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Update on Dietary Management of Childhood Functional Abdominal Pain Disorders

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INTRODUCTION

Functional bowel disorders (also termed disorders of the brain-gut axis) affect up to 20% of the world's adult and pediatric population.¹ Based on the latest Rome IV classification, pediatric functional bowel disorders associated with abdominal pain include: functional dyspepsia (which may be associated with postprandial fullness, early satiation, epigastric pain); irritable bowel syndrome (IBS) in which the abdominal pain is associated with defecation and/or changes in frequency of stool or stool form; abdominal migraine; and functional abdominal pain not otherwise specified.¹ Children with these disorders (as compared to healthy controls) have a decreased overall quality of life.²

Functional bowel disorder etiology is attributed to several potential factors. These may include: early life stress; psychosocial distress (e.g. somatization); post-infectious physiology; low-grade gut inflammation; gut microbiome abnormalities (dysbiosis); genetics; visceral hypersensitivity, and diet.³ Diet plays a significant role in the majority of children with functional bowel disorders as up to 93% identify at least one food and/or food type as being associated with a worsening in gastrointestinal symptoms.^{4–6} In adolescents with IBS, gastrointestinal symptoms associated with diet occurred more than three days per week.⁶ Subjects with functional bowel disorders (as compared to healthy controls) avoid foods more frequently and self-implement additional dietary strategies including modification (e.g. removing ingredients) of the foods they eat.^{4–6}

Despite the common clinical experience of diet being associated with worsening gastrointestinal symptoms, there are several challenges. One clinical challenge is that children with functional bowel disorders may perceive a wide variety of foods as being potential culprits; however, they do not uniformly identify the same food culprits (Table 1). In one study of children with IBS, the most frequently identified food culprit (dairy) was identified by only approximately 1/3 of the subjects.⁵ This finding is not unique to children with functional bowel disorders as adults with IBS also identify a wide variety of potential culprit foods and do not consistently identify a single food or food type as being a culprit.⁷ An additional clinical challenge relates to strength of the association of a potential food culprit and subsequent symptom generation. When asked to rate symptom correlation (rarely, sometimes, often, always) when eating a presumed symptom inducing food, children

with functional bowel disorders do not consistently identify the same foods as either often or always causing their gastrointestinal symptoms.⁴ This lack of absolute association with symptoms with perceived culprit foods may explain the high percentage of children with functional bowel disorders consuming a potential culprit food based on 24 hour dietary recall.⁴

Despite these clinical challenges, dietary intervention studies in children with functional bowel disorders have demonstrated efficacy (see below).

Carbohydrate Malabsorption

Malabsorption of individual carbohydrates (such as lactose) have been proposed to worsen gastrointestinal symptoms in children with abdominal pain related functional bowel disorders for several decades.^{8,9} More recently, potential carbohydrates which may be malabsorbed and exacerbate gastrointestinal symptoms have been grouped together. Investigators at Monash University in Australia termed such carbohydrates fermentable oligosaccharides disaccharides monosaccharides and polyols (**FODMAP**). FODMAP carbohydrates traditionally include lactose, fructose, galactans, fructans, and polyols. Common sources of FODMAP carbohydrates, their general structure, and factors related to their propensity for malabsorption may be found in Table 2.

One randomized, double-blind, placebo-controlled trial in adults with IBS found significantly higher symptom severity scores with fructose, fructans, or a combination of fructose and fructans the two versus glucose (placebo).¹⁰ A double-blind placebo controlled crossover trial identified a subset of children with IBS who were particularly sensitive (increase abdominal pain frequency) when challenged with fructans.¹¹

Physiologic Effects of Malabsorbed Carbohydrates (Figure 1)—Malabsorbed carbohydrates have a direct physiologic effect on the gastrointestinal tract; these effects include both increased osmotic activity (particularly in the small bowel) and fermentation with gas production.¹² These physiologic effects subsequently lead to gut luminal distention. In those with functional bowel disorders, this luminal distention may lead to symptoms such as abdominal pain, bloating, flatus, and changes in bowel habits.

Though FODMAP carbohydrates are grouped together, each malabsorbed carbohydrate may have a more pronounced physiologic effect in one area (e.g. small bowel water content) versus another. Using magnetic resonance imaging, fructose has been shown to significantly increase small bowel water content in both healthy adults and those with IBS.^{12,13} The increase in small bowel water content is greater with fructose as compared to fructans. In contrast, fructans increase overall hydrogen production and luminal (particularly colonic) gas distention in both healthy adults and adults with IBS. This gas production effect is higher with fructans as compared to fructose.^{12,13} When comparing adults with IBS versus healthy controls, the amount of both small bowel water content increase and colonic distention which occurred did not differ between the two groups.¹³

Other mechanisms, though not well elucidated, may also play a role in carbohydrate malabsorption related exacerbation in those with functional bowel disorders. Fermentation

of carbohydrates by the gut microbiome leads to the creation of several metabolites including short chain fatty acids. Short chain fatty acids may have physiological effects including: alteration of local ion secretion, changes in colonic motility, and activation of colonic mast cells.¹⁴ Mast cells and their mediators (including histamine) have been associated with increased visceral nociception in both adults and children with functional bowel disorders.^{15,16} Potential support for this mechanism can be found in a randomized controlled trial in adults with IBS demonstrating urinary metabolite profiles differed between those who were instructed to follow a low FODMAP diet versus those who were instructed to follow a high FODMAP diet.¹⁷ In those assigned to a low FODMAP diet, the amount of histamine decreased significantly after the dietary intervention.¹⁷ Further studies are needed to investigate additional potential carbohydrate related mechanisms in childhood functional bowel disorders.

Factors related to carbohydrate malabsorption and subsequent gastrointestinal symptom exacerbation—

Several factors may play a role in determining whether a FODMAP carbohydrate will exacerbate symptoms. These include: 1) the amount of carbohydrate ingested; 2) ingestion of the carbohydrate with a meal which in turn affects transit time to the colon; 3) small intestinal enzymatic (e.g. lactase for lactose ingestion) activity; 4) whether the meal contains microorganisms with enzymes capable of breaking down the carbohydrate; 5) colonic microbiome at time of carbohydrate ingestion and subsequent adaptation response to one's diet, and 6) host factors such as the presence or absence of either low-grade gut inflammation and/or visceral hypersensitivity.

Amount of carbohydrate ingested—Though primarily derived from adult studies, data on lactose intolerance has clearly identified a relationship between the amount ingested and subsequent symptom generation. One study in healthy adults with lactose maldigestion challenged the subjects with different lactose amounts (0, 2, 6, 12, and 20 g).¹⁸ The subjects tolerated doses of up to 6 g (representing 120 mL of milk), but symptoms began to emerge at 12 g.¹⁸ Similar findings were noted in adults challenged with increasing quantities of lactose; the severity of symptoms was primarily dependent on the amount of lactose present.¹⁹ However certain individuals with possible functional bowel disorders appeared to be more sensitive.¹⁹ The exact amount of lactose required to induce symptoms in children with functional bowel disorders is unknown.

Beyond lactose the relationship between the amount of carbohydrate ingested and subsequent symptoms has been well established. Increasing amounts of fructose has been shown to worsen gastrointestinal symptoms in children with functional abdominal pain.⁹ Similarly in adults with IBS, increasing the amount of ingested fructose and fructans is associated with more severe gastrointestinal symptoms.¹⁰

Ingestion of the carbohydrate with a meal/ transit time—Ingestion of a potentially malabsorbed carbohydrate with a meal may increase the amount threshold required for symptom induction. One study in adults with lactose intolerance found the dosage threshold prior to symptoms increased up to 18 g of lactose when other nutrients were concomitantly ingested.²⁰ Another study found that the severity of symptoms following lactose ingestion was reduced with consumption of food.²¹ Moreover, based on breath hydrogen production,

lactose given with a meal had more prolonged overall transit time before reaching the colon.
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Meals composed of various carbohydrates may have variable effects on absorption. This has been seen in particular with fructose. Concomitant ingestion of fructose with glucose appears to facilitate fructose absorption through GLUT5.²² However, concomitant ingestion of fructose with sorbitol can worsen overall fructose absorption and decrease the amount of fructose required to cause symptoms.²³ Further studies evaluating meals of various carbohydrate composition in children with functional bowel disorders are needed.

Small intestinal enzyme activity—Small intestinal enzymatic activity is required to hydrolyze certain carbohydrates which are larger than monosaccharides in order to facilitate absorption. For example, lactose is hydrolyzed by the enzyme lactase. Lactase is a β -galactosidase found on the tips of the villi of the small intestine which hydrolyzes lactose into two monosaccharides: galactose and glucose. These monosaccharides are then absorbed by the small intestine.

In humans, lactase activity is at its peak at the time of birth. However, lactase activity begins to decrease in early childhood in approximately 70% of humans so that by adulthood lactase activity is very low or undetectable.²⁴ Approximately 30% of the world's population has lactase persistence whereby lactase activity remains beyond weaning and into adulthood.²⁵ Those with lactase persistence are able to continue to hydrolyze lactose well. Lactase persistence is a genetic trait which has been associated with at least five independent functional single nucleotide variants in a regulatory region upstream of the lactase gene.²⁶ In children undergoing endoscopy, lactase activity and lactase mRNA expression from duodenal biopsies correlated strongly with one of the single nucleotide variant (−13910) genotypes.²⁷

Decreased intestinal enzymatic activity may be involved in the malabsorption of other carbohydrates in those with functional bowel disorders beyond lactose. Sucrose and starch are normally easily hydrolyzed and absorbed in the small intestine through the activity of sucrase-isomaltase and maltase-glucoamylase.²⁸ However, in children with functional abdominal pain disorders undergoing upper endoscopy, small intestinal carbohydrate enzyme deficiencies related to sucrose (sucrase activity) and/or starch (maltase activity) digestion have been identified in 20%.^{29,30} Further studies elucidating the potential role of sucrose and/or starch malabsorption in children with functional bowel disorders are needed.

Similar to lactase deficiency, sucrose/starch small intestinal enzyme deficiencies may have a genetic component. In one adult IBS study, functional variants in the sucrase-isomaltase gene were associated with an increased risk of irritable bowel syndrome.³¹ In a recently published abstract, children with functional bowel disorders (vs. a large population reference database) were found to have an increased prevalence of pathogenic sucrase-isomaltase gene variants.³² Whether these genetic components are associated with sucrose and/or starch malabsorption remains to be determined.

Meal contains microorganisms with enzymes capable of breaking down the carbohydrate—Microorganisms have the capacity to metabolize carbohydrates, and many microorganisms can metabolize carbohydrates which humans cannot.³³ Subjects who were fed dairy-based yogurts with viable microbial cultures containing beta-galactosidase activity (versus pasteurized yogurts) have demonstrated fewer signs of lactose malabsorption.³⁴ A recent systematic review identified eight probiotic strains which have been studied to ameliorate lactose intolerance either alone or within milk-related products.³⁵ Of these *Bifidobacterium animalis* appeared to be the most researched and effective strain.³⁵

Colonic microbiome at time of carbohydrate ingestion and subsequent dietary adaptation—The gut microbiome appears to have a potential role within the paradigm of carbohydrate malabsorption and subsequent development of gastrointestinal symptoms. Within a randomized double blind crossover trial of a low FODMAP vs. traditional American childhood diet in children with IBS, those children who had a 50% decrease in abdominal pain frequency on the low FODMAP diet (Responders) had a different microbiome composition as compared to those who did not achieve this level of improvement.³⁶ Specifically, Responders were enriched in both saccharolytic bacteria (including *Faecalibacterium prausnitzii*, Bacteroides and Ruminococcaceae) and two Kyoto Encyclopedia of Genes and Genomes orthologues related to carbohydrate metabolism.³⁶ Though with mixed results, studies in adults with IBS have also identified microbiome composition as a potential predictor of response to a low FODMAP diet.^{37,38}

Changes in the gut microbiome related to either chronic carbohydrate malabsorption or carbohydrate restriction may also play a role. In a small study of adults with lactose intolerance, lactose supplementation for 10 days both increased fecal microbiome β -galactosidase activity and decreased lactose-related gastrointestinal symptoms.¹⁸ In children and adults with IBS, FODMAP restriction has been found to alter both gut microbiome composition.^{17,39,40} In addition FODMAP restriction alters fecal and urinary metabolite profiles.^{17,39} The relationship of these gut microbiome related changes and relationship to gastrointestinal symptoms remains to be determined.

Host Factors—Host factors may also play a role in symptom generation in those with functional bowel disorders. Adults with lactose intolerance (vs. those who did not develop gastrointestinal symptoms after malabsorbing lactose) had increased low-grade small bowel and colonic inflammation (including increased mast cells).⁴¹ Though an association of carbohydrate intolerance and low-grade gut inflammation has not been made in children, children with IBS (vs. healthy controls) were found to have increased fecal calprotectin (a marker of inflammation).⁴²

Visceral hypersensitivity may also play a role in determining whether a host develops symptoms with carbohydrate malabsorption. Increased visceral hypersensitivity was identified in adults with functional bowel disorders who developed symptoms after ingesting lactose and lactulose.^{41,43} Children with functional bowel disorders may also have increased visceral hypersensitivity.⁴⁴

Carbohydrate Malabsorption Related Therapies in Children with Functional Bowel Disorders—Carbohydrate malabsorption related therapies in subjects with functional bowel disorders often attempt to address one or more of the factors delineated above which are associated with subsequent symptom generation.

Single carbohydrate restriction trials—Though lactose restriction for children with functional bowel disorders may be commonly used in the clinical practice setting, the majority of studies supporting this practice are uncontrolled.⁴⁵ The only two randomized control trials evaluating the need for lactose restriction in children with functional abdominal pain were negative.⁴⁵

In comparison, fructose restriction alone is more strongly supported than for lactose. One prospective randomized controlled trial in children with abdominal pain related functional bowel disorders compared a two week fructose-restricted diet versus no dietary intervention.⁴⁶ Those on the fructose-restricted diet had less severe pain. However, they did not have a decrease in pain frequency. The authors found that the improvement on the restricted fructose diet occurred irrespective of results from fructose hydrogen breath testing.⁴⁶

Low FODMAP Diet—As an alternative strategy to restricting single carbohydrates in children with functional bowel disorders, the entire group of FODMAP carbohydrates may be restricted simultaneously. A restricted (or low) FODMAP diet occurs in three phases: comprehensive FODMAP restriction; FODMAP re-introduction (during which individual FODMAP carbohydrates are used to determine which specific FODMAP carbohydrates are associated with symptoms); and FODMAP diet personalization (during which the subject tailors the low FODMAP diet to primarily avoid the FODMAP triggers that have been previously identified).⁴⁷ Working with a registered dietitian is strongly recommended to help provide appropriate education (e.g. alternatives to FODMAP carbohydrates) and guide personalization of the subject's diet.

Several randomized controlled studies in adults with IBS have demonstrated efficacy of a low FODMAP diet.^{17,40} The studies have included both those which provided the foods to subjects and those which relied on dietitian education to follow the low FODMAP diet. In children with IBS, a randomized, double blind, crossover study found that a low FODMAP diet decreased abdominal pain frequency.³⁶

Selective prebiotic supplementation—In a randomized double-blind multi-site placebo-controlled trial, adults with lactose intolerance were challenged with either a short-chain galacto-oligosaccharide or placebo.⁴⁸ The short-chain galacto-oligosaccharide increased the relative abundance of lactose-fermenting *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus*: This correlated with improved clinical lactose tolerance.⁴⁸ Whether similar strategies can be employed for other malabsorbed carbohydrates remains to be determined.

Enzyme supplementation—Enzyme therapy to help prevent a carbohydrate from being malabsorbed has been trialed for several decades – primarily with lactose. In adults with either lactose intolerance or IBS, addition of exogenous β -galactosidases (from various

microorganisms) to ameliorate lactose intolerance following a lactose challenge has been shown to be successful.^{49,50} Similarly in children with lactose intolerance enrolled in a randomized trial, subjects given lactase (versus placebo) had a decrease in clinical symptoms.⁵¹

Enzyme supplementation has also been employed as a strategy for other malabsorbed carbohydrates. In adults with fructose intolerance, the addition of xylose isomerase (which may convert fructose to glucose) during a fructose challenge both decreased breath hydrogen production and ameliorated symptoms.⁵² In adults with IBS who were sensitive to galactans, full dose (300 galactosidic units) α -galactosidase (versus either half dose or placebo) co-ingestion with a diet high in galactans ameliorated gastrointestinal symptoms.⁵³ Similar enzyme supplementation trials using these and/or other enzymes in children with functional bowel disorders are needed.

FIBER SUPPLEMENTATION

Insufficient dietary fiber intake has been associated with childhood functional bowel disorders.^{54,55} Dietary fiber is composed of both soluble (water is able to be absorbed) and insoluble components. Soluble fiber therefore has the ability to maintain hydration of stool.⁵⁶ Insoluble fiber may have the potential ability to mechanically stimulate and/or irritate the gut mucosa: This may induce a laxative effect through secretion of mucus and water resulting in more rapid colonic transit.⁵⁶ The distinction regarding the classification of fiber is important as insoluble fiber (e.g. bran) has been shown to exacerbate gastrointestinal symptoms in adults with IBS.⁵⁷

Studies related to fiber supplementation in childhood abdominal-pain related functional bowel disorders have reported mixed results. In a double-blind randomized controlled trial in children with functional abdominal pain disorders, Feldman et al. identified 10 g of corn fiber supplementation for 2 weeks was significantly more effective than placebo in decreasing abdominal pain frequency.⁵⁸ Using a randomized, four week double-blind parallel design for four weeks in children with Rome III abdominal pain-related functional bowel disorders, Romano et al. demonstrated partially hydrolyzed guar gum (5 grams/day) was significantly more effective than placebo in improving in gastrointestinal symptoms.⁵⁹ Shulman et al., in the largest fiber supplementation study in children with IBS to date, reported that psyllium fiber (6 grams for ages 7–11 years and 12 grams for ages 12–17 years) was significantly more effective at reducing abdominal pain frequency.⁶⁰ The psyllium benefit occurred irrespective of several physiologic measures which were assessed including gut microbiome composition.⁶⁰ Psyllium is a soluble fiber with high viscosity which is able to maintain its gel-like property; thereby, decreasing its fermentation by microorganisms while providing for increased water-holding capacity and regulation of stool form.⁵⁶

In contrast to the studies suggesting fiber supplementation is helpful in childhood functional abdominal pain disorders, two other randomized placebo controlled studies did not demonstrate any benefit; one used psyllium (ispaghula husk) and the other glucomannan.^{61,62}

SUMMARY

A large majority of children with functional bowel disorders have food induced symptoms. Malabsorbed carbohydrates may have both direct and microbiome-mediated physiologic effects. Several factors are associated with carbohydrate symptom generation including: 1) the amount ingested; 2) ingestion with a meal; 3) small intestinal enzymatic activity; 4) carbohydrate consumption with microorganisms capable of breaking down the carbohydrate; 5) gut microbiome, and 6) host factors. Several therapies may address carbohydrate malabsorption induced symptoms. These include dietary restriction of an individual offending carbohydrate or a more comprehensive restriction approach as seen in the low FODMAP diet. Additional approaches may include selective prebiotic, probiotic, and/or enzyme supplementation. Fiber supplementation may also be beneficial in children with functional bowel disorders.

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Fig. 1.
Physiologic effects of malabsorbed carbohydrates.

Table 1:

The top 10 most commonly identified foods in children with functional bowel disorders (N=25)⁴

Food	Number (Percentage)
Spicy Foods	17 (68%)
Cow's milk	14 (56%)
Pizza	13 (52%)
Fried foods	12 (48%)
Deep-fried foods	11 (44%)
Fast foods	10 (40%)
Sodas	10 (40%)
Cheese	10 (40%)
Ice cream	9 (36%)
Salsa	9 (35%)

Type and Sources of Fermentable Oligosaccharides Disaccharides Monosaccharides and Polyols

Table 2:

Carbohydrate	Structure	Factors related to Malabsorption	Common Food Examples
Lactose	Disaccharide	Lactase enzyme expression diminishes over time in majority of world's population	Cow's milk, cheese and other dairy products
Fructose	Monosaccharide	Passive absorption related to GLUT2 and GLUT5 transporters	Apples, pears, honey
Fructans	Oligosaccharide made of fructose polymers	Lack of human hydrolases; poorly absorbed	Wheat, onions, rye
Galactans	Oligosaccharide composed of galactose polymers	Lack of human hydrolases; poorly absorbed	Beans, legumes, asparagus
Sorbitol	Sugar alcohol	Lack of human hydrolases; passive absorption	Apricots, cherries, pears