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

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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 diarrhea[6] (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 H_2 or methane (CH_4) 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 H_2 and CH_4. Correction factors were used to correct for CO_2 and dead space by using industry standards. If there was an increase in breath H_2 or CH_4, 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 H_2 and CH_4 concentration. Fructose malabsorption was defined as a sustained increase of ≥20 parts per million (ppm) of H_2 or CH_4 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 H_2 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 H_2 or CH_4 values over time, we assessed the profiles for the area under the curve of breath H_2 or CH_4 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 definitions[6] 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 H_2 or CH_4. The peak time was defined as the time interval between the ingestion of fructose and the occurrence of peak values of H_2 or CH_4. 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 H_2 or CH_4 (Figure 1*A*). 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 H_2 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 H_2 and CH_4 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 H_2 and CH_4 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 H_2 and CH_4