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ORIGINAL ARTICLE

Fructose malabsorption in asymptomatic children and in patients with functional chronic abdominal pain: a prospective comparative study

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Abstract

The objective of this prospective cohort study was to compare fructose malabsorption in patients with functional chronic abdominal pain and in healthy children. The sample was divided into two groups: asymptomatic children and pain-predominant functional gastrointestinal disorders according to the Rome IV criteria. All children were tested for fructose malabsorption by a standardized breath hydrogen test. Hydrogen and methane were measured and the test was presumed positive when it exceeded 20 ppm above baseline. If positive, patients were given a low-fructose diet and the response was evaluated. One hundred five children were included (34 healthy children, 71 with functional chronic abdominal pain), with similar demographic characteristics in both groups (35.2% male, age 9.5 ± 2.8 years). Hydrogen levels in breath were tested through a hydrogen test for fructose demonstrating malabsorption in 58.8% of healthy children (95%CI 40.8%–76.8%) and in 40.8% of children with chronic abdominal pain (95%CI 28.7%–53.0%), removing those who had bacterial overgrowth. Twenty-one of 31 patients with symptoms and a positive test (72.4%) reported an improvement on a low-fructose diet.

Conclusion: Fructose malabsorption is more common in asymptomatic children than in patients with chronic abdominal pain. Better standardized test conditions are necessary to improve accuracy of diagnosis before using this test in clinical practice.

What is Known:
- *Although fructose malabsorption is believed to be related with chronic abdominal pain, high-quality evidence is lacking.*
- *Concerns have raised regarding the use of breath hydrogen test for fructose malabsorption in children with chronic abdominal pain.*

What is New:
- *Fructose malabsorption is not more common in children with pain-predominant functional gastrointestinal disorders than in asymptomatic children.*
- *Improvement in symptoms with low-fructose diet may indicate that, although patients with pain-predominant functional gastrointestinal disorders did not have a higher percentage of malabsorption, they had greater fructose intolerance.*

Keywords Chronic abdominal pain · Rome IV · Fructose malabsorption · Fructose intolerance · Low-fructose diet

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Abbreviations

BHT Breath hydrogen test
CAP Chronic abdominal pain
CI Confidence interval

Introduction

Fructose is a six-carbon monosaccharide which is increasingly consumed in Western diets [2, 9]. Breath hydrogen test (BHT) represents a valid and non-invasive diagnostic tool in fructose malabsorption diagnostic. Chronic abdominal pain (CAP) remains a common problem encountered by pediatricians, with a prevalence ranging from 13.5 to 26.6% [23, 26]. The etiology can be organic or functional, but in almost 85–95% of cases, the origin is functional [23]. In order to define childhood functional gastrointestinal disorders, the Rome criteria arose in 1989 leading to the Rome IV criteria recently published [15]. Although some recent studies suggest that fructose malabsorption may be a significant and treatable etiology of abdominal pain in pediatric population [6, 11], little is known about reference values of fructose absorption in healthy children [1, 14], and tests conditions are not completely standardized.

The aim of the present study was to determine fructose malabsorption in children with CAP and compare these results with those obtained in healthy children. Other purposes were to assess clinical response to a low-fructose diet in patients with CAP and to evaluate diagnostic accuracy of BHT considering different parameters (duration of the test, methane determination, bacterial overgrowth).

Methods

This is a prospective case-control study comparing the results of fructose BHT in both healthy children and patients with chronic abdominal pain.

Population study

In the first group, healthy children were recruited from four local schools through surveys. An information sheet and a previous questionnaire were given to the parents. Inclusion criteria were to be aged between 5 and 15 years, to have no digestive disease, and to have obtained the written informed consent from children's parents. Exclusion criteria were the presence of abdominal symptoms or digestive disease, any illness that could compromise the BHT, and children whose parents or caregivers cannot be expected to comply with the study procedures. The study protocol was explained to the children and their parents at school.

The second group comprised children with the same age who attended a pediatric gastroenterology unit of a tertiary care center because of CAP. These patients underwent evaluation with a complete history and physical examination. Blood test including celiac disease serology, C-reactive protein, urine test, and stool studies (culture, fat, and parasite screening) were carried out with normal results. Patients with pain-predominant functional gastrointestinal disorders (PP-FGIDs) including functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, and functional abdominal pain, not otherwise specified, who met the Rome IV criteria, were referred for BHT.

Breath hydrogen test

Fructose malabsorption was tested as determined by BHT using a standardized dose. In preparation for BTH, patients were asked to avoid antibiotics and laxatives for 2 weeks, to stop eating high fiber foods the day before, and to avoid eating and drinking 12 h before. Prior to evaluation, patients filled out a questionnaire to ensure that the given recommendations have been followed. After this, patients blew into a modified bag, and end-expiratory breath was collected. A breath sample was then injected into a gas analyzer (Quintron Breath Microlyzer™ SC®), and baseline values for hydrogen (H_2) and methane (CH_4) were measured. Patients then received a dose of 1 g/kg fructose to a maximum of 50 g, as it was done in the usual clinical practice and according to reviewed studies [13, 16, 29]. H_2 and CH_4 values were measured at time points 30, 60, 90, and 120 min in the healthy children group and at 60 and 120 min in the CAP group. Correction for CO_2 was done for accurate breath testing to compensate sampling error. A rise in breath H_2 and/or CH_4 of at least 20 ppm above baseline at 60 or 120 min was interpreted as a positive test result [6]. The test was considered suggestive of bacterial overgrowth if basal breath H_2 and/or CH_4 exceed 20 ppm [21].

Intervention

Patients with CAP and a positive BHT were asked to consume a diet low in fructose. Specific nutritional advice was provided by a dietitian, and a list that described the fructose contents of common foods was given to the parents. Foods that contained excessive amounts of fructose were avoided and other foods containing fructose were restricted. Therefore, fruits and juices with excessive fructose and sorbitol were avoided, as well as jams, nuts, and honey. Consumption of tomatoes, carrots, pumpkins, and green peas was also restricted.

The response to dietary restriction of fructose was evaluated in the following visit, 2 months later, using a standardized, non-validated, questionnaire. According to the clinical evolution with the diet, four categories were used to define dietary response: no improvement of symptoms, if there were no

changes in symptoms; low response, defined as less than 50% reduction of symptoms (in severity or frequency of complaints); good response, indicated by 50–75% reduction of symptoms; and very good response, defined as 75–100% reduction of complaints with a low-fructose diet.

Statistic analysis

This study included 105 patients, 71 in the CAP group and 34 in the healthy group (exposed/unexposed ratio = 2/1); this sample size made it possible to detect significant differences of 40 to 13%, in the prevalence of a positive BHT (security, 95%; statistical power, 80%). Descriptive analyses were performed for all variables. Continuous variables were reported using mean ± standard deviation or median and interquartile range. For dichotomous/categorical variables, absolute numbers and percentages were computed, together with its 95% confidence intervals. Qualitative variable associations were analyzed using the Pearson chi-square test or Fisher exact test. Comparisons for quantitative variables were made with Student's *t* or Mann-Whitney tests as applicable to the verification of normality using the Kolmogorov-Smirnov test. All statistical analyses were performed using SPSS version 19.0. Statistical significance was defined as a *p* value of less than 0.05 in any of the tests.

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki (7th revision), the Spanish regulations on observational studies (Order SAS 3470/2009), and Spanish personal data protection law (Law 15/ 1999). The study protocol was approved by the Ethics Committee of A Coruña, Spain. Parents or legal representatives of all patients gave written informed consent before inclusion, and patients over 12 years old also signed informed assent. All data were anonymized.

Results

Description of the study population

One hundred five patients (71 with CAP and 34 healthy children) from 5 to 15 years of age were enrolled in this study. With regard to healthy children, 1200 surveys were delivered at schools. Eighty-nine parents (7.4%; 95% confidence interval (CI) 5.9%–8.9%) filled out the information sheet and the previous questionnaire. Of these, 51.7% did not meet the inclusion criteria and 10.1% refused to participate. Finally, 34 healthy children met the inclusion criteria and agreed to participate in the study. In the same period, 71 patients with CAP who met the Rome IV criteria for PP-FGIDs, with normal complementary tests and without any specific treatment, underwent BHT for fructose. Characteristics of both groups are reflected in Table 1. They were comparable, with the exception of the personal background, with more diseases in the CAP children group, and with a predominance of the following diseases: cow's milk protein allergy, gastroenteritis and infection by *Helicobacter pylori* as abdominal diseases, and asthma as other diseases.

Description of malabsorption results

Results of BHT for fructose in both populations are represented in Fig. 1. H_2 levels in BHT for fructose were indicative of malabsorption in 46.7% of patients (95%CI 36.6%–56.7%); 20/34 of healthy children, 58.8% (95%CI 40.8%–76.8%); and 29/71 of children with CAP, 40.8% (95%CI 28.7%–53.0%), removing those who had bacterial overgrowth. The results obtained for H_2 and/or CH_4 are shown in Table 2, and levels of hydrogen and methane of the participants and the trend of elevations in Figs. 2 and 3. Maximum values of H_2 and CH_4 obtained in healthy children and children with CAP with positive BHT were compared through 60- and 120-min measurements, by selecting the maximum numerical value of each patient, obtaining greater values in healthy children, the only group with statistically significant results (see Table 3). Data showed a predominance of female sex among patients with a positive result in both groups, 65.4% (95%CI 45.2%–85.6%) in healthy children and 63.6% (95%CI 45.7%–81.6%) in children with CAP. With regard to age, a higher percentage of children under 10 years with positive BHT (60.6%) was obtained in the group of patients with CAP.

As mentioned above, the gas analyzer used for the study measured values both for H_2 and CH_4. Considering both populations, 51 patients -48.6%- were indicative of malabsorption for CH_4 in addition to H_2 (20/34 of healthy children and 31/71 of children with CAP; Table 2). Therefore, methane determination allowed at diagnosing malabsorption in 1.9% (95%CI 0.2%–6.7%) of patients with normal hydrogen levels.

Regarding the test duration, six children presenting a negative test at 60 min had a positive test at 120 min; thus, increasing the test duration to 120 min resulted in a profitability of 5.7% (95%CI 0.8%–10.6%). However, 9.5% (95%CI 3.4%–15.6%) of patients who had a positive test at 60 min presented a negative result after 120 min had passed.

Description of bacterial overgrowth results

A total of 7 out of 34 healthy children, 20.6% (95%CI 5.5%–35.6%), and 9 out of 71 children with CAP, 12.7% (95%CI 4.2%–21.1%), had levels of H_2 and/or CH_4 indicative of bacterial overgrowth. Among the 7 children of the first group, all of them had a positive H_2 and/or CH_4 BHT for fructose malabsorption, while in the second group, 2 out of the 9 patients had a positive BHT for H_2 and/or CH_4 at 60 and/or 120 min.

Table 1 Demographic characteristics of healthy children and children with chronic abdominal pain

	Total *n* = 105 (100.0%)	Healthy children *n* = 34 (32.0%)	CAP *n* = 71 (67.0%)	*p*
Age				
Mean ± SD	9.5 ± 2.8	9.5 ± 2.7	9.5 ± 2.8	0.883
Median (IQR)	9.5 (7.9–12.0)	9.0 (7.0–11.5)	10.0 (7.0–12.0)	
Sex				
Male, *n* (%)	37 (35.2%)	13 (38.2%)	24 (33.8%)	0.656
Personal background				
Abdominal complaints	15 (14.6%)	2 (5.9%)	13 (18.8%)	0.135
Other disease	28 (26.7%)	2 (5.9%)	26 (36.6%)	0.010
Family background				
Abdominal complaints	15 (14.3%)	2 (5.9%)	13 (18.3%)	0.135

CAP, chronic abdominal pain; *SD*, standard deviation

These results showed a higher rate of bacterial overgrowth between healthy children, taking into account that it was associated with a positive BHT.

Description of dietary response in the CAP patient group

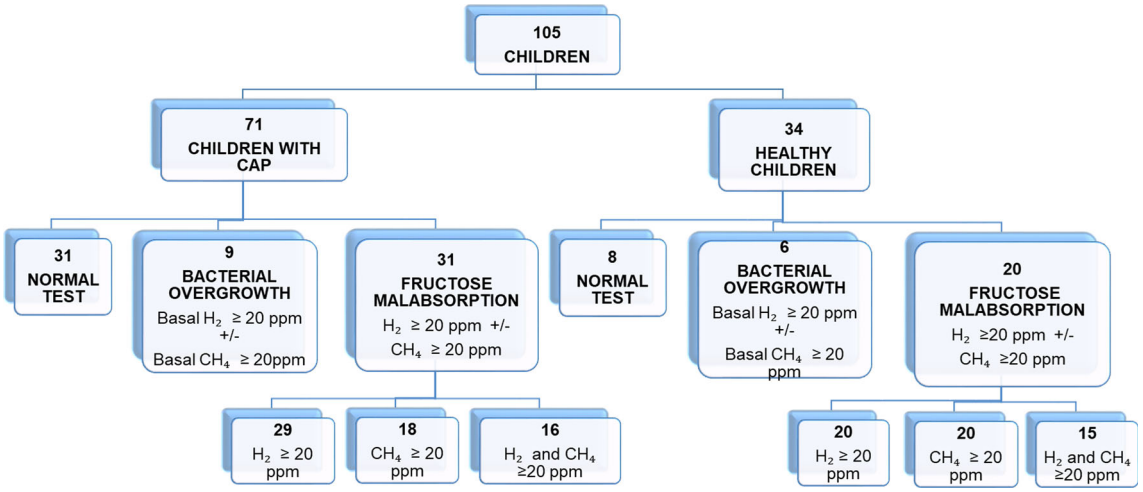
The entire 31 patients with a positive BHT for fructose were placed on a low-fructose diet for 2 months. In 29 of these, it was possible to evaluate the response to the diet. Two patients (6.9%) did not follow the recommended diet, six patients (20.7%, 95%CI 8.0%–39.7%) had a low response to dietary treatment, four patients (13.8%, 95%CI 3.9%–31.6%) had a good response, and in 17 of them (58.6%, 95%CI 39.0%–78.3%), the response was very good with a complete resolution of symptoms with the diet.

Discussion

This study analyzed fructose malabsorption in an asymptomatic pediatric population and in children with CAP. At the same time, it studied the clinical response to a low-fructose diet in children with CAP. PP-FGIDs are high-prevalence disorders in children with an impact in the quality of personal and family life [23]. The increased amount of carbohydrates consumed in the diet in the form of fruit juices [2, 16] led to the study of fructose malabsorption in CAP. Although there are some studies that link fructose malabsorption with abdominal pain [6, 29], there are many unknown questions, including the degree of fructose malabsorption that can be present in healthy children, with very few published studies in healthy population and even less in the pediatric field [28].

There are other studies that measure fructose malabsorption in pediatric CAP, but this is the largest we know dealing with healthy children [18]. In this sense, Kneepkens et al. [18], carried out a study that included 31 children (6 with gastrointestinal symptoms). Data from this study showed a higher prevalence of fructose malabsorption in healthy children (76.0%) than in children with abdominal symptoms (50.0%). Our study showed very similar results, with a positive test in 58.8% of healthy children and in 43.7% of children with CAP. The presence of previously published studies with similar results to those presented in this study raises several issues concerning this diagnostic test. BHT represents in clinical practice the reference tool in the diagnosis of fructose malabsorption. This test is based on the concept that in the human body, H_2 is only produced by intestinal bacteria. Part of the gas produced by colonic bacteria fermentation diffuses into the blood and is rapidly excreted through breath, where it can be quantified [8]. However, there is no agreement on the methodological aspects of fructose BHT as no sufficient scientific data is still available [3, 13, 30]. Several studies have been recently carried out with not very clarifying results. In this sense, Wilder-Smith et al. studied the repeatability and effect of blinding of BHT, with acceptable results for fructose intolerance (patients developing symptoms during BTH) with inadequate repeatability for fructose malabsorption [30]. On the other hand, Helwig et al. analyzed the predictive value of BHT in the diagnosis of fructose malabsorption, concluding that its value as a predictive test for the fructose-free diet outcomes is questionable [13].

The dosage of fructose used in this test is one of the most important parameters presenting variations in the reviewed studies, as the capacity of the human small intestine to absorb fructose is unclear. In the aforementioned study carried out by Kneepkens et al. [21], patients were tested for fructose malabsorption by BHT using a standardized dose of 2 g/kg body weight (maximum 50 g), a greater dose than the one used in the present study, obtaining similar results of positivity. We can also observe similar results in the study carried out by Hoekstra et al.



CAP, chronic abdominal pain; H_2, hydrogen; CH_4, methane

Fig. 1 Flowchart with patients included and breath hydrogen test results

[1], where they give a dose of 1 g/kg, and 43.8% of healthy children showed a positive test. Other authors suggest that to determine whether a child has an abnormally low absorption capacity, the appropriate fructose dose should be smaller, potentially 0.5 g/kg to a maximum of 10 or 15 g [17]. In our study, a dose of fructose of 1 g/kg (maximum 50 g) was used, since it was the dose used in our daily clinical practice, and it was described in many previously published works [13, 16, 29]. However, after a bibliographic review, we expect that prospective research must be done with a lower dose of fructose (0.5 g/kg, for example) to increase the predictive ability of the test [16]. With regard to the maximum dose, it should not be greater than 25 g, as it is the dose that healthy adults seem to have the capacity to absorb. This was evaluated in two prospective studies carried out by Rao et al. and Frieling et al., performing BHT after the oral intake of 50, 25, and 15 g of fructose. Similar results were obtained in both studies, with a positive test in only 10 and 12.5% of subjects, respectively, after 25 g load, while around 80% tested positive with 50 g [7, 24], although other authors also use 50 g (references) as a maximum dose [13, 29].

Considering cut-off values, there are no standardized diagnostic cut-off values indicative of incomplete absorption of fructose. The most popular values in literature are 10 ppm and 20 ppm. The value chosen in our study is 20 ppm, which correlates with the majority of authors [16, 19].

Another methodological aspect that differs between centers is the type of analyzer, depending on whether they analyze only H_2 in exhaled air or both H_2 and CH_4. In this study, the Quintron Breath Microlyzer™ SC that measures H_2 and CH_4 was used. Data obtained in this study indicated that the determination of CH_4 values in addition to H_2 increases the diagnostic percentage by 1.9%. This could be because there are humans, up to 28%, who have a predominance of bacteria that do not produce H_2 [9]. Recent studies recommend quantification of CH_4 associated with H_2 in order to increase the predictive ability of the test [27].

With respect to the duration of the test, there were also variations depending on the different studies. In the review article published by Gibson et al. [9], they mention studies in different countries with highly variable time duration, between 0.75 and 6 h but with standard timing of sample collection of 3 hours. Results published by Rao et al. showed that the increase in H_2 and CH_4 in healthy subjects typically occurred within 60 min, with a mean time for reaching a peak H_2 or CH_4 concentration of 77 min [24]. In our study, the test duration was of 2 h, similar to the normal small intestinal transit time, although if patients with PP-FGID had a slower

Table 2 Results of breath hydrogen test for fructose

	Total	Healthy children	CAP	*p*
Positive H_2 test	49/105 (46.7%)	20/34 (58.8%)	29/71 (40.8%)	0.180
Positive CH_4 test	38/105 (36.2%)	20/34 (58.8%)	18/71 (25.4%)	*0.002*
Positive H_2 and/or CH_4 test	51/105 (48.6%)	20/34 (58.8%)	31/71 (43.7%)	0.146

BHT, breath hydrogen test; *CAP*, chronic abdominal pain

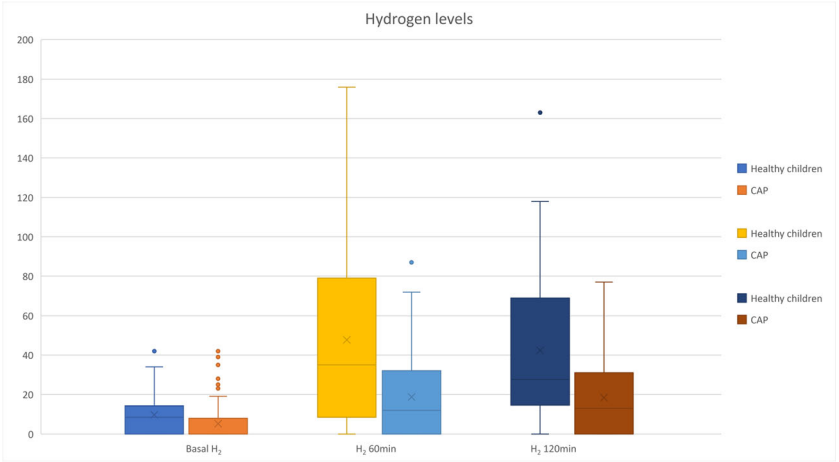


Fig. 2 Levels of hydrogen of participants and the trend of elevations

small intestinal transit, this could explain the lower percentage of abnormal results in the study group. To our knowledge, there are no studies that show that increasing the time duration longer than 2 hours increases the predictive ability of the test.

Children between 5 and 15 years old were included. Many studies performed in the pediatric population stratified by age groups show that the younger the age, the worse the absorption of fructose [5]. A study carried out in 2003–2008 [17], involving 1093 healthy subjects, revealed, using breath hydrogen levels, that fructose absorption capacity increases from birth until the age of 10, without any difference in 10 to 79 year-old patients. In the present study, we divided patients into two groups of age, depending on the fact of being younger or older than 10 years. The distribution by age showed that children younger than 10 years with CAP had 60.6% of positive results, and healthy children obtained 48.0%.

Patients with a positive BHT were strongly recommended to follow a low-fructose diet for at least 2 months. The response to dietary treatment was good or very good in 72.4% of the cases. These results are consistent with those published by Escobar et al. [6], where authors studied 222 children with CAP, and 93 of 121 (76.9%) with fructose malabsorption had a resolution of symptoms with a low-fructose diet [6]. Our study obtained similar results; however, healthy population revealed that BHT does not demonstrate more malabsorption in children with CAP than in the asymptomatic population. The fact that children with PP-FGIDs had a satisfactory response to a low-fructose diet may indicate that, although patients of this group did not have a higher percentage of malabsorption, they had greater fructose intolerance. In this sense, Hammer et al., using a sensitive symptom scoring system, found out that fructose malabsorption in children was completely unrelated to symptoms, whereas fructose sensitivity elicited during the challenge reliably correlated with ongoing bowel complaints [12]. This could be due to an increased visceral hypersensitivity or hyperalgesia in the population with CAP. This visceral hyperalgesia is one of the physiopathological factors involved in PP-FGIDs [4]. Other alternative mechanisms that could be driving symptoms include the excess of dietary intake of fructose exceeding the absorptive capacity mentioned above, and increased mucosal proinflammatory cytokines induced as a consequence of a preceding

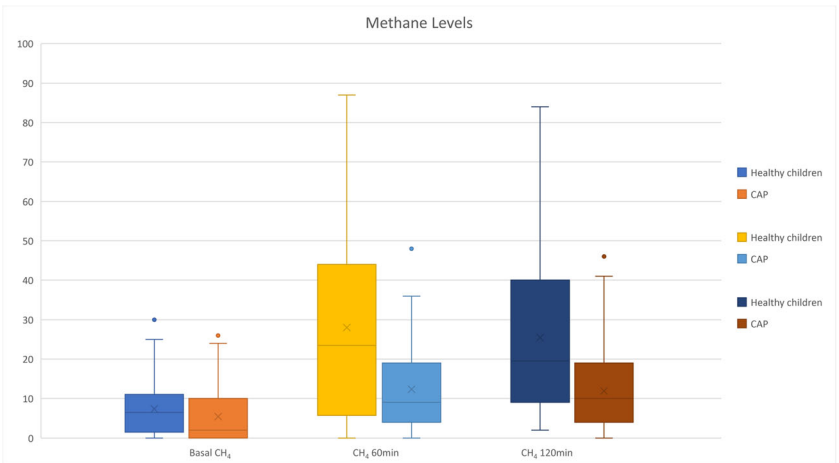


Fig. 3 Levels of methane of participants and the trend of elevations

Table 3 Maximum values of H_2 and CH_4 of patients with positive breath hydrogen test in healthy children and children with chronic abdominal pain

Variable	Healthy children	CAP	*p*
Maximum value H_2 test (ppm)			
Median (IQR)	35 (16.0–48.5)	20 (14.0–29.0)	**0.025**
Maximum value CH_4 test (ppm)			
Median (IQR)	41 (34.0–54.0)	24 (22.0–32.0)	**0.030**

BHT, breath hydrogen test; *CAP*, chronic abdominal pain; *IQR*, interquartile range; *ppm*, parts per million

acute infectious gastroenteritis [25], and demonstrated alterations in gut microbiome [20, 22]. On the other hand, the positive response observed may not be exclusively secondary to an avoidance of pure fructose, because rich foods in other FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) are also restricted by this diet, and the low-FODMAP diet seems to be effective in some children with PP-FGIDs [10]. Maagaard et al. showed a significant reduction of symptoms in patients with irritable bowel syndrome, with a percentage of satisfaction of 70% with a low diet in FODMAPs [10]. Finally, the clinical course in children with CAP shows that many improve over time with some prognosis factors involved regardless of their diet [10].

There are several limitations to this study. First is the difficulties presented to recruit healthy children for the study, since the study was carried out in a specific population, which may not be representative of the general population. In fact, 1200 information sheets were distributed and we only had an answer in 89 cases. Another concern is that we were not able to randomize or blind positive BHT patients into a low-fructose diet arm and an arm without dietary modification. In this sense, we were unable to control for any potential placebo effect, and also, children with CAP without positive BHT were not intervened with a low-fructose diet to know the response.

The present study is a prospective study that compares two pediatric populations. It is not the first study to measure fructose malabsorption in the pediatric population [6, 11] but it includes healthy population. As mentioned above, the gas analyzer used for the study measured values both for H_2 and CH_4; this can be an advantage when comparing with the results obtained in other studies that do not include it, since there is a percentage of the population that produces methane [9].

In conclusion, in the present study, pediatric patients with CAP showed fructose malabsorption in a percentage not greater than healthy asymptomatic children. Although low-fructose diet seems to be an effective treatment to improve symptoms in some children with positive BHT for fructose, many other reasons could explain this improvement. Standardized test conditions need to be studied in order to know if this test for diagnosing fructose malabsorption in children with CAP can be used in clinical practices.

Authors' contributions Oihana Martinez Azcona: acquisition, analysis and interpretation of data, redaction of the manuscript.

Ana Moreno Álvarez: design of the work, acquisition and interpretation of data, redaction and review of the manuscript.

Teresa Seoane Pillado: design of the work, statistical analysis, review of the manuscript.

Inés Niño Grueiro: acquisition and analysis of data, review of the manuscript.

Ana Ramiro Comesaña: acquisition and analysis of data, review of the manuscript.

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Marta Pérez Domínguez: acquisition and analysis of data, review of the manuscript.

Alfonso Solar Boga: design of the work, redaction and review of the manuscript.

Rosaura Leis Trabazo: design of the work, review of the manuscript.

Compliance with ethical standards The study was conducted in accordance with the Declaration of Helsinki (7th revision), the Spanish regulations on observational studies (Order SAS 3470/2009), and Spanish personal data protection law (Law 15/ 1999). The study protocol was approved by the Ethics Committee of A Coruña, Spain. Parents or legal representatives of all patients gave written informed consent before inclusion, and patients over 12 years old also signed informed assent. All data were anonymized.

Conflict of interest The authors declare that they have no conflict of interest.

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