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Fructose Malabsorption and Intolerance: Effects of Fructose with and without Simultaneous Glucose Ingestion

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Concern exists that increasing fructose consumption, particularly in the form of high-fructose corn syrup, is resulting in increasing rates of fructose intolerance and aggravation of clinical symptoms in individuals with irritable bowel syndrome. Most clinical trials designed to test this hypothesis have used pure fructose, a form not commonly found in the food supply, often in quantities and concentrations that exceed typical fructose intake levels. In addition, the amount of fructose provided in tests for malabsorption, which is thought to be a key cause of intolerance, often exceeds the normal physiological absorption capacity for this sugar. To help health professionals accurately identify and treat this condition, this article reviews clinical data related to understanding fructose malabsorption and intolerance (i.e., malabsorption that manifests with symptoms) relative to usual fructose and other carbohydrate intake. Because simultaneous consumption of glucose attenuates fructose malabsorption, information on the fructose and glucose content of foods, beverages, and ingredients representing a variety of food categories is provided.

Keywords fructose, intolerance, malabsorption, high-fructose corn syrup

INTRODUCTION

The inability to properly utilize fructose manifests in one of two forms: 1) a genetic aberration termed "hereditary fructose intolerance," resulting from a deficiency of the hepatic enzyme aldolase B, or 2) incomplete fructose absorption (often referred to as fructose malabsorption), a condition not known to be genetic in which the capacity of the gut to transport fructose across the intestinal epithelium is exceeded.

Incomplete fructose absorption is detected by breath testing for hydrogen and/or methane production after consumption of a fructose-containing beverage or food. When accompanied by gastrointestinal symptoms, this condition is increasingly referred to as dietary fructose intolerance (Skoog et al., 2008). The subject of this review is the nongenetic form of fructose malabsorption that is sometimes accompanied by symptoms and characterized by an insufficient absorptive capacity in which fructose as a monosaccharide enters the colon and is fermented by the gut flora.

In 1978, Andersson and Nygren first reported cases of fructose malabsorption in which patients received a positive result using the breath hydrogen test. Researchers reported the resolution of symptoms with a low-fructose diet. Incomplete fructose absorption is now accepted within the gastroenterological community as a consequence of normal physiology in which the absorptive capacity of the gut is exceeded (Barrett and Gibson, 2007). This capacity varies widely within the population for reasons that are yet unknown; however, it has been estimated that up to 50% of the U.S. population (Gibson et al., 2007) is unable to absorb 25 g of pure fructose as evaluated in clinical studies. In clinical trials, it was shown that up to 80% of healthy controls were unable to absorb a 50 g fructose load (Braden, 2009).

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Since the 1980s, researchers evaluating functional bowel complaints have described an increasing incidence of fructose intolerance and often speculate that the increased consumption of beverages sweetened with high-fructose corn syrup (HFCS) is a likely underlying cause (Kneepkens et al., 1984; Choi et al., 2003; Johlin et al., 2004). This perspective was also presented at the 2008 American Dietetic Association Food and Nutrition Conference and Expo in a session titled "Fructose in Obesity and Hepatic Disease: Culprit or Scapegoat?" in which the diagnosis, prevalence, and proposed treatment of fructose intolerance were described. Several articles specific to various aspects of fructose intolerance have been published recently (Beyer et al., 2005; Shepherd and Gibson, 2006; Heizer et al., 2009). However, only one study to date has included graded doses of fructose provided in the context of diet (Shepherd et al., 2008). This study includes a protocol reflecting a practical diet and pattern of intake in patients with irritable bowel syndrome (IBS). To date, no published studies have evaluated clinical data in the context of food sources and typical intakes of fructose in the healthy free-living population. In the current article, the existing clinical trial data related to fructose malabsorption and intolerance are reviewed in the context of fructose from food and beverage sources of dietary sugars as they occur in the food supply and actual intakes.

METHODS

Although there are many factors that may influence fructose absorption or aggravate gastrointestinal distress, such as dietary sorbitol (Hyams et al., 1988; Nobigrot et al., 1997; Goldstein et al., 2000; Braden, 2009; Symons et al., 2009) and fructans (polymers of fructose not hydrolyzed in the small intestine) (Shepherd and Gibson, 2006; Gibson et al., 2007), only the independent effects of fructose from food and beverage sources of dietary sugars will be addressed in this review. The studies reviewed were identified by a PubMed search in November 2008 with periodic searches since that time for relevant papers. The search terms used were "fructose intolerance" and "fructose malabsorption" with the eliminating terms "NOT hereditary" and "NOT inborn." The reference lists of relevant articles were then searched for additional information sources. Studies included in the summary table were specifically clinical trials providing fructose alone in at least one arm with breath testing, and were conducted in adults, either healthy or with compromised gut function. Studies excluded from the table examined children, provided fructose only in combination with another test substance, or included subjects with known presence of disease.

RESULTS

Of the studies identified through database and hand searching, 21 met inclusion criteria for the tabular summary of clinical trials in healthy and gut-compromised adults. Findings are described below in response to the corresponding research questions.

How Is Fructose Absorbed?

Fructose, ingested either as a monosaccharide or enzymatically cleaved from sucrose, may be transported across the intestinal epithelium by GLUT-5 or GLUT-2. Although GLUT-5 depends on a concentration gradient to move substances across the epithelium and is specific for fructose, GLUT-2 will actively transport glucose, fructose, and galactose (Gibson et al., 2007). Fructose uptake may be modified by increasing GLUT-5 expression by the presence of luminal fructose or sucrose, by co-ingestion of amino acids, or by altering the insertion of GLUT-2 into the apical membrane, such as in the case of diabetes (Hoekstra et al., 1996). Many details about the regulation of fructose uptake are still not understood (Jones et al., 2011). Riby et al. (1993) noted the facilitating effect of glucose on fructose absorption, and titration experiments in animals showed that a minimum of 1:1 is the optimal ratio of glucose:fructose. Clinical trials verify that this is likewise the case for humans (Ravich and Bayless, 1983; Rumessen and Gudmand-Høyer, 1986; Truswell et al., 1988; Densupsoontorn et al., 2007).

How Are Fructose Malabsorption and Intolerance Identified?

Fructose malabsorption is identified by a positive breath test, which is most commonly defined as a rise in hydrogen and/or methane (methane is less frequently measured) of at least 20 ppm (less often 10 ppm for methane) peaking from 1.5 to 3 hours after ingestion of the test carbohydrate. Because fermentation of a variety of carbohydrates at a previous meal may increase hydrogen breath levels, subjects are typically asked to refrain from consuming carbohydrates for 8 to 12 hours prior to the test. Unabsorbed fructose reaching the colon is fermented to short-chain fatty acids, carbon dioxide, trace gases, and hydrogen. These fermentation products may cause symptoms such as bloating, flatulence, and loose stools. Such manifestations are common for any type of undigestible carbohydrate or fiber (e.g., lactose in some races and ethnic groups). The presence of symptoms (and thus intolerance) is evaluated by visual analog scale testing or another scoring system.

What Are Dietary Sources of Fructose?

Table 1 presents the amount of total sugars, total glucose, total fructose, and net fructose per serving in sweeteners, foods, and beverages. Net fructose—the amount of fructose in excess of glucose or the difference between total fructose and total glucose—is the amount of fructose that is relevant to fructose malabsorption and intolerance given the facilitating effect of glucose on fructose absorption (Riby et al., 1993). The

Table 1 Monosaccharide and net fructose content of common foods and ingredients

		Serving Size					
Food or Ingredient	Data Source	Measure	g	Total Sugars, g	Total Glucose, g[a]	Total Fructose, g[b]	Net Fructose, g[c]
Sweeteners							
Honey	d	1 tsp	7.0	5.8	2.6	2.9	0.3
Molasses	d	1 tsp	6.7	3.7	1.8	1.8	0.1
Sugar, table	d	1 tsp	4.2	4.2	2.1	2.1	0.0
Sugar, brown	d	1 tsp	4.6	4.5	2.2	2.2	0.0
Syrup, chocolate	g	1 tsp	6.5	3.3	2.0	1.1	0.0
Syrup, corn	g	1 tsp	7.2	5.7	5.7	0.0	0.0
Syrup, high-fructose corn (HFSC-42)	g	1 tsp	6.6	4.6	2.6	1.9	0.0
Syrup, high-fructose corn (HFSC-55)	g	1 tsp	6.7	5.1	2.2	2.8	0.6
Syrup, agave nectar	h	1 tsp	6.3	4.8	0.3	4.3	4.0
Syrup, maple	d	1 tsp	6.7	4.0	2.0	1.9	0.0
Syrup, pancake	g	1 tsp	6.7	2.8	1.8	1.0	0.0
Fruits							
Agave, cooked (Southwestern)	d	—	100	20.9	2.4	18.4	16.0
Apples, raw w/ skin	d	1 med	182	18.9	6.3	12.6	6.3
Bananas	d	1 med	118	14.4	7.3	7.1	0.0
Grapes, red or green	d	1 cup	151	23.4	11.0	12.4	1.4
Oranges, navel	d	1	140	11.9	5.8	6.1	0.4
Pears	d	1 med	178	17.4	5.6	11.8	6.2
Watermelon	d	1 cup diced	152	9.4	3.4	6.0	2.6
Vegetables							
Carrots, raw	d	1 large	72	3.4	1.7	1.7	0.0
Onions, raw	d	1 small	70	3.0	1.7	1.2	0.0
Sweet potatoes, boiled	d	1 med	151	8.7	6.9	1.7	0.0
Beverages							
Apple juice	d	8 fl oz	248	23.9	8.1	15.8	7.7
Apple, grape, pear juice blend	d	8 fl oz	250	24.9	9.4	15.4	6.0
Cola (sucrose)	g	12 fl oz	369	40.5	20.3	20.3	0.0
Cola-type soft drink (HFCS)[i]	g	12 fl oz	369	41.1	18.6	22.5	3.9
Cola-type soft drink (HFCS)[i]	d	12 fl oz	369	39.0	16.5	22.5	6.0
Grape juice	d	8 fl oz	253	35.9	17.3	18.7	1.4
Lemon-lime type soft drink (sucrose)	g	12 fl oz	369	43.5	21.8	21.8	0.0
Lemon-lime type soft drink (HFCS)[i]	g	12 fl oz	369	28.5	18.9	23.8	3.3
Lemon-lime type soft drink (HFCS)[i]	d	12 fl oz	369	35.4	14.4	21.0	4.5
Lemon-lime sport drink 1	d	12 fl oz	366	22.4	9.5	12.2	2.6
Lemon-lime sport drink 2	f	12 fl oz	366	12.8	10.8	8.3	0.0
Orange juice	d	8 fl oz	249	20.7	10.2	10.5	0.4
Pear juice	e	8 fl oz	250	21.8	4.0	17.8	13.8
Dairy							
Milk, chocolate flavored, reduced fat	d	8 fl oz	250	23.9	12.1	7.0	0.0
Ice cream, vanilla	g	4 oz	66.0	12.7	7.0	4.0	0.0
Yogurt, fruit	g	8 oz	225.0	33.1	16.0	12.8	0.0
Breakfast foods							
Cereal bar, frosted and filled	g	1 bar	40.0	14.9	11.3	3.6	0.0
Cereal, ready to eat, sugared	g	1 oz	30.0	10.0	5.0	5.0	0.0
Sweets							
Candies, hard, fruit flavored	g	1 oz	14.0	10.7	7.8	3.0	0.0
Chocolate, bar, milk	g	1.55 oz	43.0	24.2	12.0	9.9	0.0
Chocolate, bar, dark	d	1.55 oz	44.0	20.3	10.2	9.8	0.0
Chocolate, bar, dark	g	1.55 oz	40.0	14.8	7.3	7.3	0.0
Cookie, chocolate chip	g	1 oz	30.0	9.7	5.0	4.7	0.0
Cookie, oatmeal raisin	g	1 oz	30.0	11.4	5.7	5.7	0.1
Cookie, sandwich, peanut butter	g	1 oz	30.0	8.9	4.5	4.4	0.0
Licorice, strawberry	g	4 pieces	45.0	18.6	15.4	2.7	0.0

[a]Total glucose = 1/2 sucrose + 1/2 lactose + maltose + glucose.
[b]Total fructose = 1/2 sucrose + fructose.
[c]Net fructose = total fructose – total glucose greater than 0.
[d]U.S. Department of Agriculture (2009).
[e]Matthews et al. (1987).
[f]Nutrition Data (2003).
[g]Manufacturer's data. For food items where only manufacturer data are presented, the USDA Standard Reference Database (2009) did not include monosaccharide information.
[h]Values for agave nectar are based on the assumption of 6.3 g per tsp, 4.8 g total sugars per tsp, and LaBelle (1999), who indicates that the carbohydrate in agave nectar is 90% fructose, 8% glucose, and 2% other carbohydrates.
[i]Average of values for products with and without caffeine.

U.S. Department of Agriculture's (USDA) Nutrient Database for Standard Reference (2009) was used as the data source where possible. If sugars data were not available in the USDA database, other recent sources were identified.

Sweeteners containing sucrose (table sugar, brown sugar, and molasses), honey, and maple syrup are fairly similar in fructose and glucose content, with glucose to fructose ratios ranging between 1.0:1.0 (sucrose-containing) and 0.9:1.0 (honey). Chocolate syrups and pancake syrups contain more glucose than fructose (1.8:1.0). Agave nectar contains appreciably more fructose than glucose (Matthews et al., 1987; Labelle, 1999). The predominant forms of HFCS used as food ingredients are HFCS-55 and HFCS-42 (Hanover and White, 1993), which contain 55% and 42% fructose, respectively. HFCS-55 is the most common form used in soft drinks, whereas HFCS-42 is more typically used in fruit-flavored drinks, confections, and baked goods.

Ventura et al. (2010) conducted a recent analysis of sugar-sweetened beverages by using a third-party laboratory. Their findings showed that the fructose content of the HFCS in the sampled beverages ranged between 47% and 65%. The authors concluded that several major brands seem to be produced with HFCS that is 65% fructose. Researchers have questioned the analytical methods applied in the study by Ventura et al. (2010) for several reasons (John White, PhD, personal communication, November 1, 2010), one being that HFCS contains 5% and 8% higher saccharides (glucose oligomers: DP2, DP3, and DP4+). The International Society of Beverage Technologists conducted a follow-up analyses demonstrating that the method applied by Ventura et al. was not sufficiently sensitive to detect maltose and higher sugars typically present in corn sweeteners (ISBT, 2010). For these reasons, the manufacturer-provided and USDA data for HFCS-sweetened beverages presented in this review must be considered reliable reference points.

Fructose is present as the monosaccharide and/or as sucrose in fruits and fruit juices; its amount is considerably greater than glucose in agave, apples, pears, and watermelon and to a lesser extent in grapes. Vegetables such as carrots, onions, and sweet potatoes contain equal or lesser amounts of fructose than glucose. Unsurprisingly, 100% fruit juices containing apple, pear, and/or grape juices contain more fructose than glucose. Data provided by U.S. manufacturers indicate that the fructose to glucose ratios in soft drinks such as colas and lemon-lime sports drinks depend on the sweeteners used, ranging from 1.2:1.0 to 0.6:1.0. In general, sweetened dairy and grain products and sweets contain less fructose than glucose or an equal ratio.

What Are the Usual Dietary Intakes of Fructose?

Marriott et al. (2009) reported the most current estimates of fructose intake in the U.S. population using dietary recall data from the 1999–2004 National Health and Nutrition Examination Survey. The total daily fructose intake of all individuals (ages 1+ years) was estimated to be 49 g at the mean and 87 g at the 95th percentile. Adolescent (ages 15–18 years) and young adult (ages 19–22 years) males have the highest total fructose intakes of 75 g at the mean and 121 to 134 g at the 95th percentile. Older adult males and females (ages 51+ years) have lower total fructose intakes of 41 g and 32 g at the mean and 60 g and 79 g at the 95th percentile, respectively. The total fructose intake of other age/sex groups falls between these ranges. Depending on the age/sex grouping and level of intake, fructose from foods containing sucrose and HFCS represent 64% to 95% of total fructose intake. These estimates of fructose intake include a variety of food and beverage sources that typically also provide glucose (either as the monosaccharide or as a component of lactose, sucrose, and starch) and are consumed throughout the day in the context of the whole diet. This is distinct from the way fructose is provided in clinical studies as pure fructose usually in a liquid bolus, which is important to consider when evaluating the results of clinical studies.

What Do Clinical Trials Tell Us?

Clinical trials that evaluated the prevalence of fructose malabsorption and intolerance and used a breath test in both healthy adults and those with compromised gut function are summarized in Table 2 and have been reviewed elsewhere (Skoog and Bharucha, 2004; Gibson et al., 2007; Heizer et al., 2009; Kyaw and Mayberry 2011). These studies provide valuable information about fructose absorption capacity. In the clinical setting, the absorption of pure fructose has been shown to range between < 5 to > 50 g, indicating wide individual variability and the possibility of very low absorptive capacity in some individuals. Studies also indicate that fructose absorption is dose-dependent (Ravich and Bayless, 1983; Rumessen and Gudmand-Høyer, 1986; Truswell et al., 1988), concentration-dependent (Ravich and Bayless, 1983; Choi et al., 2003), and facilitated by the simultaneous ingestion of glucose (Kneepkens et al., 1984; Rumessen and Gudmand-Høyer, 1986; Truswell et al., 1988; Densupsoontorn et al., 2007). For example, 10 healthy subjects were given 15, 20, 25, 37.5, and 50 g of fructose in a crossover study design and 1, 4, 5, 7, and 8 individuals obtained a positive test result for malabsorption. However, only 7, 3, and 0 individuals received a positive test result when the same subjects were provided with 50 g fructose plus 12.5, 25, or 50 g of glucose, respectively (Rumessen and Gudmand-Høyer, 1986). The latter study and others in which glucose is provided in equimolar concentrations with fructose (Kneepkens et al., 1984; Rumessen and Gudmand-Høyer, 1986; Truswell et al., 1988; Densupsoontorn et al., 2007) illustrate the facilitating effect of glucose on fructose absorption.

It has been suggested that fructose malabsorption or intolerance occurs more frequently in individuals with compromised gut function as compared with healthy individuals. Studies by Nelis et al. (1990) and Symons et al. (1992) have been cited as evidence to this effect (Heizer et al., 2009). However, fructose was provided simultaneously with varying quantities of sorbitol

Table 2 Clinical trials of fructose malabsorption and intolerance in adults

Author and Year	Study Population	Test Substance and Dose			Positive Breath Test,%n	Rise Above Baseline Required for Positive Result, ppm	Correlation of Symptoms With H2 Peak[b]	Breath Testing Regimen	
	N (M/F)	Sugar	Dose, g	Conc,%[a]				Freq, min	Dur, h
Healthy Subjects									
Beyer et al. (2005)	15 (6/9)	F	25	200 mL H_2O	53	≥20	No	30	3
	15	F	50	200 mL H_2O	73		No		
Born et al. (1995)[c]	34 (12/22)	F	25	NR	38	≥20	No	30	2
Densupsoontorn et al. (2007)	77 (37/40)	F	25	10	14	≥20	No	30	2
	9 (0/9)	F+G	25+25	20	0		No symptoms		
Hoekstra et al. (1993)	12 (5/7)	F	6 mL/kg	10	0	≥20	No symptoms	30	2.5
	12	F+Sor	6 + 0.6 mL/kg	10	0		No symptoms		
Ladas et al. (2000)	32 (15/17)	F	25	250 mL H_2O	19	≥20	No	15	6
	32	F	50	250 mL H_2O	81		No		
Madsen et al. (2006)[d]	11 (6/5)	F+Sor	25+5	10	100	≥10	No	NS	NS
	11	G	30	10	0		No		
Mitsui et al. (2001)	10 (9/1)	F+rice	17.5 + 200	5	0	≥3 over 2 samples	No symptoms	15	4
Rao et al. (2007)[d]	20 (10/10)	F	15	10	0	≥20	No symptoms	30	4 to 6
	20	F	25	10	50		No symptoms		
	20	F	50	10	69		No		
	20	F	50	33	60		No		
Ravich and Bayless (1983)	3 (NR)	F	25	10	0	≥20	No	30	4
	14 (NR)	F	37.5	10	14		No		
	16 (8/8)	F	50	10	38		No		
	14 (NR)	F	50	20	71		No		
	15 (NR)	S	50	10	0		No symptoms		
Rumessen and Gudmand-Høyer (1986)	10 (7/3)	F	15	10	10	≥20	No symptoms	15–30	4
	10	F	20	10	40		No symptoms		
	10	F	25	10	50		No symptoms		
	10	F	37.5	10	70		No		
	10	F	50	10	80		No		
	10	F+G	50+12.5	12.5	70	≥20	No		
	10	F+G	50+25	15	33		No		
	10	F+G	50+50	20	0		No		
	10	G	50	10	0		No symptoms		
	10	S	50	20	0		No symptoms		
	10	S	75	20	0		No		
	10	S	100	20	0		No		
Truswell et al. (1988)	21 (NR)	F	25	100 g/L	11		No		
	103 (31/72)	F	50	100 g/L	58	≥20	Yes	15–30	2.25
	15 (NR)	F+G	25+25	100 g/L	0		NR		
	30 (NR)	F+G (as apple juice)	25+16	60 g/L	7		NR		
	23 (NR)	G	50	100 g/L	0		No symptoms		
	15 (NR)	S	50	100 g/L	0		No symptoms		
	23 (NR)	F (as HFCS-90)	50	100 g/L	30		NR		
Subjects With Functional Gut Disorders Including IBS									
Barrett et al. (2009)[e]	201 (41/60)	F	35	17	45	≥10 over ≥2 samples	NR	15	3
	71 (23/48)[g]	F	35	17	34		NR		
	201 (41/60)	L	15	15	27		NR		
	71 (23/48)[g]	L	15	15	39		NR		
Choi et al. (2003)[d,f]	36 (9/27)	F	25	10	39		No		

(Continued on next page)

Table 2 Clinical trials of fructose malabsorption and intolerance in adults *(Continued)*

	Study Population	Test Substance and Dose						Breath Testing Regimen	
Author and Year	N (M/F)	Sugar	Dose, g	Conc,%[a]	Positive Breath Test,%n	Rise Above Baseline Required for Positive Result, ppm	Correlation of Symptoms With H2 Peak[b]	Freq, min	Dur, h
	183 (50/133)	F	50	33	73	≥20 or ≥3 over 3 samples	No	30	5
	20 (9/11)	F	50	33	80		No		
	33 (11/22)	F	50	20	70		No		
Choi et al. (2008)[d]	80 (26/54)	F	25	10	33	≥20	Yes	30	5
Corlew-Roath and Di Palma (2009)[d]	66 (9/57)	F	25	NS	3	NR	NR	NR	NR
	55 (11/34)[g]	F	25	NS	16		NR		
Fernández-Bañares et al. (1993)	25 (5/20)	F	25	10	52	≥20	No	15	3
	23 (NR)	F+Sor	25+5	250 mL H_2O	92		Yes		
	25	S	50	250 mL H_2O	68		No		
	12 (6/6)[g]	F	25	10	42		No		
	12[g]	F+Sor	25+5	250 mL H_2O	83		No		
	12[g]	S	50	250 mL H_2O	50		No symptoms		
Goldstein et al. (2000)[d]	239 (NR)	F	25	NR	44	≥20 H2; ≥4 ppm CH3	Yes	30	4
	239 (NR)	F+Sor	25+5	NR	73		Yes		
Gomara et al. 2008	9 (NS)	F	1	0.04	0	≥20	No	30	3
	10 (NS)	F	15	6.3	30		No		
	13 (NS)	F	45	19	77		No		
Johlin et al. (2004)[d]	197 (NR)	F	50	150 mL H_2O	76	≥20 or ≥3 over 3 samples	NR	30	5
Rumessen and Gudmand-Høyer (1988)	25 (2/23)	F	25	250 mL H_2O	52	≥10	Yes	15–30	4
Skoog et al. (2008)	30 (9/21)	F	40	330 mL H_2O	70	≥20	Yes	30	3
	20 (6/14)[g]	F	40	330 mL H_2O	65		Yes		
	30	F (as HFCS-55)	40	600 mL H_2O	30		No		
	20[g]	F (as HFCS-55)	40	600 mL H_2O	20		No		
Szilagyi et al. (2007)	90 (61/29)	F	25	100 to 150 mL H_2O	32	≥10 at 2 intervals	Yes	30	3

Abbreviations: Conc, concentration; Dur, duration; F, fructose; Freq, frequency; G, glucose; F + Sor, fructose + sorbitol; HFCS, high-fructose corn syrup; L, lactulose (positive control); NR, not reported; S, sucrose.

[a] Unless otherwise indicated.

[b] Assessed by reported statistical correlation, apparent dose-response pattern, or subjective assessment of reported percentages by the author of this article.

[c] Evaluated subjects for methane producers; included only H2 producers.

[d] Evaluated subjects for methane producers.

[e] Although methane production was not tested, subjects that did not increase H2 >10 ppm above baseline were considered non-H2 producers and were excluded from the analysis.

[f] Eleven percent of subjects were methanogenic.

[g] Healthy subjects were included as controls.

in those studies. Studies in which fructose alone is provided to gut-compromised individuals, show a higher incidence of symptoms (Rumessen and Gudmand-Høyer, 1988; Goldstein et al., 2000; Choi et al., 2003). However, these studies lack comparisons with a healthy group or the inclusion of a control treatment such as sucrose. In another study, the incidence of fructose malabsorption by breath testing was not different between patients with or without IBS, although symptom improvement was greater for healthy patients with fructose restriction (Corlew-Roath and Di Palma, 2009). As noted by Rangnekar and Chey (2009), the literature suggests that the prevalence of malabsorption is similar between subjects with functional bowel disorders and healthy individuals. In controlled studies, the differences observed in the incidence of fructose malabsorption

or intolerance between patients and healthy subjects is mixed (Fernández-Bañares et al., 1993; Shepherd et al., 2008; Skoog et al., 2008). In one of these controlled studies, healthy subjects did not have difficulty tolerating a test drink containing up to 50 g fructose (four of seven participants did report mild symptoms; however, it was not specified if it was taken by bolus), whereas 30% of subjects with IBS could not tolerate this dose (up to 50 g throughout the day with meals) (Shepherd et al., 2008). In two studies, no symptom differences were observed between patients and healthy subjects (Fernández-Bañares et al., 1993; Skoog et al., 2008). In the study by Skoog et al. (2008), 50% of the patients with compromised gut function also experienced symptoms after the sucrose treatment. Authors of a recent review that included studies using doses of fructose or fructose-sorbitol stated that malabsorption appears to be more common in patients with functional gut disorders, but not in patients with IBS (Kyaw and Mayberry, 2011) although in IBS, symptoms appear to be more frequent. This review highlights the difficulty of reconciling breath test results with symptoms, the latter of which is most relevant to the patient.

How do Clinical Evaluations of Fructose Malabsorption and Intolerance Compare with Usual Intake?

The application of results from clinical trials, in which fructose in large amounts is consumed in the absence of concomitant glucose to free-living individuals, is limited. In most studies, both the amount and form of fructose fail to represent free-living consumption (Skoog et al., 2008). For example, fructose is rarely consumed in isolation: it occurs as a component of HFCS and sucrose and is one of the several ingredients in foods and meals that importantly contain glucose and other macronutrients such as fiber, starch, fat, and protein. Clinical studies of fructose in forms such as HFCS and sucrose or in combination with glucose or starch show that fructose is well absorbed in both healthy individuals and individuals with compromised gut function (Ravich and Bayless, 1983; Rumessen and Gudmand-Høyer, 1986; 1988; Truswell et al., 1988; Fernández-Bañares et al., 1993; Mitsui et al., 2001; Skoog et al., 2008). Furthermore, positive breath test results are uncommon when pure fructose is provided in a dose of less than 25 g (Rumessen and Gudmand-Høyer, 1986; Rao et al., 2007; Gomara et al., 2008) or simultaneously with other carbohydrates such as starch (Mitsui et al., 2001). Given the manner in which fructose occurs in the food supply and in the diet, it would be atypical to consume 25 g of fructose in one bolus in isolation from glucose or other nutrients. For example, one would have to consume 26 fl oz (769 mL) of apple juice or more than 50 fl oz (1,500 mL) of cola sweetened with HFCS-55 to ingest 25 g of fructose in excess of glucose. In addition, the correlation of malabsorption with clinical symptoms is neither common nor consistently related to dose (Table 2). Lastly, malabsorption prevalence based on one large bolus dose of fructose without other foods may be overestimated because the breath test does not replicate conditions of fructose consumption in free-living individuals. In a randomized controlled trial, Shepherd et al. (2008) provided a fructose beverage with meals throughout the day, but did not incorporate breath testing.

What is the Importance of Baseline Fructose Intake in Assessing Dietary Fructose Restriction?

To understand the causal relationship between fructose consumption and clinical symptoms, it is useful to understand baseline fructose intake prior to fructose restriction to assess the extent of change in intake. However, this is difficult to do given the limitations of available food composition databases. Although two studies (Goldstein et al., 2000; Shepherd and Gibson, 2006) reported that subjects had an improvement in symptoms after a 1-month restriction diet, the baseline symptom data were collected after challenge with up to 35 g of fructose, as opposed to assessing symptoms when subjects ate a diet composed of a variety of foods and beverages. Similarly, Johlin et al. (2004) categorized patients as fructose intolerant after they received a positive test result on a 50 g fructose load. Symptoms were assessed before the test and an improvement was reported for those who complied with a fructose restriction diet. Choi et al. (2008) also reported a significant improvement in symptoms in IBS patients compliant with fructose restriction. Although these results are promising, the latter two studies do not characterize the fructose content of the diet, either before or after instruction. In one of the few articles to report baseline dietary fructose intake, Ledochowski et al. (2000) showed that fructose malabsorption was defined by an increase of 20 ppm of hydrogen over baseline following provision of a 50 g fructose load. Based on a dietary questionnaire, the mean daily total fructose intake of malabsorbing subjects was 20 g prior to the intervention and 5 g after dietary instruction to reduce both fructose and sorbitol intake. This modification resulted in a statistically significant ($P < 0.00001$) reduction in reported symptoms, an improvement that may be attributable to the reduced intake of fructose, sorbitol, or both (Goldstein et al., 2000; Braden, 2009). Therefore, there exists a clear need for randomized, controlled, double-blind clinical trials that clearly document dietary fructose composition to determine the frequency of intolerance, if any, in the population to HFCS-55 and other products in which the content of free fructose exceeds that of glucose, using both breath testing and symptom evaluation.

What Are Limitations of the Hydrogen Breath Test?

Results of clinical trials employing the hydrogen breath test should be interpreted in the context of the test limitations (Table 3). The testing protocol remains unstandardized (Braden, 2009) and there is some debate around the optimal parameters for testing, including the appropriate fructose dose and cut-off value for hydrogen expiration (Braden, 2009; Bate et al.,

Table 3 Limitations of clinical and dietary intervention studies of fructose malabsorption and intolerance

- Optimal hydrogen breath test parameters are still under debate and reproducibility is limited.
- Fructose is usually provided in a liquid bolus dose in isolation from glucose, after fasting, in quantities not typical to foods, potentially resulting in over diagnosis.
- Most studies do not screen for or measure methane production, potentially resulting in under diagnosis.
- Testing methods vary widely in terms of test substance amount, breath testing protocol, and comparisons with other sugars.
- Poor correlation between a positive breath test and induction of symptoms limits causal attribution.
- Baseline fructose intake prior to dietary intervention is not typically assessed or reported.

2010). Data on reproducibility are likewise limited (Gibson et al., 2007). The breath test was originally intended to assess the general absorptive capacity of a group of subjects, as opposed to "diagnosing" malabsorption in an individual (Riby et al., 1993). For some individuals who produce primarily methane as opposed to hydrogen, a methane breath test may be more appropriate because testing specifically for hydrogen can leave malabsorption undetected (Gibson et al., 2007; Braden, 2009). For example, an individual could conceivably experience symptoms even though the breath test results are negative, but the underlying causes of the symptoms are not obvious.

What Is Practical Dietary Guidance for the Potentially Fructose-Intolerant Individual?

In patients with gastrointestinal complaints, the source of the problem is often difficult to diagnose. A similar symptom profile may be observed with intolerance to a number of dietary components including fructose, sorbitol, fructo-oligosaccharides, lactose, gluten or wheat, polyols, and gas-forming foods such as cruciferous vegetables. The breath test may be of limited use in the diagnosis of fructose intolerance in an individual patient because the results may correlate poorly with the induction of symptoms (Riby et al., 1993). For the individual, however, symptom ratings are more important to quality of life than breath hydrogen test results. Therefore, an elimination diet may be the only effective means of determining the dietary culprit(s) for patients with symptoms.

For individuals who are truly fructose intolerant with notable adverse symptoms, as noted by Riby et al. (1993), "it would seem advisable . . . to avoid consumption of products in which fructose is the only carbohydrate." In practice, it is of limited value to estimate fructose intake by dietary recall given the difficulty in determining the dietary fructose:glucose ratio from food databases or label information. The American Gastroenterological Association (2010) recommends that individuals with apparent fructose intolerance limit all fruits, honey, and alcohol as well as beverages that contain HFCS. In the fructose intolerance literature, HFCS is often implicated in the descriptive sections as a key ingredient to avoid. However, it should be noted that HFCS-42 contains more glucose than fructose. HFCS-55 has slightly more fructose than glucose and therefore should not be consumed in excess (Table 1). The difference between HFCS and sucrose is slight, and HFCS is considered by health professional organizations to be similar in composition to sucrose with respect to monosaccharides (American Dietetic Association, 2008; American Medical Association, 2008). A recent review on the topic of fructose intolerance noted that fructose malabsorption is thought not likely to occur with HFCS-42 due to the ratio of fructose:glucose (Kyaw and Mayberry, 2011).

As a first step, individuals who may be fructose intolerant should be counseled to eliminate foods that contain appreciable amounts of fructose. This includes foods that contain a large amount of crystalline fructose and agave nectar, as well as large quantities of apples, pears, apple juice, pear juice, fruit juice concentrates, and beverages sweetened with HFCS-55. However, if these items are consumed along with foods that contain other sugars, carbohydrate ingredients or in a mixed meal, the likelihood of malabsorption may be reduced. Once symptoms appear to be controlled, individuals should be counseled to reintroduce foods that contain negligible amounts of net fructose (Table 1). If symptoms improve and consumption of certain foods would improve the quality of an individual's diet, foods containing appreciable amounts of net fructose should be reintroduced by balancing them with additional carbohydrates such as other sweeteners, starches, or whole grains. Sweeteners as ingredients or finished products that are unlikely to be problematic include corn syrup, brown rice syrup, sucrose (white sugar), brown sugar, raw sugar, corn syrup solids, HFCS-42, maple syrup, pancake syrup, molasses, dextrose, or dextrin.

CONCLUSIONS

Clinical symptoms may or may not relate to a positive hydrogen breath test result, but balancing dietary fructose and glucose may mitigate clinical symptoms for those individuals with apparent sensitivity to fructose. Although a fructose elimination diet will help the patient to confirm the problematic sugar, foods containing net fructose can most likely be tolerated if consumed as part of a mixed meal. Should symptoms persist, the causative component may remain elusive.

To better compare results from hydrogen breath tests and to understand the true prevalence of fructose malabsorption, revision and standardization of testing protocols are needed. Ideally, individuals should be tested not only with pure fructose but also, and perhaps more preferably, with fructose in food forms that better reflect real-life consumption.

Although it is not necessary for the fructose-intolerant individual to reduce intake of all types of sugars, the intake of added sugars should be consistent with energy and micronutrient requirements. On a population level, added sugar intake is higher

than that recommended by the U.S. Dietary Guidelines (Marriott et al., 2010). Whether intake of a particular sugar relates to gastrointestinal distress should be evaluated on a patient-by-patient basis.

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