

The Adult Carbohydrate Perception Questionnaire Identifies Patients with Lactose or Fructose Intolerance Who Respond to Diet

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Keywords

Bloating · Abdominal pain · Diarrhoea · Nausea · Flatulence

Abstract

Introduction: There is no evidence that a positive breath test is a good predictor of the success of a carbohydrate-restricted diet. Our objective was to investigate whether patients in whom lactose intolerance (LIT) or fructose intolerance (FIT) is diagnosed by validated symptom measurement respond to diet. **Methods:** Patients referred for evaluation of LIT or FIT underwent hydrogen/methane breath testing (malabsorption test) and symptom measurement with the adult Carbohydrate Perception Questionnaire (aCPQ, intolerance test) before and after 50 g lactose or 25 g fructose. Patients with a positive aCPQ received instructions on specific diets and supplements. Severity of abdominal pain, bloating, diarrhoea, flatulence, and nausea were measured using a visual analogue scale (VAS) before (VAS1, mm) and after (VAS2, mm) diet. The change in VAS for individual symptoms and overall symptoms after diet is expressed as deltaVAS (mm) and as change relative to VAS1 (%). **Results:** Forty-one patients were included (23 LIT, 8 FIT, 10 LIT+FIT). Eight patients had negative breath tests (no malabsorption). After 2 months of diet, the overall VAS and the individual symptoms decreased ($p < 0.001$). Overall VAS1 and the VAS1 for individual symptoms

correlated significantly with the decrease in deltaVAS (mm) after diet. Nineteen patients (46%) had total recovery, and additional 13 patients (32%) had improvement of >50%. Response to diet was independent of breath test results.

Conclusion: This uncontrolled and unblinded study suggests that patients with carbohydrate intolerance diagnosed by aCPQ benefit significantly from diet, independent of the presence of malabsorption. Controlled studies are required to confirm these results in larger patient groups.

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Plain Language Summary

Intolerance to lactose- or fructose-containing foods is an important reason for diarrhoea, bloating, gas in the abdomen, abdominal pain, nausea, and passing of wind through the anus. In the past, in order to diagnose intolerance, breath tests after ingestion of lactose or fructose have commonly been used, and the results of these breath tests had been used to suggest treatments like diet or food supplements. However, recent scientific publications have shown that the results of breath tests do not predict the response to treatment. It has also been suggested that the documentation of symptoms after ingestion of lactose or fructose with a questionnaire may be better in identifying patients who will benefit from treatment. Such a

questionnaire was recently developed and shown to be reliable and useful for the diagnosis of lactose or fructose intolerance. The questionnaire is called adult Carbohydrate Perception Questionnaire (aCPQ). In the current study, we demonstrated that patients with intolerance to lactose or fructose, which was confirmed by a positive result on this aCPQ, benefited significantly from the dietary treatment. The degree of symptom improvement was greatest in patients with the most severe symptoms before treatment. The response to treatment in intolerance was independent of whether or not patients had a positive breath test. The results of this study, however, are preliminary and need to be confirmed by larger controlled studies.

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Introduction

Food-associated symptoms like bloating, abdominal pain, flatulence, nausea, and diarrhoea can occur in various functional [1, 2] and structural gastrointestinal diseases [3]. These symptoms are often related to poorly digestible carbohydrates [4]. The introduction of hydrogen breath tests (H₂BT) in the 1970s [5] has focused attention to the malabsorption of specific carbohydrates, like lactose or fructose, as a cause of these symptoms. Conclusions about the general population were drawn based on case studies or small study populations [6–8]. However, it was overlooked that only some individuals with lactose malabsorption (LM) experience symptoms after lactose intake [1], and although anecdotal reports and small studies have suggested a good association between LM and improved symptoms following a lactose-free diet, a clear association has never been established in quality-controlled trials. A comprehensive review has identified 17 trials that investigated the effectiveness of lactose-restricted diets [9]. Only one study which selected patients based on malabsorption and a proven link to symptom onset showed a significant improvement in gastrointestinal symptoms [9]. Some trials showed an improvement in one or more of the individual symptoms [10], but this effect was not consistent between the trials [9]. Lack of conclusive data may be related to the use of different doses of lactose for hydrogen breath testing [9] or to combined food intolerances [11].

In later years, this breath test-centred approach was also applied for identification of malabsorption of fructose [12] (FM) and other poorly absorbed carbohydrates, and restrictive diets were imposed without verification of a link between malabsorption of the carbohydrate and the onset of symptoms in the individual patient [13]. The deficiency of data on the effect of the treatment of symptoms of lactose intolerance (LIT) may be due to the historical lack

of clear distinctions between the terms “lactose malabsorption,” “lactose maldigestion,” and “lactose intolerance.” A recent European guideline has provided a clear definition for these terms [14], with malabsorption describing the deficient absorption of a nutrient in the small intestine and intolerance describing the development of symptoms, which may be independent of malabsorption. The guideline has recommended the use of validated symptom questionnaires together with breath testing [14].

The aim of our study was to investigate whether LIT or fructose intolerance (FIT), diagnosed by a positive lactose or fructose challenge test using symptom measurement with the adult Carbohydrate Perception Questionnaire (aCPQ), which has been validated for the diagnosis of carbohydrate intolerance [15], can effectively identify patients who would benefit from dietary restriction of the respective carbohydrate for which intolerance has been documented. Visual analogue scales (VASs) were used before and after diet to measure the severity of gastrointestinal symptoms associated with carbohydrate intolerance. This study is the first to test the clinical usefulness of the recently published European Guideline, which recommends including validated symptom measurement in H₂BT [14].

Methods

Patients

Consecutive patients with chronic or relapsing gastrointestinal symptoms related to functional gastrointestinal disorders, who were referred for the evaluation of suspected intolerance of lactose or fructose between June 2017 and June 2022, were eligible for inclusion into the study if they fulfilled the following inclusion criteria: minimum age 15 years, completion of a hydrogen and methane breath test (H₂/CH₄ BT; malabsorption test), and aCPQ after a load of lactose or fructose (intolerance test), not having followed a diet for the past 4 weeks before testing, ability to attend the follow-up appointment, and documentation of LIT or FIT, or both, by means of a positive result on the aCPQ. The study period was interrupted by a nearly complete stop of patient testing during March 2020 and November 2021 due to restrictions during the COVID pandemic.

Breath and Intolerance Test after a Lactose or a Fructose Challenge

The breath and intolerance test protocol closely followed the recommendations of the European Guideline, which was published towards the end of the study period [14]. A minimum fasting period of 8 h was required before the test. Drugs that contained fermentable carbohydrates had to be avoided at least 24 h prior to the breath test. Measurements of hydrogen and methane concentration in breath (GastroCH4eck Gastrolyzer, www.bedfont.com) were obtained immediately before and at 30, 60, 120, and 180 min after ingestion of 50 g lactose or 25 g fructose suspended in 200 mL drinking water. LM or FM was indicated by an increase in breath hydrogen concentration of ≥20 parts per

million (ppm) or methane concentration of ≥ 10 ppm over baseline, respectively.

Simultaneous with the breath measurements, symptom measurements using the aCPQ were obtained. An increase of 20 mm (mm) from baseline in at least one of the five 100-mm VAS of the aCPQ for abdominal pain, nausea, bloating, flatulence, or diarrhoea in the 3 h following lactose or fructose ingestion served as the indicator of LIT or FIT [15]. For the study, the validated German version of the aCPQ was used. For future use in other countries, the questionnaire is available in validated translations into Bulgarian, English, French, German, Hungarian, Italian, Polish, Romanian, Russian, and Slovenian languages [16].

Symptom Assessment before and after Diet

The severity of five symptoms associated with carbohydrate intolerance (abdominal pain, bloating, diarrhoea, flatulence, and nausea) was rated on 100-mm VAS. The assessment period for the first measurement (VAS1) was the preceding 6 months before the breath and intolerance test. The second measurement at the time of follow-up after diet (VAS2) covered the previous 10 days. Individual symptom scores and the sum of the five scores (overall symptom score) (in mm) were analysed. A reduction in the overall score of 50–79% was defined as “clinically relevant improvement” and a reduction of $\geq 80\%$ was defined as “symptom recovery.”

Treatment Intervention

The aim of the study was to stay as closely as possible to clinical practice at our unit. Therefore, according to standard clinical practice, patients identified to have LIT or FIT were given written instructions on a lactose- or fructose-reduced diet. These instructions are in routine clinical use at our hospital and were written by dietitians and one of the authors of this manuscript (HFH). The written instructions include information on the lactose or fructose content of commonly used foods and additional advice on the optional use of lactase supplements with lactose-containing foods or xylose isomerase [17] with fructose-containing foods. Patients were educated about the dose-dependent relation between ingested carbohydrate dose and symptoms. They were encouraged to adjust their diet to the extent they deemed necessary to control their symptoms until the scheduled follow-up visit. The follow-up visit was scheduled within one to 3 months, depending on the availability of time slots in the clinic and the patient's private schedule. Patients were instructed to follow the treatment instructions until the time of the follow-up visit.

Statistical Analysis

After confirming normal distribution of the data by the Shapiro-Wilk test, paired and unpaired *t*-tests were used for analysis of dependent and independent data as appropriate; otherwise, Wilcoxon tests were used. Data were analysed for both the overall symptom scores, which present the sum of the five individual symptom scores, and for individual symptom scores. The total score ranged from 0 to 100 mm for each individual symptom and from 0 to 500 mm for the overall symptom score. The difference between VAS1 and VAS2 scores (deltaVAS) was calculated for each individual symptom in both absolute numbers (mm) and as a proportional change of VAS2 compared to VAS1 (calculated as $\text{deltaVAS}/\text{VAS1}$, in %). Data are given as mean $\pm$ standard deviation unless otherwise stated. Correlations were calculated with the Spearman test for nonparametric data.

Results

Patient Characteristics

The flowchart (Fig. 1) shows the patient selection process. During the study period, 240 patients were referred for hydrogen-methane breath and intolerance testing. One hundred ninety-nine patients were excluded because they had no intolerance or did not return for follow-up. Of the excluded patients, 34 had malabsorption but no intolerance. A total of 41 patients (30 female, 11 male, age 36 ± 17 years, age range 15–86 years) fulfilled the inclusion criteria. Twenty-three of them had LIT, 8 had FIT, and 10 had both LIT and FIT. The three groups (LIT, FIT, combined LIT+FIT) were not statistically different with regard to their patient characteristics (age distribution, gender, duration of diet) (Table 1), and therefore, data on the effect of diet are combined for the whole group of 41 patients.

Overall Symptom Scores before and after Treatment

The duration of diet was 61 ± 22 days (range 32–117) for LIT, 55 ± 14 days (range: 33–75) for FIT, and 56 ± 28 days (range 27–103) for LIT+FIT (Table 1). The overall VAS score (Fig. 2) decreased significantly from VAS1 (190 ± 85 mm) to VAS2 (53 ± 52 mm, $p < 0.001$). This represents a $67 \pm 37\%$ reduction in mean overall symptom scores after diet.

Data on overall VAS1 and VAS2 scores in each individual patient are shown in Figure 3a. All patients except patient number 24 showed a decrease in VAS scores. There was a significant positive correlation between overall VAS1 scores and the absolute decrease in overall VAS scores in mm (deltaVAS) after the treatment ($r = 0.82$, $p < 0.01$, Fig. 4a). There was no correlation ($r = 0.26$, $p > 0.05$, Fig. 4b) between overall VAS1 and the relative change of VAS (deltaVAS %).

Figure 3b shows individual data on the decrease in symptoms expressed as a percentage of the overall VAS1 (relative changes of VAS). Nineteen patients (46%) showed total recovery (more than 80% reduction in overall symptom score), and an additional 13 patients (32%) had clinically relevant reduction of more than 50%.

Individual Symptom Scores before and after Treatment

Mean VAS scores for all individual symptoms decreased significantly ($p < 0.001$) after diet (Fig. 2). There were strong positive correlations between individual symptom VAS1 scores and the absolute decrease in VAS scores for pain ($r = 0.87$, $p < 0.01$), nausea ($r = 0.87$, $p < 0.01$), bloating ($r = 0.87$, $p < 0.01$), and diarrhoea ($r = 0.89$, $p < 0.01$). For flatulence, there was a moderately positive correlation between the VAS1 score and the absolute decrease in VAS score ($r = 0.64$, $p < 0.05$).

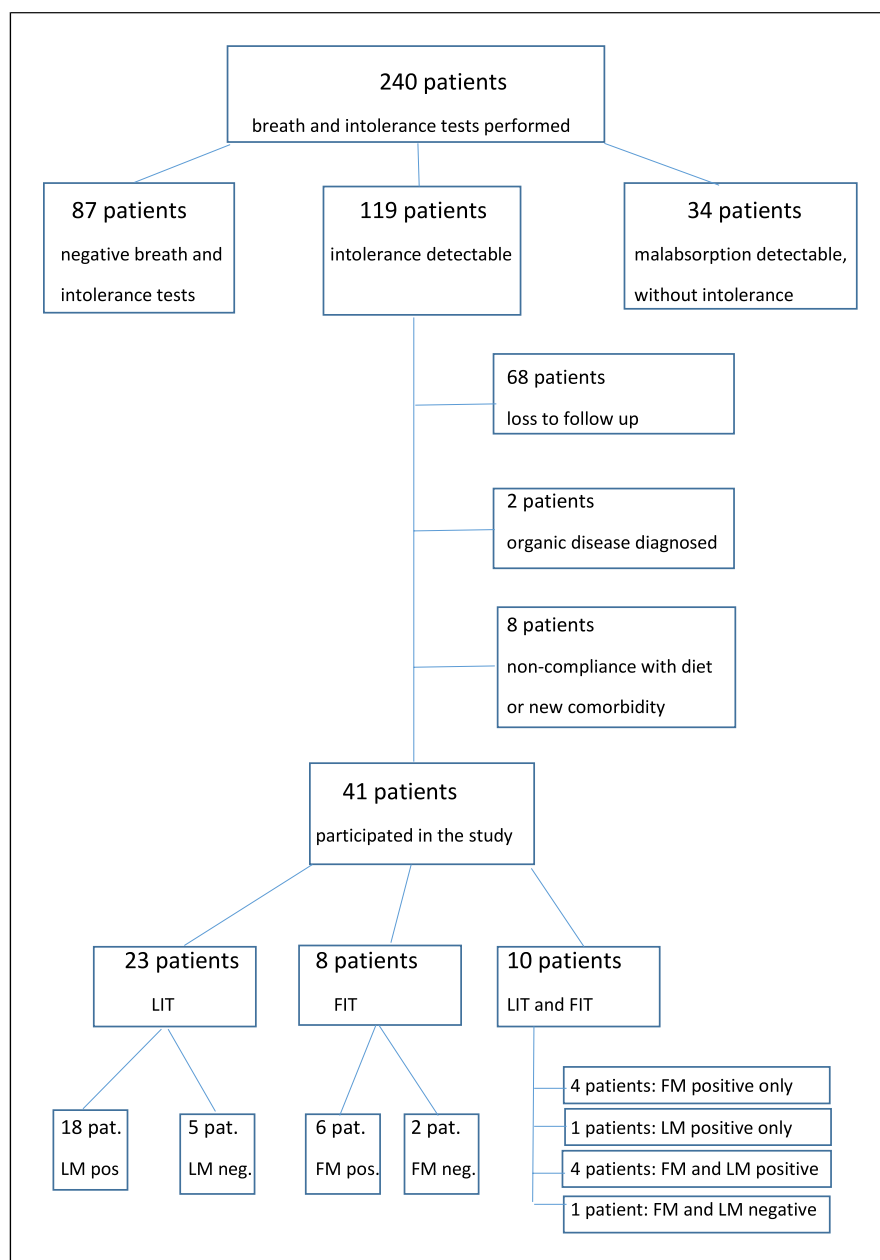


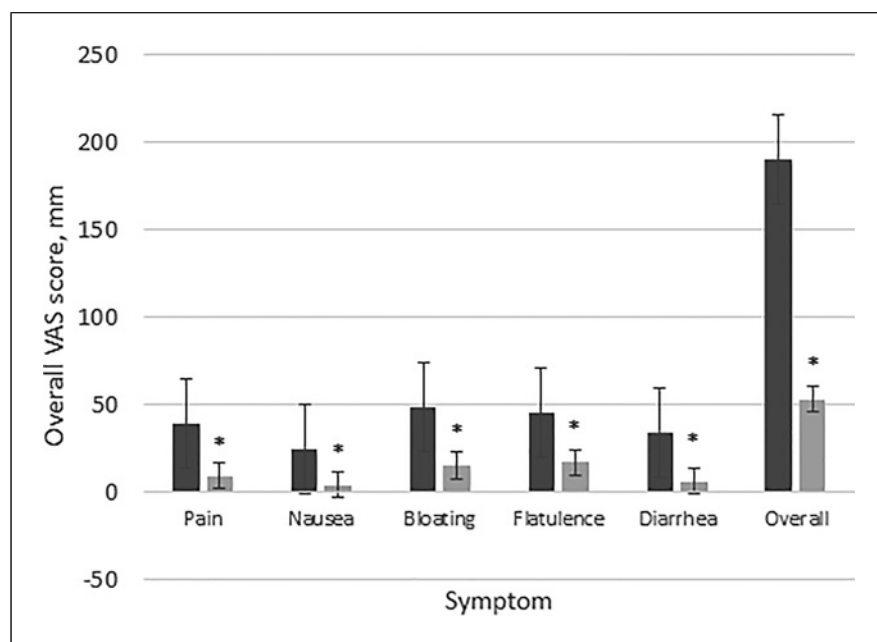
Fig. 1. Patient flowchart. Pat, patients; LM, lactose malabsorption; FM, fructose malabsorption; LIT, lactose intolerance; FIT, fructose intolerance.

Table 1. Patient characteristics

	All patients	LIT	FIT	LIT+FIT
Number	41	23	8	10
Age, mean±SD; range, years	36±17; 15–86	34±13; 19–62	46±25; 19–86	31±18; 15–71
Sex (female/male)	30 f, 11 m	14 f, 9 m	7 f, 1 m	9 f, 1 m
Duration of diet, mean±SD; range, days	58±22; 27–117	61±22; 32–117	55±14; 33–75	56±28, 27–103

LIT, lactose intolerance; FIT, fructose intolerance.

Fig. 2. Scores for individual symptoms and overall symptom scores (expressed as mm) before (VAS1) and after (VAS2) diet. Data are given as mean $\pm$ standard deviation; asterisks indicate $p < 0.0001$ for the comparison of VAS1 (black columns) with VAS2 (grey columns) for each of the individual symptoms and for overall symptoms.



Symptom Scores and Effect of Treatment in Patients with Negative Breath Test

In Figures 3a and b, patients numbered 5, 8, 10, 13, and 19 are patients with LIT who had a negative H_2/CH_4 BT; patients 29 and 31 have FIT with a negative H_2/CH_4 BT; and patient 34 had LIT+FIT and negative H_2/CH_4 BT after both lactose and fructose. For these patients with intolerance but negative breath tests, the overall VAS1 (171 ± 72 mm) was not statistically different from the VAS1 of patients with positive breath tests (195 ± 86 mm, $p = 0.48$). Additionally, the deltaVAS% was not statistically different between patients without ($75 \pm 24\%$) and with ($65 \pm 38\%$) a positive breath test ($p = 0.50$).

Discussion

In individual patients, a lactose- or fructose-reduced diet can have a remarkable positive impact on patients with carbohydrate malabsorption who suffer from abdominal pain, nausea, bloating, flatulence, or diarrhoea [18–21]. However, in contrast to the common clinical practice of using the results of breath tests for initiating diet, there is no scientific evidence of a relationship between a positive breath test and the success of a carbohydrate-restricted diet in group analyses [22–25]. A summary of published treatment trials shows that in patients with a positive breath test, the therapy has only a small overall benefit [26] and that studies with reliable data are limited. In addition, this review has suggested that those trials in which patients were

selected not only on the basis of malabsorption but also on the basis of the presence of carbohydrate-induced symptoms were the most likely to show symptom improvement. In our study, patients were selected based on evidence of carbohydrate intolerance using the aCPQ [15], regardless of whether or not they had malabsorption. The aCPQ has been validated for the diagnosis of carbohydrate intolerance [15], and its use has been recommended by a current guideline for the diagnosis of carbohydrate intolerances [14]. The questionnaire is available in validated translations into Bulgarian, English, French, German, Hungarian, Italian, Polish, Romanian, Russian, and Slovenian languages [16].

Our study demonstrates that patients who have LIT or FIT confirmed by positive symptom assessment with the aCPQ after an oral lactose or fructose load benefit significantly from the dietary treatment, which has been the routine recommendation in our clinic for many years, when there has been evidence of malabsorption by means of a breath test. The study results support the recommendations of the current guideline [14] and have the potential to enhance patient selection for dietary treatment, improve treatment success, and reduce medical costs for further diagnostic workup.

Although our patients had functional gastrointestinal symptoms compatible with IBS, which have a multifactorial pathogenesis, almost half of patients had complete recovery with dietary treatment alone and a further third had relevant clinical improvement. The extent of symptom reduction was highest in the patients with the most severe symptoms before

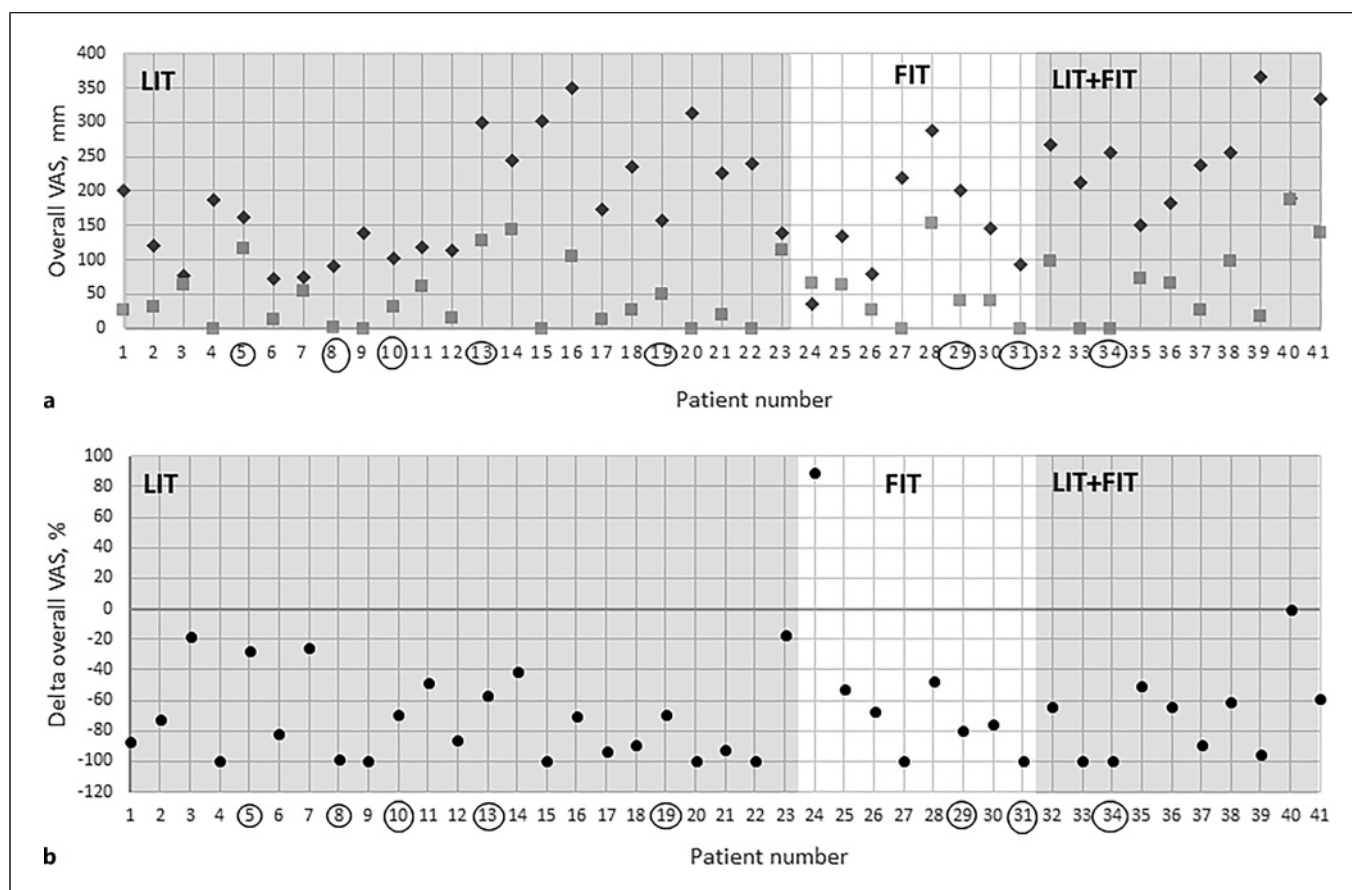


Fig. 3. a, b Individual data in 41 patients. Patients numbered 1 to 23 have lactose intolerance (LIT), patients 24 to 31 have fructose intolerance (FIT) and patients 32 to 41 have both lactose and fructose intolerance (LIT+FIT). Patient numbers with circles indicate patients with a negative breath test (no malabsorption). Patient number 24 was the only patient who had an increase in symptoms

after diet, and in patient number 40, there was only a marginal improvement of overall VAS of less than 1%. **a** Individual overall VAS values (in mm) before (black rhombus, VAS1) and after (grey square, VAS2) diet. Data points in patient 40 are overlapping. **b** Individual values of relative changes in overall VAS after diet compared to VAS1 (in %). Data points in patient 40 are overlapping.

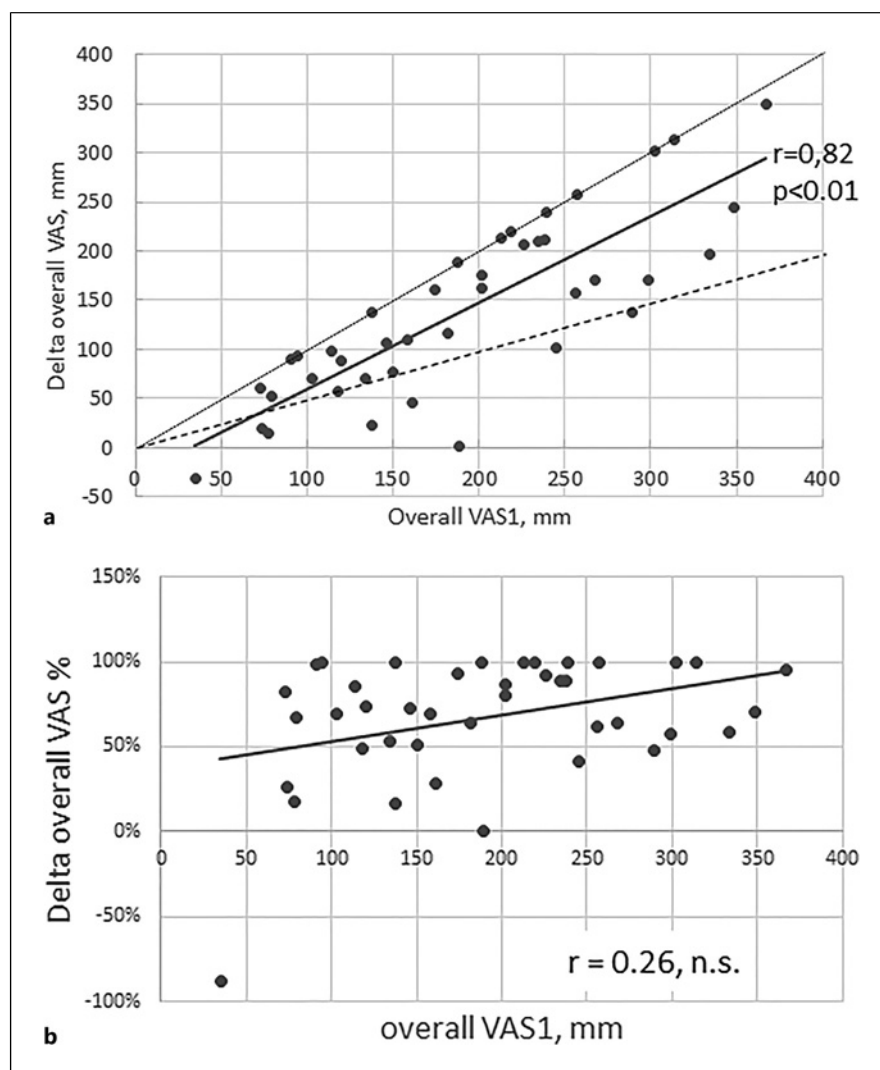
treatment. The treatment in our hospital focuses on diet, supplemented with optional dietary supplements like lactase [26] or xylose isomerase [17] when patients cannot follow the diet for personal reasons. The treatment recommendations are provided in written instructions, including information on lactose or fructose content in common foods and the dose-dependent relationship between poorly tolerated carbohydrates and symptom development.

Symptoms of carbohydrate intolerance which the patients had experienced in the 6 months before the diet and in the 10 days before the follow-up visit after having completed the period of the diet were evaluated on a VAS. Average overall VAS scores before the diet were 190 mm out of a possible 500. Among the symptoms, bloating and flatulence were the most frequently reported, while nausea was the least frequent. Nonetheless,

all the individual symptoms showed marked improvement on diet. It has to be kept in mind that the contribution of individual symptoms to the change in the overall score is by association, and they are not independent variables. We propose that a targeted dietary intervention, guided by the identification of distinct carbohydrate intolerances, might offer advantages over broader interventions like the FODMAP diet [27] in patients without verified individual symptom associations with specific foods.

The response to treatment in intolerant patients was independent of whether patients had malabsorption confirmed by a positive H₂/CH₄ BT, and the extent of response to treatment did not differ from that in intolerant patients with a negative breath test. If we had relied solely on the proof of malabsorption by a positive breath

Fig. 4. **a** Correlation between overall VAS1 (before diet, in mm) and the reduction in overall symptom scores after diet (delta overall VAS, in mm). Data points represent individual patients. The solid line (—) is the regression line ($r = 0.82$, $p < 0.01$). The dotted line (.....) indicates the line of identity (100% recovery). Patients on this line have full clinical recovery. The dashed line (-----) indicates 50% improvement. Patients above this line have clinically relevant symptom improvement. **b** Correlation between overall VAS1 (in mm) and delta overall VAS (in %). Each data point represents the data of a single patient. The solid line represents the regression line.



test to suggest a diet, 10 out of 33 patients with LIT (30%) and 4 out of 18 patients with FIT (22%) would not have received treatment, which was found to be helpful for these patients. Moreover, the cause of symptoms would have remained unclear, potentially leading to additional testing or symptomatic treatment attempts. Additionally, 34 patients referred for testing had malabsorption but were asymptomatic after the lactose/fructose load, and we chose not to include them in the study. We cannot rule out the possibility that these patients might have also benefited from treatment, and future studies will need to explore this further.

The discrepancy between intolerance and malabsorption could be due to false-negative breath tests, but the combined measurement of H_2 and CH_4 excretion in breath minimized this possibility [28]. Other factors

contributing to intolerance symptoms in patients with negative breath tests might include mechanisms like symptom expectations (nocebo effect), visceral hypersensitivity, food allergy, alterations of microbiome [29], or unidentified mechanisms.

In keeping with recommendations in the European Guideline, relatively high doses of lactose and fructose are used in our breath test routine; however, a smaller lactose dose is recommended for testing of LIT [14]. As malabsorption is dose dependent [30], a lactose/fructose challenge using lower doses would presumably have resulted in fewer malabsorbers. Our treatment results suggest that the doses used for intolerance testing in our study are adequate for the time being. One patient in our trial showed an increase in symptoms after treatment, but in a personal interview, this 77-year-old lady reported a

significant improvement in her symptoms with the diet. We suspect that this patient may not have used the VAS scoring adequately. Patient number 40, a 27-year-old female, experienced improvement in diarrhoea but worsened flatulence, with no change in nausea or bloating. She did not score pain both before and after the diet.

Our study is limited by the lack of blinding for both the measurement of carbohydrate intolerance and diet. Therefore, a placebo or nocebo effect of the dietary intervention cannot be excluded. However, blinded testing for food intolerance is not required in routine clinical practice [14, 31]. Future controlled studies may consider blinding for breath testing or treatment with dietary supplements, but it may be impossible for intolerance testing, symptom assessments, or dietary interventions. We also did not assess the patient's compliance with dietary instructions, supplement use, or other dietary changes which might have occurred in parallel to lactose or fructose reduction. Patients were informed of the dose-dependent nature of the symptoms and were advised to follow the diet as strictly as they found helpful to minimize the impact on their quality of life [27]. A potential limitation may be that patients may have had difficulty remembering symptoms for the 6 months prior to the testing (VAS1) and that therefore the calculation of deltaVAS (VAS1 minus VAS2) may not have been accurate.

A considerable number of patients diagnosed with LIT or FIT and receiving written treatment instructions did not attend the follow-up visit. The impact of this high dropout rate on our results is uncertain. We hypothesize that they were satisfied with treatment and did not see the need to attend the second visit. Alternatively, it is possible that they were dissatisfied with an unsuccessful treatment and therefore did not attend a second visit. We consider this latter scenario to be less likely because, after an unsuccessful treatment, the patients would have had the option of a further gastroenterological evaluation, which patients in our institution very often take advantage of. An additional cause for drop-outs was regulatory restrictions during the COVID period. Future studies should explore ways to decrease dropout rates through validated telephone or online-video interviewing for follow-ups.

In order to detect the optimal tolerated dose of a specific carbohydrate for an individual patient, future studies may consider testing a range of doses and carbohydrates in randomized order in blinded patients [32]. The cost-utility ratio of such an approach with repeated tests in the clinic needs to be studied before recommending it for routine clinical practice. However, the

availability of the aCPQ as a mobile application (Carboception App, currently only in German) will make home-based testing more feasible in the future.

The results of our uncontrolled study allow the generation of hypotheses for future controlled studies and make it reasonable to develop protocols for treatment studies based on the identification of intolerance with the aCPQ, for example, placebo-controlled studies of the effect of dietary supplements. The effect of a lactose-free diet on gastrointestinal symptoms should be assessed and compared in patients with the four following clinical situations: (1) LM plus LIT, (2) LM only, (3) LIT only, and (4) none of the above, preferably in a multicentre collaboration with well-characterized patients with functional gastrointestinal disorders according to the current Rome criteria.

Statement of Ethics

The study protocol was following the principles of the Declaration of Helsinki and reviewed and approved by the Ethics Committee of the Medical University Graz, Austria (EK 34-321 ex 21/22, 1124-2022). Written informed consent was not required because the study involved analysis of data which were obtained during routine clinical care without any additional measures going beyond routine medical care.

Conflict of Interest Statement

Heinz Hammer and Johann Hammer are shareholders of Carboception GmbH. Christin Klare has no conflict of interest to report.

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Author Contributions

C.K.: study design, data analysis, and first draft of the manuscript. J.H.: data analysis and interpretation and writing the manuscript. H.F.H.: study concept and design, data interpretation, and writing and finalizing the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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