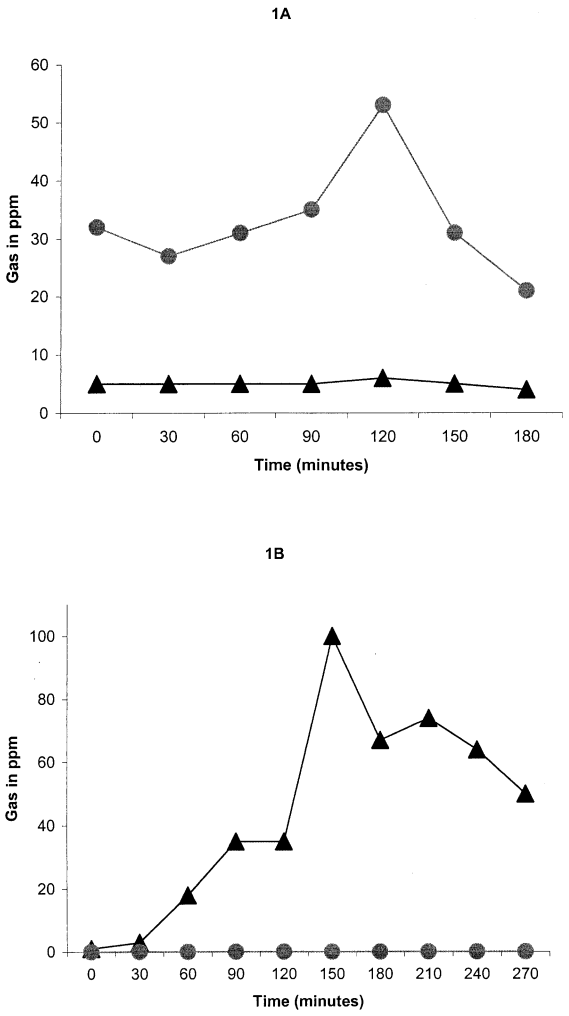

Figure 1. *(A)* Patient with elevation of breath methane (circles) and a flat breath hydrogen (triangles) response after ingestion of fructose. *(B)* Elevation of breath hydrogen level (triangles) with a flat methane response (circles).

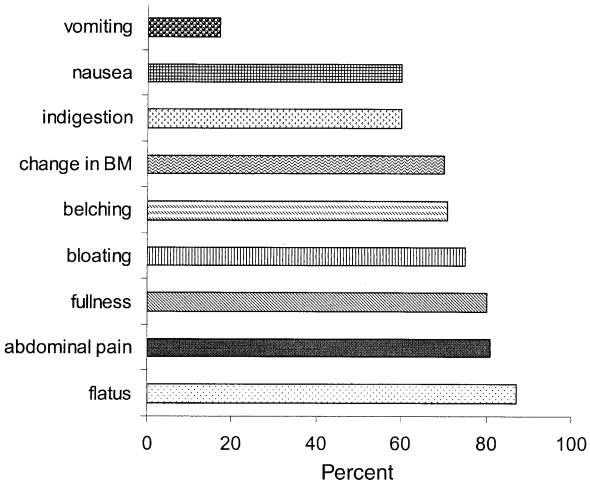

Figure 2. Prevalence of unexplained GI symptoms in patients with a positive fructose breath test. BM = bowel movement.

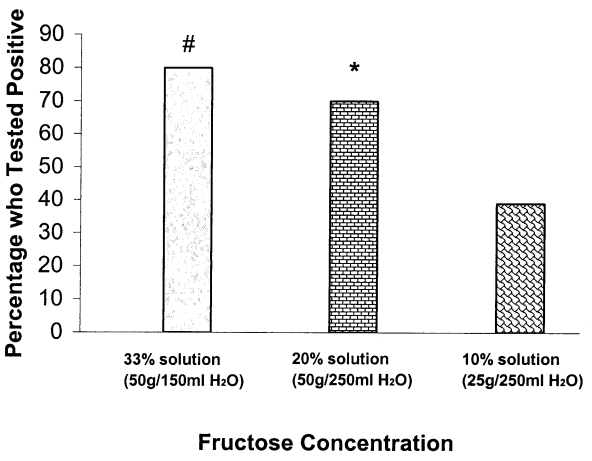

Figure 3. Percentage of patients with a positive fructose breath test after ingestion of three different concentrations of fructose. $*p = 0.01$, $\#p = 0.005$.

ilarly, we compared the symptom prevalence at baseline between the three fructose solutions with the Fisher exact test. Finally, the differences in the positive yield between the three fructose solutions was assessed with the Fisher exact test.

RESULTS

A total of 183 patients (50 men, 133 women; mean age 49 yr, range 20–90 yr) were evaluated for fructose intolerance over 2 yr.

Fructose Breath Test

Of the 183 subjects, 134 patients (73%; 36 male, 98 female) had a positive fructose breath test, and 49 patients (27%; 10 male, 39 female) had a negative test. Among the 134 patients, 119 patients (89%) had elevated breath H_2 values only, 10 patients (7%) had elevated H_2 and CH_4, and 5 patients (4%) had elevated CH_4 only. Thus, 11% of patients had methanogenic flora. Among those who tested positive, 101/134 patients (75%) had their predominant symptom(s) reproduced during the fructose challenge.

Analysis of Symptom Patterns

The questionnaire analysis revealed that all of our patients had at least one GI complaint. Patients who tested positive for fructose breath test were analyzed separately from those who tested negative. The prevalence of each symptom among the patients who tested positive is shown in Figure 2. The prevalence of symptoms among those who tested negative was similar (data not shown), and there was no statistical difference. For example, a change in bowel movement was reported by 73%, abdominal pain by 80%, and bloating by 80% of patients who tested negative. The questionnaire data regarding the frequency, duration, and intensity of each symptom were analyzed separately and compared between the fructose tolerant and intolerant groups. There was no statistical difference between the groups.

Coexisting Conditions

The prevalence of coexisting conditions is shown in Table 1. The referring gastroenterologist felt that these conditions were either treated or unlikely to be responsible for the patient's symptom(s). They were grouped as peptic disorders (gastroesophageal reflux disorder, peptic ulcer disease, gastritis, or *Helicobacter pylori* infection), pancreatic disorders (sphincter of Oddi dysfunction), liver disorders (hepatitis or cirrhosis), unexplained symptoms including IBS, and lactose intolerance (elimination of lactose did not resolve the patient's symptoms).

Effects of Fructose Concentration

Between January and June of 2001, 89 patients underwent fructose breath test with three different concentrations. The prevalence of coexisting conditions in this group was similar to those observed in our earlier study and is shown in Table 1.

A 10% solution (25 g in 250 ml water) was given to 36 patients (9 male, 27 female, mean age 44 yr, range 14–69 yr). Of these, 14 (39%) had a positive breath test and 22 (61%) had a negative test (Figure 3). Among those who tested positive, 43% had their symptoms reproduced during the test (Table 2). Detailed symptom analysis is shown in Table 2.

A 20% solution (50 g in 250 ml water) was given to 33 patients (11 male, 22 female, mean age 46 yr, range 22–86 yr). Among these, 23 (70%) had a positive breath test (Figure 3), and among those who tested positive, 19 (83%) had their symptoms reproduced during the test (Table 2).

A 33% solution (50 g in 150 ml water) was given to 20 patients (9 male, 11 female, mean age 50 yr, range 23–76 yr). Here, 16/20 (80%) tested positive (Figure 3), and among these, 88% had their symptoms reproduced during the test (Table 2).

There was no statistical difference between patients who received either the 20% or the 33% fructose solution, but

Table 2. Number of Subjects Who Tested Positive and Reported Abdominal Symptoms With Each Concentration of Fructose Solution

	Test Result	Abdominal Pain	Diarrhea	Bloating	Gas
Fructose 25 g/250 ml (n = 36)	Positive (n = 14)	4 (29%)	1 (7%)	1 (7%)	1 (7%)
	Negative (n = 22)	2 (9%)	2 (9%)	1 (5%)	1 (5%)
Fructose 50 g/250 ml (n = 33)	Positive (n = 23)	5 (22%)	14 (61%)	4 (17%)	5 (22%)
	Negative (n = 10)	2 (20%)	4 (40%)	5 (50%)	1 (10%)
Fructose 50 g/150 ml (n = 20)	Positive (n = 16)	8 (50%)	5 (31%)	4 (25%)	4 (25%)
	Negative (n = 4)	1 (25%)	1 (25%)		

Most subjects reported more than one symptom.

both of these groups showed a higher yield ($p \leq 0.01$) of positive tests compared with those who received a 10% solution (Figure 3). The prevalence of symptoms at baseline among those who tested positive was similar to those who tested negative for each fructose solution. Also, these data are similar to the data shown in Figure 2 and hence are not reported.

DISCUSSION

In this study, we found that 134 patients (73%) with unexplained GI symptoms had a positive breath test after ingestion of 50 g of fructose. In approximately 75% of these patients, the typical symptom(s) that led to a GI evaluation was reproduced during the test. This data suggests a high prevalence of fructose intolerance in our study population.

This high prevalence of fructose intolerance may be due to a malabsorption disorder or our testing conditions, in particular the dose and concentration of fructose. In a previous study, Rumessen and Gudmand-Hoyer (6) reported that 9/25 patients (36%) with functional bowel disorders had fructose malabsorption. One possible reason for the higher prevalence in our study could be the concentration of fructose solution. We used a 50 g fructose solution, whereas Rumessen and Gudmand-Hoyer used a 25 g fructose solution. Because fructose is absorbed through facilitative diffusion (1), it is theoretically possible that the maximum absorptive capacity can be overwhelmed when challenged with a hyperosmolar (50 g) solution as opposed to a more dilute and lower concentration (25 g) of fructose solution. This hypothesis was further reaffirmed by our second study, which showed marked differences in the yield of positive test based on the fructose concentration. Whereas the positive breath test for a 20% and 33% solution of fructose was 72% and 80% respectively, the yield for a 10% fructose solution was significantly lower ($p < 0.01$) at 39%. Thus, the higher yield of positive tests in our initial study appears to be related to the use of a larger dose of fructose.

These observations raise the question, what constitutes an abnormal fructose test? Is the inability to digest 50 g of fructose abnormal? In one study, it was demonstrated that 38% of normal healthy volunteers malabsorbed 50 g of fructose, whereas in another study 80% of healthy volunteers malabsorbed this dose (3, 10). Because there is no active transport mechanism for fructose or an enzyme that facilitates its absorption, it is likely that fructose absorption can be erratic and unpredictable in most individuals and could depend on solvent factors, including co-ingestion of glucose and other sugars (11). To better understand fructose absorption, studies that examine the dose–response curves of fructose absorption in healthy subjects is desirable, but these have not been performed.

However, as can be seen from our large group of patients, the true prevalence of fructose intolerance may lie between 38% and 80%. If so, this is a significant proportion of patients whose symptoms may potentially benefit from avoiding dietary fructose. Recently, it has been reported that up to 70% of patients may obtain relief of symptoms on a fructose-free diet (12). This observation was also supported by another study, which demonstrated that fructose withdrawal led to improvements in GI symptoms, psychological moods, and depression (13). Thus, in our current dietary culture, in which artificial sweeteners, soft drinks, fruit juice, and other products rich in high fructose corn syrup are consumed in high proportion, identification of patients with fructose intolerance may prove beneficial in the management of patient's symptoms.

A noninvasive fructose breath test seems to be the best way of identifying these patients (14). The symptom profiles *per se* did not reveal any differences among those who were fructose intolerant compared with those who tolerated fructose. In our study, symptoms by themselves were insufficient to diagnose fructose intolerance, because 25% of patients with fructose intolerance had no symptoms during the fructose challenge.

Approximately 11% of our patients had methanogenic flora. This emphasizes the need to test breath samples for H_2 and CH_4. Furthermore, the use of CH_4 analysis during the fructose breath test may have also accounted for the higher positive yield in our study. Another possibility for a higher yield in our studies could be bacterial overgrowth. However, nearly all of our patients either had a negative glucose breath test or were treated for bacterial overgrowth, making this less likely. Finally, the rapid dumping of fructose solution into the colon may also increase the positive yield of the fructose breath test. Recent studies from our group showed that in 7/11 patients (64%) who received a 33% fructose solution, a positive breath test was associated with dumping of fructose and not with bacterial overgrowth (15). This observation was further reaffirmed by the finding of our second study, which showed a higher yield for fructose intolerance among those who received either the 20% or the

33% solution compared with those who received the 10% solution. Furthermore, only 14% of patients with a negative breath test experienced symptoms with a 10% solution, whereas nearly 50%–60% of patients reported symptoms with the 20% or the 33% solution. This suggested that dumping of a hyperosmolar solution may either cause a rise in breath hydrogen and/or methane levels or produce symptoms during the breath test. Thus, in some patients, the consequences of a hyperosmolar load rather than the malabsorption of carbohydrate may produce symptoms.

Although our study revealed a high yield of fructose intolerance, it must be pointed out that this may not reflect the prevalence of fructose intolerance in the community or in patients with nonspecific GI symptoms. Our patients comprised a highly selected group of individuals who were referred to a tertiary care center. We are unaware of any data that has examined the prevalence of fructose intolerance in the community setting. Furthermore, our data suggest that the testing conditions may also influence the results of the fructose breath test. We would also like to emphasize that this was not a controlled study. Nevertheless, the high prevalence of fructose intolerance in our study reaffirms previous studies (2, 4, 5) suggesting that some patients with unexplained symptoms may have fructose intolerance. Without excluding this possibility, many patients may be mistakenly labeled as having irritable bowel syndrome. Hence, we would recommend that patients with unexplained symptoms should be tested with a noninvasive breath test before dismissing their symptoms as either nonspecific or before making a diagnosis of functional bowel disorder, because fructose intolerance is treatable.

ACKNOWLEDGMENTS

We thank all of our colleagues in the Division of Gastroenterology/Hepatology and in particular Drs. K. Bielefeldt and K. Schulze for their support with this study. We also thank Dr. B. Zimmerman from the Clinical Research Center for her help with the biostatistical analysis and Grant RR00059 from the General Clinical Research Center Program, NIH.

Reprint requests and correspondence: Satish S.C. Rao, M.D., University of Iowa Hospital and Clinics, Division of Gastroenterology, 4612 JCP, 200 Hawkins Drive, Iowa City, IA 52242.

Received Sep. 9, 2002; accepted Dec. 30, 2002.

REFERENCES

1. Rumessen JJ. Fructose and related food carbohydrates. Sources, intake, absorption, and clinical implications. Scand J Gastroenterol 1992;27:819–28.
2. Riby JE, Fujisawa T, Kretchmer N. Fructose absorption. Am J Clin Nutr 1993;58:748–53.
3. Ravich WJ, Bayless TM, Thomas M. Fructose. Incomplete intestinal absorption in humans. Gastroenterology 1983;84: 26–9.
4. Suarez FL, Savaiano DA, Levitt L. Comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. N Engl J Med 1995;333:1–4.
5. Mishkin D, Sablauskas L, Yalovsky M, Mishkin S. Fructose and sorbitol malabsorption in ambulatory patients with functional dyspepsia. Comparison with lactose maldigestion/malabsorption. Dig Dis Sci 1997;42:2591–8.
6. Rumessen JJ, Gudmand-Hoyer E. Functional bowel disease: Malabsorption and abdominal distress after ingestion of fructose, sorbitol, and fructose-sorbitol mixtures. Gastroenterology 1988;95:694–700.
7. Hyams JS. Sorbitol intolerance: An unappreciated cause of functional gastrointestinal complaints. Gastroenterology 1983; 84:30–3.
8. Bohmer CJ, Tuynman HA. The clinical relevance of lactose malabsorption in irritable bowel syndrome. Eur J Gastroenterol Hepatol 1996;8:1013–6.
9. Read NW, Al-Janabi MN, Bates TE, et al. Interpretation of the breath hydrogen profile obtained after ingesting a solid meal containing unabsorbable carbohydrate. Gut 1985;26:834–42.
10. Rumessen JJ, Gudmand-Hoyer E. Absorption capacity of fructose in healthy adults. Comparison with sucrose and its constituent's monosaccharides. Gut 1986;27:1161–8.
11. Hommes FA. Inborn errors of fructose metabolism. Am J Clin Nutr 1993;58:789–95.
12. Johlin FC, Panther M, Kraft N. A fructose restricted diet and dietary counseling in patients with dietary fructose intolerance demonstrates significant reduction in symptoms and an improvement in quality of life proportionate to the amount of fructose eliminated. Gastroenterology 2001;120:A1374 (abstract).
13. Ledochowski M, Widner B, Bair H, et al. Fructose- and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. Scand J Gastroenterol 2000;35:1048–52.
14. Romagnuolo J, Schiller D, Bailey R. Using breath test wisely in a gastroenterology practice: An evidence-based review of indications and pitfalls in interpretation. Am J Gastroenterol 2002;97:1113–26.
15. Summers RW, Johlin FC. Fructose intolerance is due to rapid orocecal transit and not small bowel bacterial overgrowth. Gastroenterology 2001;120:A1369 (abstract).

APPENDIX

Appendix 1. A Sample of the Symptom Questionnaire That Was Used for the Evaluation of Symptoms at Baseline

Please circle the most appropriate response that best describes your symptom(s)

Frequency	Intensity	Duration
0 = none	0 = none	0 = none
1 = less than one episode/wk	1 = mild	1 = less than 10 min
2 = one episode/wk	2 = moderate	2 = 10–30 min
3 = more than one episode/wk	3 = severe	3 = greater than 30 min

	Frequency	Intensity	Duration	Comments
Abdominal pain	0123	0123	0123	
Belching	0123	0123	0123	
Bloating	0123	0123	0123	
Fullness after meals	0123	0123	0123	
Indigestion	0123	0123	0123	
Nausea	0123	0123	0123	
Diarrhea	0123	0123	0123	
Vomiting	0123	0123	0123	
Flatulence/gas	0123	0123	0123	