



Fructose malabsorption syndrome

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Purpose of review

Fructose malabsorption is associated with gastrointestinal symptoms. This review examines new findings on the physiology, assessment and therapy of fructose malabsorption in functional gastrointestinal disorders.

Recent findings

Additional GLUT transport mechanisms that regulate fructose absorption might be involved in symptom adaptation to high-fructose diets. Although glucose is known to facilitate fructose absorption, erythritol promotes malabsorption. The methodologies of fructose breath testing and its clinical utility have been questioned by findings of unrealistic testing dose and poor reproducibility. Although fructose restriction appears to benefit children with functional abdominal pain, fructose restriction itself may not be the key player. In irritable bowel syndrome, fructose restriction within a diet low in other fermentable carbohydrates (fermentable, oligosaccharide, disaccharide monosaccharide and polyols) produced good symptom control compared with habitual diet, but such therapy resulted in significantly reduced bifidobacteria. Fructose absorption and subsequently, abdominal pain and nausea are improved by a novel enzyme therapy that converts fructose to glucose for absorption.

Summary

New insights into factors affecting fructose absorption may have therapeutic applications. Doubts surrounding clinical utility of fructose breath testing are emerging. Although restriction of fructose and other fermentable, oligosaccharide, disaccharide monosaccharide and polyols have efficacy for functional gastrointestinal symptoms, potentially negative effects on microbiota deserve attention.

Keywords

dietary therapy, fructose malabsorption, functional abdominal pain, irritable bowel syndrome

INTRODUCTION

Dietary fructose exists mainly in three forms – as a monosaccharide, as sucrose, a disaccharide of fructose and glucose, and in chains as fructans. As only monosaccharides can be absorbed from the small intestine, this form is being considered in the current review. Common food sources are fruits, honey and food products sweetened with high fructose corn syrup (HFCS) [1]. Incomplete absorption of fructose was first implicated in children with chronic diarrhea. High intake of fruit juices containing fructose in excess of glucose was associated with toddler diarrhea and other pediatric gastrointestinal problems [2]. A body of evidence has now established a role for fructose malabsorption in symptom induction for functional bowel disorders [3].

The purpose of this review is to discuss recent publications addressing issues of relevance to the absorption of fructose from the small intestine and its clinical evaluation, and the association of this with functional gut disorders in adults and children.

REGULATION OF FRUCTOSE ABSORPTION FROM THE SMALL INTESTINE

The mechanisms by which fructose is absorbed from the small intestine are not thoroughly understood. Fructose transport across the intestinal epithelium involving two major GLUT pathways (GLUT-2 and GLUT-5) is well established [4]. However, the situation appears more complex than that with the recent identification of other GLUT pathways. Data from human cell cultures and animal experiments demonstrate a potentially important role of a GLUT-8 pathway [5]. Significant fructose uptake was shown when Caco2 epithelial cells were

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Curr Opin Clin Nutr Metab Care 2013, 16:473–477

DOI:10.1097/MCO.0b013e328361c556

KEY POINTS

- The efficiency of fructose absorption can be modulated by coingestion of other sugars or polyols, by the use of an enzyme catalyzing fructose conversion to glucose, and possibly by endogenous transport systems.
- Methodological and interpretative issues with breath hydrogen testing for fructose malabsorption limit its clinical value.
- Fructose restriction as part of a diet low in poorly absorbed and highly fermentable carbohydrates is an effective therapy for functional bowel symptoms but may have negative impact on colonic microbiota

incubated in high concentrations of fructose via mechanisms of GLUT-8 suppression. Additionally, a high-fructose diet stimulated a three-fold increase in GLUT-12 expression to accommodate this fructose load in mice fed such diets. In the presence of GLUT-8, however, utilization of the GLUT-12 absorptive pathway is minimized. It is not known what other factors control GLUT-8 expression [5[¶]]. These findings suggest that the GLUT-8–GLUT-12 fructose regulatory pathway provides an additional adaptive mechanism to accommodate large amounts of fructose. It is tempting to speculate that this new mechanism might play a role in adaptation to high free fructose intake often seen in Western diets, but its presence in normal and function in the human small intestine requires elucidation.

Both naturally occurring sugars (such as glucose and sorbitol) and those added to high-fructose foods may affect its absorption [6]. This hypothesis was recently tested in healthy adults using erythritol, a well absorbed polyol thought to facilitate fructose absorption by enhancing tight-junction permeability [7^{¶¶}]. In this cross-over trial, solutions containing equimolar concentrations of fructose (50 g) alone or in combination with glucose (50 g) or erythritol (33.3 g) were used to determine interaction of the molecules in their absorption as indicated by breath hydrogen production, and their ability to induce gastrointestinal symptoms. Compared with hydrogen production after fructose, the fructose–glucose mix produced a four-fold reduction in breath hydrogen [7^{¶¶}] as documented previously [6]. In contrast, coingestion of fructose and erythritol doubled hydrogen production after ingestion of fructose alone and increased the frequency of symptoms [7^{¶¶}]. As erythritol is poorly fermented by colonic bacteria [8], this increased hydrogen production was related to reduced absorption of fructose. These findings were unlikely to be due to reduced transit time (i.e., less time for

fructose to be absorbed) due to the increased osmolality of the solution ingested as the time of first hydrogen rise after ingestion was not different between challenges. It was more likely a reflection of erythritol interfering with the absorptive pathway of fructose at the epithelial level. As the low-caloric, nonglycemic and nonfermentable properties of erythritol make it attractive as a sweetener, its interaction with dietary fructose in the present study would be unfavorable for patients with irritable bowel syndrome (IBS) as fermentation of short-chain carbohydrates such as fructose is a major trigger of abdominal symptoms (see below).

FUNCTIONAL ABDOMINAL PAIN SYNDROME AND FRUCTOSE-RESTRICTED DIETS

Upon fermentation of fructose by bacteria in the distal small intestine and colonic lumen, there is rapid accumulation of gaseous products, which distends intestinal wall. By virtue of its small molecular size, fructose creates an osmotic force that increases water influx and subsequent retention in the lumen of both the small and large intestine [9]. In patients with functional bowel disorders in which visceral hypersensitivity is a prominent feature, a combination of one or both of these physiological effects within the intestinal tract may, therefore, cause gastrointestinal symptoms such as abdominal pain and bloating [10]. Hence, recent studies have focused on the association of fructose malabsorption in children with functional abdominal pain syndrome and fructose-restricted diets (FAPS), a disorder characterized by amplification of normal visceral sensations [11,12], as well as purported benefits of fructose-restricted diet as a therapeutic option.

First, Gijsbers *et al.* [13[¶]] examined the role of fructose malabsorption in a large cohort of children with FAPS. According to breath hydrogen testing, a high proportion of children (76/171, 65%) with fructose malabsorption were identified. Eight of the children with positive breath tests, all of whom had reported pain relief with short-term elimination of dietary fructose, were then subjected double-blind, placebo-controlled challenges (DBPC) for fructose. In none were symptoms induced by fructose. The authors concluded that fructose malabsorption does not explain FAPS in the study population [13[¶]]. Unfortunately, there were a couple of issues that make such a conclusion somewhat tenuous. First, differences in the fructose loads used between tests – 25 g fructose in the DBPC compared with a dosage of 2 g/kg (with a maximum of 50 g) in the breath tests – were not considered. The latter dose would likely have exceeded the absorption threshold and

produced symptoms. Secondly, the nature of the diet that had shown efficacy in the children was not described. For example, it was unclear whether fructose in excess of glucose alone was targeted or whether the poorly absorbed fructo-oligosaccharides were also included in the exclusion diet.

Another open, uncontrolled study investigating the efficacy of a fructose-restricted diet in children with FAPS also found a high prevalence (42% of 117) of fructose malabsorbers following a 1 g/kg fructose load [14[¶]]. Seventy-five of these children followed a dietician-administered low-fructose diet for 4 weeks. Pain frequency and intensity improved significantly in most children within 2-weeks of dietary initiation. Stool frequency, nausea and analgesic use were also reduced [14[¶]]. However, whether the improvement in pain was directly attributed to a reduced fructose intake remains uncertain for two reasons. First, in the absence of a control treatment group, the benefits may have been purely related to placebo effects. Patients with poor compliance to the diet still achieved some pain relief. Secondly, the restriction of polyols (co-existing with fructose in fruits and artificially sweetened gum) as well as the described simultaneous reduction of food containing the nonabsorbable oligosaccharides (such as onions and cauliflower) may well have contributed to this positive result.

It is clear from both of these studies that symptom induction and improvement was not simply and directly related to the presence of a positive hydrogen response after fructose ingestion. Symptoms arising from fructose ingestion in some children may be generated from osmotically induced distension of the small intestine, even when little fructose reaches the colonic microbiota. Moreover, symptoms might relate more to oligosaccharides and polyols than to fructose (see below). These observations imply that breath testing demonstration of poor fructose absorptive capacity has little clinical predictive value and that dietary manipulation needs not to focus on fructose alone, but also on other fermentable short-chain carbohydrates. The limitation of detailed descriptions of the diets used hindered interpretation. Despite these two publications, clarity on the dietary approach and value of breath tests in children with FAPS remain unresolved.

FRUCTOSE RESTRICTION AS A PART OF THE LOW FERMENTABLE, OLIGOSACCHARIDE, DISACCHARIDE MONOSACCHARIDE AND POLYOLS DIETARY THERAPY FOR FUNCTIONAL SYMPTOMS

Two reviews have summarized the mounting evidence for dietary management of functional bowel

symptoms to be expanded beyond restriction of specific carbohydrates such as fructose [3[¶],15[¶]]. Fructose co-exists in food with other poorly absorbed carbohydrates which have been given the umbrella term of fermentable, oligosaccharide, disaccharide monosaccharide and polyols (FODMAPs) [1,16]. Although no studies have directly compared the efficacy of restricting all FODMAPs compared with fructose alone in managing symptoms of FBD, Staudacher *et al.* have shown that, in a group of patients with IBS, restricting all FODMAPs is efficacious [17^{¶¶}]. Forty-one diarrhea-predominant IBS patients were randomized to a diet low in FODMAPs or continued with their usual diet (controls) for 4 weeks. As a result, 68% patients on the low FODMAP intervention documented adequate symptom control compared with 23% without dietary modification. Specifically, overall symptoms and bloating were reduced with FODMAP restriction. Although no effects were found on stool consistency and self-reported diarrhea, the proportion of patients with normal stool consistency was higher in the intervention group [17^{¶¶}]. The positive results of this study further support data from previous interventional trials in which better symptom response occurred on a low FODMAP diet compared with a high FODMAP diet [18] and in comparison with standard IBS dietary advice [19] in patients with IBS. Hence, successful dietary management of functional symptoms may warrant consideration of other FODMAPs, not just fructose alone.

Of equal importance, however, was their finding that reduction of the intake of carbohydrates with prebiotic properties is associated with changes in fecal microbiota, with a significant reduction of putatively health-promoting bacteria such as bifidobacteria. Although it is not known if such a change is indeed associated with a poorer health outcome, the findings do act as a reminder that changing the diet may have other health impact that may not be favorable. Evidence that fructose is prebiotic is not strong, but diets that reduce fructose intake (as exemplified by the studies above) often also reduce oligosaccharides which are prebiotic.

THE CLINICAL VALUE OF BREATH TEST DEMONSTRATION OF FRUCTOSE MALABSORPTION

There is considerable methodological heterogeneity in key aspects of breath tests which can vary outcomes significantly, including the fructose dose used and cutoff values of hydrogen production that define malabsorption. Furthermore, the importance of symptom induction during testing is controversial. A small but detailed study of 17 healthy

young women aimed to address the issue of fructose dose [20]. Using 20-ppm as the breath hydrogen cutoff for a positive test, 53% were positive after 50 g fructose challenge compared with less than 10% after 25 or 15 g [20]. Furthermore, three out of eight patients with a negative test after 50 g had a positive test on rechallenging, although results continued to be negative after 25 g. All patients remained asymptomatic throughout the study. The average fructose intake of these participants, quantified using food questionnaires, did not exceed 25 g per day (mean 19 g per day). The authors concluded that a 50 g dose is inappropriate as it represents an unrealistic intake in one sitting, is not reproducible and a positive result is, therefore, unlikely to be meaningful. Likewise, in another study, 29% patients were not able to reproduce a positive response to 25–30 g fructose at the start of the study [21[■]]. All these patients had prior fructose malabsorption according to breath tests conducted within 12 months. It was also noted that testing conditions and antibiotic use at the time of retest were similar to their initial breath test.

Both studies highlight the difficulties with reproducibility and interpretation. If ‘fructose malabsorption’ was a diagnosis that caused problems in isolation, then its value in clinical decision-making would be highly questionable. However, fructose is rarely ingested in isolation – most foods with fructose in excess of glucose also contain clinical relevant amounts of sorbitol, which has the same physiological effects when malabsorbed [22]. Indeed the two have greater effects than one alone. One interpretation of fructose breath tests is that complete absorption of a big load (e.g., 25 or 35 g) indicates that the contribution of ingested fructose to symptom genesis is small. However, the data outlined above that coingestion of erythritol markedly reduces fructose absorption indicates that the breath test using fructose alone does not mimic ‘real life’ situations in which complex combinations of carbohydrates are ingested via food. As also suggested by the pediatric study above [13[■]], the true value of the breath test in clinical practice must, therefore, be considered dubious.

LOOKING BEYOND THE GUT: SYSTEMIC CONSEQUENCES OF UNABSORBED FRUCTOSE

A cross-sectional study comparing the prevalence of ‘chronic illnesses’ in two cohorts of IBS patients – 32 with fructose malabsorption according to a 50 g breath hydrogen challenge and 30 with complete fructose absorption, alluded to the relationship of incomplete fructose absorption with higher

frequencies of skin inflammation and of chronic respiratory and urogenital infections [23[■]]. Curiously, patients with fructose malabsorption had higher urinary fructose output, putatively due to defects with the GLUT-5 fructose transporter in various organs. Furthermore, a ‘fructose exclusion diet’, which was not defined in the study, exhibited improvement in the likelihood of chronic illness [23[■]]. This study, though provocative, had multiple methodological flaws – details regarding characteristics of selected patients and their selection process were absent. The nature of the diet used and the details of the follow-up data were poorly documented. Given the problems with breath test reproducibility as outlined above, the findings of this study must be viewed skeptically. However, the concepts that urinary fructose excretion be used as a marker of defective GLUT-5 and that chronic illness might be associated with fructose malabsorption are worthy of a properly constructed study.

NOVEL STRATEGIES TO ASSIST IN FRUCTOSE ABSORPTION

Dietary restriction of excess fructose not only is a burden for patients, especially if followed for long-term, but also limits food variety. Hence, research is focused on designing strategies to reduce the need for fructose restriction. The use of the facilitative effect of glucose on fructose absorption, as described above, has been proposed to improve fructose absorption [24] but its application in dietary practice has not been evaluated. Manipulation of the GLUT-8 pathway could also be targeted in future studies to address fructose malabsorption [5[■]].

Another novel therapy utilizing enzymatic conversion of fructose to glucose was assessed in a randomized, cross-over trial using xylose isomerase in 65 individuals with gut symptoms and fructose malabsorption [21[■]]. The treatment group was allocated three enzyme capsules to be taken with 25 g fructose in solution whilst the control group had capsules without the enzyme with the fructose drink. Breath testing and symptoms were recorded. Administration of the enzyme decreased breath hydrogen excretion accompanied by reduction in abdominal pain and nausea. Bloating, which was reported to be most severe, was, however, not different between the enzyme or placebo group. This could be because fructose has a minimal role in the pathogenesis of bloating. Adverse events did not appear to be well documented, but presumably were few; the enzyme has been approved by the US Food and Drug Administration as ‘Generally Recognized As Safe’ [21[■]]. Although this enzyme is a promising strategy for individuals who experience

symptoms from even moderate amounts of fructose, further studies are needed to reproduce the positive results of the enzymes with foods containing significant amounts of excess fructose as well as to examine its long-term safety profile.

CONCLUSION

Although malabsorbed fructose is likely to be pathogenically important in the functional gastrointestinal symptoms in adults and children, the guidance that breath hydrogen tests offer in deciding this is in an individual has been seriously questioned on the basis of a clinical study in children with FAPS, of studies examining the dose of fructose used in those tests, and of the reproducibility of these tests. Dietary manipulation remains the key to the therapeutic approach in patients with functional gut symptoms, but the failure to define the nature of the 'fructose-reduced' diets used in the publications reviewed hindered interpretation of the study findings. However, new insights into fructose absorptive mechanisms and the evaluation of orally administered xylose isomerase in converting fructose to a readily absorbable form (glucose) offer some hope of nondietary approaches to improving fructose absorption.

Acknowledgements

No funding was received for the writing of this review.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
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