Hydrogen excretion in pediatric lactose malabsorbers: relation to symptoms and the dose of lactose

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Abstract

Introduction: Lactose malabsorption arises from lactase deficiency and may lead to lactose intolerance – gastrointestinal symptoms after lactose ingestion. Occurrence and severity of the symptoms are influenced by many factors, including the dose of lactose and the intensity of its colonic fermentation to short chain fatty acids and gases.
Material and methods: The hydrogen breath test (HBT) after 30 g or 50 g of lactose was performed in 387 children. Further analysis included children who had a positive HBT result. The HBT parameters were net hydrogen concentration in each breath and total net hydrogen concentration during the HBT. The time of the first hydrogen rise was also calculated. HBT parameters were analyzed according to symptoms occurrence (lack or present), symptoms severity (lack, moderate or severe) and the dose of lactose (30 g or 50 g).
Results: One hundred and six children (12.1 years, 46 boys) had a positive HBT result. Symptoms occurrence was positively related to net hydrogen concentration at 30 min, 60 min and 90 min ($p < 0.001$ at each time point), as well as to the total net hydrogen concentration ($p < 0.001$). There were no differences in hydrogen excretion between subjects with moderate and severe symptoms after lactose ingestion. Symptoms were more frequent in subjects given 50 g of lactose than in those given 30 g of lactose (79% vs. 47%, $p = 0.003$). In both dose groups symptoms occurrence was related to hydrogen excretion.
Conclusions: Symptoms occurrence is closely related to hydrogen excretion and to the dose of ingested lactose.

Key words: children; gastrointestinal diseases, hydrogen breath test, lactose intolerance, lactose malabsorption.

Introduction

Deficiency of digestive enzymes may result in various health complications related to malnutrition [1]. Calcium deficit, which may arise from the difficulties in milk ingestion, may be linked to osteoporosis, type 2 diabetes, metabolic syndrome and cardiovascular disease [2, 3]. The key enzyme involved in the digestion of milk sugar, lactose, is lactase (β-galactosidase). When lactase deficiency occurs, undigested lactose enters the colon, where it is hydrolyzed to glucose and galactose molecules by the bacterial enzyme β-galactosidase. Subsequently, these monosaccharides are fer-

mented to gases (hydrogen, methane and carbon dioxide) and short chain fatty acids (SCFAs). This condition is called lactose malabsorption and may result in gastrointestinal symptoms [4].

In clinical practice, lactose malabsorption is diagnosed with the hydrogen breath test (HBT), the examination consisting in breath hydrogen measurement after an oral lactose load. Although the HBT is used to detect the extent to which maldigested lactose is fermented and absorbed in the colon, it does not determine the actual activity of lactase [5]. The weak relationship between lactose digestion degree and total breath hydrogen after lactose ingestion is explained by colonic factors, which influence lactose fermentation intensity [6]. The activity of colonic microflora seems to be an important factor determining hydrogen content in breath during HBT, as well as symptoms occurrence and their severity after lactose ingestion [4, 6]. Studies showed that only some lactose malabsorbers (LM) developed gastrointestinal symptoms after lactose ingestion, known as lactose intolerance [5, 6]. Abdominal pain, flatulence, cramps, bloating and nausea are associated with gas production, whereas loose stool or diarrhea are linked to osmotic load due to the accumulation of unfermented sugar in the colon [4].

The aim of the present study was to evaluate the influence of hydrogen excretion during a standard 90 min HBT with 30 g or 50 g of lactose on symptoms occurrence and severity in pediatric LM.

Material and methods

The hydrogen breath test was performed in 387 children diagnosed and treated in 2nd Department and Clinic of Pediatrics, Gastroenterology and Nutrition (Wroclaw, Poland) in the years 2010–2013. Children underwent the HBT after an overnight fast and were asked to brush their teeth before the examination. Hydrogen content in five breaths was evaluated using the Gastro+ Gastrolyser (Bedfont Scientific, Ltd.) – one before and four after a test meal (15 min, 30 min, 60 min, 90 min). The test meal was lactose monohydrate (Pharma Cosmetic, Inc.), dissolved in 250 ml of water. The dose of lactose was body weight-dependent – children up to 30 kg were given 30 g of lactose, while children over 30 kg were given 50 g of lactose. An increment of hydrogen by 20 ppm above the basal breath, in at least one breath, indicated a positive HBT result. Children with a positive HBT result were described as LM. During the study, children (and/or their caregivers) were asked to report gastrointestinal symptoms such as abdominal pain, cramping, bloating, flatulence, nausea and loose stool/diarrhea. Children with one or more symptoms after lactose ingestion were identified as lactose intolerants (LI), while those without symptoms were identified as lactose tolerants (LT). Abdominal pain, cramping, bloating, flatulence and nausea were defined as moderate symptoms, while severe symptoms were associated with one loose stool or diarrhea.

Analyses involved only children with a positive HBT result who met the inclusion criteria: (1) had no gastrointestinal disease or had one of the following – upper gastrointestinal tract disease (gastro-esophageal reflux disease or gastric ulcer disease), lower gastrointestinal tract disease (malabsorption syndrome or inflammatory bowel disease) or functional gastrointestinal disorder (functional constipation or irritable bowel syndrome); (2) had a basal breath hydrogen level lower than 20 ppm; (3) had no chronic pulmonary diseases or cow's milk allergy; (4) had no antibiotic treatment during the last month.

The HBT data collection included five parameters: hydrogen concentration in each breath after lactose ingestion minus basal hydrogen concentration (net H_2 concentration at 15 min, 30 min, 60 min and 90 min) and the sum of net H_2 concentrations from 15 min to 90 min (total net H_2 concentration). Mean values of each breath were used to estimate the time of the first rise of hydrogen concentration by 20 ppm using a linear regression equation.

The protocol of the study was approved by the local Ethic Committee of Medical University of Wroclaw. Informed consent was obtained from children's caregivers and children ≥ 16 years of age.

Statistical analysis

Hydrogen concentrations were presented as mean and standard error of the mean (SEM). The distribution of the data was tested using the Kolmogorov-Smirnov test. Differences in HBT parameters between multiple groups were assessed using univariate ANOVA (parametric) or the Kruskal-Wallis test (non-parametric) with the Scheffe test (parametric) or Mann-Whitney *U* test (non-parametric) as a post-hoc test. Two unpaired groups were compared with Student's *t* test (parametric) or Mann-Whitney *U* test (nonparametric). Qualitative data were tested using Pearson's χ^2 test. A *p*-value below 0.05 was considered significant. All statistical analyses were performed using Statistica 10 software (StatSoft, Inc.). Time of the first rise of hydrogen concentration was calculated using Excel 2011 software (Microsoft, Inc.).

Results

One hundred and six children (12.1 years, 46 boys) were selected for the study from 387 children who underwent the HBT (Table I). Symptoms occurrence was positively related to net H_2 concentration at 30 min, 60 min and 90 min, as well

Table I. Characteristics of subjects

Diagnosis	Subjects, *n* (%)	Age (min.–max.) [years]	Males, *n* (%)
Healthy	35 (33.0)	12.17 (4.29–17.56)	17 (48.6)
Upper gastrointestinal tract disease:	26 (24.5)	11.98 (2.86–17.98)	13 (50.0)
Gastro-esophageal reflux disease	14	11.68 (2.86–17.98)	6 (42.9)
Peptic ulcers	12	12.33 (6.08–17.78)	7 (58.3)
Lower gastrointestinal tract disease:	25 (23.6)	12.06 (5.27–17.90)	11 (44.0)
Malabsorption syndromes	15	10.94 (5.27–16.75)	6 (40.0)
Inflammatory bowel disease	10	13.74 (8.59–17.90)	5 (50.0)
Functional gastrointestinal disorder:	20 (18.9)	12.13 (4.17–17.99)	5 (25.0)
Constipation	11	10.30 (4.17–16.19)	1 (9.1)
Irritable bowel syndrome	9	14.36 (9.25–17.99)	4 (44.4)
Total	106 (100.0)	12.08 (2.86–17.99)	46 (43.4)

Table II. Statistical significances of differences in H_2 parameters between symptom groups (*p*-values according to *t* test, ANOVA and Scheffe test as post-hoc, or their nonparametric counterparts)

Net H_2 concentration	Lack – present	Lack – moderate – severe	Lack – moderate	Lack – severe	Moderate – severe
15 min	0.072	0.088	–	–	–
30 min	< 0.001	< 0.001	< 0.001	0.002	0.443
60 min	< 0.001	0.004	0.008	0.031	0.992
90 min	< 0.001	< 0.001	0.001	0.007	0.974
Total	< 0.001	< 0.001	0.002	0.005	0.907

as to the total net H_2 concentration. Children with no symptoms exhaled about 50 ppm of hydrogen less than subjects with moderate and severe symptoms (68 ppm, 119 ppm and 121 ppm of total net H_2 concentration; $p < 0.001$ according to univariate ANOVA). However, there was no difference in hydrogen excretion parameters between moderate LI and severe LI (Table II and Figure 1). Lactose tolerants achieved the first hydrogen increment in 56 min of the test ($R^2 = 0.992$). Lactose intolerants, regardless of the symptoms severity, achieved the hydrogen increment faster than LT (in 39 min, $R^2 = 0.993$ for moderate symptoms, and 37 min, $R^2 = 0.999$ for severe symptoms).

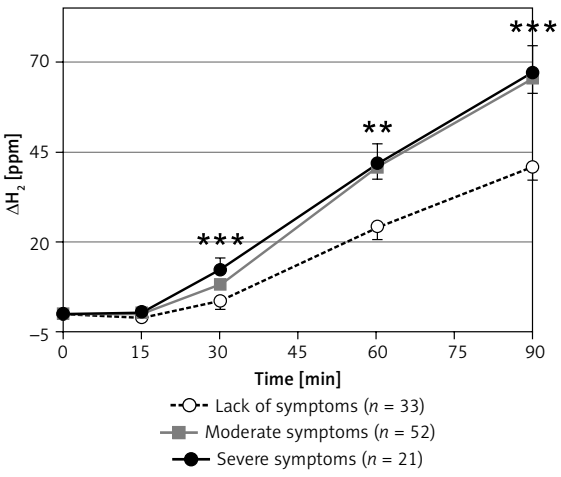

Figure 1. Net H_2 concentration increment during 90 min hydrogen breath test in relation to occurrence and severity of symptoms after lactose ingestion (**$p < 0.01$, ***$p < 0.001$ according to univariate ANOVA or non-parametric Kruskal-Wallis test)

Thirty-four children were given 30 g of lactose and 72 children were given 50 g of lactose. The dose of lactose was positively related to the net H_2 concentration at 90 min and to the total net H_2 concentration ($p = 0.007$ and $p = 0.046$). These differences disappeared when analyses were performed in groups of LT and LI separately. Symptoms after lactose were significantly more frequent after 50 g of lactose compared to 30 g (79% vs. 47%, Table III). In both dose groups hydrogen excretion differed between individuals with and without symptoms. Statistically significant differences in net H_2 concentration between LT and LI appeared later in children who received 30 g of lactose than in those given 50 g of lactose (Figures 2 A and B). Gastrointestinal disease type did not influence any HBT parameter (data not shown).

Table III. Frequency of symptoms and dose of lactose ($\chi^2 = 11.834$; $p = 0.003$ according to Pearson's χ^2 test)

Symptoms	Dose of 30 g, *n* (%)	Dose of 50 g, *n* (%)	Total, *n* (%)
Lack	18 (53.0)	15 (20.8)	33 (31.1)
Moderate	13 (38.2)	39 (54.2)	52 (49.1)
Severe	3 (8.8)	18 (25.0)	21 (19.8)
Total	34 (100.0)	72 (100.0)	106 (100.0)

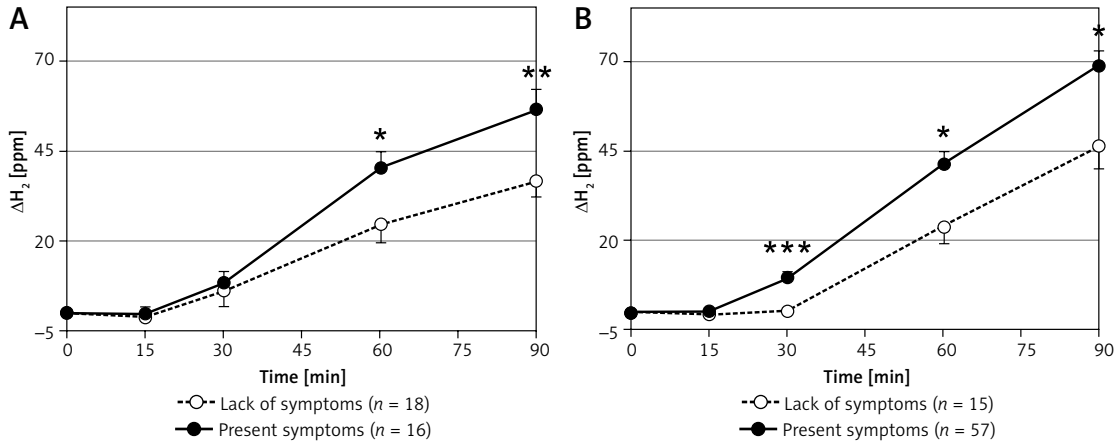

Figure 2. Net H_2 concentration increment during 90 min hydrogen breath test after ingestion of 30 g (**A**) or 50 g (**B**) of lactose in relation to symptoms occurrence (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ according to unpaired Student's *t* test or non-parametric Mann-Whitney *U* test)

Discussion

Our study showed a significant relation of hydrogen excretion to symptoms occurrence after lactose ingestion in LM. Net H_2 concentration in breath samples from 30 min to 90 min and total net H_2 concentration were significantly higher in LI compared to LT. Several other studies have evidenced the relation of hydrogen excretion to symptoms occurrence after lactose ingestion. A strong positive correlation of lactose intolerance severity, expressed as total symptom score, with total hydrogen excretion was also found [7–9]. Excessive gas excretion was especially related to borborygmi and bloating [8]. According to our knowledge, only one study has found no relation between hydrogen excretion and symptoms severity [10]. All the studies contained both individuals with positive and negative HBT results, while combining these groups may inadvertently increase the relation of gas production and symptoms severity. Bianchi *et al*. found a high positive relation of hydrogen peak value with symptoms score in all participants, but not in a subgroup of LM [7]. Considering the above issues, all analyses in the present study were confined to individuals with positive HBT results.

Although our results showed differences in hydrogen excretion between LT and LI, no differences in HBT parameters between LI with moderate and severe symptoms were obtained. Moreover, children with lactose intolerance (regardless of symptoms severity) revealed shorter time of the first hydrogen rise compared to LT. The occurrence and severity of symptoms after lactose ingestion depend on many factors, including lactase activity, oro-cecal transit time (OCTT), lactose fermentation, colonic absorption capacity and visceral sensitivity [4]. It was demonstrated that LT had a higher degree of lactose digestion and longer OCTT than LI. However, there were no differences in these parameters between LI with and without diarrhea [6].

The occurrence of diarrhea is a result of high osmotic load due to accumulation of sugar in the colon. On one hand, lactose fermentation to SCFAs and gases is an important mechanism reducing osmotic load. However, excessive SCFA production reduces intraluminal pH, which inhibits bacterial fermentation of lactose [11]. Our subjects with moderate and severe symptoms revealed similar levels of hydrogen excretion; thus symptoms severity cannot be explained by the mentioned pattern. The intensity of symptoms may be traced to the buffer capacity of the colon, rather than to the net hydrogen production. On the other hand, hydrogen content in the breath is not proportional to its production in the gastrointestinal tract. At low intestinal hydrogen production, 65% of this gas is removed by the respiratory tract, but at high hydrogen production only 25% of this gas is exhaled [12]. It is plausible that intestinal production of hydrogen is significantly different in moderate LI and severe LI.

Our study showed that LT achieved the first hydrogen rise about 17–19 min later than LI with moderate and severe symptoms. When using lactulose, an indigestible sugar fermenting in the colon as lactose, this time may be connected with OCTT or small intestinal bacterial overgrowth. It has been demonstrated that hydrogen rise time is negatively related to abdominal pain after lactulose ingestion, and tends to be shorter in individuals with diarrhea, compared to individuals without diarrhea [13]. It was found that healthy LM, but tolerant, had longer OCTT than LI, and it was related to the lactose digestion degree [6]. However, another study showed similar OCTT in LM and LI (59 and 58 min respectively) [10].

In the present study two different doses of lactose were used, depending on patients' body weight. The dose of 50 g of lactose was associated with a higher incidence of symptoms compared to the dose of 30 g. Dose of lactose is positively related to symptoms occurrence, severity and their number during HBT [9]. It has been reported by many authors that 50 g of the sugar (an equivalent of 1 L of milk) is a highly non-physiological dose, especially in countries with high prevalence of primary hypolactasia [14, 15]. A dose of 25 g of lactose was suggested as an adequate dose to diagnose lactose malabsorption with reduced gastrointestinal symptoms [15]. Our study demonstrated that children who were given 30 g of the sugar exhaled significantly less hydrogen in 90 min of the HBT, compared to children given the higher dose. However, the distinctions disappeared when our subjects were divided additionally into symptom groups (lack or presence). Hydrogen excretion after a lower dose of lactose differed between LT and LI from 60 min of the HBT, whereas after a higher dose of lactose it did so from 30 min. Other studies also showed that symptoms occurrence may be associated with excessive gas production only after 50 g, and not after 25 g, of lactose [14].

Our study was conducted on healthy children and children with various gastrointestinal diseases. We found no differences in net H_2 concentration at any time of HBT, nor in total net H_2 concentration, between studied groups. This allowed us to merge the mentioned groups, in order to analyze HBT parameters regardless of diagnosis. A few other studies also found no differences in hydrogen excretion after lactose between healthy subjects and those with IBS, in spite of a higher frequency of lactose intolerance in patients [8, 9]. However, there is lack of studies presenting HBT parameters in other gastrointestinal diseases such as inflammatory bowel diseases and malabsorption syndromes.

The limitation of our study was the short duration of the HBT (90 min), which might exclude subjects with a slow hydrogen rise in the breath. It is assumed that HBT should not be shorter than 120–180 min, which gives high sensitivity and specificity [15–17]. It was shown that the first rise of hydrogen may appear between 15 and 165 min of the HBT after ingestion of 50 g of lactose, but most LM achieve their 20 ppm rise by 120 min of the test [17]. However, there are studies indicating a shorter time of the first hydrogen rise in LM [16, 18]. The second limitation of the present study was that only hydrogen was measured, whereas some individuals may exhale also or only methane. There is only one study where methane measurement has been included. It was found that excretion of both hydrogen and methane significantly influences symptoms severity, but total methane concentration is not related to ailments [7].

In conclusion, based on the presented results we conclude that only symptoms occurrence, but not their severity, is related to hydrogen excretion during the HBT. The dose of lactose positively influences symptoms occurrence and severity in LM. Breath hydrogen excretion after lactose is not affected by gastrointestinal disease type.

Conflict of interest

The authors declare no conflict of interest.

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