

Ability of the Normal Human Small Intestine to Absorb Fructose: Evaluation by Breath Testing

SATISH S. C. RAO, ASHOK ATTALURI, LESLIE ANDERSON, and PHYLLIS STUMBO

Department of Internal Medicine and Clinical Research Center, University of Iowa Carver College of Medicine, Iowa City, Iowa

Background & Aims: Fructose consumption is increasing, and its malabsorption causes common gastrointestinal symptoms. Because its absorption capacity is poorly understood, there is no standard method of assessing fructose absorption. We performed a dose-response study of fructose absorption in healthy subjects to develop a breath test to distinguish normal from abnormal fructose absorption capacity. **Methods:** In a double-blind study, 20 healthy subjects received 10% solutions of 15, 25, and 50 g of fructose and 33% solution of 50-g fructose on 4 separate days at weekly intervals. Breath samples were assessed for hydrogen (H_2) and methane (CH_4) during a period of 5 hours, and symptoms were recorded. **Results:** No subject tested positive with 15 g. Two (10%) tested positive with 25 g fructose but were asymptomatic. Sixteen (80%) tested positive with 50 g (10% solution), and 11 (55%) had symptoms. Breath H_2 was elevated in 13 (65%), CH_4 in 1 (5%), and both in 2 (10%). Twelve (60%) tested positive with 50 g (33% solution), and 9 (45%) experienced symptoms. The area under the curve for H_2 and CH_4 was higher ($P < .01$) with 50 g compared with lower doses. There were no gender differences. **Conclusions:** Healthy subjects have the capacity to absorb up to 25 g fructose, whereas many exhibit malabsorption and intolerance with 50 g fructose. Hence, we recommend 25 g as the dose for testing subjects with suspected fructose malabsorption. Breath samples measured for H_2 and CH_4 concentration at 30-minute intervals and for 3 hours will detect most subjects with fructose malabsorption.

During the last decade, sucrose consumption has increased by at least 25 lb/y.¹ The source of sweetener has also changed from cane sugar (as sucrose, a disaccharide of glucose and fructose) to corn sweetener (primarily equal molar quantities of the monosaccharides sucrose and fructose). Thus the average consumption of fructose as a monosaccharide has increased dramatically.

Fructose is a 6-carbon sugar that occurs naturally in fruits such as apples, peaches, and prunes, and honey contains as much as 35 g/100 g edible portion.² It is also produced enzymatically from corn as high fructose corn syrup, and this form of fructose is commonly used in many food sweeteners, soft drinks, diabetic and diet foods.^{1,3} Dietary fructose might be ingested as a monosaccharide (eg, high fructose corn syrup) or as a disaccharide (sucrose, eg, table sugar). Sucrose is split by sucrase to produce equal amounts of glucose and fructose and in this form is usually completely absorbed.

Fructose is mostly absorbed in the small intestine through glucose transporter-5 transporter-mediated facilitative diffusion. This is an energy-independent process, and consequently its absorptive capacity is carrier limited.⁴ Glucose promotes intestinal fructose absorption by solvent drag and passive diffusion.^{2,5} However, excessive dietary intake of fructose as a monosaccharide can easily overwhelm the absorptive capacity of the small intestine, leading to incomplete absorption of fructose (fructose malabsorption). The unabsorbed fructose can serve as an osmotic load and is thereby rapidly propelled into the colon, where its contact with anaerobic flora causes fermentation and production of gas, bloating, and diarrhea⁶ (dietary fructose intolerance).

Breath hydrogen (H_2) tests have been advocated for the assessment of dietary fructose malabsorption.^{5,7,8} In a previous study of patients with unexplained gastrointestinal symptoms, 134 of 183 (73%) patients had a positive fructose breath test, indicating fructose malabsorption. We found that 39% of patients exhibited fructose malabsorption when tested with a dose of 25 g and 66% with a dose of 50 g of fructose at 10% concentration,⁶ suggesting that fructose malabsorption might be dose-related and confirming previous observations.^{5,7,8} Furthermore, a higher concentration of fructose was associated with a higher incidence of malabsorption.⁸ Hence, not only the dose but also the concentration of fructose might affect its absorption. In addition, 101 of 134 (75%) of patients with a positive breath test result had their predominant symptom(s) reproduced during the breath test, suggesting dietary fructose intolerance.⁶

A recent study of irritable bowel syndrome subjects with fructose intolerance and a positive breath test result showed that dietary restriction of fructose improved symptoms.⁹ This observation was confirmed by 2 other recent studies.^{10,11} These studies suggest that the recognition of dietary fructose intolerance might be clinically useful. However, the appropriate dosage and concentration of fructose that should be used in clinical practice to distinguish a normal from an abnormal capacity to absorb dietary fructose are not clearly known.¹²

Here we tested the following hypotheses: (1) 15-g and 25-g doses of fructose are more completely absorbed than a 50-g dose of fructose, and (2) 10% fructose solution (lower osmolarity) is more completely absorbed than a 33% fructose solution

Abbreviations used in this paper: CH_4 , methane; H_2 , hydrogen; ppm, parts per million.

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(higher osmolarity). To test these hypotheses, we performed a randomized, double-blind, dose-response study of 3 different doses and 2 different concentrations of fructose and assessed its absorption and tolerance in healthy subjects.

Methods

Healthy volunteers with no previous history of gastrointestinal disorders or surgeries, antibiotic use (within 3 months), and who were not taking any medications (except oral contraceptive pills or multivitamins) were recruited through a hospital advertisement. They were asked to fill out a health symptom questionnaire and undergo a routine physical examination. Only subjects who were asymptomatic fulfilled the aforementioned inclusion criteria, and had a normal physical examination were eligible to participate.

Study Protocol

The study required 4 visits to the motility laboratory at weekly intervals. Subjects were asked to complete a bowel symptom questionnaire in which they recorded their baseline symptoms. One day before each visit, subjects were asked to consume a lactose-free and fructose-restricted diet to avoid high baseline values of breath H₂ or methane (CH₄) from the presence of unabsorbed carbohydrates. No food or drink was allowed for at least 8 hours before the study. Subjects were asked to brush their teeth before the test and to refrain from smoking, drinking, sleeping, or exercising during the study.

At each visit, a baseline breath sample was obtained. Thereafter, in a random order on 4 separate days, 1 of the following 4 solutions was administered to each subject: 15 g of fructose dissolved in 150 mL of water (10% solution), 25 g of fructose in 250 mL of water (10% solution), 50 g of fructose in 500 mL of water (10% solution), or 50 g of fructose in 125 mL of water (33% solution). The drink was served at room temperature (approximately 70°F) in a 600-mL opaque coffee mug to camouflage the volume of each solution, and the subjects were asked to drink each solution within 10 minutes. The subject, the research assistant who administered the drink, and the individual who collected and analyzed the breath samples were each blinded to the type of solution. Next, breath samples were collected at 30-minute intervals for 4–6 hours. End expiratory breath samples were collected in a modified (Haldane-Priestley) bag (QuinTron, Milwaukee, WI). A 20-mL sample of air was withdrawn from the bag and injected into a gas chromatography analyzer (QuinTorn Microlyzer Self Correcting Model SC; QuinTron) for detection of H₂ and CH₄. Correction factors were used to correct for CO₂ and dead space by using industry standards. If there was an increase in breath H₂ or CH₄, samples were collected until the values returned to baseline or 5 hours had elapsed. During the study if the subject experienced any symptoms (abdominal pain, cramping, belching, bloating, fullness, nausea, diarrhea, vomiting, and flatulence) after ingestion of fructose, its severity was documented on a visual analogue scale.

Measurements and Analysis

The breath samples were analyzed for H₂ and CH₄ concentration. Fructose malabsorption was defined as a sustained increase of ≥ 20 parts per million (ppm) of H₂ or CH₄ or

both over the baseline value or a successive incremental increase of at least 5 ppm over the basal value that was sustained over 3 consecutive breath samples. For example, if a basal breath test sample showed a H₂ concentration of 4 ppm and samples obtained at 2, 2½, and 3 hours were 11, 16, and 22 ppm, then the test was designated as an abnormal breath test. By plotting the breath H₂ or CH₄ values over time, we assessed the profiles for the area under the curve of breath H₂ or CH₄ for each subject and for each concentration of fructose. The area under the curve was not used to define a positive test result but was used to provide a semiquantitative assessment of the overall volume of gas produced and an index of fructose malabsorption. We modified our definition of a positive fructose breath test result from previously published definitions⁶ to decrease the false-positive rate. Repeated-measures analysis of variance was used to compare the area under the curve data for each concentration. The onset time was defined as the interval between ingestion of fructose and the onset of a sustained increase in breath H₂ or CH₄. The peak time was defined as the time interval between the ingestion of fructose and the occurrence of peak values of H₂ or CH₄. A dose-response curve was plotted for each subject to assess their ability to absorb fructose.

Results

Twenty subjects (male/female, 10/10; mean age, 31 years; range, 19 to 70 years) participated in the study.

Dose-Related Fructose Absorption

Fifteen-gram dose. All 20 subjects were able to absorb 15 g of fructose without significant elevation of breath H₂ or CH₄ (Figure 1A). None of the subjects reported any symptoms.

Twenty-five-gram dose. Eighteen subjects were able to absorb 25 g of fructose, whereas 2 subjects (10%) had a positive breath test result (Table 1). The peak H₂ concentration in these 2 subjects was 26 and 106 ppm, respectively. However, neither subject reported any symptoms. Thus, it appears that most subjects can absorb and tolerate this dose of fructose. The overall area under the curve of breath H₂ and CH₄ profile was significantly higher ($P < .05$) than that obtained with the 15-g dose of fructose (Figure 2). A subanalysis after excluding the 2 subjects with a positive test result showed that there was no significant difference between the 2 groups ($P > .05$). None of the subjects with a negative breath test result reported symptoms during the test.

Fifty-gram dose (10% w/v). Four subjects were able to absorb 50 g of fructose, whereas 16 subjects (80%) exhibited a positive breath test result (Table 1). The mean area under the curve of breath H₂ and CH₄ profile was significantly higher ($P = .006$) than that obtained with either the 15-g or 25-g dose of fructose, but it was not different to that of the 33% fructose solution (Figure 2). Also, 69% of subjects with a positive breath test result reported symptoms during the test: gas (30%), belching (15%), abdominal pain (15%), diarrhea (15%), and bloating (10%). In addition, 25% of subjects with a negative breath test result also reported similar symptoms (Table 1).

Fifty-gram dose (33% w/v). Eight subjects (40%) were able to absorb 50 g of fructose at this higher concentration, whereas 12 subjects (60%) had a positive breath test result (Table 1). The mean area under the curve of breath H₂ and CH₄

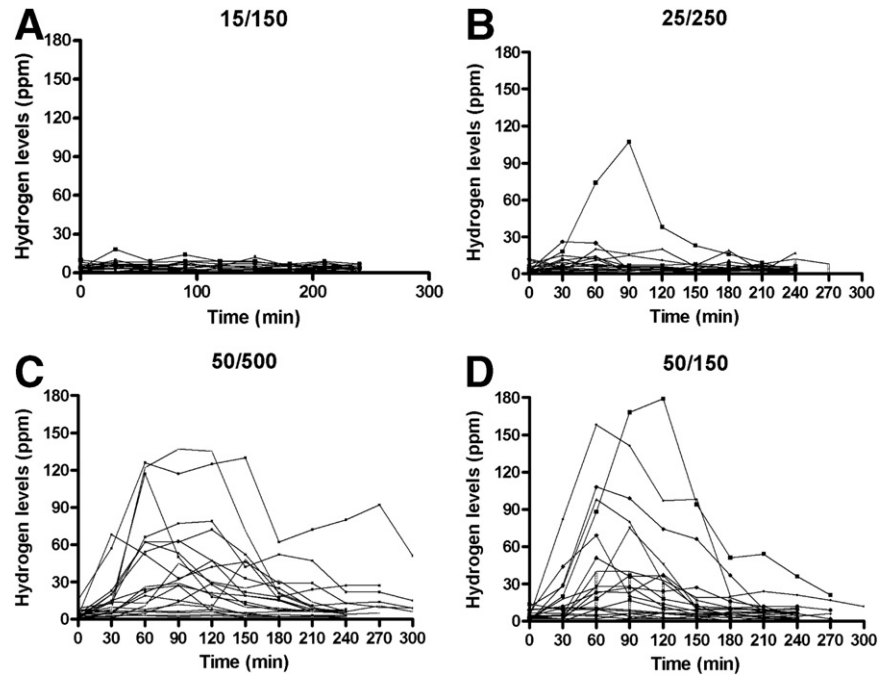


Figure 1. Individual profiles of H₂ concentration (ppm) in expired air after ingestion of different fructose loads. (A) 15 g fructose in 150 mL water (10% solution); (B) 25 g fructose in 250 mL water (10% solution); (C) 50 g fructose in 500 mL water (10% solution); (D) 50 g fructose in 150 mL water (33% solution).

profile was significantly higher ($P < .05$) when compared with that after ingestion of either 15 g or 25 g fructose. Seventy-five percent of subjects with a positive test result experienced symptoms during the test: gas (30%), bloating (15%), belching (15%), abdominal pain (10%), headache (10%), and diarrhea (5%). Also, 25% of subjects with a negative breath test result reported symptoms.

Characteristics of Breath Hydrogen and Methane Responses

Six subjects (30%) had methanogenic flora,¹³ of which 4 subjects exhibited fructose malabsorption. After fructose malabsorption, an increase in breath H₂ or CH₄ always occurred within 3 hours. For a positive breath test result, the onset time for an increase in breath H₂ or CH₄ ranged between 30–54 minutes (Table 1). The time interval between the ingestion of fructose and a peak H₂ or CH₄ concentration ranged between 74–90 minutes (Table 1). Both the onset time and the time for reaching peak concentration were not significantly ($P > .05$) different between the 4 doses, although there was a trend toward a faster onset and a higher peak for the higher doses and for the 33% concentration (Table 1). The mean baseline H₂

values were similar across study days: 3.4, 3.8, 4.5, and 4 ppm, respectively, for the 15-g, 25-g, 50-g (10%), and 50-g (33%) doses. The mean baseline CH₄ values were also similar: 4.5, 3.9, 4.9, and 5.3 ppm, respectively.

There was no difference ($P > .05$) between male and female subjects in either the incidence of fructose malabsorption or the prevalence of symptoms during the test. For example, after a 50-g (10%) dose, 9 of 10 (90%) men and 7 of 10 (70%) women had a positive breath test result ($P > .05$), and 6 of 10 (60%) men and 5 of 10 (50%) women reported symptoms during the breath test.

Adverse Effects

Two subjects developed significant bloating, discomfort, and pain with a 50-g dose that subsided after a few hours. Several others experienced transient symptoms as summarized above.

Discussion

The capacity of the human small intestine to absorb fructose is unclear. Some studies have suggested that healthy

Table 1. Characteristics of the Breath H₂ and CH₄ Profiles and Symptoms After Ingestion of Fructose

	Fructose	15 g	25 g	50 g (10%)	50 g (33%)
% of subjects with a positive breath test result	H ₂ only	0	10	65	50
	CH ₄ only	0	0	5	0
	Both	0	0	10	10
% of subjects with symptoms during the test	Positive test	0	0	69	75
	Negative test	0	0	25	25
Onset time (min) ^a		N/A	30 ± 0	54 ± 31	45 ± 15
Peak time (min) ^a		N/A	90 ± 0	81 ± 45	74 ± 27

N/A, not applicable.

^aMean ± standard error of the mean.

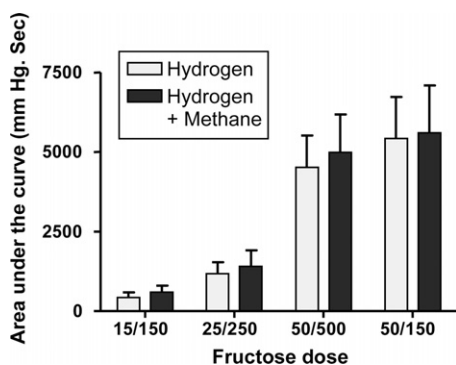


Figure 2. H₂ and CH₄ concentration (area under the curve in mm³) after ingestion of different doses of fructose (mean \pm standard error of the mean).

humans malabsorb fructose at doses as low as 5 g,⁵ although others have found malabsorption at doses of 37.5 g or higher.⁸ Consequently, the assessment of dietary fructose malabsorption has remained problematic.² Our objectives were to examine fructose absorption in healthy subjects and to facilitate the development of a breath test that can be used in patients with suspected dietary fructose malabsorption to distinguish a normal from an abnormal capacity to absorb dietary fructose.

We found that our healthy subjects were able to completely absorb a 15-g dose of fructose. This finding differs from that of Rumessen and Gudmand-Hoyer,¹⁴ who reported that 1 subject (10%) malabsorbed after ingestion of either 5 or 10 g of fructose, and 4 subjects (40%) malabsorbed after receiving a 20-g dose. Unlike their study, we used strict criteria for selecting our healthy subjects and restricted their dietary intake of carbohydrate on the day before the study to prevent high basal values of H₂ or CH₄ that could influence test interpretation. Second, we performed a randomized, double-blind study at weekly intervals in equal number of men and women and measured both H₂ and CH₄, whereas the previous study was single-blinded and not always randomized, the studies were repeated after 2 days, and there was male predominance. Third, the observation that healthy subjects malabsorb doses of fructose as low as 5–15 g most likely stems from repeated studies in a single subject who, although healthy, might have unrecognized fructose malabsorption.

After ingestion of 25 g fructose, 2 of our subjects exhibited evidence for fructose malabsorption. In one subject there was a significant increase in breath hydrogen with a peak H₂ concentration of 106 ppm. The second subject exhibited a modest increase with a peak H₂ concentration of 26 ppm. However, both subjects were asymptomatic. These findings are consistent with those of others who found either no malabsorption⁸ or 19% malabsorption with a 25-g dose.⁷ Also, similar to our study, none of the subjects in these previous studies were symptomatic.

In contrast, when a 50-g dose of fructose was administered, the majority of subjects exhibited malabsorption. In these subjects there was significant elevation of breath H₂ or CH₄ concentration. Furthermore, approximately 50% of subjects reported mild to moderate belching, bloating, or diarrhea. These observations emphasize that a 50-g dose is inappropriate and unphysiologic for the evaluation of subjects with suspected fructose malabsorption.

Thus, although the absorption capacity is variable in healthy subjects, a dose of 25-g fructose might represent a critical threshold for bolus ingestion of this sugar, above which significant malabsorption can occur. This finding supports our hypothesis. Interestingly, about 31% of subjects who received the 50-g dose of fructose at a concentration of 33% and 25% of subjects who received the 10% concentration did not report any symptoms, despite the evidence for malabsorption. Thus, the breath test appears to be quite sensitive for detecting fructose malabsorption and by itself might overestimate the true prevalence of dietary fructose intolerance. Hence, an assessment of symptoms both during and immediately after the test together with a positive breath test result provides the best evidence for a diagnosis of dietary fructose intolerance. Likewise, symptoms alone after ingestion of fructose might not accurately predict fructose malabsorption, because 10%–20% of healthy subjects experienced mild gastrointestinal symptoms without any evidence for fructose malabsorption. Also, subjects who have a normal fructose breath with a 25-g dose might still have dietary fructose intolerance if they ingest a higher amount (>25 g) of fructose in their diet. This limitation of the breath test should be considered in the evaluation of these patients. A prospectively maintained food diary along with dietary consultation can be very useful in the clinical evaluation of these patients.

Approximately 30% of our study population had methanogenic flora, and 4 subjects had elevated CH₄ levels after ingestion of fructose. In 2 subjects (10%), there was an exclusive increase of CH₄ only, suggesting that any hydrogen produced was shunted into the methanogenic pathway.¹³ Thus, when compared with another study,⁸ the higher yield of a positive breath test in our study might in part be due to the assessment of CH₄ production. Consequently, an assessment of both will facilitate a more accurate detection of fructose malabsorption and reduce the incidence of false-negative test results.

A previous study reported that fructose malabsorption increased from 37.5% to 71.4% when the concentration of ingested fructose increased from 10% to 20%.⁸ However, at a similar dose (50 g) and at a higher concentration of fructose (33% solution), we were unable to identify a concentration-dependent malabsorption of fructose, which negated our hypothesis. Thus, our study suggests that fructose malabsorption is more likely to depend on the amount of fructose consumed rather than the concentration of fructose. It is also possible that the healthy upper gut is capable of handling the higher osmotic concentration, or that fructose absorption is independent of its concentration gradient in the lumen.¹⁵

We collected breath samples for a total duration of 5 hours. Reviewing the profiles for the area under the curve, it became apparent that the increase in H₂ or CH₄ typically occurred within 60 minutes, and the mean time for reaching a peak H₂ or CH₄ concentration was 77 minutes (range, 30–180 minutes). Hence, an abnormal breath test result was usually apparent within 180 minutes. Consequently, by analyzing breath samples that are obtained for a total duration of 3 hours and at 30-minute intervals, it should be possible to detect most subjects with fructose malabsorption.

One other possibility for an abnormal fructose breath test result is small bowel bacterial overgrowth. This is unlikely because we examined asymptomatic healthy individuals. Also, a previous study showed that after ingestion of fructose along

with a radioisotope meal, both symptoms and an increase in breath H_2 always coincided with the arrival of isotope in the cecum.¹⁶ Thus, in our study, a positive breath test result most likely resulted from fructose malabsorption.

Our study confirms previous observations that the incidence of gastrointestinal symptoms after ingestion of fructose is quite variable in healthy subjects.⁵⁻⁸ Thus, symptoms or a breath test alone is unlikely to accurately detect dietary fructose malabsorption. However, the genesis of symptoms and the threshold for reporting symptoms might vary across individuals and can depend on various factors including health status, patient expectation, genetic predisposition, environmental factors, individual variation in sensory thresholds, the rate of gas production, the shunting of gas into alternate pathways, as well as its absorption, consumption, and transport.^{10,14,17-20}

In summary, our study revealed that healthy subjects completely absorbed a dose of 15 g fructose. About 10% of subjects malabsorbed a dose of 25 g, but they were asymptomatic. Therefore, 25-g fructose can distinguish a normal from an abnormal capacity to absorb fructose, and a positive breath test result with this dose suggests an abnormally low capacity to absorb dietary fructose. Thus, 25 g of fructose is the appropriate dose for testing subjects with suspected dietary fructose malabsorption. Breath samples obtained at 30-minute intervals and for a duration of 3 hours and analyzed for both H_2 and CH_4 concentration will detect most individuals with dietary fructose malabsorption.

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Address requests for reprints to: Satish S. C. Rao, MD, PhD, FRCP (LON), Department of Internal Medicine, Division of Gastroenterology/Hepatology, 200 Hawkins Dr, 4612 JCP, Iowa City, Iowa 52242-1009. e-mail: satish-rao@uiowa.edu; fax: (319)353-6339.

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