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Implementation and interpretation of hydrogen breath tests

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Abstract
Hydrogen breath tests are non-invasive and safe diagnostic tools used to investigate functional intestinal disorders. For the diagnosis of fructose or lactose malabsorption as well as for the detection of small intestinal bacterial overgrowth syndrome, hydrogen breath tests are even regarded as gold standard. However, standardization of the testing procedure and the interpretation of the test results are still lacking. In this paper, reliable information on the implementation of the most common hydrogen breath tests and precise guidelines for the interpretation of the test results are presented.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

At present, it is known that the exhaled breath of human beings contains at least 2000 different substances and that, apart from breathing, the lung's further essential function is the excretion of volatile substances [1–3]. Hydrogen breath tests are based on the physiological fact that healthy humans when fasting and at rest do not exhale hydrogen. As hydrogen is only generated during anaerobic metabolism and the human organism at rest does not have anaerobic metabolism, the hydrogen excreted with the exhaled air must originate from anaerobic bacteria [4]. The large bowel contains an enormous number of bacteria that are predominantly anaerobes and produce a large quantity of hydrogen. It is assumed that the large intestine contains around 10^{15} bacteria whilst there is only a very small quantity of anaerobic bacteria in the small intestine [5]. Under normal conditions, the bacterial concentration in the small intestine is no higher than 10^2 up to a maximum of 10^5. If the bacterial concentration is above 10^5 bacteria ml^{-1} of the small intestinal content, a small intestinal bacterial overgrowth syndrome (SIBOS) exists [6–8]. Anaerobic bacteria prefer to metabolize sugar molecules, which, as part of a fermentation reaction, are initially broken down into short-chain fatty acids (SCFA), carbon dioxide (CO_2) and hydrogen (H_2), as illustrated in figure 1.

A large part of the CO_2 remains in the intestines and leads to the symptom of bloating. SCFA generate an osmotic gradient and, by doing so, absorb water into the intestinal lumen, which leads to the symptom of diarrhea. The hydrogen generated in the intestines passes the intestinal wall, ends up in the bloodstream, is transported to the lungs and excreted as part of the exhaled breath. There is strong evidence that the exhaled hydrogen indicates the quantity and the metabolic activity of anaerobic bacteria in the intestines. Exhaled hydrogen can be measured in parts per million (ppm) non-invasively and relatively easily with hand-held breath test devices [9–11]. The time at which the hydrogen concentration rises during a breath test gives an indication as to the part of the intestines where the fermentation takes place [12].

2. Sample

This paper reflects our findings based on a total of $N = 3374$ patients, who visited a doctor's office for internal medicine in Innsbruck, Austria, presenting functional intestinal symptoms.

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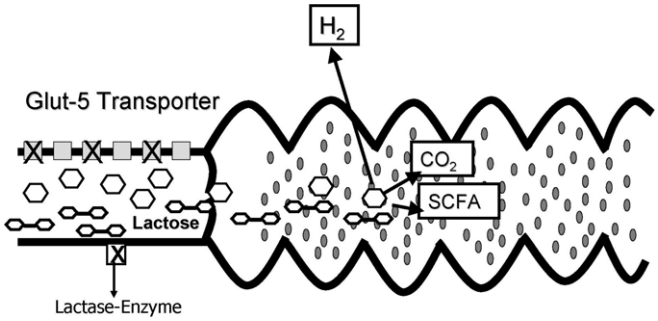

Figure 1. Fermentation reaction of sugar molecules (lactose) in the intestines as found in lactose malabsorption.

The data were collected from January 1997 to April 2008. The mean age of our patients was 42.9 years (range 3.2–87.5 years), including 31.5% ($n = 1064$) male and 68.5% ($n = 2310$) female subjects. We carried out 1783 fructose, 1590 lactose, 271 lactulose, 200 sorbitol, 14 xylose and 9 xylitol load tests on our patients. The investigation conforms with the principles outlined in the Declaration of Helsinki, and informed written consent was obtained from each participant to be included in this analysis.

3. Preparation for the test

Prior to the test, the patient should fast for at least 12 h. During this time, he must not drink anything apart from water. In particular, he must be advised to avoid milk and/or fruit juices on the day prior to the test. The last meal on the day preceding the test should not be too ample and should ideally not consist of any fiber. On the day prior to the test, products such as onions, leeks, garlic, cabbage, pickled cabbage or beans should be avoided. Twelve hours prior to the test, the patient should stop smoking and chewing gum [13]. If, due to an oversight, the patient does smoke, it is still possible to conduct the test at a low basal H_2 value (<5 ppm). If, repeatedly, increased basal H_2 values are measured in a patient, it is recommended to measure the exhaled content of carbon monoxide (CO) to establish whether the patient did smoke shortly before the test.

Apart from vitamins, laxatives and antibiotics, medicines can be taken with pure water on the day of the examination. Wearers of dentures must not use an adhesive on the day of the test. The claim that it is contraindicated to brush the teeth prior to the breath test because most types of toothpaste contain sorbitol or xylitol is incorrect. In our sample we have never encountered problems due to patients' brushing teeth in the morning. In contrast, when patients fail to brush their teeth, increased basal H_2 concentrations may occur and even distort the test result. Besides, carrying out the test on patients who did not brush their teeth beforehand is unpleasant for the patient and the staff involved.

3.1. What must be done prior to starting the breath test?

First of all, it is most important to establish that there are no contraindications against the breath test. This applies above all to children with suspected hereditary fructose intolerance. In the case of hereditary fructose intolerance (HFI), a fructose load is strictly contraindicated as it could generate severe hypoglycaemia. As the clinical symptoms of HFI and fructose malabsorption can be very similar, particular care needs to be taken with regard to children. In such cases, a molecular genetic test to establish HFI should always be carried out prior to a fructose load test. In very rare cases, mainly in compound heterozygotic cases where the clinical course of the condition is not quite severe, it is possible that HFI is not diagnosed until adulthood [14].

Table 1. Contraindications for hydrogen breath tests.

Absolute contraindications
• Known or suspected hereditary fructose intolerance (CI for fructose load test, sorbitol load test)
• Known or suspected (postprandial) hypoglycaemia
Relative contraindications
• Administration of antibiotics (in the last four weeks)
• Colonoscopy (in the last four weeks)
• Irrigoscopy (in the last four weeks)
• Fluoroscopy of the small bowel according to Sellink (in the last four weeks)
• Ileostomy (except for the diagnosis of SIBOS)

Additionally the patient's current and most recent medication needs to be documented. Antibiotics continue to distort the test result of the hydrogen breath test to up to four weeks after they have been discontinued [15]. Therefore, it is recommended not to carry out the test if this has been the case. Equally, the taking of laxatives, in particular of lactulose (*Laevolac*®) should be discontinued at least three days prior to the test. After a colonoscopy the intestinal flora needs up to four weeks to recover. Therefore, hydrogen breath tests should not be carried out before this time has passed. In any case, after a colonoscopy, one has to wait until the patient has had at least three normal bowel movements. The same applies after the execution of other intestinal examinations where prior 'bowel cleaning' has been carried out, such as, for example, after an irrigoscopy, a Sellink procedure or other bowel tests [16]. A list of contraindications for hydrogen breath tests is featured in table 1.

3.2. Emergency medication

Whilst emergencies associated with breath tests tend to be rare, it is still important to be prepared for all eventualities. If complaints occur, they tend to be migraine attacks, headaches or stomach cramps. However, in rare cases, patients may experience panic attacks, dizziness, allergy-like reactions or tachyarrhythmias. Appropriate emergency medications should be stocked by a breath test laboratory (antihistamines, cortisone, migraine drugs, spasmolytics, paracetamol etc).

3.3. Fasting state

The fasting state has to be validated. This is usually done by a basal H_2 measurement. The basal H_2 level should be below 10 ppm (better <5 ppm). If the basal H_2 is 10 ppm or above, the

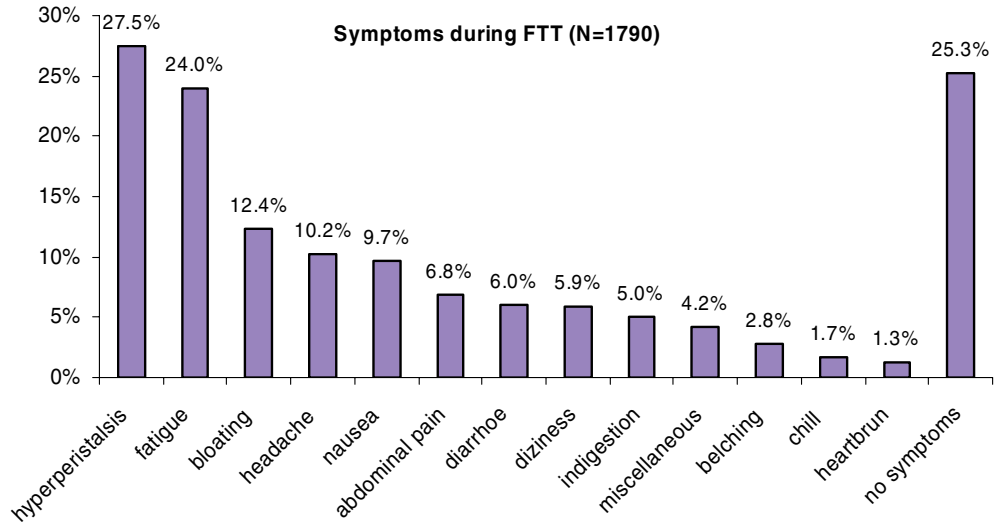

Figure 2. Frequency of symptoms during fructose tolerance test ($N = 1790$).

breath test cannot be used. In such a case, the patient should be asked to return on another day and to fast for at least 16 h before undergoing the breath test again. Beside fibre the last meal prior to the test should not contain milk (dairy products) either, if lactose intolerance is suspected. If potential fructose intolerance is suspected, the last meal should additionally be devoid of fruit. Furthermore, it is advisable that, on the morning of the day when the test is carried out, the patient drinks a glass of hot water. This assists the peristalsis and produces a 'wash out' of the bowel bacteria, which contribute to the production of fasting breath hydrogen.

3.4. Documentation

The production of comparable and reliable results of hydrogen breath tests does not just require a standardized implementation of the breath test but also exact documentation. Apart from measured H_2 levels, it is above all necessary to establish the symptoms that existed each time a measurement is taken. The establishment of symptoms is essential for the interpretation of the test results and is of major importance for the clinical consequences. The symptoms that may occur during a test are not at all limited to gastrointestinal symptoms such as bloating, hyperperistalsis, diarrhea or abdominal pain. Frequently, the patient experiences extra-intestinal symptoms such as fatigue, dizziness, headache or heartburn (see figure 2).

4. Implementation of hydrogen breath tests

Each breath test starts with an initial measurement in the fasting state (basal value) prior to the patient having been administered a test substance. The procedure of exhaling should be carried out according to the instructions of the manufacturer of the breath test device. As hydrogen is distributed differently depending on the body position, the patient must adopt the same position as during the basal measurement [17]. When outpatient, non-bedridden patients are tested, we recommend to conduct measuring on a sitting subject. Before the measuring can take place the patient should sit down for at least 1 min. During the test, patients should remain in the waiting room as physical activity may distort the measured results. Nervousness, stress and other causes leading to hyperventilation may also distort the readings [13]. The simultaneous presence of other subjects in the waiting room does not interfere with H_2 breath test results. If it has been established that the subject has no more than 10 ppm (better <5 ppm) of H_2 in his respiratory air, the load test can begin.

4.1. Dosage, concentration, readings

The dosage and the concentration of the test substance as well as the speed of consuming it affect the test result. Evidence-based standards concerning the dosage, its concentration, the significance of H_2 levels, the frequency of measurement and the period over which measurements should be taken are actually lacking and are discussed controversially [16, 18–24]. False-positive and false-negative results have to be taken into consideration. More detailed information based on our clinical experience is described in section 6 below. Generally after measuring the basal fasting value (0 min), the amount of H_2 in the exhaled air is measured at 30 min intervals over the course of at least 2 h plus an additional measurement at 15 min. This means that H_2 readings are taken at 0 min (before the load) as well as at 15, 30, 60, 90 and 120 min. If more information about the effect of the tested substance on the small intestine is required, i.e. if small intestinal bacterial overgrowth syndrome (SIBOS) is suspected, it is useful to add another reading after 45 min.

5. Guidelines for the interpretation of breath test results

The interpretation of hydrogen breath test results is based on three crucial factors: H_2 exhalation level, appearance of

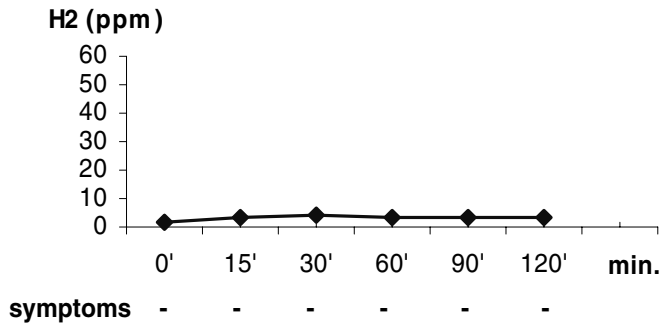

Figure 3. Negative breath test. Test result: no H_2 increase, no symptoms. Interpretation: normal findings.

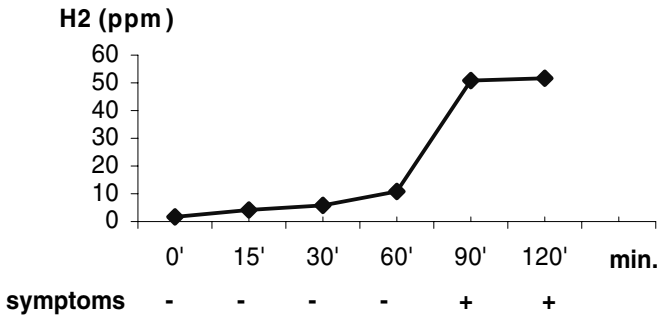

Figure 4. Positive breath test and symptoms. Test result**:** H_2 increase and symptoms, both after 60 min. Interpretation**:** intestinal intolerance of the test substance.

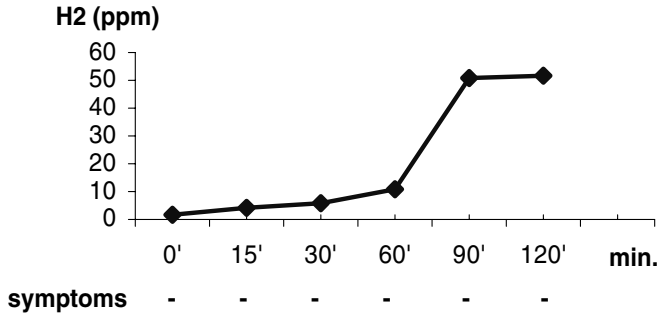

Figure 5. Positive breath test without symptoms. Test result: H_2 increase after 60 min, no symptoms. Interpretation**:** malabsorption of the test substance (without intolerance).

symptoms and the time-dependent change of these two factors during the test period. Differences in the H_2 concentration of 2–3 ppm during measurements taken in quick succession must be considered as random variation because the measuring uncertainty of the equipment is within this range. If, under the same trial conditions, the measured hydrogen values differ by more than 5 ppm, the device should be re-adjusted.

5.1. The negative breath test

If there is no malabsorption of the test substance, there is no significant increase in hydrogen levels, i.e. readings vary by less than 5 ppm above or below the basal value, and there are no symptoms. Only if both criteria apply (lack of H_2 increase and lack of symptoms) normal findings should be diagnosed (see figure 3).

If clinical complaints occur but are not accompanied by an increase in H_2 levels, a lack of H_2 production (non-H_2-producer) should be considered. In order to make a safe diagnosis of non-H_2-production, a lactulose test must be carried out. If a lactulose load still does not produce an increase in H_2 levels, the subject is very likely to be a 'non-H_2-producer' (see below under sections 6.4 and 7).

Additionally false-negative results may occur due to a longer oro-cecal transit time, i.e. it is possible that the test was finished before a measurable increase in H_2 levels could be established. If a slow transit time is suspected (in cases where patients tend to complain about constipation with very rare bowel movements) it is reasonable to take additional readings after 150 and 180 min, respectively. However, if for logistical reasons this is not feasible, it is useful to ask the patients to provide a feedback on experienced complaints such as bowel rumbling, bloating or diarrhea during the afternoon after the test.

5.2. The positive breath test

In general, an increase in hydrogen concentrations of more than 20 ppm above the basal value is considered to be a positive test result (significant H_2 increase). A significant H_2 increase and the appearance of symptoms, both occurring at about 60 min after starting the test, are diagnosed as an intestinal intolerance of the test substance (see figure 4). Generally, it should be possible to measure the maximum increase at the earliest after 60 or—even better—after 90 min as it takes that long until the non-absorbed proportion of the test substance has arrived in the large intestine.

If there is a significant H_2 increase after 60 min but clinical complaints (symptoms) are lacking, a malabsorption of the test substance (instead of an intestinal intolerance) has to be diagnosed (see figure 5). Generally we recommend the term 'intolerance' if positive breath test results occur together with symptoms in contrast to the term 'malabsorption', indicating a positive breath test but no appearance of symptoms.

If the value rises more than 10 ppm but less than 20 ppm above the basal value, the test result is considered as 'borderline positive'. Again it needs to be taken into consideration, at what time this borderline H_2 increase occurs. An increase of more than 10 ppm above the basal value within 30 min is seen as indicative of a test substance-dependent small intestinal bacterial overgrowth syndrome (SIBOS). There are essentially two possibilities for this particular H_2 profile:

(a) The curve shows a dual-peak profile (see figure 6) i.e. an H_2 increase in the first 30 min is followed by a drop in the H_2 concentration, which is once more followed by an H_2 increase after 60 min. This indicates that there is a SIBOS with a still intact function of the ileo-cecal valve and that the bacteria in the small intestine are able to metabolize the test substance. The second peak (after 60–90 min) means that a major part of the test substance could not be absorbed, and is therefore fermented in the large intestine (malabsorption). If, during the test, the subject experiences discomfort, an intestinal intolerance of the test substance with

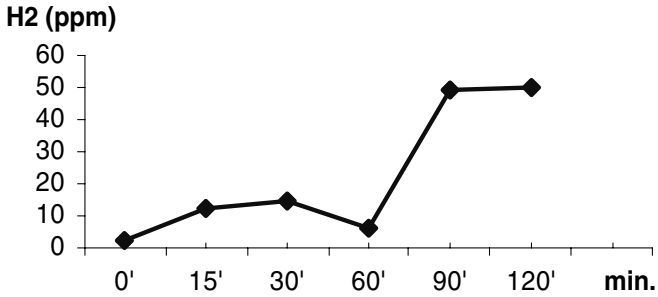

Figure 6. Breath test curve with dual-peak profile. Test result: H_2 increase within 30 min, drop of H_2 level, second H_2 peak after 60 min. Interpretation**:** malabsorption/intolerance (depending on appearance of symptoms) with SIBOS and intact ileo-cecal valve.

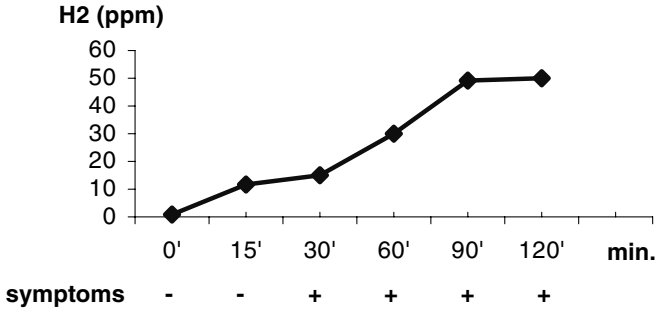

Figure 7. Breath test curve with early increase. Test result: H_2 increase within 60 min, no drop until 90th min and appearance of symptoms. Interpretation: intestinal intolerance and backwash ileitis.

a test substance-dependent SIBOS and intact ileo-cecal valve has to be diagnosed. If there is no discomfort during the test, a malabsorption of the test substance with test substance-dependent SIBOS with intact ileo-cecal valve would need to be diagnosed. If the clinical complaints only occur during the first 60 min and disappear relatively quickly afterwards, this would indicate that the complaints were caused by the overgrowth in the small intestine rather than by the malabsorption of the test substance in the large intestine.

(b) The curve shows an early increase (before 60 min) that remains at least 20 ppm above the basal value without a drop in the H_2 concentration until the 90th minute. This curve has a quasi dual-peak shape without a 'valley' between the first and the second peaks (see figure 7). In such a case, the assumption is that stool from the large intestine (cecum) has 'flown back' into the small intestine (terminal ileum) via the ileo-cecal valve. This is not a particularly rare occurrence because, in the case of malabsorption due to fermentation, a great deal of pressure can be produced in the cecum. The ileo-cecal valve is extended and becomes 'leaky'. What is less well known is the fact that there is antiperistaltic movement in the cecum in order to 'knead through' the mashed food. During this process, the contents of the large intestine flow back into the small intestine if the ileo-cecal valve leaks, which results in bacterial overgrowth in the terminal ileum while the rest of the small intestine has not yet been overgrown with bacteria. Such cases are referred to as 'backwash ileitis'. As a situation such as this is almost always associated with complaints, an intestinal intolerance of the test substance with backwash ileitis would need to be diagnosed. If the patient does not complain of discomfort during the test, he needs to be examined in order to establish whether he is sensitive to palpatory pressure applied on the right lower abdomen at the intersection between the small and the large intestines. If there is no sensitivity to palpatory pressure and if the H_2 level shows an image as in figure 7, the correct diagnosis should be 'malabsorption of the test substance with reflux of bowel content via the ileo-cecal valve without backwash ileitis'.

Table 2. Types of hydrogen breath tests.

- Fructose tolerance test (FTT)
- Lactose tolerance test (LTT)
- Glucose load test (GLT)
- Lactulose test (LT)
- Sorbitol tolerance test (STT)
- Fructose–sorbitol tolerance test (FSTT)
- Xylitol tolerance breath test (XTT)

Table 3. Indications for the fructose tolerance test.

- Suspected gastro-intestinal fructose intolerance
- Investigation of irritable bowel syndrome
- Intolerance of sweets, honey or fruits
- Investigation of bloating, meteorism, flatulence, diarrhea, steatorrhea (fatty stools)
- Monitoring celiac disease and other conditions that may be associated with villous atrophy
- Chronic inflammatory bowel diseases (often combined with carbohydrate malabsorption)

6. Types of hydrogen breath tests

Actually, any sugar, sugar alcohol, di-, oligo- or polysaccharide can be tested for resorption via the hydrogen breath test. Depending on which test is to be carried out, the subject is given a load of different test substances. Hydrogen breath tests are most frequently used for the diagnosis of fructose malabsorption, lactose malabsorption and SIBOS. Table 2 offers an overview of the currently common types of hydrogen breath tests.

6.1. The fructose tolerance test (FTT)

The fructose tolerance test has been established as the gold standard to diagnose fructose malabsorption (FM) and intestinal fructose intolerance (IFI). The most frequent indications for the FTT are listed in table 3.

The fructose tolerance test is not suitable to diagnose hereditary fructose intolerance (HFI). If HFI is suspected, the hydrogen breath test is contraindicated as it could generate severe hypoglycaemia. In cases where HFI cannot be safely excluded in advance, it is essential to carry out a molecular genetic analysis beforehand.

6.1.1. Implementation and interpretation of the fructose tolerance test. For the fructose tolerance test (FTT) we recommend a load of 25 g fructose dissolved in

Table 4. Indications for the lactose tolerance test.

- Suspected primary or secondary lactose intolerance
- Investigation of irritable bowel syndrome
- Intolerance of milk, dairy products, pastries or chocolate
- Investigation of bloating, meteorism, flatulence, diarrhea, steatorrhea (fatty stools)
- Monitoring celiac disease and other conditions with villous atrophy if primary LI has been excluded via molecular genetic tests
- Chronic inflammatory bowel diseases (often combined with carbohydrate malabsorption)

Table 5. Indications for the glucose load test.

- Suspected SIBOS
- Exocrine pancreatic insufficiency
- Cirrhosis of the liver
- Secondary lactose intolerance
- Irritable bowel syndrome
- Duodenal diverticula
- Investigation of steatorrhea (fatty stools) or creatorrhea (foul smelling stools with protein maldigestion)
- Intolerance of sugar and sweets

250 ml of water. Some colleagues still use loads up to 50 g in 250 ml of water. Whilst such a high dosage leads to more side effects during the course of the test, it does not make it easier to differentiate between malabsorbers and healthy subjects. In addition, the high quantity of 50 g does not correspond to a physiological fructose-related load in real life situations. Children are given 1 g/kg BW up to a maximum of 25 g of fructose dissolved in 10 ml of water/kg BW up to a maximum of 250 ml of liquid. The H_2 values are measured at 0, 15, 30, 60, 90 and 120 min after the fructose load. In order to detect a fructose-dependent SIBOS, we recommend to add a further reading after 45 min. An increase of H_2 levels of more than 20 ppm above the basal value is defined as a positive test result (significant H_2 increase). The results of the fructose tolerance test are interpreted according to the guidelines described in the section above. A fructose malabsorption (positive test result but no appearance of symptoms) does not require dietary intervention. The determination of blood sugar levels while carrying out the breath test does not provide additional information regarding IFI and FM and must be considered as obsolete.

6.2. The lactose tolerance test (LTT)

The enzyme lactase is responsible for breaking down the disaccharide lactose and dividing it into its two components glucose and galactose. Lactose cannot be resorbed in its non-split form. The lactose tolerance test (LTT) is used to diagnose lactose maldigestion (LM) or lactose intolerance (LI) independently of the cause of the lactose malabsorption. The most frequent indications for a lactose tolerance test are listed in table 4. The H_2 breath test is currently considered to be the most cost effective and reliable method to diagnose malabsorption of lactose [25, 26].

6.2.1. Implementation and interpretation of the lactose tolerance test. We recommend to give 50 g of lactose dissolved in 250 ml of water (in children: 2 g/kg BW dissolved in 10 ml/kg BW up to a maximum of 50 g in 250 ml). As lactose dissolves less well in water, it is recommended to use warm water. Like for the fructose tolerance test, the H_2 level is measured at 0, 15, 30, 60, 90 and 120 min after the lactose load. In order to find out whether or not there is lactose-dependent SIBOS, a further reading after 45 min is useful. An increase of H_2 levels of more than 20 ppm above the original value is defined as a positive test result (significant H_2 increase). The results of the lactose tolerance test are interpreted according to the guidelines described in the section above. If malabsorption is not accompanied by clinical complaints, lactose maldigestion (LM) is diagnosed; if there are complaints, lactose intolerance (LI) should be diagnosed. However, some patients show only a slight increase in the H_2 concentration after 90 and 120 min, which has not yet reached significant levels of 20 ppm above the basal value. In such cases, the test should definitely be continued and another reading should take place at 150 and at 180 min. It needs to be taken into consideration that some patients do not exhibit diarrhea, bloating or abdominal cramps until up to 8 h after the administration of lactose. Therefore, it is reasonable to ask the patient to provide feedback to the testing laboratory if he or she experiences complaints during this time. If this is the case, the test needs to be repeated with the H_2 measurements taking place hourly for up to 8 h (without food intake between readings).

Further testing methods to diagnose lactose intolerance are the ^{13}C-lactose breath test (stable isotope ^{13}C) and the molecular genetic test to establish mutation of the LCT genes LCT-13910T>C and LCT-22018A>G. The ^{13}C-lactose breath test offers the advantage that it can be used to diagnose lactose maldigestion independently of the intestinal flora (e.g., in non-H_2-producers). Due to its radioactive load, the ^{14}C-lactose test (radioactive isotope ^{14}C) must be considered as obsolete and should no longer be carried out.

We were able to show that the molecular genetic test does not replace the LTT breath test [27]. If the LTT breath test is positive, it is possible to distinguish secondary lactose intolerance from primary lactose intolerance by conducting a complementary molecular genetic test. In our patient collective, approximately 10% with a positive breath test had secondary lactose intolerance, which indicates that in such cases a molecular genetic test is useful [27].

6.3. The glucose load test (GLT)

Under physiological conditions, glucose is readily absorbed in the small intestine [28]. However if there is a bacterial overgrowth in the (upper) small intestine, bacterial fermentation of glucose and production of H_2 can take place prior to the absorption of glucose. Table 5 shows the most important indications for the glucose tolerance breath test.

A study carried out by Casellas *et al* found that by using GLT it was possible to establish that 40% of patients with exocrine pancreatic insufficiency suffered from bacterial overgrowth [29]. This frequency of SIBOS should justify the

Table 6. Indications for the lactulose test.

- Establishing oro-cecal transit time
- Establishing non-H_2-producers
- Small intestine bacterial overgrowth (SIBOS)
- Investigation of constipation

routine use of a GLT on patients with exocrine pancreatic insufficiency. In addition, up to one third of the patients with liver cirrhosis were found to have bacterial overgrowth [30], which represents a risk for the development of spontaneous bacterial peritonitis [31]. In our own sample the use of a GLT shows that around 80% of the patients with secondary lactose intolerance suffered from SIBOS, which had caused the lactose intolerance and which, in all cases, was reversible after the use of antibiotic therapy (unpublished data).

6.3.1. Implementation and interpretation of the glucose load test. As part of the GLT the subject is given a load of 50 g of glucose dissolved in 250 ml of water. The hydrogen levels are measured each 15 min after the glucose load (0, 15, 30, 45 and 60 min). This test is generally not carried out on children. However, a load of 2 g/kg BW up to a maximum of 50 g dissolved in 10 ml/kg BW up to a maximum of 250 ml would be possible. When carrying out the glucose load test, the aim is not to establish whether glucose reaches the large intestine but whether, in the upper section of the digestive system, there are signs of a measurable anaerobic metabolic activity, which is reflected in an H_2 increase. This means that any increase of more than 10 ppm above the basal value is to be considered as significant and hints at a small intestinal bacterial overgrowth.

6.4. The lactulose test (LT)

Lactulose is a synthetic disaccharide consisting of fructose and galactose. Lactulose cannot be absorbed in humans and is therefore always fermented. If a lactulose load still does not produce an increase in hydrogen levels, a 'non-H_2-production' most likely exists. The common indications for the lactulose breath test are summarized in table 6.

6.4.1. Implementation and interpretation of the lactulose test. We recommend to give 10–20 g of lactulose (this equals around 1 to 2 tablespoons of *Laevolac*®) as this dose rate limits the discomfort whilst the H_2 increase is still sufficient to achieve good test results. If, within 3 h, no H_2 increase (<5 ppm) is reported, it is quite safe to assume that we are dealing with a non-H_2-producer. For the evaluation of the oro-cecal transit time readings should also take place every 30 min over a 3 h period. Normally, lactulose reaches the large intestine within 70–90 min. This means that an H_2 increase of at least 20 ppm above the basal value must, at the latest, occur in the 90th minute. If this does not occur, an extended oro-cecal transit time can be assumed. Extended oro-cecal transit time is mainly seen in patients suffering from 'slow-transit constipation', and is in most cases a sign of disturbed motility affecting the entire digestive system.

6.5. The sorbitol tolerance test (STT) and the fructose–sorbitol tolerance test (FSTT)

The STT is used to diagnose sorbitol intolerance (SI). Two types of sorbitol intolerances are differentiated: pure sorbitol and sorbitol-dependent fructose malabsorption [32]. The latter is of clinical significance because fructose and sorbitol are very frequently both part of the same food (e.g., fruits). The most frequent indications for the sorbitol tolerance test are suspected sorbitol intolerance (intolerance of chewing gums, boiled sweets, diabetic products) and borderline positive results in the fructose tolerance test.

As part of a sorbitol tolerance test, the subject is given a load of 12.5 g of sorbitol dissolved in 250 ml of water whilst, during the fructose–sorbitol load test, the subject receives a

Table 7. Implementation of hydrogen breath tests.

Test substance	Dosage	Readings (min)	Positive test result (increase over basal value)	Remark
Fructose	25 g in 250 ml water children: 1 g/kg BW in 10 ml water/kg BW (max. 25 g)	0–15–30–60–90–120[a]	>20 ppm	
Lactose	50 g in 250 ml water children: 1 g/kg BW in 10 ml water/kg BW (max. 50 g)	0–15–30–60–90–120[a]	>20 ppm	
Glucose	50 g in 250 ml water children: 1 g/kg BW in 10 ml water/kg BW (max. 50 g)	0–15–30–45–60	>10 ppm	
Lactulose	10–20 g	0–15–30–60–90–120–150–180	<10 ppm (non-H_2-production) >20 ppm (evaluation of transit time)	
Sorbitol	12.5 g in 250 ml water	0–15–30–60–90–120[a,b]	>20 ppm	Not on children
Fructose–sorbitol	12.5 g fructose + 12.5 g sorbitol in 250 g water	0–15–30–60–90–120[a,b]	>20 ppm	Not on children
Xylitol	12.5 g in 250 ml water	0–15–30–60–90–120[a,b]	>20 ppm	Not on children

[a] Additional reading after 45 min for evaluation of test substance dependent SIBOS.
[b] Additional reading after 150 min and 180 min if slow transit time is suspected.

load of 12.5 g of sorbitol + 12.5 g of fructose dissolved in 250 ml of water. This test is generally not carried out on children. The H_2 values are measured at 0, 15, 30, 60, 90 and 120 min after the test-substance load. An increase of H_2 levels of more than 20 ppm above the basal value is regarded as a positive test result. The results are interpreted according to the guidelines described in the section above.

6.6. The xylitol tolerance test (XTT)

Xylitol is a sugar substitute and, as such, is often added to the so-called 'sugar-free' food under the name E-967. The xylitol tolerance test (XTT) is used to diagnose xylitol intolerance. Xylitol is not sufficiently absorbed by many people so that, not infrequently, irritable bowel symptoms can be triggered by food containing xylitol. In spite of this, the XTT is only carried out rarely. From a clinical point of view, the characteristics of xylitol are very similar to those of sorbitol. Indications for a xylitol tolerance test are suspected xylitol intolerance (intolerance of chewing gum, boiled sweets, diabetic products etc.) and borderline positive results in the fructose tolerance test or sorbitol tolerance test. We recommend to give a load of 12.5 g of xylitol dissolved in 250 ml of water. This test is generally not carried out on children. Readings of the H_2 level should be taken at 0,15, 30, 60, 90 and 120 min after the xylitol load. H_2 levels of more than 20 ppm above the basal value indicate a positive test result, and should be interpreted according to the guidelines described in section 5. Table 7 offers an overview of the design parameters for the implementation of the most common hydrogen breath tests.

7. Non-H_2-production

If a patient neither shows an increase in the hydrogen concentration of the respiratory air nor any simultaneous symptoms, such findings are—as a rule—to be considered as normal. If a patient shows symptoms during or within 6 h after the test (in particular, if he suffers from bouts of diarrhea during this time) whilst no H_2 increase could be established during the breath test, a lack of H_2 production needs to be considered and a lactulose test should be carried out to confirm the lack of H_2 production. A non-H_2-production can, on the one hand, be due to a predominance of intestinal bacteria, which metabolize hydrogen themselves [33] (e.g., acetogenic bacteria, methanogenic bacteria, nitrate-reducing bacteria, sulphate-reducing bacteria). This can happen so quickly that hydrogen cannot be absorbed in sufficient quantities to be excreted via the lungs. On the other hand, due to a recent antibiotic therapy or the preparation of a colonoscopy, hydrogen producing bacteria may have been reduced to a point where hydrogen cannot be produced in sufficient quantities. However, there are rare exceptions where an H_2 increase has been established during the fructose load test or the lactose load test whilst, the lactulose test shows no H_2 increase. In such a case, it is assumed that the intestines predominantly contain no bacteria that are able to split lactulose into fructose and galactose. Whilst this is a very rare occurrence, it does happen at times.

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