Fructooligosaccharides and lactulose cause more symptoms in lactose maldigesters and subjects with pseudohypolactasia than in control lactose digesters\textsuperscript{1,2}

Ulla Teuri, Heikki Vapaatalo, and Riitta Korpela

**ABSTRACT**

**Background:** Many lactose maldigesters tolerate more lactose in experimental studies than in everyday life, in which their symptoms may result from other carbohydrates as well.

**Objective:** The question of whether the symptoms caused by large quantities of carbohydrates are more severe in lactose maldigesters than in control lactose digesters or in lactose digesters who report milk to be the cause of their gastrointestinal symptoms (pseudohypolactasic subjects) was studied in a randomized, double-blind, crossover study. Comparisons between commonly used diagnostic methods for lactose maldigestion were also made.

**Design:** The subjects were 40 women aged 20–63 y from 3 groups: lactose maldigesters (n = 12), pseudohypolactasic subjects (n = 15), and control lactose digesters (n = 13). The subjects were given either 50 g lactose, 50 g sucrose, 25 g lactulose, or 25 g fructooligosaccharides. After carbohydrate ingestion, urine was collected and the breath-hydrogen concentration was measured every 30 min for 3 h. Blood glucose was measured every 20 min for 1 h and subjective gastrointestinal symptoms were monitored for 8 h with a questionnaire.

**Results:** When lactulose and fructooligosaccharides were ingested, the lactose maldigesters (P = 0.04 and 0.09, respectively) and the pseudohypolactasic subjects (P = 0.006 and 0.01, respectively) reported more symptoms than did the control lactose digesters. Sucrose caused more symptoms in the lactose maldigesters than in the control lactose digesters (P = 0.05).

**Conclusions:** Lactose maldigesters and lactose digesters with pseudohypolactasia experience more symptoms than control lactose digesters after a single intake of large amounts of indigestible carbohydrates. Lactose maldigesters also experience more symptoms after ingesting sucrose. *Am J Clin Nutr* 1999;69:973–9.

**KEY WORDS** Breath-hydrogen test, fructooligosaccharides, galactose, gastrointestinal symptoms, pseudohypolactasia, lactose, lactose intolerance, lactulose, sucrose, women, Finland

**INTRODUCTION**

Lactose is hydrolyzed by lactase in the small intestine. In cases of lactose maldigestion, lactose passes to the large intestine without hydrolysis and is fermented there by the bacterial flora. In lactose-intolerant subjects this causes gastrointestinal symptoms such as flatulence, bloating, abdominal pain, borborygm, and diarrhea. Many lactose-intolerant subjects claim that they cannot tolerate any lactose at all in everyday life. However, most lactose maldigesters can tolerate, at a single challenge, ≤12 g lactose without experiencing any symptoms, as was shown in double-blind trials (1). Suarez et al (2) showed that only two-thirds of the self-diagnosed, severely lactose-intolerant subjects were found to be lactose maldigesters and they experienced only minimal gastrointestinal symptoms after ingesting 12 g lactose in milk. Other studies have also shown that many of those who claim to be milk intolerant appear not to be lactose maldigesters when double-blind studies were conducted (3, 4). However, symptoms caused by milk may be similar in lactose maldigesters and in digesters who claim to be milk intolerant (3). There also seem to be many lactose maldigesters who experience symptoms when there is milk in their diet even when there is no, or very little, lactose in the milk (4, 5).

The only direct diagnostic method of testing lactose maldigestion is jejunal biopsy, which is invasive and thus not used routinely; therefore, indirect methods are more common. The specificity and sensitivity of indirect methods vary in different studies from 76% to 100% (6).

Besides lactose, other carbohydrates pass into the large intestine (7), of which, in addition to dietary fiber, resistant starch forms a significant part (8). Oligosaccharides from vegetables, fructose in excess of glucose, and large quantities of sorbitol and xylitol are not absorbed in the small intestine. Because these carbohydrates, except for insoluble dietary fiber, are efficiently hydrolyzed and fermented in the large intestine, symptoms may result. Honey contains fructose in excess of glucose and has a laxative effect in some people (9). If there is a great deal of fructooligosaccharide-containing food such as wheat and onion in the diet, some people may experience symptoms (10, 11).

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Because the symptoms caused by nonabsorbable carbohydrates resemble those of lactose in lactose maldigesters, our hypothesis was that symptoms caused by other carbohydrates are often mistakenly considered to be caused by lactose. The primary aim of this study was to examine whether the symptoms caused by large quantities of carbohydrates are more severe in lactose maldigesters than in control lactose digesters or in lactose digesters who report milk to be the cause of their gastrointestinal symptoms (pseudohipolactasic subjects). The secondary aim of the study was to examine how well, under strictly controlled experimental conditions, different methods used for diagnosing lactose malabsorption—the measurement of blood glucose, breath hydrogen, and urine galactose excretion, and symptom scores—agreed with each other.

**SUBJECTS AND METHODS**

**Subjects**

Forty-two volunteers were recruited for the study and gave their informed consent to participate. The study protocol was approved by the Ethical Committee of the Faculty of Agriculture and Forestry, University of Helsinki. Two volunteers were dropped from the study: one because of noncompliance and the second because of gastrointestinal complaints unrelated to the study. The final group consisted of 40 women whose mean age was 39 y (range: 20–63 y). The women had no diagnosed gastrointestinal diseases, had received no antibiotic treatment for ≥2 wk before the study, and were not taking any medication that might have affected the gastrointestinal tract. Three groups were recruited: those who considered themselves to be lactose digesters and had no gastrointestinal complaints (n = 17); those who thought they experienced symptoms after ingesting milk, but who had either not undergone a lactose tolerance test or, if they had, the results had been negative (n = 13); and those who had undergone a lactose tolerance test and the results had been positive (n = 10).

We tested all the subjects to determine whether they had lactose malabsorption, after which they were divided into the final groups. The test for lactose malabsorption was included as 1 of 4 interventions during the study (50 g lactose in 300 mL water). This dose is commonly used, especially when testing for lactose malabsorption with the glucose and urinary galactose tests (6).

Three tests were used to determine lactose malabsorption: measurements of breath-hydrogen, blood glucose, and urinary galactose concentrations. Subjects with peak breath-hydrogen concentrations > 20 ppm above basal excretion within 3 h, a peak rise in blood glucose < 1.1 mmol/L within 1 h, or a urinary galactose content < 20 mg within 3 h are classified as lactose maldigesters. In the present study, subjects were considered to be lactose maldigesters if 2 of these 3 tests gave positive results. Ten of the 12 lactose maldigesters had positive results from all 3 tests. The subjects were then reclassified into 3 groups: lactose malabsorbers (n = 12), control lactose digesters (n = 13), and pseudohipolactasic subjects, ie, lactose digesters who originally believed milk to be the cause of their symptoms, but whose test results showed that they did not suffer from lactose malabsorption (n = 15).

The lactose maldigesters group (n = 12) was formed from the following group of original recruits: 24% (4/17) of those who considered themselves to be lactose digesters, 23% (3/13) of those who thought they had symptoms when they ingested milk, and 50% (5/10) of those who had been diagnosed previously as being lactose intolerant on the basis of a lactose intolerance test.

**Experimental design**

The study was a randomized, double-blind, 4-period crossover study. Results of the following interventions were compared: 50 g lactose (Valio Ltd, Lapinlahti, Finland), 50 g sucrose (Sucrose Pharma; Porkkala Sugar Refinery Ltd, Porrkala, Finland), 25 g lactulose (Duphalac; Solvay Duphar, Weesp, Netherlands), and 25 g fructooligosaccharides (Rafitolose P95: Orafti SA, Oreye, Belgium). Subjects were randomly assigned to 1 of the 4 possible intervention sequences, which determined the order of carbohydrate interventions. There was a 1–2 wk washout period between interventions. All carbohydrates were administered in 300 mL tap water. β-Carotene coloring (Yellow Color; Kemisk Industri Soro A/S, Rodovre, Denmark) and lemon flavoring (Lemon NI: Pelaron SA, Louvain-La-Neuve, Belgium) were added to all solutions to make them similar in color and taste. On the test day, after an overnight fast of ≥ 10 h, subjects ingested 1 of the 4 carbohydrate solutions. Breath-hydrogen concentrations were measured every half hour for 3 h and urine was collected for the same length of time (6). The blood glucose concentration was measured every 20 min for 1 h after ingestion of the sugar solution and subjects noted any gastrointestinal symptoms on a questionnaire for 8 h after ingestion. After 3 h, subjects were offered a standard meal, which was similar throughout the study period and in each experimental session. The meal consisted of rice with minced meat, fruit juice, and bread. Subjects had been asked to avoid, on the day before the study, irritating foods such as beans and fresh rye bread and food that they knew would cause them gastrointestinal symptoms. If subjects had gastrointestinal symptoms on the experimental day, the study was postponed.

Breath-hydrogen concentrations were measured with a breath-hydrogen sensor (Solid hydrogen leak detector 8505; Sensistor AB, Linköping, Sweden) (12). The peak increase in breath-hydrogen concentration (in ppm) above baseline over 180 min was noted and the area under the 3-h hydrogen curve (in ppm) was calculated (AUC/180). There were no significant differences in baseline hydrogen concentrations, either between groups or between periods.

A capillary blood sample was taken from the tip of a finger for blood glucose measurement with an automatic blood glucose meter (Glucometer Elite; Kyoto Daiichi, Kagaku, Japan) (13). The maximal rise in blood glucose (mmol/L) was noted.

For determination of urinary galactose excretion, a fasting urine sample was obtained before the carbohydrate challenge and another sample was collected 3 h after the challenge. The samples were stored at −20°C until assayed with a commercially available test kit (Galac MPR 1 Galactose; Boehringer Mannheim, Mannheim, Germany) (14) with an automatic spectrophotometer (Elan Analyzer 6150; Eppendorf-Netheler-Hinz, Hamburg, Germany).

On the test day, the subjects used a ranked scale (0 = none, 1–3 = slight, 4–6 = moderate, 7–9 = moderately severe, and 10 = severe) to rate flatulence, abdominal bloating, abdominal pain, borborygmi, and the degree of loose stools or diarrhea. Ratings were made before intake of the test solution, every hour for 3 h after intake, and 6 and 8 h after intake. The maximum symptom score of each symptom obtained during the first 3 h after intake and during the first 6 h after intake were noted. An overall measurement of the degree of the symptoms (ie, the sum of symptoms score) was calculated by adding together the maximum symptom scores of these 5 symptoms (possible score: 0–50). A sum of symptoms score ≥12 indicated clinically significant symptoms.
Food-related symptoms questionnaire

Before the study began, subjects completed a questionnaire about their usual reactions to 19 foods known to often cause gastrointestinal symptoms (0 = does not cause symptoms, 1 = causes symptoms only when a great deal is eaten, 2 = causes symptoms when normal amounts are eaten, 3 = causes symptoms even when a small amount is eaten). There were no questions concerning milk products. The mean symptom score for each subject was calculated and then the mean scores for each group were calculated.

Statistics

Results are expressed as means ± SEMs. The primary variables were the increase in breath-hydrogen concentration (AUC/180), the maximal increase in blood glucose concentration, and the sum of symptoms scores (during the first 3 and 6 h after intake). Because of skewed distributions in the sum of symptoms scores, they were logarithmically transformed before the analysis. In analyzing the primary variables, a mixed-effects analysis of variance model was applied. Intervention, period, and carryover were included as fixed-effect factors; subject effect was included as a random-effect factor. Because a carryover effect and a period effect were ruled out for all variables tested, the final model was an analysis of variance with group and intervention as main fixed effects, a group-by-intervention interaction, and a random subject effect (as the explanatory variables). To further examine the interaction between group and intervention, pairwise post hoc analyses were carried out by using Fisher’s least-significant-difference method and a repeated-measures contrast analysis to compare the groups and the interventions, respectively.

The secondary variables were separate abdominal symptoms. Ordered symptom scores during the first 6 h for flatulence, abdominal bloating, abdominal pain, borborygmi, and the degree of loose stools or diarrhea were analyzed separately by using nonparametric statistical methods. The differences between groups were tested by using the Kruskal-Wallis test. In cases in which the Kruskal-Wallis test was significant (P < 0.05), pairwise comparisons between groups were made by using the Mann-Whitney U test. These tests were conducted separately for each intervention.

The 3 diagnostic tests used (rise in breath-hydrogen concentration, rise in blood glucose concentration, and amount of urinary galactose) were compared by calculating the percentages of concordance with clinically significant gastrointestinal symptoms (ie, a sum of symptoms score ≥12 out of a possible 50).

For the questionnaire about foods, differences between groups were tested with the Kruskal-Wallis and Mann-Whitney U tests. The analyses were carried out by using the STATISTICA/W statistical package (release 5; StatSoft Inc, Tulsa, OK) and SPSS (release 7.5.1; SPSS Inc, Chicago).

RESULTS

Lactose malabsorption

When the ability to digest lactose was evaluated, the breath-hydrogen and blood glucose tests gave the same result in 80% (32/40) of the subjects, the breath-hydrogen and urinary galactose tests gave the same result in 87.5% (35/40) of subjects, and the blood glucose and urinary galactose tests gave the same result in 82.5% (33/40) of subjects. The kappa coefficients were 0.57 (95% CI: 0.31, 0.84), 0.72 (0.49, 0.95), and 0.61 (0.35, 0.87), respectively. The first value showed moderate agreement and the last 2 showed good agreement on the kappa coefficient scale. On the basis of the kappa coefficients, the concordance with clinically significant symptoms was good with the urinary galactose test (0.64; 95% CI: 0.38, 0.90), moderate with the breath-hydrogen test (0.50; 0.21, 0.79), and fair with the blood glucose test (0.39; 0.08, 0.70).

Breath-hydrogen excretion

In the analysis of hydrogen production (AUC/180), the main group effect, the effect of intervention, and the interaction between group and intervention were all significant (P < 0.001). Further analysis indicated that there were no significant differences between groups after ingestion of sucrose and fructooligosaccharides (Table 1). However, after ingestion of lactose and lactulose, lactose maldigesters produced significantly more hydrogen than did the control lactose digesters (P < 0.001 and P = 0.02, respectively) and pseudohypolactasic subjects (P < 0.001 and P = 0.005, respectively).

Symptoms

In the analysis of the 6-h sum of symptoms scores, the main effect of group was significant (P < 0.001), the effect of intervention was significant (P < 0.001), and the interaction between group and intervention was also significant (P = 0.05). After ingesting sucrose, the lactose maldigesters experienced more severe symptoms than did the control lactose digesters (P = 0.05), although the symptoms were slight (Table 2). The symptoms caused by lactose

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**TABLE 1**

Hydrogen production during the first 3 h after sucrose, lactose, lactulose, and fructooligosaccharide intakes

<table>
<thead>
<tr>
<th>Carbohydrate intervention</th>
<th>Control lactose digesters (n = 13)</th>
<th>Pseudohypolactasic subjects (n = 15)</th>
<th>Lactose maldigesters (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak H2 ppm</td>
<td>AUC/180 ppm</td>
<td>Peak H2 ppm</td>
</tr>
<tr>
<td>50 g Sucrose</td>
<td>2.4 ± 1.2</td>
<td>5.8 ± 0.9</td>
<td>2.3 ± 1.0</td>
</tr>
<tr>
<td>50 g Lactose</td>
<td>5.8 ± 2.1</td>
<td>7.1 ± 1.4</td>
<td>10.3 ± 4.1</td>
</tr>
<tr>
<td>25 g Lactulose</td>
<td>39.0 ± 5.6</td>
<td>28.8 ± 4.6</td>
<td>42.1 ± 8.3</td>
</tr>
<tr>
<td>25 g Fructooligosaccharides</td>
<td>78.2 ± 11.1</td>
<td>42.8 ± 5.0</td>
<td>82.1 ± 11.2</td>
</tr>
</tbody>
</table>

1 ± SEM. Peak H2, the maximum hydrogen production value above baseline during the first 3 h; AUC/180, the area under the breath-hydrogen-excretion curve divided by the measurement time (180 min).

2 Significantly different from control lactose digesters and pseudohypolactasic subjects, P < 0.05 (Fisher’s least-significant-difference test).
TABLE 2
All symptoms and sum of symptoms scores during the first 6 h after the carbohydrate interventions in the different groups*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Control lactose digesters (n = 13)</th>
<th>Pseudohypolactasic subjects (n = 15)</th>
<th>Lactose maldigesters (n = 12)</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sucrose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.8 ± 1.5</td>
<td>1.3 ± 1.6</td>
<td>1.1 ± 1.3</td>
<td>0.50</td>
</tr>
<tr>
<td>Borborygmi</td>
<td>0.4 ± 0.7†</td>
<td>0.0 ± 0.0†</td>
<td>1.0 ± 1.0†</td>
<td>0.03</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>0.3 ± 1.1†</td>
<td>1.7 ± 2.9†</td>
<td>2.2 ± 2.9†</td>
<td>0.02</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.4 ± 0.8</td>
<td>0.3 ± 1.0</td>
<td>1.3 ± 1.9</td>
<td>0.11</td>
</tr>
<tr>
<td>Loose stools</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Sum of symptoms</td>
<td>1.8 ± 0.9†</td>
<td>3.3 ± 1.1</td>
<td>5.5 ± 1.7†</td>
<td>—</td>
</tr>
<tr>
<td><strong>Lactose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.9 ± 1.0†</td>
<td>2.7 ± 2.9†</td>
<td>5.3 ± 3.1†</td>
<td>0.003</td>
</tr>
<tr>
<td>Borborygmi</td>
<td>0.3 ± 0.9†</td>
<td>1.1 ± 2.0†</td>
<td>4.8 ± 3.4†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>0.5 ± 1.4†</td>
<td>2.3 ± 3.4</td>
<td>3.4 ± 3.5‡</td>
<td>0.04</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.5 ± 1.0†</td>
<td>0.5 ± 1.1‡</td>
<td>2.4 ± 2.9‡</td>
<td>0.02</td>
</tr>
<tr>
<td>Loose stools</td>
<td>0.0 ± 0.0†</td>
<td>0.4 ± 1.1‡</td>
<td>4.3 ± 4.6‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of symptoms</td>
<td>2.2 ± 1.4†</td>
<td>6.9 ± 1.8†</td>
<td>20.3 ± 4.2‡</td>
<td>—</td>
</tr>
<tr>
<td><strong>Lactulose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.7 ± 2.7§</td>
<td>5.5 ± 2.3†</td>
<td>5.3 ± 2.7†</td>
<td>0.02</td>
</tr>
<tr>
<td>Borborygmi</td>
<td>2.1 ± 1.6§</td>
<td>3.8 ± 2.7†</td>
<td>4.8 ± 2.8†</td>
<td>0.04</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1.5 ± 2.4</td>
<td>3.9 ± 3.6</td>
<td>3.8 ± 2.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.5 ± 1.9</td>
<td>3.0 ± 3.4</td>
<td>1.6 ± 1.8</td>
<td>0.54</td>
</tr>
<tr>
<td>Loose stools</td>
<td>3.1 ± 3.8</td>
<td>5.2 ± 4.8</td>
<td>3.8 ± 4.7</td>
<td>0.45</td>
</tr>
<tr>
<td>Sum of symptoms</td>
<td>10.8 ± 2.2§</td>
<td>21.4 ± 2.9§</td>
<td>19.2 ± 2.6§</td>
<td>—</td>
</tr>
<tr>
<td><strong>Fructooligosaccharides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>5.0 ± 2.5</td>
<td>6.9 ± 2.9</td>
<td>5.4 ± 2.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Borborygmi</td>
<td>2.2 ± 2.3</td>
<td>3.7 ± 2.9</td>
<td>4.6 ± 2.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1.7 ± 2.3§</td>
<td>4.7 ± 3.0†</td>
<td>3.5 ± 2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.2 ± 2.6</td>
<td>1.9 ± 2.3</td>
<td>1.8 ± 1.8</td>
<td>0.97</td>
</tr>
<tr>
<td>Loose stools</td>
<td>0.2 ± 0.8</td>
<td>3.1 ± 4.2</td>
<td>2.3 ± 3.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Sum of symptoms</td>
<td>11.2 ± 1.8§</td>
<td>20.3 ± 2.7§</td>
<td>17.7 ± 2.9</td>
<td>—</td>
</tr>
</tbody>
</table>

*SEM. The Mann-Whitney U test was used for pairwise comparisons of the different symptoms; Fisher’s least-significant-difference test was used for pairwise comparisons of the sum of symptoms scores.

†Kruskal-Wallis test.

‡Significantly different from the pseudohypolactasic subjects, P ≤ 0.05.

§Significantly different from the control lactose digesters, P ≤ 0.05.

¶Significantly different from the lactose maldigesters, P ≤ 0.05.

were significantly more severe in the lactose maldigesters than in the other 2 groups (P < 0.001). The lactose maldigesters and the pseudohypolactasic subjects experienced more severe symptoms than the control lactose digesters (P = 0.04 and 0.006, respectively) after lactulose was ingested, but there were no significant differences between the lactose maldigesters and the pseudohypolactasic subjects. After ingesting fructooligosaccharides, the pseudohypolactasic subjects experienced more severe symptoms than the control lactose digesters (P = 0.01), as did the lactose maldigesters, although not significantly so. The results of symptoms analyses during the first 3 h after ingestion (Figure 1) were consistent with those during the first 6 h after ingestion.

All subjects experienced a similar degree of symptoms after the lactulose and fructooligosaccharide interventions. There were no significant differences in the severity of symptoms after sucrose and lactose ingestion in either pseudohypolactasic subjects or control lactose digesters. Flatulence after the lactulose load was more severe in the lactose maldigesters and pseudohypolactasic subjects than in the control lactose digesters (P = 0.04 and P = 0.008, respectively) during the first 6 h after ingestion (Table 2). Lactose maldigesters also experienced more borborygmi than the control lactose digesters after ingesting lactulose (P = 0.02). Lactulose caused loose stools or diarrhea during the 6-h period in about half of the subjects in all groups. The symptoms caused by lactulose continued to increase for 6 h after its intake in all groups (Figure 2).

After the fructooligosaccharide challenge, the pseudohypolactasic subjects experienced significantly more abdominal distention than did the control lactose digesters during the first 6 h after ingestion (P = 0.009) (Table 2). Fructooligosaccharides caused loose stools or diarrhea during the 6-h period in 8% of the control lactose digesters, in 47% of the pseudohypolactasic subjects, and in 33% of the lactose maldigesters. The symptoms caused by fructooligosaccharides continued to increase for 6 h after its intake in all groups (Figure 2).

**Blood glucose and urinary galactose**

In the final analysis of the rise in blood glucose concentration, the main effect of group was significant (P = 0.001), the effect of intervention was significant (P < 0.001), and the interaction between group and intervention was also significant (P < 0.001). The rise in blood glucose concentration after sucrose ingestion was 2.8 ± 0.2 mmol/L in the whole study population. The increase in blood glucose concentration after the lactose challenge was significantly lower in the lactose maldigesters (0.6 ± 0.4 mmol/L) than in the control lactose digesters (2.3 ± 1.0 mmol/L, P < 0.001) and pseudohypolactasic subjects (1.9 ± 0.6 mmol/L, P < 0.001).
There was no rise in blood glucose concentration after the lactulose and fructooligosaccharide interventions. The amount of urinary galactose 3 h after lactose ingestion was $9 \pm 2.6$ mg in the lactose maldigesters ($n = 12$) and $43 \pm 2.8$ mg in the lactose digesters ($n = 28$). The amount of galactose excreted in the urine after ingestion of the 3 other carbohydrates varied between 0 and 2 mg/3 h.

**Food-related symptoms questionnaire**

The mean symptom scores for usual symptoms experienced after the ingestion of 19 specified foods were as follows: $0.7 \pm 0.1$ in the control lactose digesters, $1.1 \pm 0.1$ in the lactose maldigesters, and $1.3 \pm 0.2$ in the pseudohypolactasic subjects. The pseudohypolactasic subjects reported experiencing significantly more symptoms from these foods than did the control lactose digesters ($P = 0.01$). The differences between the lactose maldigesters and the control lactose digesters and between the lactose maldigesters and the pseudohypolactasic subjects were not significant.

**DISCUSSION**

In the present study, we compared the gastrointestinal symptoms experienced by 3 groups of women (control lactose digesters, lactose maldigesters, and pseudohypolactasic subjects) after ingestion of sucrose, lactose, lactulose, or fructooligosaccharides to test the hypothesis that lactose maldigesters are more sensitive than control lactose digesters to large carbohydrate loads. We found that symptoms from all 4 carbohydrates were more severe in the lactose maldigesters than in the control lactose digesters.

**Tests for lactose maldigestion**

In this study we compared 3 methods regularly used for diagnosing lactose maldigestion. Although the results of the diagnostic methods differed slightly from each other, the kappa coefficients between them indicated moderate or good agreement. The symptoms caused by the lactose load must be taken into account when lactose intolerance is tested for, although even if people suffer symptoms from 50 g lactose, the dose commonly used for diagnosing lactose maldigestion (6), they may tolerate smaller amounts well. Fifty grams of lactose has been shown to cause symptoms in some lactose digesters (15). However, urinary galactose seemed to correlate most accurately with the symptoms and could therefore be regarded as the most reliable method for diagnosing lactose intolerance.

Interestingly, only half of those who said they were lactose intolerant—on the basis of a previous test—received a diagnosis of lactose maldigestion in the present study. One possible explanation for this is that some of the subjects may have suffered from secondary lactose maldigestion during the first diagnosis. Another explanation could be that the diagnostic method used previously had given a “borderline value,” which the physician had interpreted as indicating lactose intolerance because of the symptoms the subjects reported experiencing after ingesting milk. The use of 3 diagnostic methods in the present study increased the reliability of the diagnosis.

Of those who believed that milk was a cause of their gastrointestinal symptoms, 25% proved to be lactose maldigesters. Finnish people are very much aware of lactose intolerance. Because milk and milk products are such a large part of their diet, they often associate gastrointestinal problems with milk ingestion. It is possible that the pseudohypolactasic subjects actually experienced gastrointestinal symptoms when they drank milk, as suggested previously by others in a study in which the lactose digesters who claimed that milk was a cause of their symptoms had as many symptoms from 18 g lactose in milk as did the lactose maldigesters (3). In addition, in a study with teenagers, it was concluded that factors other than lactose malabsorption may have been responsible for the mild symptoms experienced after milk ingestion (16). Therefore, other components of milk should be studied to determine if they could be responsible for the symptoms.

The same proportion of lactose maldigesters was found among those who believed that they experienced symptoms from milk and those who did not. It is possible that the lactose intakes of these...
unexpected lactose maldigesters were so low that they had not previously experienced symptoms. This finding agrees with the fact that most lactose maldigesters tolerate 12 g lactose in milk (1).

Symptoms caused by carbohydrates

Lactulose and fructooligosaccharides are not hydrolyzed in the small intestine, so they are good standards for comparing the symptoms experienced by different subjects when equal amounts of carbohydrate pass into the large intestine. The pseudohypolactasic subjects experienced more severe symptoms than the control lactose digesters after ingesting lactulose and fructooligosaccharides. Thus, indigestible carbohydrates other than lactose may actually have been the cause of the symptoms in the pseudohypolactasic subjects. It remains to be shown whether a fructooligosaccharide challenge could be used in combination with a lactose intolerance test to differentiate dyspeptic patients with normal lactose digestion who experience severe symptoms after consumption of indigestible carbohydrates from subjects who are lactose intolerant.

Note that the lactose maldigesters also suffered severe symptoms after ingesting indigestible carbohydrates other than lactose. As is true for pseudohypolactasic subjects, lactose maldigesters may also misinterpret the cause of their symptoms as lactose when other carbohydrates may actually be the cause. This is one possible explanation for the discrepancy between the claims of lactose maldigesters and the results of experimental studies. Lactose maldigesters claim that small amounts of lactose cause them symptoms, whereas double-blind studies in which they ingested large amounts of lactose have shown otherwise (2, 17). It was also shown that a diet with lactose-free milk caused more symptoms in the lactose maldigesters than in the lactose digesters (5).

Sucrose was chosen for this study because it is a digestible carbohydrate that is completely absorbed in the small intestine (18). Fifty grams of sucrose does not cause symptoms in healthy people (18), but it does cause mild symptoms in subjects with functional bowel disease (19). Patients with functional bowel diseases, including irritable-bowel syndrome (IBS), also experienced more severe symptoms from indigestible carbohydrates such as lactulose and a combination of sorbitol and fructose than did healthy, control subjects (19). The symptoms of IBS resemble those of lactose intolerance, and these 2 disorders may be easily confused. IBS might explain some of the symptoms experienced by the pseudohypolactasic subjects and the lactose maldigesters after lactulose and fructooligosaccharide ingestion, although we did not examine IBS in this study. In a study in which the diagnosis of lactose intolerance was based on subjective evaluations, patients with IBS were found to be more lactose intolerant than subjects without IBS (20). IBS may partly explain the large number of pseudohypolactasic subjects in the present study.
The symptoms experienced by all 3 groups in the present study continued to increase for 6 h after lactulose and fructooligosaccharide ingestion. The standard meal offered at 3 h may have resulted in extra stimulation to the intestine; however, there was no increase in symptoms after 3 h when sucrose was ingested. The data from the completed questionnaires supported the results of the present study, showing that the pseudohypolactasic subjects and, to some extent the lactose maldigesters, experienced symptoms from certain foods other than milk products more often than did the control lactose digesters.

**Hydrogen production after lactulose ingestion**

Because small intestinal lactase does not hydrolyze lactulose (21), the reason why the lactose maldigesters produced more hydrogen after lactulose ingestion than did the pseudohypolactasic subjects and the control lactose digesters is not clear. The amount of lactose in the lactulose product used (0.5 g/portion) could not have caused any extra hydrogen production in the lactose maldigesters. Lactose maldigesters may have a shorter transit time, which results in greater hydrogen production during the first hours after ingestion. It is also possible that those bacteria that utilize both lactose and lactulose (21) are more prevalent in the large intestine of lactose maldigesters because of a presumably small amount of lactose in their diet. This might have caused quicker utilization and thus greater hydrogen production from lactulose in the lactose maldigesters than in the other groups in the present study. However, when lactose maldigesters are fed high amounts of lactose regularly, the colonic microflora adapt, resulting in less hydrogen production over time (22).

**Conclusions**

First, the results indicate that lactose maldigesters and lactose digesters with pseudohypolactasia experienced more symptoms than did control lactose digesters after a single large intake of indigestible carbohydrates. Lactose maldigesters also experienced more symptoms than control lactose digesters after ingestion of large amounts of sucrose. The results suggest that in subjects with pseudohypolactasia, the cause of symptoms may be indigestible carbohydrates rather than lactose. Second, the 3 diagnostic methods used agreed reasonably well in diagnosing lactose maldigestion.

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