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ORIGINAL ARTICLE

Gastroenterology

Assessment of dietary interventions including low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet as management for fructose intolerance

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Abstract

Objectives: Abdominal pain remains one of the most common referral reasons to pediatric gastroenterology. Dietary intolerances are often considered but due to various factors are hardly pursued. We observed that diet review in large number of children with abdominal pain was high in sugary foods which led to food intolerance investigation and dietary intervention.

Methods: A retrospective review was conducted of patients presenting with abdominal pain, diarrhea, or vomiting and negative GI evaluation, who underwent fructose breath testing. Patients younger than 20 years old who were seen between June 1, 2018 and March 1, 2021 were included. Statistical analysis was performed in R.

Results: There were 110 pediatric patients during the study period who underwent fructose breath testing, with 31% male and 69% female. The average age was 12.14 ± 4.01 years, and the average BMI was 21.21 ± 6.12. Abdominal pain was the most common presenting symptom (74.5%) followed by diarrhea and vomiting. Seventy-seven patients (70%) had a positive fructose breath test and were diagnosed with dietary intolerance to fructose. The 56 (67.5%) of those patients experienced symptoms during the breath test. Forty-three patients improved with dietary intervention. Twenty-seven on low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet and 16 on other diets.

Conclusions: Based on analysis of our cohort of children with abdominal pain and high incidence of fructose intolerance as well as improvement in symptoms, following dietary changes, this condition should be considered and treated. Further investigation is needed to improve diagnostic testing but also into understanding mechanisms behind symptom presentation in this population.

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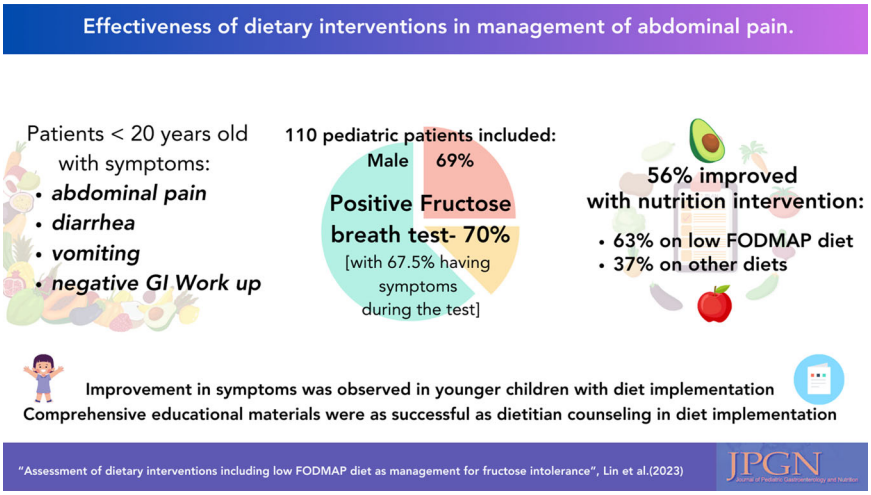

KEYWORDS

abdominal pain, diet, fructose intolerance, low FODMAP

1 | INTRODUCTION

Abdominal pain remains one of the top reasons for pediatric gastroenterology referrals. Although, the differential is broad, most common screening studies may not yield a diagnosis. Dietary contribution to symptoms is not always assessed and nutrition approaches are not commonly utilized. Dietary fructose intolerance diagnosed via breath test has been implicated in chronic abdominal pain.[1–3] The low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet has been commonly utilized to address symptoms of chronic abdominal pain[4,5] and specifically in dietary fructose intolerance with an elimination and reintroduction phase.[6] However, the low FODMAP diet comes with a concern of prebiotic source restriction which may lead to downstream microbiome modifications. Prebiotics are a type of fiber rich, non-digestible food components that support beneficial bacterial growth in the intestines and are found in fructooligosaccharides and galactooligosaccharides.[7] The significant increase in simple sugar consumption among children in the United States, primarily through sugar sweetened beverages and sugar additives (mostly in the form of high fructose corn syrup), accounts for an estimated 14% of the daily caloric intake. This increase in sugar consumption has resulted in an increased incidence of metabolic dysregulation, leading to risks of obesity, type 2 diabetes and, metabolic dysfunction associated steatotic liver disease.[8] In addition, based on studies on dental caries, the World Health Organization (WHO) recommends limiting the intake of free sugars to <10% of one's total energy intake.[9] Anecdotally, our clinical team has observed simple carbohydrate intolerance in the form of dietary fructose intolerance that presents with abdominal pain, diarrhea, and gassiness. There is currently no good diagnostic testing for fructose intolerance, although fructose hydrogen breath test is the most utilized.

What is Known

- Dietary fructose intolerance is a known contributor to abdominal pain in children.
- Fructose breath test is sometimes utilized to aid the diagnosis.
- Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet has been commonly implemented to improve symptoms.

What is New

- Fructose breath test should be considered if work up for abdominal pain, diarrhea and vomiting does not yield a diagnosis.
- Improvement in symptoms was observed in younger children with diet implementation.
- Comprehensive educational materials are as successful as dietitian counseling in diet implementation.

Fructose is a 6-carbon monosaccharide molecule that is naturally present in a variety of foods. Foods high in fructose include certain fruits, vegetables, and honey. Fructose is also produced enzymatically from corn as high fructose corn syrup (HFCS), which is commonly found as a sweetener in many foods and soft drinks. Based on the United States Department of Agriculture data, HFCS consumption has increased by

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more than 1000% between 1970 and 1990.[10,11] In addition, daily sugar consumption was estimated at 10 g per day in 1800 and is now estimated at 75–100 g per day.[10] Fructose is absorbed via the facilitative transporter GLUT5, and its absorption occurs independently of glucose. The absorption of fructose is a lot slower than that of glucose and galactose but faster than sugar alcohols like sorbitol and xylitol. The small intestine has limited capacity to absorb fructose with an estimated absorption of 20–50 g a day. With increased fructose consumption, there is an increased amount of fructose and other sugars, that will be unabsorbed.[12]

Unabsorbed fructose attracts water to the small intestine and is then quickly transported to the colon where it is metabolized by bacteria. This bacterial metabolism of fructose in the colon results in production of gases including H_2, CO_2, and CH4, as well as likely a large number of undefined metabolites. The absorption and malabsorption complexity of fructose is quite individual dependent. Factors that impact fructose absorption include the intestinal absorptive surface, processing by intestinal bacteria, age, and gender. A mouse model of fructose malabsorption showed microbiota dependent metabolism,[13] highlighting the interaction between the intestinal microbiome and food one consumes. A previous study showed variable success of dietary interventions in children with abdominal pain, with the prevalence of simple carbohydrate malabsorption in this population reported to be high.[3] Unfortunately, dietary intolerances to fructose, and also FODMAPs are still poorly recognized[14] and there are limited studies on the prevalence in children. These intolerances frequently lead to unexplained gastrointestinal (GI) symptoms such as abdominal pain, bloating, gas, flatulence, abdominal distension, nausea, and diarrhea. The exact underlying mechanism of dietary intolerances are still being investigated. However, it does not appear that the absorptive capacity of the small intestine is affected in dietary intolerance of fructose, as a study by Wilder-Smith et al. (2014) did not show a difference in expression of GLUT-2/-5 transporters responsible for fructose absorption in patients with dietary fructose intolerance compared to controls.[15] It is postulated that GI symptoms are a result of intestinal microbiome alteration, but these studies are inconclusive with few on the pediatric population.[16–19]

As general GI symptoms can be seen with dietary fructose intolerance, the presence of these symptoms in absence of other common pediatric GI conditions should warrant clinical suspicion and diagnostic work-up for dietary fructose intolerance. The challenge is that healthy children and children with abdominal pain appear to have the same degree of dietary fructose intolerance[20] so relying on GI symptomatology alone may not sufficiently identify dietary fructose intolerance. A low FODMAP diet consisting of an elimination and reintroduction phase has been utilized to alleviate symptoms in children with functional GI conditions.[6] The objective of this retrospective review is to describe the pediatric population at our institution who have dietary fructose intolerance based on a positive fructose breath test and to assess the effectiveness of dietary interventions, including the low FODMAP diet.

2 | METHODS

A retrospective review was conducted of patients presenting with abdominal pain, diarrhea, or vomiting as their primary symptom with an unremarkable GI evaluation who underwent fructose breath testing at the Pediatric Gastroenterology satellite clinic of Doernbecher Children's Hospital, Oregon Health & Science University in Eugene, Oregon. Patients under the age of 20 years old who were seen between June 1, 2018 and March 1, 2021 were included in the study. Data was collected on the initial GI evaluation before referral for a fructose breath test. This study was approved by OHSU IRB.

The fructose breath test was performed based on previously published guidelines[2,3,21] utilizing Quintron which measures production of hydrogen and methane gases.[1] Briefly, patients were instructed to follow a blend diet consisting of water, eggs, rice, chicken, fish, turkey, and white bread, with limited spices (salt and pepper only) for 12 h and fasting for 12 h before the test. A 1 g/kg of fructose (maximum 25 g) dissolved in water was given orally with breath sample collected before fructose ingestion and at 30, 60, 90 and 120 min. A positive fructose breath test result was defined a greater than 20 ppm difference in hydrogen level between baseline and either the first or second measurement. For patients with methanogenic flora presence, a difference of 12 pm or greater in methane level between baseline and either the first or second measurement was considered a positive fructose breath test. Patients with a positive fructose breath test were referred to our GI dietician and recommended to follow a low FODMAP diet trial. The dietician had prior training and clinical experience in counseling on the low FODMAP diet implementation as well as in other diets such as the specific carbohydrate diet among others. A chart review was conducted to determine if a patient was able to be seen by the dietician (insurance constraints might have limited access), if the family reported successfully implementing of the low FODMAP diet, and if there was symptom resolution. For patients who were unable to follow the low FODMAP diet or who experienced persistence of symptoms, alternative dietary counseling was offered.

Internal Review Board (OHSU IRB) approval was obtained for the study. Statistical analysis was

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performed using R (version 4.2.1). Categorical variables (sex and symptoms: abdominal pain, diarrhea, vomiting, cramping, nausea, and gas) were described using number and percentage. Continuous variables (age in years, BMI) were described with mean and standard deviation. A chi square test was performed comparing clinical outcomes between patients who received dietary counseling and those who did not. Multivariate logistic regression was performed with hydrogen breath test result as the outcome variable with sex, age, BMI, abdominal pain, diarrhea, vomiting, cramping, and nausea as covariates. A separate multivariate logistic regression was performed using patients with positive hydrogen breath test with response to dietary intervention as the outcome variable and sex, age, BMI, abdominal pain, diarrhea, vomiting, cramping, and nausea as covariates.

3 | RESULTS

There were 110 pediatric patients during the study period with a negative GI work-up who underwent fructose breath testing, with 31% male and 69% female. The 95 out of 110 were non-Hispanic (86%), 12 Hispanic (11%) and 3 did not answer ethnicity question. The average age was 12.14 ± 4.01 years (range 3–19 years), and the average BMI was 21.21 ± 6.12 (range 13.52–41.51). Abdominal pain was by far the most common presenting symptom for those who underwent fructose breath testing (74.5%) followed by diarrhea and vomiting (Table 1). The diagnostic workup was based on the patient's presenting symptom, history, and clinical exam. As an example, the diagnostic workup for abdominal pain most commonly included a fecal calprotectin, celiac antibodies, and inflammatory markers (Table 2).

An EGD was performed in 57% of patients, which included disaccharidase testing in 48% of cases. Eight subjects were found to have low lactase level, however, did not improve on lactose free diet alone. Eighteen subjects were found to have elevated calprotectin with 4 over 150. Twenty-eight underwent a colonoscopy with normal results.

TABLE 1 Presenting symptoms of pediatric patients ($n = 110$) who underwent fructose breath testing.

Symptom	*n* (%) (*n*)
Abdominal pain	82 (74.5%)
Diarrhea	27 (24.5%)
Vomiting	21 (19.1%)
Nausea	19 (17.3%)
Gas	5 (4.5%)
Cramping	4 (3.6%)
More than one symptom	48 (44%)

TABLE 2 Workup for abdominal pain in pediatric patients ($n = 110$) who underwent fructose breath testing.

Test	*n* (%)
Fecal calprotectin	95 (86%)
Celiac antibodies	92 (84%)
ESR	85 (77%)
CRP	81 (74%)
H. Pylori (by fecal antigen)	57 (52%)
EGD	63 (57%)
Disaccharidases	53 (48%)
Colonoscopy	28 (25%)

Abbreviations: CRP, C-reactive protein; EGD, Esogastroduodenal endoscopy; ESR, Erythrocyte sedimentation rate.

A total of 77 patients (70%) had a positive fructose breath test and were diagnosed with dietary intolerance to fructose. There were no patients with methane level changes during the fructose breath test. Of the patients with a positive fructose breath test, 56 (67.5%) experienced symptoms during the breath test, with the majority having the same symptoms as at initial presentation. Three patients also underwent a glucose breath test which was negative.

All patients with a positive fructose breath test were referred to a dietician, but only 44 (57%) were seen by a dietitian. For patients who worked with a dietician, 32 patients (73%) reported improvement of their symptoms with dietary changes compared to 2 (5%) who did not experience improvement of symptoms, with 5 (11%) being unable to follow through with the proposed dietary changes and 5 lost to follow up (Figure 1). Dietitian met with patient and family following the breath test for two visits with second visit at 6-12 weeks after the first. Symptom assessment and diet recall was performed at that time. Pre low FODMAP implementation, diet commonly consisted of: sugary cereals, juice, soda, sweet pastries, sweetened milk, ultra-processed foods, fruits, legumes, pastas. Three patients were on gluten free diet before breath test and one on a lactose and gluten free diet. Low FODMAP diet implementation followed a 2-week all high FODMAP food eliminations, followed by one high FODMAP food reintroduction at a time for 6-8 weeks. Patients were instructed to monitor symptoms during reintroduction phase. While all patients were initially started on a low FODMAP diet, additional dietary changes such as a low fructose diet were recommended by the dietician if their symptoms persisted or if patients had trouble adhering to the low FODMAP diet. Of the 32 patients who experienced improvement of symptoms, 21 (66%) experienced improvement on a low FODMAP diet. Reasons for

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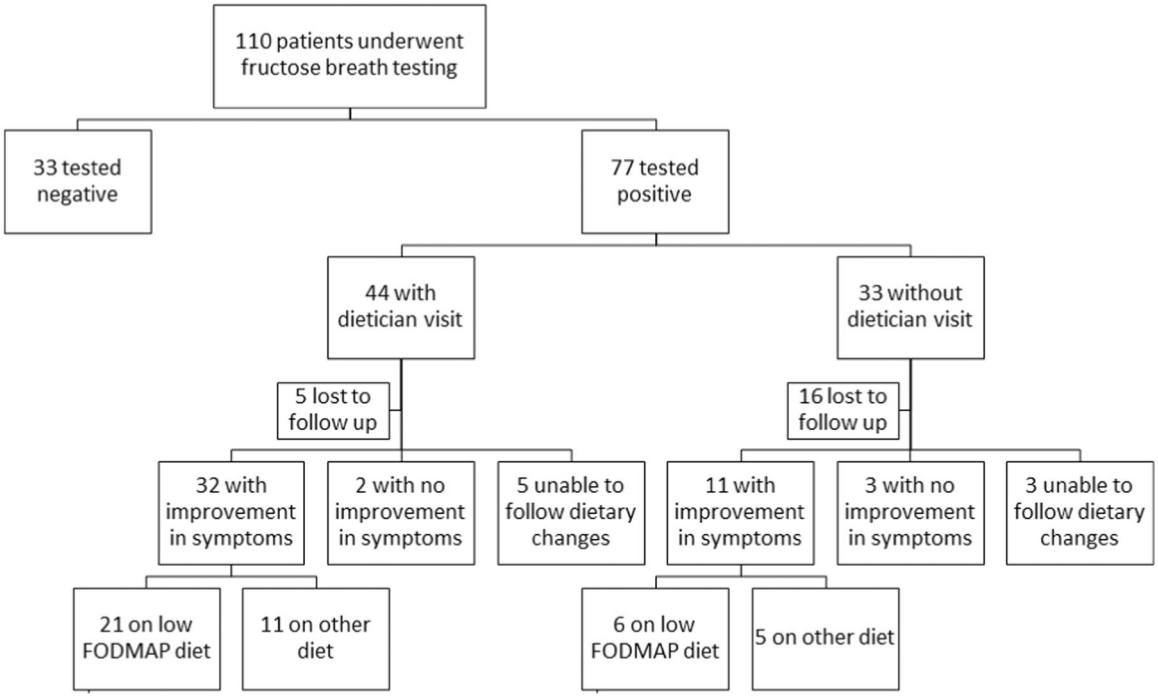

FIGURE 1 Dietitian visit and improvement in symptoms in pediatric patients with fructose intolerance. FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols.

low FODMAP diet noncompliance included: autism with food selectiveness, avoidant restrictive eating disorder, low weight, or poor weight gain where diet restriction was not recommended, inability to implement full diet. In those instances, diets were modified and included: low fructose (limited foods with high fructose corn syrup, sodas, juices, selected high fructose fruits and vegetables), low sugar (total, daily sugar intake limited to 25 g); two patients with family history of Inflammatory Bowel Disease chose to follow the specific carbohydrate diet with improvement.

Thirty-three patients who were referred but unable to see a dietician, were provided with patient education materials on the low FODMAP diet or other dietary changes to try without specific dietician guidance. Only 17 patients had follow-up in clinic to assess the impact and efficacy of dietary changes with 11 (65%) reporting improvement of their symptoms compared to three patients reporting no improvement, and three others reporting being unable to follow the recommended dietary changes.

3.1 | Statistical analysis

There was no significant difference in symptom improvement with dietary changes whether the patient had formal dietician counseling or not. No association was found between age, sex, BMI, or presenting symptoms and a positive fructose breath test. For patients with a positive fructose breath test who initiated dietary changes, younger age was associated with improvement of symptoms following dietary intervention (odds ratio = 0.72, 95% confidence interval [0.52, 0.89]).

4 | DISCUSSION

We present a retrospective single center review of children who presented with common GI symptoms who underwent breath testing for suspected dietary fructose intolerance and subsequently received low FODMAP diet counseling. Abdominal pain, vomiting, and diarrhea are common GI symptoms in pediatrics, each with a broad spectrum of potential etiologies. For example, the differential diagnosis for abdominal pain in children is broad and encompasses infectious, inflammatory, structural, malabsorptive, and functional etiologies, among others. For children with functional GI disorders such as disorders of the gut-brain interaction, the challenge is finding a balance in necessary diagnostic testing based on the history and physical. In addition, as dietary intolerances can contribute to these symptoms, a breath test may be considered as part of the diagnostic work-up.[22]

In our retrospective study, over a 3-year period between June 1, 2018 and March 1, 2021 there were 110 pediatric patients with GI symptoms who underwent testing for fructose intolerance at our institution. The majority of patients who were tested presented with abdominal pain and many were experiencing multiple GI symptoms. The breath test was ordered

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after an initial negative work-up as determined by the primary GI provider. For example, the initial workup for abdominal pain included testing for inflammatory and malabsorptive issues (Table 2) to assess for chronic conditions such as inflammatory bowel disease or celiac disease which require specific interventions. Additional diagnostic testing was based on the patient's symptoms such as assessing for infectious etiologies or obtaining an upper endoscopy to assess for ulcers or anatomic etiologies. In our study, of the patients who underwent fructose breath testing, 70% had positive tests with most experiencing their presenting GI symptoms, which suggests that dietary intolerances should be considered in patients who have an initial negative diagnostic work-up as clinically indicated. Previous studies have varied in reports of symptom correlation with a positive fructose breath test with younger age being associated with fructose malabsorption.[23,24] In our patient population, there was no association between age, BMI, or presence of symptoms with a positive fructose breath test. However, age of patient was associated with an improvement in symptoms following dietary intervention in patients with a positive fructose breath test. It is possible that younger children are more likely to follow dietary regimens set for by their parents, thus leading to symptomatic improvement.

The low FODMAP diet approach is nutritionally adequate and multiple studies have reported its efficacy in improving functional bowel symptoms.[16,25–28] However, the low FODMAP diet can be hard to follow, and patients may intentionally ingest offensive foods even with an understanding of subsequent symptoms.[25] In our study, there were multiple reasons why patients did not try or were non-adherent to a low FODMAP diet, most commonly including difficulties with tolerance and adherence. The efficacy of low FODMAP diet in fructose intolerance is based on the assumption that the intestinal microbiome contributes to symptoms in fructose intolerance. Small bacterial communities are usually present in the small intestine with the bulk of the microbiome located in the colon. The implication is that increased consumption of sugars including fructose, has altered the carbohydrate sources available to the microbiome, leading to microbe adaptation through gene modifications with subsequent metabolic impact. However, besides a proven link between dietary trehalose promoting survival of Clostridium difficile,[29] the exact downstream effect of those changes in human metabolism is not fully understood. Animal studies suggest that dysbiosis induced by high fructose diet leads to increase in intestinal permeability, leakage of bacterial endotoxins and induction of inflammation through toll-like receptors.[5,30]

The majority of our patients with dietary fructose intolerance who were started on and adherent to dietary changes experienced improvement or resolution of symptoms with most patients being on a low FODMAP diet. Given the nuances of the FODMAP diet and challenges with adherence, our hypothesis was that formal counseling by a dietician would be beneficial for patients, but there was no significant difference in symptom improvement if a patient was seen by a dietician compared to following patient education materials. It is possible that the patients and families were quite motivated to follow dietary changes, thus making it more likely for them to commit to a specific diet. In addition, perhaps the dietary education materials given to patients who weren't seen by a dietician were quite comprehensive as these were the same handouts provided by the dietician. It is also possible that other than low FODMAP diet options would not have been explored without dietitian's guidance.

Limitations of the study include generalizability of the results as this is a retrospective review from a single center. In addition, while most patients with a positive fructose breath test experienced their presenting symptoms, it is possible that the patient's GI symptoms are not primarily attributed to dietary fructose intolerance. Lastly, sample size was also limited by follow-up data available as 21 patients who started dietary therapy did not have a follow-up visit to allow for assessment of dietary therapy impact.

5 | CONCLUSION

In conclusion, patients with dietary fructose intolerance can experience improvement in their symptoms with dietary therapies and specifically with the low FODMAP diet. Despite the diet specifics which can make adherence difficult, the low FODMAP diet was able to be successfully followed by the majority of our patients, both with and without the guidance of a dietician. While a formal counseling by a dietician seems preferable, with dedicated GI provider patient education along with comprehensive diet educational materials, it is possible for families to successfully follow these complex diets.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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