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Comparison of breath testing with fructose and high fructose corn syrups in health and IBS

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Abstract

Although incomplete fructose absorption has been implicated to cause gastrointestinal symptoms, foods containing high fructose corn syrup (HFCS) contain glucose. Glucose increases fructose absorption in healthy subjects. Our hypothesis was that fructose intolerance is less prevalent after HFCS consumption compared to fructose alone in healthy subjects and irritable bowel syndrome (IBS). Breath hydrogen levels and gastrointestinal symptoms were assessed after 40 g of fructose (12% solution) prepared either in water or as HFCS, administered in double-blind randomized order on 2 days in 20 healthy subjects and 30 patients with IBS. Gastrointestinal symptoms were recorded on 100-mm Visual Analogue Scales. Breath hydrogen excretion was more frequently abnormal ($P < 0.01$) after fructose (68%) than HFCS (26%) in controls and patients. Fructose intolerance (i.e. abnormal breath test and symptoms) was more prevalent after fructose than HFCS in healthy subjects (25% vs 0%, $P = 0.002$) and patients (40% vs 7%, $P = 0.062$). Scores for several symptoms (e.g. bloating $r = 0.35$) were correlated ($P \leq 0.01$) to peak breath hydrogen excretion after fructose but not HFCS; in the fructose group, this association did not differ between healthy subjects and patients. Symptoms were not significantly different after fructose compared to HFCS. Fructose intolerance is more prevalent with fructose alone than with HFCS in health and in IBS. The prevalence of fructose intolerance is not significantly different between health and IBS. Current methods for identifying fructose intolerance should be modified to more closely reproduce fructose ingestion in daily life.

Keywords

bloating; fructose intolerance; functional bowel disorder; high fructose corn syrup; irritable bowel syndrome

BACKGROUND

The introduction of high fructose corn syrups (HFCS) as alternative sweeteners to sucrose in the 1960s resulted in a dramatic increase in the monosaccharide form of fructose in the US food supply.[1] HFCS became, and remain, widely used as sweeteners in beverages, dairy products, canned, baked and processed foods worldwide.[2]

Fructose monosaccharide is absorbed by carriermediated facilitated diffusion, an energy-independent process. The fructose carrier is a member of the glucose transport (GLUT) family of genes encoding for facilitative sugar transporters and is referred to as GLUT 5[3] and the rate of fructose absorption is between that of mannose and glucose.[4] Sucrose is cleaved to glucose

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and fructose by sucrase, an enzyme located in the brush border of small intestine enterocytes. For unclear reasons, the absorptive capacity for fructose derived from sucrose exceeds that of fructose monosaccharide. Unabsorbed fructose is fermented by colonic bacteria producing short-chain fatty acids, hydrogen, carbon dioxide and trace gases. Hydrogen must be excreted in breath and flatus and/or consumed by colonic bacteria as it cannot be metabolized by humans. A rise in breath hydrogen (and/or methane) following substrate ingestion is the basis for detecting incomplete fructose absorption and estimating fructose absorptive capacity. The absorptive capacity for fructose in healthy individuals ranged from less than 5 g to greater than 50 g[5] and was both dose and concentration dependent.[5,6]

Fructose intolerance is diagnosed when gastrointestinal symptoms accompany a positive breath test. The amount and concentration of fructose used to detect incomplete absorption by breath-testing has varied among studies. The frequency of incomplete fructose absorption increases as the dose and concentration increase. Up to 50% of healthy subjects incompletely absorbed 25 g fructose (10%) and up to 80% incompletely absorbed 50 g.[5–7] Increasing the concentration from 10% to 20% increased the frequency of incomplete absorption from 37.5% to 71.4%.[6] In uncontrolled studies, the prevalence of incomplete fructose absorption (25 g) was higher in patients with functional bowel disorders, i.e. 36–75%[8–11] compared to the prevalence (i.e. 0–50%) reported in healthy subjects.[5–7] Although it has been suggested that fructose intolerance causes gastrointestinal symptoms in some patients,[11] the only controlled study did not demonstrate a higher prevalence of incomplete fructose absorption and gastrointestinal symptoms in irritable bowel syndrome (IBS).[10] Moreover, glucose greatly facilitates fructose absorption in health;[5,7,12,13] and both natural and processed dietary sources of fructose usually contain glucose. FDA Regulation 21, Section 184.1866 requires 'HFCS' to represent the two fractions HFCS-42 and HFCS-55. Although the name suggests otherwise, glucose is the predominant sugar in HFCS-42 (42% fructose, 53% glucose and 5% oligosaccharides).[14] HFCS-55 (42% glucose, 55% fructose and 3% oligosaccharides) contains a small excess of fructose.[14] Thus, breath testing with pure fructose may not reflect fructose ingestion under normal circumstances. Because glucose increases fructose absorption,[5,7,12,13] breath testing with fructose alone may overestimate the true prevalence of incomplete fructose absorption in controls and IBS.

Our hypothesis was that fructose intolerance (i.e. positive hydrogen breath test and gastrointestinal symptoms) would occur more frequently with pure fructose compared to fructose provided as HFCS in healthy subjects and in IBS.

METHODS

This was a double-blind, randomized, crossover study comparing symptoms and fructose absorption after fructose alone to HFCS. The study was approved by and all the procedures followed were in accordance with ethical standards of the Mayo Clinic Institutional Review Board.

Subjects

Twenty healthy subjects were recruited by public advertisement and 30 patients with a functional bowel disorder were recruited from our outpatient practice. All participants had an interview and a physical examination prior to enrolment, and patients underwent appropriate investigations to exclude organic disease.[15] Exclusion criteria for healthy subjects and patients included significant cardiovascular, respiratory, neurological, psychiatric, or endocrine disease; anxiety or depression as assessed by the Hospital Anxiety and Depression Questionnaire;[16] medications likely to affect gastrointestinal motility (e.g. opiates, anticholinergic agents, adrenergic agents and calcium channel blockers); and abdominal surgery (other than appendectomy, cholecystectomy, or hernia repair). In addition, subjects

who used antibiotics at any time during a 2-month period before the study were excluded. A validated questionnaire was used to exclude IBS, functional bloating, diarrhoea, or constipation in controls.[17] Subjects were reimbursed for participating in this study.

Breath tests

Subjects were asked to abstain from pastas, legumes, dairy, fruits, fruit juices and products containing HFCS or fructose along with tobacco products and to limit caffeinated beverages (i.e. two per day) for 24 h prior to breath tests. Mints and chewing gum were also not permitted during the 12-h fasting period before the test for both study days. After mouth rinsing with an antibacterial mouthwash, subjects were randomized, in a double-blind fashion, to one of two sugar solutions [i.e. 40 g of fructose in 330 mL of tap water (12%) or 40 g of fructose as 95 g HFCS-55 (77% dry weight) in tap water to total 600 cc (12%)] provided in identical, covered, opaque containers with a straw. The randomization sequence was generated by the study biostatistician (ARZ) and provided to the pharmacy. These fructose concentrations approximate that of cola sweetened with HFCS-55 (some colas are sweetened with sucrose). Subjects were not informed of the volumes of these solutions and neither subjects nor study personnel administering the test were allowed to hold the container. Subjects were asked to consume solutions within 10 min and to remain sedentary during the study.

Breath samples were collected every 30 min after the test meal for 3 h after the sugar solution was given and analysed for hydrogen concentration. End expiratory breath samples were collected in a modified (Haldane-Priestley) bag (Quintron, Milwaukee, WI, USA). A 20 mL sample of air was withdrawn from the bag and injected into a gas chromatography analyser (Quinn Torn Microlyzer Self Correcting Model SC; Quintron) for detecting breath hydrogen levels. Correction factors were used to correct for CO_2 and dead space using industry standards. Incomplete fructose absorption was defined as a rise in breath hydrogen of ≥20 ppm over the baseline value, which is highly specific for identifying carbohydrate malabsorption.[18]

Symptoms

Symptoms were recorded on separate 100-mm Visual Analog Scales (VAS) for each symptom (i.e. abdominal bloating, flatulence, nausea and abdominal pain) at baseline and every 30 min after the test meal for 3 h.[11] These symptom scores were summarized by adding values for each symptom over 3 h. A 10-mm increase in symptom scores for any symptom over baseline was considered abnormal. Because baseline symptom scores averaged <5, the 10-mm absolute increase is greater than the 10% change considered abnormal in previous studies.[19,20] Subjects also recorded the consistency of every bowel movement during the 3-h postmeal period on a Bristol scale.[8] The same procedure was repeated with the other sugar solution 2–7 days later.

Statistical analysis

The prevalence of an abnormal breath hydrogen response after fructose *vs* HFCS were compared separately in controls and in IBS by McNemar's test for paired discrete data. The area under the curve (AUC) for hydrogen breath excretion after fructose and HFCS were compared by paired *t*-tests or signed-rank tests. The relationship between symptoms and the breath hydrogen response was analysed by Spearman's correlation coefficient. The Breslow–Day test was used to compare the association (i.e. between symptoms and a positive breath test) between health and IBS. Statistical analyses were carried out using the SAS software package (SAS Institute, Cary, NC, USA).

The sample size of 20 controls and 30 patients was expected to provide 10 discordant pairs of controls and 16 discordant pairs of patients using conservative estimates based on previous studies. The null hypothesis was that the discordant pairs would be equally split between those intolerant to fructose and not HFCS *vs* the reverse (intolerant to HFCS and not fructose). This

hypothesis was tested separately in patients and controls using McNemar's test (applying the exact binomial distribution). Due to the discreteness of the binomial distribution, conservative twosided α-levels were necessary to select the rejection regions (degree of imbalance) in the anticipated number of discordant pairs for each subject group. For example, there was 81% power to reject the null hypothesis if the true proportion of fructose intolerant but not HFCS intolerant pairs was 0.92 or greater (reject the null at an α-level of 0.021). Similarly, there was 82% power if the true proportion of fructose intolerant but not HFCS intolerant pairs is 0.86 or greater (α = 0.021).

RESULTS

Clinical and demographic features

All subjects completed both breath tests. Age, but not gender or BMI, was associated ($P < 0.01$) with subject group (healthy subjects *vs* patients) (Table 1). Patients had symptoms of diarrhoea predominant IBS ($n = 12$), constipation-predominant IBS ($n = 4$), alternating IBS ($n = 10$), or functional diarrhoea ($n = 4$).[21] In addition, 22 patients reported significant abdominal bloating.

Hydrogen breath tests

After fructose, an abnormal breath hydrogen response was observed in 13 of 20 (65%) healthy subjects and in 21 of 30 (70%) patients (Table 1). In contrast to fructose, an abnormal breath hydrogen response was less frequently ($P < 0.01$) observed after HFCS [i.e. in four of 20 (20%) healthy subjects and in nine of 30 (30%) IBS patients]. Among subjects who had an abnormal breath test for fructose and HFCS, breath hydrogen peaks were observed 125 ± 12 min (mean ± SEM) after HFCS and 102 ± 9 min after fructose ($P = 0.125$ by sign test).

Four of 13 healthy subjects and nine of 21 patients who had incomplete fructose absorption after fructose alone also had abnormal breath hydrogen responses after HFCS. No subjects had the combination of an abnormal breath hydrogen response after HFCS and a normal breath hydrogen response after fructose alone. Breath hydrogen responses (i.e. peak and AUC) after fructose and HFCS were not different between health and IBS (Fig. 1). The order of testing (i.e. fructose first *vs* HFCS first) did not affect the results of breath hydrogen tests.

Symptoms

Baseline symptom scores (i.e. prior to sugars) averaged <5 for each symptom and were not significantly different between study days (data not shown). After sugar ingestion, overall symptom scores were not significantly different between fructose and HFCS or between healthy subjects and patients (Table 2). Seven of 20 healthy subjects (35%) and 15 of 30 patients (50%) had one or more symptoms (i.e. a ≥10-mm increase in symptom scores over baseline) during a fructose hydrogen breath test, but only two healthy subjects (10%) and only 14 of 30 patients (47%) had one or more symptoms during a HFCS breath test (Table 3). Bloating was the most common symptom after fructose alone.

Taken together, five healthy subjects (25%) and 12 patients (40%) had fructose intolerance as defined by symptoms and an abnormal breath hydrogen response (Table 3). Thus, the odds ratio for an abnormal symptom response to fructose in those with an abnormal breath hydrogen response relative to those with a normal breath hydrogen response was somewhat higher in patients (OR, 2.67; 95% CI, 0.52–13.66) than in controls (OR, 1.56; 95% CI, 0.21–11.37), but this was not statistically significant ($P = 0.68$). No healthy subjects and only two patients (7%) were intolerant to HFCS ($P = 0.72$). However, intolerance was more prevalent after fructose than after HFCS in patients ($P = 0.002$) and to a lesser extent in controls ($P = 0.062$). As there

were no controls and only two patients intolerant to HFCS, a comparison of the homogeneity of the intolerance response between controls and patients could not be tested.

Symptom scores for bloating ($r = 0.36$, $P = 0.01$), flatulence ($r = 0.43$, $P = 0.002$), and pain ($r = 0.36$, $P = 0.01$) but not nausea were related to peak breath hydrogen excretion after fructose; this association was not different between health and IBS. In contrast, symptom scores were not correlated with peak breath hydrogen excretion after HFCS.

Four subjects had bowel movements during the 3-h study. Of these four subjects, two had bowel movements on both study days. The two other subjects had bowel movements after fructose or HFCS on one study day only.

DISCUSSION

Previous studies observed incomplete absorption after 50 g of fructose in 37.5%, 58% and 80% of healthy subjects and after a lower threshold (i.e. 25 g) in 36–75% of patients with IBS.[5,6,8,9,11] Confirming these studies, our data demonstrate that a majority of healthy subjects (i.e. 65%) and patients with functional bowel symptoms (i.e. 70%) incompletely absorbed (40 g) fructose when ingested alone.[5–7] In contrast, a lower proportion of healthy subjects (i.e. 20%) and patients (i.e. 30%) incompletely absorbed (40 g) fructose provided as HFCS, which is generally used to sweeten processed foods rather than fructose alone. Moreover, the prevalence of incomplete fructose absorption after fructose alone or after HFCS was not significantly different between healthy subjects and IBS. Taken together, these findings suggest that breath testing as commonly practiced (i.e. 25 g or more of pure fructose) may overestimate the prevalence of incomplete fructose absorption in daily life. Perhaps, a smaller test dose (e.g. 10 g) of fructose or HFCS-55 instead of fructose will provide a more specific measure of incomplete fructose absorption, but even HFCS may overestimate the prevalence of incomplete fructose absorption intolerance because HFCS are usually ingested with other foods that contain glucose and may also enhance fructose absorption. Both sugar solutions contained 40 g of fructose, approximating the fructose content of two cans of cola (closer to 44 g). The HFCS-55 study solution used in this study provided an excess (as compared to glucose) of 9.5 g fructose as a 12% solution, mimicking the ingestion of two cans of cola sweetened with HFCS-55 consumed in isolation. While ingestion of 40 g of fructose provided as HFCS may be commonplace in the diet of some individuals, it is extremely unlikely that 40 g of fructose in isolation would be consumed unintentionally. We speculate that the prevalence of incomplete fructose absorption with the other commonly used fraction of HFCS (i.e. HFCS-42) is even lower because it contains an excess of glucose and should be completely absorbed.

Among subjects with an abnormal breath hydrogen test, breath hydrogen excretion peaked at approximately 2 h after the substrate was administered. Indeed, only four of 47 abnormal breath tests were characterized by peak breath hydrogen excretion at 60 min and in only one subject, a control, was peak breath hydrogen excretion observed at 30 min. Although peak breath hydrogen excretion earlier than 60 min after substrate ingestion may be due to small intestinal bacterial overgrowth,[22] this healthy subject also had normal fasting breath hydrogen excretion, arguing against bacterial overgrowth. It is less widely recognized that early breath hydrogen peak excretion may reflect rapid orocecal transit.[23] We did not measure breath methane excretion as only a small proportion of subjects (i.e. 4% in a recent study) exclusively produce methane.[11]

On the basis of uncontrolled studies, it has been suggested that incomplete fructose absorption is more common (i.e. 36–75%) in patients with functional bowel disorders,[8–11] than in healthy subjects (i.e. 0–50%).[5–7] However, our data confirm the findings of the only previous controlled study,[10] which demonstrated that intolerance for a variety of sugars [i.e. lactose (50

g), fructose (25 g), sorbitol (5 g), fructose plus sorbitol (25 + 5 g) and sucrose (50 g)] is not more prevalent in IBS than in health. Despite these findings, it is conceivable that fructose intolerance may contribute to gastrointestinal symptoms in a minority of patients with IBS.

After ingestion of fructose alone, symptoms were correlated to peak breath hydrogen excretion as suggested previously.[8] Symptoms may be caused by intestinal distention due to osmotic effects of fructose and/or by colonic distention, secondary to colonic bacterial fermentation of incompletely absorbed sugars. Visceral hypersensitivity may also explain symptoms after ingestion of fructose in IBS. However, in a previous study, symptoms after ingestion of fructose—sorbitol were not associated with increased perception of jejunal balloon distention.[24] Symptoms were not correlated to breath hydrogen excretion after HFCS, suggesting they are not attributable to colonic fermentation, but may have been due to other factors such as volume.

Glucose increases fructose absorption[5,7,12,13] presumably by solvent drag and passive diffusion.[12,25–27] The extent to which glucose increases fructose absorption depends on the proportion of glucose relative to fructose.[5] An equimolar dose of glucose normalized fructose absorption in healthy subjects[5,13] and glucose at one-half the fructose dose decreased the prevalence of incomplete absorption by over 50%.[5] In addition, it is conceivable that glucose delays gastric emptying, thereby facilitating fructose absorption.[28]

In summary, our data demonstrate that fructose intolerance is more prevalent after fructose alone than after HFCS in health and IBS. The prevalence of fructose intolerance is not significantly different between health and IBS.

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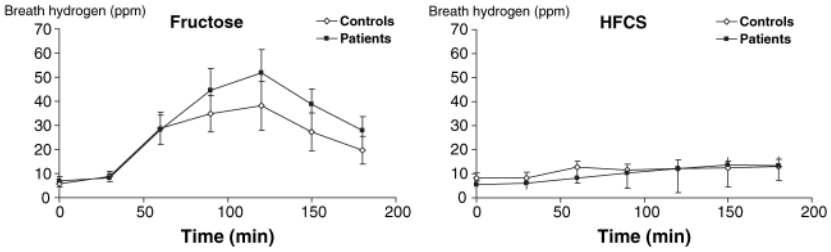

Figure 1.

Comparison of breath hydrogen excretion after fructose (left panel) and high fructose corn syrup (HFCS; right panel) in healthy volunteers and patients. Breath hydrogen excretion was not significantly different between healthy volunteers and patients.

Table 1

Demographic characteristics

Variable	Controls (n = 20)	Patients (n = 30)
Age (years) (mean ± SE)	28 ± 3	41 ± 2
Number of females	14 (60)	21 (60)
BMI (kg m^{-2}) (mean ± SE)	24 ± 1	26 ± 1
Breath hydroge response		
Abnormal – fructose	13 (65)	21 (70)
Abnormal – HFC	4 (20)	9 (30)
Abnormal – fructose and HFCS	4 (20)	9 (30)
Normal – fructose HFCS	7 (35)	9 (30)
Symptoms after fructose		
Flatulence	4 (20)	9 (30)
Bloating	5 (25)	10 (33)
Nausea	2 (10)	8 (27)
Abdominal pain	2 (10)	9 (30)
Symptoms after HFCS		
Flatulence	2 (10)	6 (20)
Bloating	1 (5);	10 (33)
Nausea	0	8 (27)
Abdominal pain	0	9 (30)

All values except age and BMI are *N* (%) of group total. HFCS, high fructose corn syrup; BMI, body mass index.

Table 2

Comparison of symptoms after fructose and HFCS in controls and IBS

Median (IQR) Visual Analog Scales scores (mm)								
	Bloating		**Nausea**		**Flatulence**		**Pain**	
	F	**HFCS**	**F**	**HFCS**	**F**	**HFCS**	**F**	**HFCS**
Healthy subjects	3.5(0, 30.5)	0 (0, 14.0)	0 (0, 13.0)	0 (0, 9.0)	9.5 (0, 31.0)	0 (0, 19.0)	0 (0, 18.0)	0 (0, 13.0)
Patients	18.0 (1, 87)	15.0 (0, 98)	13.0 (0, 29)	7.5 (0, 40)	13.0 (1, 74)	6.0 (0, 38)	14.5 (0, 55)	10.0 (0, 56)

Values represent the cumulative symptom score recorded at six time points over 3 h (i.e. maximum = 400). F, fructose; HFCS, high fructose corn syrup; IBS, irritable bowel syndrome.

Table 3

Comparison of symptoms and breath hydrogen responses in controls and IBS

Variable	Controls (*n* = 20)	Patients (*n* = 30)
Normal fructose breath test	7 (35)	9 (30)
Number with symptoms	2/7 (28)	3/9 (33)
Abnormal fructose breath test	13 (65)	21 (70)
Number with symptoms	5/13 (38)	12/21 (57)
Normal HFCS breath test	16 (80)	21 (70)
Number with symptoms	2/16 (12)	12/21 (57)
Abnormal HFCS breath test	4 (20)	9 (30)
Number with symptoms	0/4 (0)	2/9 (22)

Values in parenthesis are in percentage. IBS, irritable bowel syndrome; HFCS, high fructose corn syrup.