

# The Predictive Value of the Hydrogen Breath Test in the Diagnosis of Fructose Malabsorption

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## Keywords

Fructose malabsorption diagnosis · Hydrogen breath test · H<sub>2</sub>-exhalation · Fructose-free diet · Irritable bowel syndrome

## Abstract

**Background:** Fructose malabsorption is commonly diagnosed by the hydrogen fructose (H<sub>2</sub>) breath test. However, the mechanisms behind fructose malabsorption in humans are not well understood and the clinical relevance of this test is considered controversial. Hence, the main aim of this study is to evaluate the predictive value of the H<sub>2</sub> breath test. **Methods:** Regarding exclusion criteria, the study enrolled 562 consecutive patients, enlisted to a gastroenterology clinic between 2009 and 2011 for testing malabsorption. In the final data analysis, 246 patients were included. Ecotrophologists used 3 categories to rate dietary success: complete response, partial response and no response to the diet. They also rated the occurrence of abdominal pain, diarrhoea and bloating during the H<sub>2</sub> breath test. Ordinal regression analysis using SPSS was performed to evaluate whether H<sub>2</sub> breath test results – measured as the maximum H<sub>2</sub> level, the maximum increase in H<sub>2</sub>, and the area under the curve (AUC) – predicted dietary success or failure. Correlation anal-

yses were applied to test whether symptoms of fructose malabsorption correlated with the H<sub>2</sub> breath test measures. Finally, we evaluated whether cut-off-values of 40 or 60 parts per million (ppm) serve better than the test measure of 20 ppm to diagnose fructose malabsorption. **Results:** When a fructose-free diet was administered it was found that 103 patients (41.9%) were complete responders, 116 (47.2%) were partial responders and 27 (11%) were non-responders. The H<sub>2</sub> breath test with the 20 ppm cut-off-value, that is, the maximum H<sub>2</sub> level, the maximum increase in H<sub>2</sub>, and the AUC did not predict dietary response (all 95% CI ns). This was also the case when using 40 or 60 ppm as cut-off-values (all 95% CI ns). Abdominal pain during the test correlated significantly with the AUC. Diarrhoea and bloating correlated significantly with the AUC, the maximum H<sub>2</sub> level and the maximum increase in H<sub>2</sub> ( $p < 0.05$ ). **Conclusions:** The H<sub>2</sub> breath test produced no predictive value for the fructose-free diet outcomes; its value as a predictive test is therefore questionable. However, the symptoms of fructose malabsorption correlated significantly with the H<sub>2</sub> breath test measures, and this is an indication that there is at least a degree of validity of the H<sub>2</sub> breath test beyond the simple detection or exclusion of fructose malabsorption.

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## Introduction

Primary fructose malabsorption is a highly prevalent disorder and a frequent gastrointestinal diagnosis. It ranges from 38 to 80%, depending on the diagnostic fructose dose, in patients with unexplained gastrointestinal symptoms tested in a gastroenterology clinic [1–3]. While fructose intolerance is characterized by an inherent liver enzyme defect, primary fructose malabsorption is probably marked by an ineffective monosaccharide transportation system in the small bowel. In affected patients, this incomplete absorption of fructose causes potential problems like flatulence, diarrhoea and abdominal pain. In healthy people, carbohydrates are digested and reabsorbed via the brush border of the small bowel [4]. In patients with fructose malabsorption, it is assumed that the absorption of fructose is impaired and this leads to a higher concentration of fructose in the colon. In the colon, fructose is metabolized by bacteria to short-chain fatty acids, hydrogen and methane, and this leads to flatulence and diarrhoea [5, 6]. Besides the primary fructose malabsorption described above, there is also secondary fructose malabsorption. In cases of inflammation of the upper small intestine such as Morbus Whipple, Coeliac or Crohn's Disease, or acute infectious diseases, the malabsorption is caused by a destruction of the membrane, and is therefore called secondary malabsorption [7]. Causes of this type of fructose malabsorption are different from the causes of primary fructose malabsorption. The focus of this paper lies in primary fructose malabsorption.

Primary fructose malabsorption is commonly diagnosed by a hydrogen fructose ( $H_2$ ) breath test [7]. The  $H_2$  breath test is the standard test in daily patient care. With the high rates of gastrointestinal complaints and the high prevalence of fructose malabsorption, physicians frequently apply this test. However, it has not been well evaluated. A better understanding of the test would be helpful in the following areas of work: the physicians' work, medical advice and the administration of the  $H_2$  breath test in daily care. The test rationale is that bacteria metabolize the unabsorbed fructose producing  $H_2$  as a by-product.  $H_2$  is then reabsorbed and excreted through the breath, where it can be easily measured. An increase from the baseline of more than 20 parts per million (ppm) of the  $H_2$  concentration in the exhaled air is seen as a significant increase, which justifies the diagnosis of fructose malabsorption [8–10]. This significance value has been extrapolated from the lactose breath test. Evidence of the correct diagnosis is a clinical improvement

after fructose reduction. A fructose-restricted diet should improve symptoms of fructose malabsorption, but to date it is unclear whether the  $H_2$  breath test does predict this improvement. Therefore, the main aim of the study was to evaluate the predictive value of the  $H_2$  breath test on the clinical response of patients diagnosed with fructose malabsorption. It was expected that the higher the  $H_2$  breath test measures were, the better the response to the fructose-free diet would be. Hence, we tested whether 3 common measures of the  $H_2$  breath test – the maximum  $H_2$  level, the maximum increase in  $H_2$  and the area under the breath test curve (AUC) – predict the same response to a 10-day fructose-free diet as that rated by the patient.

Furthermore, patients with fructose malabsorption experience symptoms of bloating, abdominal pain and diarrhoea. A significant relationship between the main symptoms of fructose malabsorption, (bloating, abdominal pain and diarrhoea) and the  $H_2$  breath test measures, (the maximum  $H_2$  level, the maximum increase in  $H_2$ , and the AUC) during testing would support the diagnostic value of the test.

Additionally, as the significance value of 20 ppm to diagnose fructose malabsorption is extrapolated from the lactose breath test, there might be other, more appropriate cut-off values. Hence, we tested whether 40 or 60 ppm might serve as a better cut-off value in predicting dietary response.

To conclude within the present study, we evaluated the predictive value of the  $H_2$  breath test by testing 3 research questions (RQ):

RQ 1: Do the  $H_2$  breath test results predict dietary response?

RQ 2: Do the  $H_2$  breath test results correlate with symptoms of fructose malabsorption?

RQ 3: Is the significance value of 20 ppm the most adequate cut-off value?

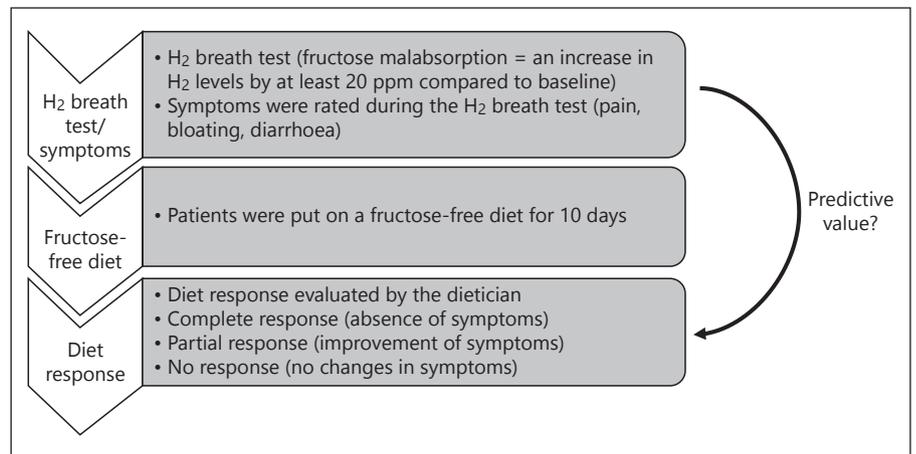
## Methods

### *Design*

The present study involved a non-interventional data collection, approved by the Ethical Committee of Lower Saxony, Hannover, Germany and was performed in concordance with the Helsinki Declaration.

### *Patients*

Five hundred sixty two consecutive patients, admitted to an out-patient clinic for Internal Medicine between 2009 and 2011, who fulfilled the inclusion and exclusion criteria were tested for fructose malabsorption, participated in the study.



**Fig. 1.** Study overview.

### Diet

Patients diagnosed with fructose malabsorption were consulted by an experienced Ecotrophologist and put on a fructose-free diet for 10 days. Dietary instructions were given in a face-to-face manner. Fruits with high fructose content and products enriched with fructose were excluded. Adherence to the diet was determined by a daily log in which patients documented all meals. At the end of the diet an Ecotrophologist evaluated the dietary success using a standardized questionnaire.

The following categories were used to define dietary response at the end of the fructose fasting period: complete response, defined as the absence of symptoms; partial response, defined as the improvement of symptoms; and no response, indicated by no changes in symptoms.

### Exclusion Criteria

Patients with secondary causes of fructose malabsorption, (gastroenteritis or duodenitis, coeliac disease, Crohn's disease, ulcerative colitis, liver disease, pancreatic disease and lymphatic disease) and patients who also had lactose malabsorption were diagnosed and excluded from the analysis. In addition, patients with other reasons for gastrointestinal disorders (i.e., pancreas or liver disease, inflammatory bowel disease, food allergy) and non-compliant patients detected by the Ecotrophologist, who screened the nutrition protocol, were excluded. Patients who did not show clinical symptoms of fructose malabsorption (i.e., bloating, diarrhoea or abdominal pain) were identified as false positive responders and also excluded from the analysis.

### Diagnostic Procedures

#### H<sub>2</sub> Breath Test

Fructose malabsorption was determined by the H<sub>2</sub> emission levels in the breath, measured by the H<sub>2</sub> breath test at the beginning of the study before the 10-day diet. H<sub>2</sub> emissions indicate failure of the gastrointestinal tract to absorb the fructose. It was measured as the amount of end-expiratory H<sub>2</sub> levels in the breath before and after the ingestion of a specific amount of fructose (50 g fructose diluted in 250 mL water). Measurements were conducted after an overnight fasting period of at least 10 h. Patients were not allowed to take any medication or to use toothpaste prior to the test. H<sub>2</sub> concentrations were determined at 15-min intervals for 3 h in total using the Gastrolyzer Breath H<sub>2</sub> Monitor (Bedfont Scientific LTD,

ME1 3QX, England). Fructose malabsorption was defined as an increase in H<sub>2</sub> levels by at least 20 ppm compared to baseline. Peak H<sub>2</sub> concentrations, areas under the curve and the maximum increase of H<sub>2</sub> were determined for each patient.

#### Lactulose Test

In order to identify false non-responders and to determine the orocecal transit time we performed an H<sub>2</sub> breath test with lactulose (10 g lactulose diluted in 100 mL water). The H<sub>2</sub> breath test was performed as described above.

#### Lactose Test

In order to identify and exclude patients with additional secondary lactose intolerance, we performed an H<sub>2</sub> breath test with lactose (50 g lactose diluted in 300 mL water). The H<sub>2</sub> breath test was performed as described above.

#### Symptoms

A 4-point scale was used to determine the subjective severity of bloating, abdominal pain and diarrhoea during the H<sub>2</sub> breath test, with the following ratings: 0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms and 3 = severe symptoms. See Figure 1 for a study overview.

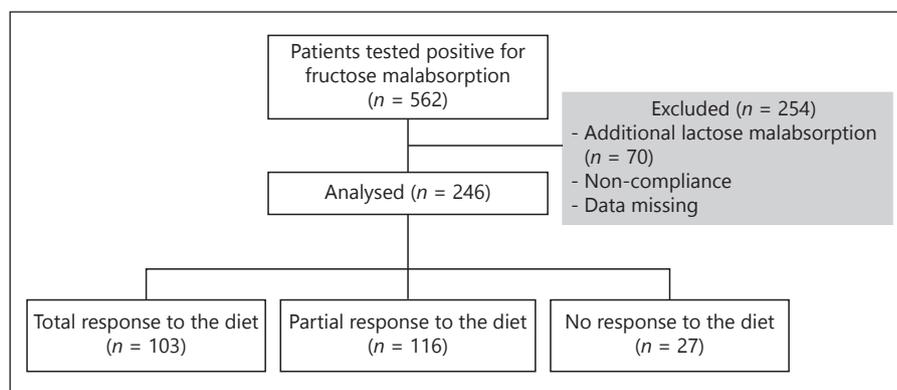
#### Data Analysis

All analyses were performed using the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, version 22.0). For hypothesis testing, ordinal regression and nonparametric correlation analyses were performed. For all analyses when not indicated otherwise, bootstrapping drawing 5,000 bootstrap-samples were used and the level of statistical significance was set at  $p = 0.05$ .

## Results

From 562 patients tested for fructose malabsorption, 338 were positive for fructose malabsorption (66.5%). Seventy patients were also tested positive for lactose malabsorption and were excluded from the analysis. In 7 pa-

**Fig. 2.** Flowchart of patient numbers: tested, excluded, analysed and the response rates.



**Table 1.** Sociodemographic characteristics of the study sample

	Total (n = 246)	No response (n = 27)	Partial response (n = 116)	Total response (n = 103)
Gender, f/m	202/44	22/5	95/21	84/19
Age, years (M ± SD, range)	39.21±18.08	50.7±19.9, 14–82	40.0±18.4, 8–83	35.6±15.9, 5–77

f, female; m, male; M, mean; no bootstrapping was applied.

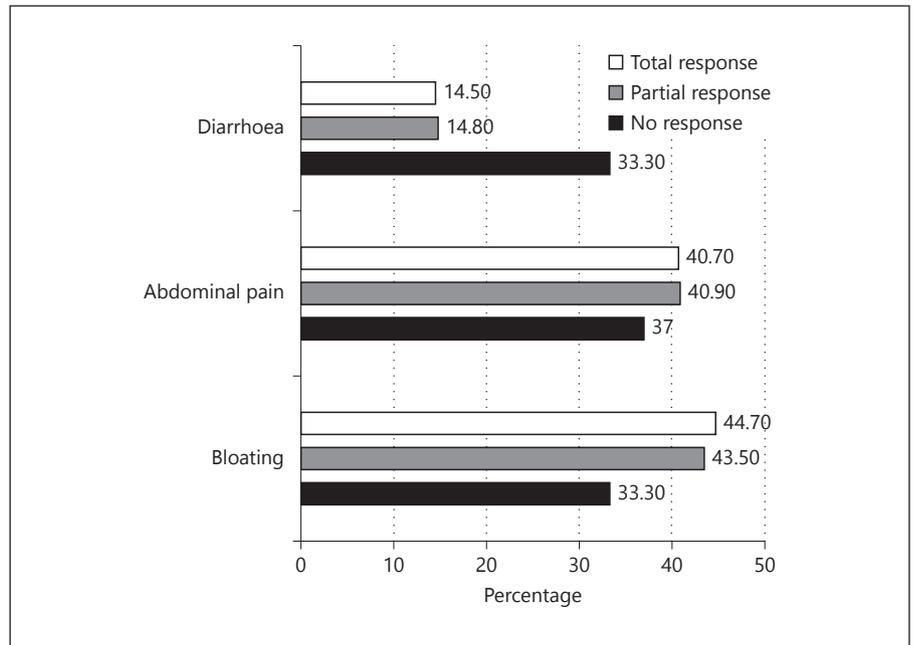
**Table 2.** Descriptive statistics

	Mean	SD	Minimum	Maximum
Maximum H <sub>2</sub> , ppm				
No response group	95.78	46.62	24	201
Partial response group	104.17	63.21	14	255
Total response group	104.67	61.67	19	255
Maximum increase, ppm				
No response group	92.07	50.25	18	201
Partial response group	97.35	60.30	13	255
Total response group	96.16	57.55	12	239
AUC, ppm				
No response group	577.89	325.25	110	1,342
Partial response group	622.39	483.88	0	2,363
Total response group	670.13	487.36	43	2,674

AUC, area under the curve.

tients, no symptoms occurred during testing and 5 patients were not compliant to the diet. For 10 patients, not all data was available and 246 patients fulfilled all criteria (Fig. 2). Twenty-seven patients were non-responders, 116 were partial responders and 103 were total responders (see Table 1 for sociodemographic characteristics). Lactulose breath test revealed no false non-responders. Preliminary analysis of variance analyses showed a significant effect between age and dietary response for the 3 groups (F-val-

ue [2, 243] = 8.08,  $p < 0.001$ ), with significant differences between the total response group and the no-response group (mean difference [MD] = -15.16, SD = 3.80,  $p < 0.001$ ), and between the no-response group and the partial response group (MD = -10.91, SD = 3.76,  $p < 0.05$ ). Therefore, we controlled for age within the analyses. Descriptive statistics regarding the maximum H<sub>2</sub> level, maximum increase in H<sub>2</sub> and the AUC are shown in Table 2 and in Figure 4 for diarrhoea, abdominal pain and bloating.



**Fig. 3.** Percentage of diarrhoea, abdominal pain and bloating (defined as percentage of patients who rated their symptoms as 2 or 3 on a scale from 0 to 3) per group during the H<sub>2</sub> breath test.

**Table 3.** Correlations between study variables

Scale	Dietary response	Bloating	Abdominal pain	Diarrhoea	Maximum H <sub>2</sub>	Maximum increase
Dietary response	–					
Bloating	0.03					
Abdominal pain	0.03	0.26***				
Diarrhoea	0.13*	0.20**	0.30***			
Maximum H <sub>2</sub>	–0.02	0.15*	0.12	0.23***		
Maximum increase	–0.01	0.15*	0.11	0.25***	0.98***	
AUC	–0.05	0.17*	0.19**	0.22***	0.93***	0.88***

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ ; ( $n = 246$ ).  
AUC, area under the curve.

### Testing of the Hypotheses

Our first research question was to evaluate whether the H<sub>2</sub> breath test results predict dietary response. Ordinal regression analyses revealed that the H<sub>2</sub> breath test had no predictive value on dietary response. Neither the total maximum, nor the maximum increase, nor the AUC predicted dietary response. Figure 3 shows the mean ppm trajectories for the 3 dietary response groups during the course of the 13 H<sub>2</sub> breath test time points.

Our second research question was to evaluate whether the H<sub>2</sub> breath test results correlate with the symptoms of fructose malabsorption. Spearman correlation analyses showed, that diarrhoea and bloating were significantly

correlated to all 3 measures of the H<sub>2</sub> breath test (all  $p < 0.05$ ), whereas abdominal pain was correlated only with the AUC (Table 3).

Our third research question was to evaluate whether the significance value of 20 ppm is the most adequate cut-off value. We therefore tested whether cut-off values of 40 and 60 ppm might have a higher predictive value than 20 ppm. Repetition of the ordinal regression analyses using 40 and 60 ppm as cut-off values revealed that there was no significant predictive value of the H<sub>2</sub> breath test for either of these. Neither the total maximum, nor the maximum increase, nor the AUC predicted dietary response (data not shown).

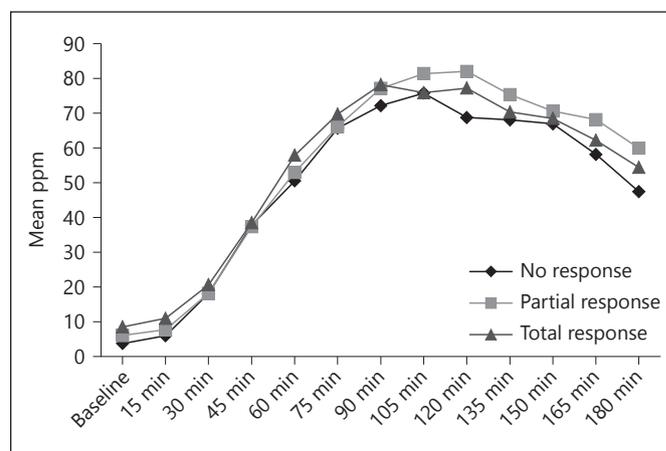
## Discussion

The present study answered 3 main questions: First, regression analyses showed that the H<sub>2</sub> breath test did not predict response to a 10-day fructose-free diet. Second, the symptoms of fructose malabsorption – diarrhoea, abdominal pain and bloating – correlated significantly to H<sub>2</sub> breath test measures. Diarrhoea had an especially strong relationship to the H<sub>2</sub> breath test measures. Third, cut-off values of 40 and 60 ppm did not have a higher predictive value than the 20 ppm cut-off-value on patients' response to the fructose-free diet. Therefore, our results show a low predictive value of the H<sub>2</sub> breath test in predicting response to a fructose-free diet. These findings are in line with the findings of previous studies that showed that H<sub>2</sub> breath tests can only be used to detect or exclude fructose malabsorption [11]. However, in our sample, diarrhoea shows a strong correlation to H<sub>2</sub> breath test measures. Within the study by Symons et al. [11], diarrhoea was not among the symptoms recorded. The simultaneous evaluation of H<sub>2</sub> breath test measures and diarrhoea as a symptom might yield additional value in diagnosing fructose malabsorption. Furthermore, when diagnosing primary fructose malabsorption, it is important to exclude patients with other causes for gastrointestinal disorders such as ulcerative colitis, Crohn's disease or celiac disease. While the diagnosis for most of these diseases is often unambiguous, in a subgroup of patients, a clear cause for the symptoms cannot be detected using the diagnostic standard procedures. These patients frequently fulfil the criteria of irritable bowel syndrome (IBS).

Diarrhoea, abdominal pain and bloating are commonly experienced by patients with IBS. Provocation studies, where fructose is ingested by patients with fructose malabsorption, induce symptoms more easily in subjects with IBS than in those without [12, 13], pointing to the fact that fructose has an unspecific impact rather than a specific effect in this set of patients.

Furthermore, we found that younger patients had a significantly better response to the fructose-free diet, while there was no difference in the adherence to the diet. Since young age is a risk factor for being affected by a post-infectious IBS [14], it might be the case that the younger patients in our patient cohort also were affected by IBS.

A fructose-reduction diet influences the intraluminal microbiota [15–17], which is discussed as a co-factor in the pathophysiology in a subgroup of patients with IBS [18, 19]. In our group of patients, diarrhoea was the most prevalent symptom in the no-response-group dur-



**Fig. 4.** Trajectories of hydrogen parts per million (ppm) for the 3 dietary response groups no response, partial response, and total response during the course of the 13 test time points.

ing the application of fructose. In addition, a fructose-restricted diet like the FODMAP (Fermentable Oligo-, Di-, Mono-Saccharides and Polyols) diet in general has shown a significant improvement of symptoms in patients with IBS [20]. The fructose-induced distension of the colon is especially reduced after a FODMAP diet [20]. The distension of the colon plays a crucial role in the pathophysiology of IBS [21–24], but is not associated with a positive H<sub>2</sub> breath test [20]. If the bowel distension after fructose exposure is independent of the production of H<sub>2</sub> in IBS patients, again, fructose must be rated as an unspecific rather than a specific stimulus for the symptoms induced.

In conclusion, the H<sub>2</sub> breath test did not predict the response to a 10-day fructose-free diet. Although symptoms of fructose malabsorption correlated significantly to the H<sub>2</sub> breath test measures, higher cut-off values of 40 and 60 ppm did not give a higher predictive value of patients' response to the fructose-free diet than the 20 ppm cut-off-value. Therefore, our results show a low predictive value of the H<sub>2</sub> breath test in predicting response to a fructose-free diet. Only the fact that symptoms and the H<sub>2</sub> breath test measures correlated significantly gives a little evidence for the predictive value of the test.

### Strengths and Limitations

When studying fructose malabsorption, the choice of dosage is critical. Previous studies have shown the frequency of fructose malabsorption in healthy volunteers to be 50% up to 80% if tested with 25 or 50 g of fructose respectively. Studies show that a high percentage of

healthy people have a positive H<sub>2</sub> breath test when tested with 50 g fructose [25, 26]. Because (1) of an overlap between fructose malabsorption with IBS [27], (2) the good clinical response in the case of fructose malabsorption and (3) to avoid false negative testing. Convenience food has often an underestimated content of fructose. For example, a cinema food and drink snack with a medium size Coke (500 mL) and medium size Popcorn (250 g) contains more than 50 g fructose [28]. Therefore, we decided to investigate patients with 50 g fructose as a pretest and to define the fructose malabsorption in those patients who responded to the fructose restricted diet. We tested with 50 g and identified 66.5% of the patients who were positive for fructose malabsorption. This conforms to other studies that wanted to avoid false negative malabsorption test results due to testing with 25 g fructose [29]. After the fructose-free diet, 41.9% of the diagnosed patients were complete responders, 47.2% were partial responders and 11% were non-responders. Therefore, the majority of the patients showed an improvement of symptoms after the fructose-free diet, which further confounds the validity of testing with 50 g fructose. These high-rate findings are congruent with findings of other groups [27, 30, 31]. But, a dosage of 50 g fructose might lead to a substantial amount of false positive respondents. Patients who did not show clinical symptoms of fructose malabsorption (i.e., bloating, diarrhoea or abdominal pain) therefore were identified as false positive responders and excluded from the analysis (Fig. 2). However, as a significant proportion of the population produce methane gas and many of these patients have very low H<sub>2</sub> concentrations, it cannot be ruled out that at least some patients were nonetheless false negative patients. In our clinical observation, we found 18% H<sub>2</sub> non responder. In our daily practice, all patients with unclear diagnostic parameters (including the non-responders) were advised to carry out a nutrition protocol. Then we performed the dietician advice based on the protocol. This was a very heterogeneous group and in the retrospective way it was not possible to use them as a control group.

Furthermore, a 4-point scale was used to determine the severity of bloating, abdominal pain and diarrhoea during the H<sub>2</sub> breath test. This was not a validated scale, which is another limitation to this study.

To conclude, the findings of the present study support the low specificity of the fructose H<sub>2</sub> breath test and lead to the necessity to confirm diagnosis by response to a fructose-free diet. Future research is necessary to confirm our findings.

### Study Highlights

#### What is Current Knowledge?

- In fructose malabsorption, fructose is poorly absorbed in the small intestine. When fructose enters the colon fermentation, it leads to an increase of colonic gas with intestinal symptoms like bloating, pain and diarrhoea.
- The H<sub>2</sub> breath test is a common method used to detect fructose malabsorption, which is a high prevalence disorder in healthy subjects without symptoms, leading to a low specificity of the test.
- A fructose-restricted diet often leads to a positive clinical improvement in those tested but not in all patients.

#### New Findings

- The H<sub>2</sub> breath test did not predict response to a 10-day fructose-free diet.
- The symptoms of fructose malabsorption: diarrhoea, abdominal pain and bloating were significantly correlated to H<sub>2</sub> breath test measures.
- Cut-off values of 40 and 60 ppm did not have a higher predictive value on patients' response to the fructose-free diet than 20 ppm.
- Even when there is a high prevalence of fructose malabsorption and when the fructose H<sub>2</sub> breath test is performed with 50 g fructose, over 90% of the patients respond to a fructose-free diet.

### Disclosure Statement

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