Fructans of chicory: intestinal transport and fermentation of different chain lengths and relation to fructose and sorbitol malabsorption

Jüri J Rumessen and Eivind Gudmand-Høyer

ABSTRACT Fructans (fructooligosaccharides and inulin) are of increasing interest to clinical nutritionists as functional food additives. The chemically closely related food carbohydrates fructose and sorbitol are implicated in functional bowel disease. Intestinal handling of these carbohydrates is incompletely understood. Intestinal transport, transit, and fermentation (breath hydrogen and methane, venous acetate, blood glucose, and urine fructans) after ingestion of 10–30 g short- and long-chain fructans from chicory were studied by single-blind, crossover randomization in 10 healthy adults. Responses were compared with responses after ingestion of lactulose, fructose, and sorbitol. Breath hydrogen and venous acetate production increased in proportion to increasing fructan dose and were similar to responses to lactulose. The transit times of long-chain fructans were longer than those of short-chain fructans (75 compared with 30 min, P < 0.001). Semi-quantitative estimates of unabsorbed carbohydrate were not significantly different with either short-chain fructans or lactulose as nonabsorbable standards. Venous acetate curves were less precise estimates of the magnitude of carbohydrate malabsorption than were breath-hydrogen curves (P < 0.01). All subjects showed malabsorption of 50 g fructose, resulting in significantly more symptoms than 20 g fructose (P < 0.05). Ingestion of sorbitol with equimolar amounts of glucose did not reduce malabsorption or abdominal distress. Abdominal symptoms after fructans increased with increasing dose and decreasing chain length. The overall gastrointestinal effects of short-chain fructans seem similar to those of lactulose. Fructans with different chain lengths may have different physiologic properties and further studies of fructans in disease states are warranted.

KEY WORDS Acetate, breath tests, fructans, fructose, breath hydrogen, inulin, carbohydrate malabsorption, oligosaccharides, sorbitol, lactulose, chicory, humans, adults

INTRODUCTION Fructans (fructose oligosaccharides) are naturally occurring, nonstructural plant storage carbohydrates. Fructans consist of fructose polymers with a glucose molecule at the end. The chain length (DP, degree of polymerization) varies from 2 units (for sucrose, DP = 1) up to several hundred; inulin is a fructan with a chain length of ≈35 (1). Fructans occur primarily in cereals, onions, asparagus, scorzonera, and Jerusalem artichokes. Fructans are also present in several nonedible plants such as chicory (2).

We previously studied fructans from Jerusalem artichokes with regard to transit, absorption, and blood sugar regulation in healthy subjects (3). Like dietary fiber and resistant starch, fructans are not absorbed in the small intestine but are fermented in the colon to gases (hydrogen, methane, and carbon dioxide), lactate, and short-chain fatty acids (acetate, butyrate, and propionate) (4, 5). Fructans have attracted increasing attention in clinical nutrition (6). Fructan ingestion may have a positive influence on lipid metabolism and blood sugar regulation in diabetics (7) and on large bowel function (8, 9). Dietary fructans increase the density and proportion of colonic bifidobacteria, which may be health promoting (8–12). Short-chain (DP = 3–5) fructans are commercially available as nonabsorbable sweeteners (13, 14). It is therefore important to extend our knowledge of the physiologic properties of fructans as they relate to basic human digestive physiology and to clinical nutrition. In particular, the physiologic effects of fructans of different chain lengths have not been addressed previously.

In the present study, we report the findings of a randomized study of fructans from the root of chicory. Fructans were studied with respect to intestinal transit, absorption, fermentation, influence on blood sugar, and symptom-provoking effects in the gastrointestinal tract of healthy adult subjects (2–5, 15–17). The fructans were treated with enzymes (endo-inulases) to produce 2 different well-defined chain lengths (short and long), and the physiologic properties and gastrointestinal effects of different chain lengths could therefore be compared directly. The responses were also compared with responses from similar studies of the closely related, partially resistant food carbohydrates fructose and sorbitol. This study therefore addressed and extended several findings of mechanisms and quantitation of fructose and sorbitol absorption as well as carbohydrate malabsorption in general (2, 16, 18–21).
SUBJECTS AND METHODS

Subjects
Ten healthy, nonobese subjects (5 women and 5 men aged 18–25 y) participated. All subjects had normal results from blood screening tests at study entry and had no history of diabetes or gastrointestinal or pulmonary disease. They were not taking any medication. The study was carried out in accordance with the Helsinki Declaration II, and the study protocol was approved by the Copenhagen County Medical Ethics Committee.

Fructans
We used unbranched chains of fructofuranose units in β-(2–1’)-glycosidic binding, containing a single glucose moiety (inulin; 1–3). Fructans were prepared from inulin extracted from the root of chicory (Cichorium intybus, compositae; Orafti, Tienen, Belgium). By controlled hydrolysis of inulin with the enzyme endoinulase (Novo Nordisk A/S, Copenhagen), 2 fructan products of different chain lengths were produced for investigation. Short-chain fructans (FASC, Raftilose; Ferrosan A/S, Søborg, Denmark) were composed of fructose chains with a DP < 10 (median: DP = 3, according to the supplier) with or without a glucose molecule attached at the end. FASC contained fructose (0.8%), glucose (0.1%), sucrose (6.7%), and fructan (92.4%). Long-chain fructans (FALC, Raftiline; Ferrosan A/S) consisted of fructose chains of different lengths (51% with a DP > 12, 42% with a DP > 21, according to the supplier). FALC contained fructose (0.6%), glucose (0.5%), sucrose (3.2%), and fructan (95.7%).

Study design
The 10 adult subjects were initially challenged with a 15-mL lactulose solution [4-(β-d-galactopyranosyl)-d-fructose, Duphalac; Duphar, Weesp, Netherlands] containing 10.05 g lactulose, 0.9 g lactose, and 1.650 g galactose in 100 mL tap water. All subjects generated a significant, sustained rise in hydrogen concentration > 10 ppm in end-expiratory air (4, 16, 18, 22). Subsequently, the following tests were given in random order on a single-blind (subject blind) basis on different days separated by 3 mo (median: 3 mo): 1) 20 g lactulose (Duphalac) in 200 mL tap water; 2) 10 g FASC in 100 mL purified water; 3) 20 g FASC in 200 mL purified water; 4) 30 g FASC in 300 mL purified water; 5) 20 g FALC in 200 mL tap water; 6) 20 g fructose (d-fructofuranose; Roquette Freres, Lille, France) in 200 mL tap water; 7) 50 g fructose in 500 mL tap water; 8) 20 g sorbitol (d-glucitol; Merck, Darmstadt, Germany) in 200 mL tap water; and 9) 20 g sorbitol + 20 g glucose (Roquette Freres) in 200 mL tap water (thus keeping the sorbitol concentration constant at 10%) (Table 1). One subject, an 18-y-old man, discontinued the study after completing the initial screening and tests no. 2, 4, 7, and 8 because of elevated serum aspartate aminotransferase and serum lactate dehydrogenase values at the fifth visit. Both values were normal at the second visit, and they were completely normalized 3 wk after dropout. The abnormalities were ascribable to the subject’s status as a top trained athlete, great muscle mass, and excessive physical exercise at the time of enzyme elevation. The other 9 subjects completed all tests and no other laboratory test abnormalities were noted.

Breath tests
Interval samples of end-expiratory hydrogen and methane concentrations were collected in duplicate from the mouth of each subject in 20-mL plastic syringes fitted with a T-piece after a 12-h overnight fast (4, 16, 18, 22, 23). Samples were taken before ingestion of the above test substances for hydrogen every 15 min until a sustained rise in hydrogen concentrations > 10 ppm was reached, and subsequently every 30 min until 12 h (4 h for the initial 10-g lactulose screening). Methane concentrations were measured every 30 min. Concentrations used for calculation were means of duplicate samples (16, 18). All hydrogen and methane concentrations were measured simultaneously in the same breath sample on a compact gas chromatograph (model DP microlyzer; Quintron Instrument Co, Inc, Milwaukee) (18). Subjects with occasional fasting (initial values = time 0) hydrogen concentrations ≥30 ppm were not studied, and their test was scheduled for another day. Before breath collection, all subjects rinsed their mouths with a 0.1% chlorhexidine solution. A standard meal of 100 g minced meat and 50 g boiled rice was given at time 5 h (16, 18). Smoking and sleeping were not allowed and the subjects were nonambulant.

Blood glucose was determined from samples taken from an indwelling venous catheter before and every 30 min until 3 h after tests 3, 4, 6, 7, and 8. Venous acetate was measured by capillary electrophoresis (24) before and every 30 min until 7.5 h after tests 1–4 and 6–8 (Table 1). In tests 2–4, urine was collected for 24 h and the presence of fructans in urine was analyzed by enzymatic determination of fructose (3).
TABLE 2

Orocecal transit times (OCTT) in healthy adults after ingestion of fructans in different doses and of different chain lengths

<table>
<thead>
<tr>
<th>Substance</th>
<th>OCTT (min)</th>
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<tbody>
<tr>
<td>Lactulose, 20 g (n = 9)</td>
<td>45 (15–225)</td>
</tr>
<tr>
<td>FASC 10 g (n = 10) (60–240)</td>
<td>105</td>
</tr>
<tr>
<td>20 g (n = 9)</td>
<td>30 (15–105)</td>
</tr>
<tr>
<td>30 g (n = 10)</td>
<td>53 (0–165)</td>
</tr>
<tr>
<td>FALC, 20 g (n = 9)</td>
<td>75 (15–180)</td>
</tr>
<tr>
<td>Fructose, 50 g (n = 10)</td>
<td>45 (15–270)</td>
</tr>
<tr>
<td>Sorbitol, 20 g (n = 10)</td>
<td>30 (15–75)</td>
</tr>
<tr>
<td>Sorbitol + glucose, 20 g + 20 g (n = 9)</td>
<td>90 (45–150)</td>
</tr>
</tbody>
</table>

1 Median; range in parentheses. If breath-hydrogen concentration rose between 0 and 15 min after fructan ingestion OCTT was set to 0. FASC, short-chain fructans; FALC, long-chain fructans.

2,3 Significantly different from 20 g FASC: 2P < 0.01, 3P < 0.05.

4 Significantly different from sorbitol + glucose, P < 0.01.

Symptom scores

Gastrointestinal symptoms were recorded and scored as reported previously (3, 18). Scores were completed by the subjects throughout all tests and included the occurrence of flatulence, distension, borborygmi, abdominal pain, diarrhea, and nausea. All subjective symptoms were rated by the study subjects (none; 0; mild; 1; moderate; 2; or severe; 3) at fixed (0.5-h) intervals for 7 h after ingestion (14 times), and a total symptom score for each of the tests was calculated.

Calculations and statistics

For breath tests, the following variables were determined for the different tests (3, 4, 15, 16, 18): 1) the interval between ingestion of the test substance and the initial sustained rise in breath hydrogen ≥10 ppm from basal concentrations [the lowest previous concentration; orocecal transit time (OCTT)] (15); 2) the triangulated areas under the hydrogen or methane concentration-time curves, which were calculated after the initial sustained rise for hydrogen and methane until 12 h as incremental areas under the concentration versus time curves (AUC) (16); later measurements below basal values were set to 0.

The accuracy of the technique with which the doses known to be unabsorbed (10 and 30 g FASC, and 20 g FALC) could be calculated from hydrogen excretion after their ingestion was assessed by using equivalent doses of the unabsorbable standards, the 20-g lactulose challenge (test 1) and the 20-g FASC challenge (test 3), as reported previously (3, 16, 18–21). The deviation from the expected value was calculated as the numerical value of the difference between calculated values and the known malabsorbed amount (expected value) (16). The malabsorbed fractions of 50 g fructose and 20 g sorbitol were also estimated with use of both the lactulose and the FASC standards.

For blood gases and fasting venous acetate concentrations (baseline), maximum increases in concentration from baseline (peaks) and AUCs of positive incremental areas above baseline for 3 h (glucose) or 7.5 h (acetate) were calculated. Individual total AUCs of the acetate response after the 20-g lactulose and after the 20-g FASC tests were used to calculate the malabsorbed amount of carbohydrate after 10 and 30 g FASC, and the precision of the quantitative estimates was compared with hydrogen curves as above (16). Acetate responses after 20 g lactulose in one subject and after 20 g sorbitol in another were not analyzed because of errors in specimen handling.

Nonparametric statistical tests were used throughout [exact Wilcoxon test for paired replicates, Page’s test, and Friedman’s two-way analysis of variance (ANOVA) with multiple comparisons procedures] (3, 16, 25). Response variables for each type of measurement were compared pairwise for the 9 randomized test substances whenever relevant. Data from the subject discontinuing the study (described above) were analyzed and included in comparisons where available (tests 2, 4, 7, and 8, not in the symptom scores). A P value <0.05 (two sided) was considered statistically significant. Assistance with statistical analysis was provided by Spadille Biostatistik ApS, Fredensborg, Denmark. The computer software programs SAS (version 6.10; SAS Institute, Cary, NC) and STATXACT TURBO (version 2.0; Cytel Software Corp, Cambridge, MA) were used for the analyses.

RESULTS

All 10 subjects generated a significant sustained rise in hydrogen concentration after challenge with 10 g lactulose (median peak: 37 ppm; range: 26–77 ppm). Significant methane production was detected in 2 subjects, in 1 subject after all tests, and in the other only after test 4 (data not shown). These profiles were not analyzed further.

Orocecal transit times

OCTTs were calculated by using the hydrogen profiles (Table 2). OCTTs after 20 g FASC, 20 g lactulose, 20 g sorbitol, and 50 g fructose were not significantly different. In 2 subjects, a sustained rise in hydrogen concentration was not apparent until 5 h after ingestion of 50 g fructose. The median OCTT in the 3 subjects with apparent malabsorption of 20 g fructose was 15 min. Analysis of fructan OCTTs disclosed that FALC had longer OCTTs than FASC in similar doses and that 20 g FASC was transported faster than both 10 g FASC and 30 g FASC. By two-way ANOVA (Friedman’s test), 10 g FASC had significantly longer OCTTs than 20 g FASC. When 20 g sorbitol was given with 20 g glucose, a significant prolongation of OCTTs was apparent by pairwise comparison (Wilcoxon’s test) but not by ANOVA.

Hydrogen production

The integrated hydrogen responses after the different tests are shown in Table 3. AUCs after 20 g lactulose were not significantly different from similar doses of FASC, FALC, or sorbitol, although there was a trend toward higher hydrogen production after FASC (Table 3). Hydrogen production increased with increasing FASC dose; hydrogen production was significantly higher after 20 and 30 g FASC than after the 10-g dose (by ANOVA). Addition of 20 g glucose to the 20-g sorbitol solution did not change the hydrogen evolution significantly, whether measured as AUCs (Table 3) or as peak incremental increases in hydrogen concentration above basal values (data not shown). A sustained rise in hydrogen production was seen in 3 of 9 subjects after 20 g fructose; all 10 subjects had apparent malabsorption (ie, produced significant amounts of hydrogen) after 50 g fructose.

Acetate production

The AUCs for serum acetate concentration above fasting values for 7.5 h after tests 1–4 and 6–8 (Subjects and Methods) are
TABLE 3
Incremental areas under the breath-hydrogen concentration versus time curves (AUCs) over 12 h in healthy adults after ingestion of different substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>AUC (ppm·min/10²)</th>
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<tbody>
<tr>
<td>Lactulose, 20 g (n = 9)</td>
<td>220 (106–424)²</td>
</tr>
<tr>
<td>Lactulose, 10 g (n = 10)</td>
<td>139 (110–486)³</td>
</tr>
<tr>
<td>Lactulose, 20 g (n = 10)</td>
<td>306 (241–570)²</td>
</tr>
<tr>
<td>Lactulose, 30 g (n = 10)</td>
<td>368 (256–615)⁴</td>
</tr>
<tr>
<td>FALC, 20 g (n = 9)</td>
<td>247 (118–491)</td>
</tr>
<tr>
<td>Fructose, 20 g (n = 9)</td>
<td>8 (0–44)²</td>
</tr>
<tr>
<td>Fructose, 50 g (n = 10)</td>
<td>82 (34–331)</td>
</tr>
<tr>
<td>Sorbitol, 20 g (n = 10)</td>
<td>245 (117–370)</td>
</tr>
<tr>
<td>Sorbitol + glucose, 20 g + 20 g (n = 9)</td>
<td>211 (115–290)</td>
</tr>
</tbody>
</table>

¹Median; range in parentheses. FASC, short-chain fructans; FALC, long-chain fructans.
²Significantly different from 20 and 50 g fructose, P < 0.01.
³Significantly different from 20 and 30 g FASC, P < 0.01.
⁴A sustained rise in breath-hydrogen concentration was apparent in 3 of 9 subjects.

summarized in Table 4. Serum acetate AUCs had a somewhat different pattern from that of AUCs of hydrogen production. The acetate production increased with increasing dose of FASC, but the difference was not significant for the highest dose (Wilcoxon’s and Friedman’s tests). Acetate responses after 20 g lactulose and 20 g FASC were similar. The acetate response did not differ significantly after the 2 fructose doses (tests 6 and 7) but was significantly lower than after 20 g lactulose (P < 0.01, Wilcoxon’s and Friedman’s tests). After 20 g sorbitol, the rise in venous acetate was significantly smaller than that after similar doses of lactulose and FASC (Wilcoxon’s test). Thus, acetate responses appear to be less sensitive indexes of the magnitude of carbohydrate malabsorption than are hydrogen responses.

Quantitation of malabsorbed carbohydrate

Hydrogen production: precision of estimates with different nonabsorbable standards

The malabsorbed amounts of 10 and 30 g FASC, 20 g FALC (assuming quantitative malabsorption of these fructans), 50 g fructose, and 20 g sorbitol were estimated by comparison of total AUCs of the respective individual hydrogen-production curves with those of the individual 20-g lactulose tests and those of the individual 20-g FASC tests (16, 18). With use of 20 g lactulose as the standard, the median calculated amount malabsorbed after 10 g FASC was 12.7 g, as compared with 10.0 g with 20 g FASC as the standard (P > 0.10). For 30 g FASC, the median calculated malabsorbed amount was 30.8 g with the lactulose standard and 24.4 g with the 20-g FASC standard (P > 0.10). For 20 g FALC, similar calculations showed 22.7 g and 16.2 g, respectively (P = 0.08). Thus, there were no significant differences between deviations of calculated malabsorbed amounts from expected amounts between the 2 standards, 20 g FASC and 20 g lactulose, for any test, and the overall median deviations were 2.5 g (25%) for 10 g FASC, 6.1 g (20%) for 30 g FASC, and 4.4 g (22%) for 20 g FALC. Apparently, the precision of quantitative estimates for these tests were not significantly different for the 2 nonabsorbable standards.

The median calculated malabsorbed amount of fructose after the 50-g test was 6.6 g with lactulose as the standard and 5.4 g with 20 g FASC as the unabsorbable standard (P > 0.10). Similar estimates after 20 g sorbitol were 21.1 and 13.4 g, respectively (P > 0.01). Thus, there were no significant differences in the quantitative estimates based on total hydrogen production with use of 20 g lactulose or 20 g FASC as unabsorbable standards, except for sorbitol, for which the estimates derived with the use of the 20-g FASC standard were significantly lower.

Acetate production: precision of estimates with different nonabsorbable standards

Quantitation procedures similar to those described above were carried out with AUCs of total acetate versus time curves. As for the breath-hydrogen curves, the calculated malabsorbed amounts after the 10- and 30-g FASC tests were not significantly different with use of the acetate versus time curves after 20-g FASC or 20 g lactulose as unabsorbable standards (data not shown, P > 0.10; n = 8).

Precision of estimates, hydrogen compared with acetate

The precision of quantitative estimates was also compared between hydrogen curves and acetate curves for the same tests (10 and 30 g FASC) and for both 20-g standards. With 20 g FASC as the standard, the calculated amounts after 30 g FASC were significantly more precise when the hydrogen curves were used (P < 0.01; median deviations 5.9 compared with 13.2 g). A similar trend was apparent for 10 g FASC (P = 0.16). With 20 g lactulose as the standard, a trend toward more precise estimates of the same substances was also apparent when hydrogen curves were used (P = 0.11 for 30 g FASC and P = 0.20 for 10 g FASC). Thus, the precision of quantitative estimates tended to be higher when quantitative estimates were based on hydrogen production than when based on acetate production.

Blood glucose and urine fructan

Blood glucose was measured for 3 h after ingestion of 20 and 30 g FASC, 20 and 50 g fructose, and 20 g sorbitol. Maximum incremental rises (peak rises) in blood glucose or AUCs were not
Intestinal handling of fructooligosaccharides

Most studies of fructan ingestion in humans have been carried out with short-chain fructans, containing ≤4 fructose units (6–7, 8, 14, 26–30). In our previous studies of fructans from Jerusalem artichokes (Helianthus tuberosus) with longer chain lengths (=50% with > 4 fructose units), we found that median OCTTs were 3 and 2.5 h for 10- and 20-g doses, respectively, and that the substances were apparently completely unabsorbed and fermented (3). In recent studies of ileostomists and healthy subjects after ileal intubation and aspiration, 87–89% of short-chain fructans and inulin from Jerusalem artichokes was recovered (29, 31). These figures agree well with those of the breath-hydrogen studies mentioned above (3). The OCTTs in the ileostomy model (31) were somewhat longer than those found in the study by Rumessen et al (3), perhaps reflecting adaptive changes in the pathophysiologic ileostomy model and possibly also because of the somewhat longer chain lengths of the fructans used in the ileostomy model (65% with >4 fructose units). In the present study, and in accordance with previous studies (3), fructans were undetected in urine, signaling no or negligible small intestinal absorption of intact molecules. With other detection systems, a fraction of 1% of intact short-chain fructans have been estimated to be absorbed by the small intestine under similar conditions (29).

The present study seems to be the first to have directly compared the physiologic responses after ingestion of 2 different chain lengths of fructans. In the present investigation, the short-chain product (FASC) had a median DP of 3, whereas the other fructan product (FALC) had considerably longer chain lengths (42% with chain lengths > 21). We found a median OCTT of 0.5 h after 20 g FASC, whereas 20 g FALC resulted in significantly longer OCTTs, comparable with OCTTs after similar doses of fructans from Jerusalem artichokes (3). Because of an increased osmotic load, the OCTT will generally decrease with increasing dose of unabsorbable carbohydrate (3, 16). However, in the present study, the OCTTs after 30 g FASC (median: 53 min) were significantly longer than those after 20 g FASC (median: 30 min). This finding disagrees with findings from long-chain fructans in ileostomy models (31), and our data are inadequate to offer a direct explanation. Delayed gastric emptying of a large single dose of 30 g in intact individuals is a possibility, and such an effect may also contribute to other measures of abdominal discomfort with higher doses of fructans (14, 27, 28).

Hydrogen and acetate are end products of the colonic bacterial fermentation of the carbohydrate substrates, and increased production is reflected by rises in end-expiratory hydrogen concentrations and venous acetate concentrations, respectively (4). These indexes are therefore indirect measures of colonic fermentation, and in the present study, there was increased hydrogen and acetate production with increasing doses of fructans. No

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**DISCUSSION**

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significant qualitative or quantitative differences in fermentation pattern were apparent between equivalent doses of short-chain fructans, long-chain fructans, and the nonabsorbable disaccharide lactulose. However, a difference was noted for estimates of sorbitol absorption, possibly unmasking a trend in the primary comparisons. In vitro studies have suggested that acetate production from fructans in fecal inocula is lower than that of lactulose (30). The physiologic relevance of this observation is unclear, the effect is apparently not mirrored in venous acetate concentrations.

Fructans may be nutritionally important because of their various physiologic effects, which are primarily related to their fermentation in the lower gastrointestinal tract. Fructans may serve as low-energy, nonglycemic dietary supplements for diabetic and obese persons, as dietary fiber, sugar substitutes, or even a fat replacement (3, 6). In agreement with studies of Jerusalem artichoke fructans (3), chicory fructans did not significantly raise blood glucose. The energy production of ingested fructans may be about one-half that of sucrose (29). A health-promoting effect of fructan ingestion has been proposed because fructans are preferential substrates for bifidobacteria, which concomitantly reduce other potentially pathogenic colonic bacterial species and reduce colonic reductive enzymes implicated in carcinogenesis (8–12, 28). Dietary fructans reduce the numbers of Salmonella spp. in chicken colon (32), and in humans, a daily intake ≤5 g/d may have a bifidogenic action (9, 11, 12, 28). It has never been shown, however, that this effect contributes to prevention or reduced severity of manifest gastrointestinal infections in humans, not to mention possible effects on neoplasia. Because of their physiologic properties, fructans may also be beneficial to constipated individuals or even in the treatment of hepatic encephalopathy because their OCTT and fermentation profiles are so similar to those of lactulose. It is likely that clinical, systemic, and colonic effects vary with different chain lengths of the fructans.

Ingestion of fructans is limited by various abdominal symptoms such as osmotic diarrhea, pain, bloating, and flatulence due to colonic fermentation and production of bacterial end products. A dose of 5 g/d seems to be well tolerated (28), whereas higher doses may induce annoying symptoms during chronic ingestion, primarily excessive flatulence (14, 27, 28). In single doses of 10–20 g, Jerusalem artichoke fructans were generally well tolerated (3). In the present study, mostly mild symptoms were disclosed after similar single doses of chicory fructans. The symptoms tended to increase with increasing carbohydrate load, and the number of symptoms produced after consumption of 30 g FASC and 20 g lactulose were significantly greater than those after consumption of 20 g fructose, which was apparently completely absorbed in two-thirds of the subjects. During chronic ingestion of unabsorbable sugars, adaptive changes in symptom profiles may occur (33), but this effect may not be apparent during fructan ingestion (27).

**Fructan, fructose, and sorbitol absorption: relations to quantitation**

In our previous quantitation studies of carbohydrate malabsorption, we investigated the reliability of lactulose as an unabsorbable reference standard for quantification of fructose malabsorption (2, 19) and the relation between the amount of malabsorbed carbohydrate and different indexes of end-expiratory hydrogen production (4, 16). We also speculated that other indirect indexes besides breath hydrogen could improve the precision of quantitative estimates of carbohydrate malabsorption (4, 16). Although theoretically attractive, concomitant methane measurements appear to be of only marginal value because both hydrogen and methane excretion in methane producers tend to be somewhat erratic (18). Similarly, acetate, another major end product of colonic bacterial fermentation, has shown some proportionality in venous concentration after different incompletely absorbed carbohydrate loads (34–38). In the present study, we tested whether increases in venous acetate concentrations after different unabsorbable carbohydrate loads were comparable in precision with breath-hydrogen responses with respect to semiquantitative estimates of the unabsorbed amount of carbohydrate (4, 16, 18, 36). We found a clear trend toward more precise quantitative estimates based on hydrogen production than on increases in venous acetate, a difference that was significant for larger doses of fructans. Furthermore, the acetate responses after the 2 doses of fructose were similar, despite clearly different rates and magnitudes of malabsorption. We therefore conclude that venous acetate responses are less precise and less sensitive indexes of the magnitude of carbohydrate malabsorption than are end-expiratory hydrogen concentrations. A likely explanation for this is that acetate, in contrast with hydrogen, is also produced from endogenous, noncolonic sites (36).

It could be speculated that for quantitative estimates of fructose malabsorption, nonabsorbable standards with chemical compositions more similar to that of fructose would be more precise than lactulose (which is a synthetic disaccharide of galactose and fructose) for comparison of breath-hydrogen responses. This hypothesis was tested in the present study, and we found that quantitative estimates of fructan and fructose malabsorption were similar whether short-chain fructose units (20 g FASC) or 20 g lactulose were used as nonabsorbable standards.

Estimates of sorbitol absorption, however, differed significantly with consistently lower estimates for the quantity malabsorbed after 20 g FASC was used as the reference, which also reflects the nonsignificant trend toward higher hydrogen production after FASC consumption after lactulose. This may confirm results from previous studies suggesting that the hydrogen production from malabsorbed sorbitol may be higher than that from equal amounts of lactulose (39), and consequently, that the absorption capacity for sorbitol may have been underestimated previously (2). The present study suggests, with use of FASC as the reference, that a mean of about one-third of a 20-g sorbitol load is absorbed. In analogy with lactose intolerance, patients with irritable bowel syndrome (21, 40) or even healthy individuals (20, 41) may have discomfort with malabsorption of even small amounts of fructose, sorbitol, or both, also reflected in the present study of healthy subjects, in whom symptom scores after 50 g fructose were significantly greater than those after 20 g. Patients with irritable bowel syndrome may therefore benefit from a fructose- and sorbitol-free diet (5, 21, 42).

We hypothesized previously the existence of separate and specific mechanisms of small intestinal fructose absorption: one, a low-capacity glucose-independent facilitated fructose transporter, the other, a high-capacity glucose-dependent fructose transporter, possibly hydrolase related (2, 19). Because fructose given as sucrose or invert sugar is apparently completely absorbed (2, 19), such mechanisms could explain why adults frequently show apparent malabsorption after loads of free fructose and also why these responses are predictive of the malabsorption of fructose in excess of glucose (19). This hypothesis, including
the possible involvement of a hydrolase-related effect, has received support from independent studies in rats (43–45); the observed phenomena could involve basolateral fructose transporters (46). However, recent breath-test studies of fructose absorption in children suggested that this clear-cut effect of glucose on fructose absorption is less specific because it is apparently mimicked by ingestion of the amino acid l-alanine instead of glucose, and because addition of the β-glucosidase inhibitor acarbose does not abolish the effects of added glucose on fructose absorption (47, 48). In keeping with this, a recent perfusion study of the duodenojejunum of healthy adults suggested that under these circumstances, free fructose is apparently not absorbed by a disaccharidase-related transport system but that facilitated diffusion and the paracellular pathway are the major transport mechanisms (49). Because supraadditive malabsorption has been shown after mixtures of free fructose and sorbitol (20, 21), sorbitol may interfere with the transport mechanism for free fructose but not with that of fructose given as sucrose (20).

Such differences between mechanisms for fructose and sorbitol malabsorption are supported by several other lines of evidence. Recent perfusion studies in human small intestine do not support a facilitating effect of glucose on sorbitol absorption (50). In accordance with this, we could not detect an effect of concomitant ingestion of equimolar amounts of glucose on sorbitol absorption in the present study, a finding supported by similar symptom scores. In other studies, the rate of sorbitol malabsorption was significantly reduced when sorbitol was ingested with glucose or lipids (51), or with glucose and l-alanine (47). However, in these studies the concentrations and volumes of the sorbitol solutions as well as the amounts of glucose added were different from those of the present study and also different in the conditions compared. The present study was designed to keep the concentration of sorbitol constant in the conditions compared. A nonspecific effect of the presence of nutrients other than fructose on gastric emptying or small intestinal motility is a likely confounder. For practical purposes, the present study showed that sorbitol causes overt malabsorption, even in small doses, and this malabsorption is not alleviated by concomitant ingestion of similar amounts of glucose. This situation therefore clearly differs from that after ingestion of fructose (2, 5, 19–21). This points to a more specific nature of the glucose-associated fructose absorption, although there may be considerable species differences. The possibility of specific interactions between fructose and sorbitol absorption is still unsettled.

In conclusion, the present findings have put the magnitudes of fructose and sorbitol absorption into further nutritional perspective. We showed that the fermentation patterns of fructans with different chain lengths are similar but that the transit time increases significantly with increasing chain length. The intestinal handling of fructans is similar to that of lactulose and both substances may be useful as nonabsorbable standards for the study of fructose absorption. There seems to be no advantage of measuring venous acetate concentrations for semiquantitative estimates of carbohydrate malabsorption. Distressing abdominal symptoms seem to occur only after single doses of fructans > 20 g. The postulated health-promoting effects of fructan ingestion in various diseases and conditions merit further direct studies.

We are grateful to G Bishoff, LM Hansen, J Purtoft, and I Staack for skillful technical assistance.

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