Adding glucose to food and solutions to enhance fructose absorption is not effective in preventing fructose-induced functional gastrointestinal symptoms: randomised controlled trials in patients with fructose malabsorption

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Abstract
Background: In healthy individuals, the absorption of fructose in excess of glucose in solution is enhanced by the addition of glucose. The present study aimed to assess the effects of glucose addition to fructose or fructans on absorption patterns and genesis of gastrointestinal symptoms in patients with functional bowel disorders.

Methods: Randomised, blinded, cross-over studies were performed in healthy subjects and functional bowel disorder patients with fructose malabsorption. The area-under-the-curve (AUC) was determined for breath hydrogen and symptom responses to: (i) six sugar solutions (fructose in solution) (glucose; sucrose; fructose; fructose + glucose; fructan; fructan + glucose) and (ii) whole foods (fructose in foods) containing fructose in excess of glucose given with and without additional glucose. Intake of fermentable short chain carbohydrates (FODMAPs; fermentable, oligo-, di-, monosaccharides and polyols) was controlled.

Results: For the fructose in solution study, in 26 patients with functional bowel disorders, breath hydrogen was reduced after glucose was added to fructose compared to fructose alone [mean (SD) AUC 92 (107) versus 859 (980) ppm h–1, respectively; \( P = 0.034 \)]. Glucose had no effect on breath hydrogen response to fructans (\( P = 1.000 \)). The six healthy controls showed breath hydrogen patterns similar to those with functional bowel disorders. No differences in symptoms were experienced with the addition of glucose, except more nausea when glucose was added to fructose (\( P = 0.049 \)). In the fructose in foods study, glucose addition to whole foods containing fructose in excess of glucose in nine patients with functional bowel disorders and nine healthy controls had no significant effect on breath hydrogen production or symptom response.

Conclusions: The absence of a favourable response on symptoms does not support the concomitant intake of glucose with foods high in either fructose or fructans in patients with functional bowel disorders.

Introduction
Fructose is a dietary 6-carbon monosaccharide that is present in commonly consumed foods such as apples, pears and fruit juices, and is also used as a sweetener. It is also found as part of the disaccharide sucrose and the plant oligosaccharide fructan. Fructose has been implicated in multiple health problems, such as obesity and depression, although it is unknown whether the relationship is cause and effect. Dietary fructose is one inducer of abdominal symptoms in patients with functional bowel disorders (FBD), including irritable bowel
syndrome (IBS). This is a result of its slow absorption in the small intestine with resultant passive diffusion increasing small intestinal luminal water content and, in some individuals, its malabsorption with fermentation in the proximal colon. Restricting the intake of fructose in excess of glucose is part of the dietary restriction in the low FODMAP (fermentable, oligo-, di-, monosaccharides and polyols) diet, which provides symptom improvement in IBS (5–8). An alternative strategy is to improve the rate of absorption of fructose.

Small intestinal fructose absorption principally involves the transporters, GLUT5 and GLUT2 (9). GLUT5 is specific to fructose and provides carrier-mediated facilitative diffusion. However, its low capacity leads to slow uptake of luminal fructose that occurs along the length of the small intestine (10). In the presence of high luminal glucose concentrations, GLUT2 can insert into the apical membrane, providing a high capacity pathway for fructose absorption (11). Hence, the concentration of luminal glucose plays a key role in the rate of fructose absorption. At equal or greater concentrations of glucose, fructose will be largely absorbed rapidly via GLUT2 (12). When fructose is present in excess of glucose, it is dependent upon the slower GLUT5 pathway (13,14), and hence fructose molecules remain in the small intestinal lumen for longer. The passive diffusion exerted by fructose in the lumen is the most likely reason for the increased luminal water content and distension (13). Some fructose fails to be absorbed and enters the large intestine resulting in malabsorption (9). The degree of malabsorption will depend not only upon the efficiency of GLUT5, but also the dose of fructose and the time available for its absorption (9). The malabsorbed fructose which reaches the large intestine is then available for fermentation by the colonic microbiota, resulting in hydrogen and/or methane production, depending on the type of microbiota present. Some of this gas produced can then travel to the lungs via the bloodstream, and can be measured through exhaled breath (16).

One therapeutic technique used to enhance the absorption of fructose is to elevate the concentration of luminal glucose by its co-ingestion with foods containing fructose in excess of glucose. When glucose is added to ingested fructose solutions or fruit juices in healthy subjects, both fructose malabsorption (using breath hydrogen as a marker) (17–21) and small intestinal water content (using magnetic resonance imaging) (15) are reduced. The optimal reduction in breath hydrogen has been observed when glucose and fructose are in a ratio of 1 : 1 (17). However, whether this strategy improves fructose absorption and subsequent symptom induction when the fructose is contained within whole food, as well as solutions, has not been investigated in patients with FBD.

The present study aimed to address the hypotheses that glucose addition to solutions and whole foods containing fructose in excess of glucose will enhance fructose absorption and improve symptoms in patients with FBD. Randomised, blinded, cross-over studies in patients with FBD and in healthy subjects with fructose malabsorption were undertaken using breath hydrogen and symptoms as end-points.

**Materials and methods**

**Subjects**

Subjects were recruited via advertising through the Monash University website, social media, dietitian private practice clinics and breath-testing clinics, in Melbourne, Australia. Inclusion criteria required participants to be aged 18–70 years, and, within the past 3 months, to have fructose malabsorption identified by breath hydrogen rise of ≥15 ppm after 35 g of fructose. Two groups of fructose malabsorbers were recruited: healthy subjects (without gastrointestinal symptoms) and patients with FBD, as determined by a gastroenterologist using the Rome III criteria. Exclusion criteria included inadequate breath hydrogen production (<15 ppm) after 35 g of fructose, pregnancy or breastfeeding, diabetes, other gastrointestinal disorders such as coeliac disease, antibiotic or probiotic use in the past 2 weeks, and the taking of colonoscopy preparations in the past 4 weeks. Those who expressed interest but had a positive fructose breath test more than 3 months prior were asked to repeat the fructose breath test prior to enrolment and only if fructose malabsorption was retained were they then invited to enrol.

**Study protocol: fructose in solution**

The fructose in solution study was a randomised, double-blind, placebo-controlled, cross-over trial. After careful instruction, participants were asked to complete tests involving six separate sugar solutions (Table 1) performed at home on separate days at least 2 days apart. The solutions used included glucose alone, sucrose alone (negative controls), fructose alone (fructose control), fructose and glucose (co-administration intervention), fructans (positive control), and fructans and glucose (co-administration intervention). A dose of 25 g of fructose was used, with equal quantities of glucose added to the combined solution to give a total of 50 g. To provide an equivalent dosage, 50 g of sucrose and 50 g of glucose were used. As a positive control for induction of symptoms, a fructan (Oligofructose Orafti P-95; Beneo-Orafti, Oreye, Belgium) was used because they are short-chain (degree of polymerisation of four) and not digested in the small intestine. A dose of 10 g was used as larger
quantities were more likely to be poorly tolerated (22), with the equivalent glucose of 25 g added to the combined solution. Dosage and volumes used for the sugar solutions were chosen to ensure a suitable osmolarity to be tolerated by the participants as shown in Table 1. The order of sugar solution consumption was randomised (www.randomizer.org). All sugar solutions were made up to 375 mL in water and had 3 g of orange sugar flavouring (containing 3 g of sucrose; Vitafresh, Hansells, Auckland, New Zealand) added. Solutions were labelled ‘A’ to ‘F’ by a department member who was not involved in data collection or analysis to aid in the blinding of both participants and researchers.

Participants were instructed to follow a diet low in FODMAPs and fibre, which they provided themselves for 24 h prior to each test. After an overnight fast, a baseline breath sample was taken, the sugar solution was consumed within 5 min and breath samples collected every 20 min for the next 4 h. Participants were asked to refrain from eating during this time. Hourly breath samples were taken for a further 8 h. Participants were provided with lunch, dinner and snacks to consume after the test solution. All of the food provided was low in FODMAPs (including lactose-free) to minimise other sources of breath hydrogen production. Samples of the meals and snacks made were analysed for their total FODMAP content according to previously described protocols (1,23). The nutrient analysis (analysed using FOODWORKS PROFESSIONAL, version 7; Xyris Software Pty Ltd, Brisbane, QLD, Australia) and FODMAP content of the foods consumed are provided in the Supporting information (Table S1).

Study protocol: fructose in foods

The fructose in foods study was a randomised, single-blind, cross-over trial using whole foods as the source of fructose with and without added glucose. During a 36-h low FODMAP run-in period, followed by a 24-h test day, all food was provided (see Supporting information, Table S2). Breath hydrogen samples were collected hourly for 14 h on two consecutive days, commencing before breakfast each day. For the test day, participants were randomised to either a diet high in fructose with no added glucose (high fructose diet) or high in fructose with glucose added to give a 1 : 1 ratio of free fructose to free glucose (fructose/glucose co-administration diet). Following a 1-week washout period, participants crossed over to the alternative diet. For both test diets, foods included were naturally high in fructose in excess of glucose (including watermelon, apple/guava juice, pear and apple muffins). The remainder of the diet was low in total FODMAP content.

For the fructose/glucose co-administration diet, glucose was co-ingested by participants in tablet form (Glucodin tablets; Reckitt Benckiser, West Ryde, NSW Australia) when whole pieces of fruit were eaten (see Supporting information, Table S2). Participants were asked to consume the glucose tablets at the time of meal consumption. Glucose powder (Glucodin Powder; Reckitt Benckiser) was added during the baking process for apple muffins and premixed with apple/guava juice. For the high fructose diet, sucrose cubes and powder replaced the glucose to aid in blinding the participants.

The high fructose foods provided 11 g of fructose in excess of glucose. The diets provided during the two run-in periods were identical. The two high fructose diets were also identical apart from the addition of sucrose and/or glucose. There were no differences in macronutrient content between the two test diets, including total carbohydrate, starch, dietary fibre and total sugar levels.

Hydrogen breath testing

The methodology for the breath testing followed that reported previously by Ong et al. (8). Breath samples were collected in collection bags (Wagner Analysen Technik Pty Ltd, Carlton, VIC, Australia). Breath hydrogen concentrations were analysed using a gas chromatography (Microlyzer Model DP Plus and Model SC; Quinton Instrument Co., Milwaukee, WI, USA). The machine was calibrated prior to sample analysis.

Symptom scores

At the end of the each day, participants were asked to score their symptoms on a previously validated 100-mm
visual analogue scale (VAS) (24). The symptom diaries requested participants to rate overall abdominal symptoms, abdominal pain, bloating, wind, nausea and fatigue. Participants were also asked ‘During the past day, were your symptoms adequately controlled (meaning not troublesome for you) – yes or no?’.

Ethics approval
All participants provided informed consent prior to commencing the study. Ethics approval was received for the fructose in solution study from The Alfred Ethics Committee (Number 124/12) and Eastern Health Research and Ethics Committee (E57/1112). For the fructose in foods study, approval was received from Deakin University Human Research Committee (EC 37-2008) and Eastern Health Ethics committee (E52/0708). The trials were registered with the Australian New Zealand clinical trials registry (Number ACTRN12614000176662 and ACTRN12616000766415).

Statistical analysis
For the fructose in solution study, a sample size of 20 participants in the FBD subgroup was required to detect a 30% change in the primary end-point, breath hydrogen, with a power of 80%. \( P \leq 0.05 \) was considered statistically significant. An interim analysis after 16 patients with FBD had completed the fructose in solution study was planned. This was performed by an independent statistician examining only the primary end-point. An additional 10 participants with FBD were then recruited. No power calculations were conducted for the healthy subgroup or the whole food study.

Statistical analysis was carried out using IBM SPSS, version 22 (IBM Corp., Armonk, NY, USA). Breath hydrogen data are displayed as both average and area-under-the-curve (AUC) using the mean (SD), as reported previously (8). Per-protocol analyses were undertaken, hydrogen data were corrected for baseline and outliers (>2 SD above mean) were removed. For the fructose in solution study, hydrogen data were assessed at both the 4- and 12-h time points via one-way repeat analysis of variance and pairwise comparisons with Bonferroni correction. Greenhouse–Geisser correction was used for problems with homogeneity of covariance. For the fructose in foods study, hydrogen production between the two test diets was compared using paired \( t \)-tests. The symptom data for both the fructose in solution and fructose in foods studies were analysed using nonparametric analysis and outliers were removed (>2 SD above mean). Friedman’s test and Wilcoxon signed ranks test were used and expressed using the median and interquartile range.

As a result of uneven subject numbers in the FBD versus healthy subject groups in the fructose in solution study, no statistical comparisons could be made between the two groups.

Results

Subjects
In the fructose in solution study, 26 FBD [mean (range) age 40 (22–65) years; 23 female] and six healthy [mean (range) age 35 (26–52) years; five female] participants were recruited. Functional bowel disorder subtypes included 21 IBS (three constipation-predominant; nine diarrhoea-predominant; eight mixed; one un-subtyped); one functional constipation, three functional bloating and one functional diarrhoea. In the fructose in foods study, 10 FBD [mean (range) age 50 (31–76) years; nine female] and nine healthy [mean (range) age 47 (22–65) years; nine female] participants were recruited, one FBD participant was a clear outlier and was removed from all analysis. Participants with FBD were well matched demographically with the healthy subjects in each part of the study. Details of the subject recruitment process and subsequent participation are provided in the Supporting information (Fig. S1). For the fructose in solution study, intake of individual FODMAP subgroups and total FODMAP intake were similar across the test days, with the exception of the content of the sugar solutions. Intake of macronutrients and fibre was similar between the healthy and FBD subgroups, with the exception of fat during the fructose + glucose sugar solution test day which was significantly higher in the FBD group (\( P = 0.005 \)) as shown in the Supporting information (Table S1). All subjects consumed the entire 375 mL of sugar solution.

Fructose in solution

Breath hydrogen excretion
Average breath hydrogen production across the 12-h collection period for the FBD subject group is shown in Fig. 1(a). The 4-h breath hydrogen response expressed as AUC following the fructose test drink [mean (SD) fructose 859 (984) ppm \( 4 \) h\(^{-1} \)] was reduced with the addition of glucose [fructose + glucose, 92 (107) ppm \( 4 \) h\(^{-1} \); \( P = 0.034 \); \( t \)-test], which was similar to that with glucose alone [glucose, 143 (186) ppm \( 4 \) h\(^{-1} \); \( P = 1.00 \)] (Fig. 2). The greatest production of breath hydrogen was in response to fructans [fructan, 2951 (1415) ppm \( 4 \) h\(^{-1} \)] and this was unaffected by the addition of glucose [fructan + glucose, 2200 (1421) ppm \( 4 \) h\(^{-1} \); \( P = 1.000 \)]. The AUC data when expressed over the 12-h period were similar (Fig. 2), except there was no longer any statistical
Average hydrogen production following ingestion of various sugar solutions in (a) patients with functional bowel disorders (FBD) \((n = 26)\) and (b) healthy subjects in the fructose in solution study \((n = 6)\). There was significantly greater breath hydrogen response to fructans compared to that to fructose \((P < 0.001)\) in the FBD group. Breath hydrogen response from FBD and healthy subgroups were similar.

Hydrogen response expressed as area-under-the-curve (AUC) for the functional bowel disorders (FBD) subgroup at 4 and 12 h following ingestion of various sugar solutions in the fructose in solution study \((n = 26)\). Breath hydrogen response following fructose alone [mean (SD) 859 (980) ppm 4 h\(^{-1}\)] was significantly greater than that when glucose was added to fructose \([92 (107) \text{ ppm } 4 \text{ h}^{-1}; P = 0.034; \text{t-test}]\). There was no significant difference in breath hydrogen response with the addition of glucose to fructans \((P = 1.000)\). The AUC data when expressed over the 12-h period was similar, except there was no longer any statistical difference between fructose alone and fructose with added glucose \([1527 (1319) \text{ versus } 1023 (1097) \text{ ppm } 12 \text{ h}^{-1}]\).
difference between fructose alone and fructose with added glucose \([1528 (1319) \text{ versus } 1023 (1097) \text{ ppm } 12 \text{ h}^{-1}; P = 1.00] \). There was significantly greater breath hydrogen response to fructans compared to fructose \((P < 0.001)\).

The pattern of breath hydrogen responses in the six healthy participants was similar compared to the patients with FBD, as shown for the 12-h data in Fig. 1(b). The breath hydrogen response to 25 g fructose [mean (SD) \(1186 (786) \text{ ppm } 12 \text{ h}^{-1} \)] or to fructans [13300 (5291) ppm \(12 \text{ h}^{-1} \)] did not significantly change with addition of glucose \([2035 (1106) \text{ ppm } 12 \text{ h}^{-1}; P = 0.157 \) and \(12874 (4876) \text{ ppm } 12 \text{ h}^{-1}; P = 1.000, \) respectively\].

Breath hydrogen response after fructans was significantly higher compared to that following fructose \((P = 0.000)\).

**Symptoms**

As shown in Fig. 3, the addition of glucose did not alter the overall symptom score compared to those for either fructose (median 15, interquartile range 2–46 versus 5, 1–35; \(P = 0.236, \) Wilcoxon signed-rank test) or fructans alone (19, interquartile range 2–32 versus 17, 2–46; \(P = 0.926)\). The addition of glucose to fructose worsened nausea (1, interquartile range 0–3 versus 2, 1–11; \(P = 0.049)\).

From minimal baseline symptoms reported, no differences for overall or individual symptoms were observed in the healthy subgroup for any of the sugar combinations. Three subjects experienced symptoms \(\geq 20 \text{ mm} \) above baseline and these comprised of overall symptoms and bloating following fructan with glucose \((n = 1)\), wind following fructan \((n = 1)\), lethargy following sucrose \((n = 1)\) and bloating following glucose \((n = 1)\).

**Fructose in foods**

**Breath hydrogen excretion**

For breath hydrogen excretion, only subjects who had a significant rise in breath hydrogen and hence still demonstrated fructose malabsorption following ingestion of the high fructose foods were analysed. An increase in breath hydrogen \(\geq 15 \text{ ppm} \) was noted in five FBD participants and five healthy controls. As shown in Fig. 4, addition of glucose to the diet high in fructose in excess of glucose had no discernible effect on the increment of breath hydrogen production in those with FBD [mean (SD) \(5049 (1949) \text{ versus } 4362 (1641) \text{ ppm } 14 \text{ h}^{-1}; P = 0.620\)] but tended to fall in the healthy controls [8690 (4540) versus 4809 (2504) ppm \(14 \text{ h}^{-1}; P = 0.076)\].

**Figure 3** Visual analogue scale (VAS) symptom scores in the functional bowel disorders (FBD) subgroup following ingestion of various sugar solutions in the fructose in solution study \((n = 26)\). No statistical differences were shown with the addition of glucose to fructose or fructans with the exception of nausea which was increased when glucose was added to fructose compared to fructose alone (median 1, interquartile range 0–3 versus 2, 1–11; \(P = 0.049)\).
This two-part study has shown that, although the addition of glucose in excess of fructose without glucose or with glucose in the fructose in foods study (n = 5). Both groups had a significant increase in breath hydrogen with the addition of the foods containing fructose in excess of glucose compared to the low FODMAP run-in period (FBD mean (SD) 1030 (324) versus 5049 (1949) ppm 14 h⁻¹, P = 0.016; Healthy 756 (624) versus 8690 (4540) ppm 14 h⁻¹, P = 0.019; paired t-test). During the fructose/glucose co-administration diet, breath hydrogen remained higher for the FBD group [1719 (1944) versus 4362 (1641) ppm 14 h⁻¹, P = 0.017]; however, in the healthy group, this change was no longer seen [920 (984) versus 4809 (2504) ppm 14 h⁻¹, P = 0.061]. AUC, area-under-the-curve; H₂, breath hydrogen production.

**Symptoms**
All nine patients with FBD were analysed in terms of symptom response. Overall symptoms were not changed with the addition of glucose [median 27, interquartile range 13–47 versus 33, 9–49; P = 0.990]. The addition of foods containing fructose in excess of glucose was associated with a worsening of symptoms (VAS increase of ≥10 mm from baseline) in three of five with fructose malabsorption and two of four without on breath hydrogen criteria.

**Discussion**
This two-part study has shown that, although the addition of glucose to fructose in sugar solution and whole food can reduce breath hydrogen, it does not assist in improving symptoms associated with fructose intake in FBD. The practice of adding glucose to meals containing fructose in excess of glucose to enhance absorption of fructose and consequently reduce symptoms is largely based upon breath hydrogen response following challenges in healthy subjects with pure sugar solutions (15,17–19,21). The present study confirms this response also occurs in patients with FBD. However, whether this strategy has any clinical utility must be questioned because the present study failed to show the addition of glucose to fructose solutions had any significant impact on symptom induction and does not appear to improve fructose absorption or symptoms when applied to whole food containing fructose in excess of glucose.

The patterns of breath hydrogen responses to sugars in the six healthy controls in the present study confirmed previous demonstrations that fructose malabsorption is a normal physiological phenomenon (25) and that equimolar glucose is effective in promoting rapid fructose absorption (17). In 11 FBD patients with fructose malabsorption and 15 controls, small bowel biopsy found no differences in expression of GLUT5 and GLUT2 transporters (26). Minimal symptoms were produced in our healthy controls, as would be expected in an asymptomatic population. Thus, the methodologies and protocols used in the present study were valid. The lack of symptom response in the healthy controls also emphasises that dietary fructose is of relevance only when fructose malabsorption occurs in the presence of functional gastrointestinal symptoms.

The major focus of the present study was the responses in patients with FBD, which have received minimal attention. First, there is a disparity between fructose malabsorption and symptom induction by foods containing fructose in excess of glucose in patients with FBD. This suggests that malabsorption of fructose is not the main mechanism by which fructose induces symptoms, which rather may arise principally as a result of small intestinal distension from the passive diffusion created by slowly-absorbed fructose. This was illustrated by Murray et al. (15), where magnetic resonance imaging in 16 healthy controls demonstrated that the degree of distension was independent of the malabsorption of fructose. In a study of symptoms experienced by 1372 FBD patients undergoing a fructose breath test, symptoms during breath testing...
correlated more strongly with symptom response to subsequent dietary change rather than malabsorption during the breath test (27). In another study involving 306 patients, only a weak correlation between a positive 25 g of fructose breath test and symptoms was found (28). For mannitol or sorbitol, both slowly absorbed FODMAPs similar to fructose, the development of symptoms in patients with IBS after an acute challenge bore no relationship to whether malabsorption occurred (29).

Second, glucose enhanced fructose absorption in the FBD group. One feature of the patients in the present study was that their breath hydrogen response to 25 g of fructose was not vigorous. This dose was chosen for practical reasons to permit glucose matching without reducing the tolerability of the final solution. The patients were identified as fructose malabsorbers after routine clinical testing with 35 g of fructose. Malabsorption of fructose is dose-dependent (30); for example, in 20 healthy subjects, none malabsorbed a dose of 15 g, 10% malabsorbed 25 g and 80% malabsorbed 50 g (31), and most healthy subjects can absorb up to 25 g of fructose (13,32). Thus, it was not surprising then that breath hydrogen responses to 25 g of fructose were relatively attenuated. However, they still permitted the positive effect of glucose on improving the absorption of fructose solutions.

Third, despite such reduction in fructose malabsorption, supplemental glucose had no consistent and statistically significant effect on fructose-induced symptoms in the patients with FBD, except paradoxically by increasing nausea. The mechanism for the increase in nausea is unknown, although it may be related to the high sugar load given. These results further challenge the importance of fructose malabsorption per se on symptom genesis. However, it might have been anticipated that the reduction of its malabsorption assessed by breath hydrogen would have reflected improved fructose absorption in the small bowel and thus reduced the small bowel water content increase caused by passive diffusion, as demonstrated on magnetic resonance imaging (15). Such an observation raises the question of what does generate abdominal symptoms when free fructose is ingested in patients with IBS.

Fourth, and as anticipated, the addition of glucose to fructans did not provide any reduction in breath hydrogen or symptom induction. Fructans are oligosaccharides consisting of short chains of fructose units with a single D-glucosyl unit at the nonreducing end (33). Mammals lack the enzymes to hydrolyse the glycosidic linkages with subsequent malabsorption and delivery of fructans to the large intestine. This was reflected in the relatively vigorous hydrogen response to 10 g of fructans compared to a small response to 25 g of fructose. Glucose addition delayed the rise in breath hydrogen response to fructan, which is possibly related to changes in intestinal transit, although the magnitude of the rise in breath hydrogen was unchanged. The practice of adding glucose to reduce symptoms associated with high fructan foods that has been anecdotally reported to occur commonly in the community should be strongly discouraged.

It was important to observe whether concomitant glucose ingestion could influence the rate of food-delivered fructose absorption. The results of the present study indicate that such a strategy is not successful. Breath hydrogen responses were not significantly attenuated in patients or in healthy controls and food-induced symptoms were not altered. The lack of positive effects may be related to mixing issues with the gastrointestinal tract and/or the fact that the rapid absorption of glucose may reduce its luminal concentration relative to fructose that is being less rapidly released from food during digestion. Whatever the explanation, the results provide further evidence that glucose co-ingestion is an ineffective strategy to reduce fructan-related abdominal symptoms. Such a conclusion is welcome given the potential negative health implications of strategically increasing the intake of refined sugar and total energy intake.

The challenges and limitations of designing and implementing dietary studies to control for confounding factors were exemplified in the present study (34). In an attempt to limit such factors, the present study was carefully designed to ensure randomisation, blinding of subjects in both studies, as well as investigators in the fructose in solution study, the use of a placebo and a cross-over design. The control of diet through providing low FODMAP meals was used to limit the effects of variations in food choice by the subjects. Moreover, a combination of hydrogen breath testing and symptom scores enabled accurate associations to be made. Despite such methodological rigour, the effects of small amounts of fermentable undigested carbohydrates present in the meals provided were still evident with the increased variability of the 12-h breath hydrogen data. Furthermore, designing a diet in which foods containing fructose in excess of glucose but not of other potentially malabsorbed sugars is difficult because fructose in excess of glucose often co-exists with sorbitol in foods. The use of pear that contains sorbitol may have confounded results. Hence, the approach taken in the present study was to concurrently test both foods and pure sugar solutions. Physiological observations with pure sugar solutions may not reflect the physiology when those sugars are presented in a food matrix. Malabsorption from food is likely to be less than sugar solutions as a result of slower gastrointestinal transit. For example, hydrogen and symptom responses have been found to be greater following ingestion of fructose in excess of glucose compared to high
fructose corn syrup containing glucose (35). It may also reflect the limited release of fructose when contained within the food matrix, hence limiting absorption. One could also argue that, if fructose in excess of glucose is difficult to find without the presence of other FODMAPs, then the use of glucose may be of limited benefit because of the presence of other FODMAPs whose absorption is independent of glucose. Glucose and sucrose given on alternate diets did not appear the same and, despite the use of orange flavouring to disguise taste, the sweetness of the sugar solutions did vary, which may have influenced the blinding. However, it is unlikely that subjects would understand these differences and should not have affected the placebo response. In addition, the different sugar content of the solutions leads to differences in osmolarity, which may have affected symptom response, although this is unlikely because the solutions with highest osmolarity had the lowest breath hydrogen and symptom response.

In conclusion, when applied to pure sugar solutions, adding glucose to solutions in excess of fructose improves its absorption, although it appears to have an attenuated effect, if any, when added to whole food containing fructose in excess of glucose. In both studies, no evidence was obtained that this approach reduced the induction of gastrointestinal symptoms in patients with FBD. The addition of glucose had no impact on the effect of fructans. These observations, together with the potential induction of nausea, do not support the strategy of adding glucose to lessen the impact of dietary FODMAPs on functional gastrointestinal symptoms.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT guidelines. The trials were registered with the Australian New Zealand clinical trials registry (ANZCTR) (Number ACTRN12614000176662 and ACTRN12616000766415) http://www.anzctr.org.au/.

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Conflict of interests, source of funding and authorship

LAR and JSB declare that they have no conflicts of interest.

CJT was supported by an Australian Postgraduate Award Scholarship. The Department of Gastroenterology financially benefits from the sales of a digital application and booklets on the low FODMAP diet. PRG has published an educational/recipe book on diet. JGM declares no conflict of interest.

JGM, JSB and PRG designed the study. CJT and LAR conducted the research. CJT, JGM and PRG analysed data. CJT, PRG, JGM and JSB wrote the paper. CJT had primary responsibility for final content. All authors read and approved the final manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References


Supporting information
Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Subject recruitment process and subsequent participation..
Table S1. Actual dietary intake on the test day of each sugar solution during the fructose in solution study.
Table S2. Diets provided during the fructose in food study.