

Review article: fructose malabsorption and the bigger picture

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SUMMARY

Fructose is found widely in the diet as a free hexose, as the disaccharide, sucrose and in a polymerized form (fructans). Free fructose has limited absorption in the small intestine, with up to one half of the population unable to completely absorb a load of 25 g. Average daily intake of fructose varies from 11 to 54 g around the world. Fructans are not hydrolysed or absorbed in the small intestine.

The physiological consequences of their malabsorption include increasing osmotic load, providing substrate for rapid bacterial fermentation, changing gastrointestinal motility, promoting mucosal biofilm and altering the profile of bacteria. These effects are additive with other short-chain poorly absorbed carbohydrates such as sorbitol.

The clinical significance of these events depends upon the response of the bowel to such changes; they have a higher chance of inducing symptoms in patients with functional gut disorders than asymptomatic subjects. Restricting dietary intake of free fructose and/or fructans may have durable symptomatic benefits in a high proportion of patients with functional gut disorders, but high quality evidence is lacking.

It is proposed that confusion over the clinical relevance of fructose malabsorption may be reduced by regarding it not as an abnormality but as a physiological process offering an opportunity to improve functional gastrointestinal symptoms by dietary change.

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INTRODUCTION

Fructose is a six-carbon monosaccharide that is making an increasing contribution to the Western diet. It is ingested in three forms: a pure monosaccharide, the disaccharide, sucrose, where fructose is complexed with glucose and hydrolysed by sucrase to its constituents and polymerized forms as oligosaccharides and polysaccharides. Polymerized forms are variably described as inulins, fructans and fructo-oligosaccharides (FOS; Figure 1). Over the past 30 years, fructose in its many forms has excited interest from its potential roles in symptom generation in patients with irritable bowel syndrome (IBS), as a prebiotic,¹ as a contributor

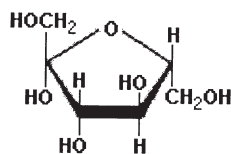
to the obesity crisis (particularly in the US), in the pathogenesis of non-alcoholic fatty liver disease, in influencing the glycaemic index of foods and in the pathogenesis of dental caries (reviewed by Gaby²). This review aims to address one aspect of this spectrum – the effects and clinical significance of its malabsorption in the small intestine.

DIETARY INTAKE OF FRUCTOSE

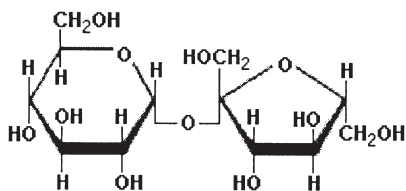
Investigating dietary fructose intake relies on food consumption surveys. This is complicated by the presentation of fructose in its free and various bound forms. Accurate data are therefore unattainable, but researchers have made some attempt at estimating dietary intake of the sugar. Park and Yetley³ examined the results from the US Department of Agriculture Food Consumption Survey 1977–1978 and found that the daily intake of total fructose was 40–54 g (mean 37 g). The majority of fructose was from added sources such as soft drinks, compared with natural sources such as fruit, contributing 24 g and 13 g daily, respectively. While sucrose intake appears to have fallen, there has been a marked rise in free fructose ingestion in the US, it being a four-fold increase in 10-year-old children⁴ and nearly 20% increase in the population as a whole.⁵ This high level of free fructose stems from the use of high fructose corn syrups (HFCS) as an added sweetener in food manufacturing, a cheaper alternative to sucrose and comprising up to 80% fructose. This has resulted in a significant increase in fructose intake over the past few decades in the US with the rise in consumption of HFCS known to have been >1000% between 1970 and 1990.⁶ This more recent data, alongside possible underreporting in food consumption surveys suggests that Park and Yetley's³ figure of 37 g fructose consumed daily is likely to be an underestimate of the current daily intake in the US.

The daily per capita consumption of fructose varies across the world, depending significantly on dietary habits and the use of fructose as a sweetener. Finnish researchers examined the diets of 12- to 17-year-old adolescents and found the average fructose intake to be 11–20 g daily,⁷ about one quarter of that reported from the US.³ The majority of fructose was derived from natural sources such as fruits and vegetables with added fructose contributing much less than one half (5 g) compared with 80% in the US.

Fructose



Sucrose



Inulin

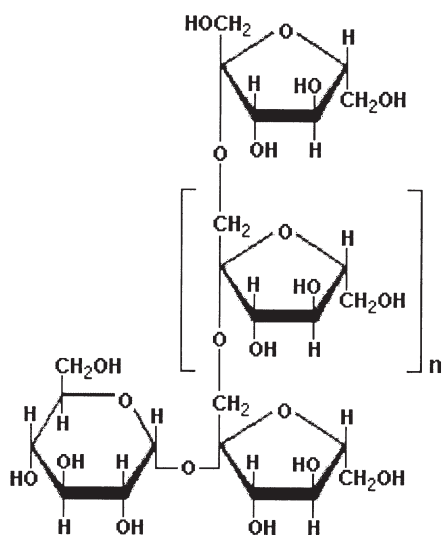


Figure 1. The major forms in which fructose is present in the diet. Sucrose is a disaccharide of glucose and fructose. The fructans found in the diet are inulins and comprise a variable number of repeating fructose units (degree of polymerization) shown in the brackets and labelled 'n'. For fructo-oligosaccharides or oligofructose, n is <10.

When used as a sweetener in soft drinks such as in the US, fructose consumption can quickly approach levels at which malabsorption is seen in healthy adults. Evidence suggests that when solutions containing 25–50 g of fructose (equivalent to >500 mL HFCS-sweetened soft drink) are used in hydrogen breath testing, >50% of healthy subjects demonstrate malabsorption of fructose and consequently experience symptoms of abdominal pain, wind and loose bowels.⁸ The high fructose content in sports drinks has also been implicated in adverse athletic performance and abdominal symptoms.^{9, 10}

Fructans, the linear or branched fructose polymers are found in various plants including chicory roots Jerusalem and globe artichokes, garlic, onion, wheat, asparagus, leek, rye, barley and banana.^{11–13} Estimates of daily per capita intake of fructans have varied widely from 1 to 10 g,^{13, 14} but are likely to underestimate actual intake because the fructan content of foods is incompletely documented. More detailed assessment only exists for the US where the average fructan intake has been estimated at 3.91 g/day.¹⁴ Intake of fructans can only be assessed indirectly by extrapolating from dietary trends, but does seem to be increasing. The intake of major sources of fructans, such as pasta, pizza, cakes and bread, has increased substantially in the US and Europe over the last 20 years.^{5, 15–19}

DEFINITIONS

Interpretation of published literature has been hampered by variations in the use of terminology. Definitions applied to the present review are presented in Table 1. The use of the terms inulin, fructan, oligofructose and FOS has been confusing. It is particularly important that the difference is understood between **hereditary fructose intolerance** (a rare, autosomal recessive disorder)²⁰ and **fructose malabsorption** (often referred to as 'fructose intolerance'), a very common physiological state and the topic for this review. A new term, Fermentable Oligosaccharides, Disaccharides and Monosaccharides And Polyols (FODMAPs), has recently been introduced to define a previously seemingly unrelated group of poorly absorbed short-chain carbohydrates and sugar alcohols that have a similar fate in the distal small bowel and colon.²¹

PHYSIOLOGY OF INTESTINAL ABSORPTION OF FRUCTOSE AND ITS CONTROL

Absorption of free fructose and sucrose

Small intestinal absorption of carbohydrates relies upon their hydrolysis by luminal and brush border hydrolases to the hexose monosaccharides, glucose,

Table 1. Definitions

Hereditary fructose intolerance	Rare, inherited condition where a deficiency of fructose-1,6-bisphosphate aldolase results in infantile vomiting, liver failure and failure to thrive ²⁰
Fructose malabsorption (intolerance)	Any situation in which free fructose is available to fermentative metabolism by luminal bacteria before it can be absorbed across the small intestinal mucosa
Free fructose	Fraction of fructose present as a free hexose in excess of glucose
Fructan	Oligosaccharides and polysaccharides of fructose units with a glucose terminal end
Inulin	A subgroup of fructans with β 1-2 fructose–fructose bonds with a degree of polymerization (DP) 2–60+ ⁹⁴
Fructo-oligosaccharide (FOS), oligofructose	Fructans with a DP of <10 ⁹⁴
Galacto-oligosaccharides (GOS)	Oligosaccharides with a β -fructosidic linkage and an α -galactosidic linkage. The main dietary forms are raffinose, which comprises one fructose, one glucose, and one galactose molecule, and stachyose, which is raffinose with an additional galactose molecule
Polyols	Sugar alcohols including sorbitol, xylitol, mannitol and maltitol
FODMAPs	Fermentable Oligosaccharides, Disaccharides and Monosaccharides And Polyols. This is a collective term that includes all poorly absorbed short-chain carbohydrates and sugar alcohols ²¹

galactose and fructose, with subsequent transport across the small intestinal epithelium. Recent advances in the understanding of hexose absorption have indicated that the vast majority of absorption occurs via three major transporters:

1 SGLT1 is the sodium/glucose-galactose co-transporter that is present in the apical (brush border) membrane of the small intestinal epithelium.²² SGLT1 can transport glucose and galactose against a concentration gradient and is responsible for transport of luminal glucose when luminal concentrations are relatively low.

2 GLUT5 is a facultative transporter (i.e. it depends upon a concentration gradient for movement of substrate across the transporter) and is specific for fructose.²³ It is found in the apical membrane. As fructose is cleared rapidly from the circulation, luminal uptake of fructose is ensured. This uptake mechanism is of low capacity but is present along the length of the small intestine.²⁴

3 GLUT2 is a low affinity, facultative transporter that will carry glucose, fructose and galactose.²⁵ It is present constitutively on the basolateral membrane, where it transports hexoses down a concentration gradient out of the cell. Recently, GLUT2 has been recognized to be present on the apical membrane under specific circumstances.²⁶ It appears to be rapidly and reversibly inserted into the apical membrane when SGLT1 transports glucose. The presence of GLUT2 in the brush border membrane will result in a high capacity, low affinity pathway for absorption of glucose, galactose and fructose.^{27, 28} This system permits lower luminal concentrations of glucose to be taken up by the cells via an active process, which in turn activates a system that can more efficiently take up all hexoses. This may also represent what has been described as

the 'diffusional pathway' previously thought to occur via the paracellular route.²⁹ The system offers a ready explanation for the observed facilitation of fructose uptake by glucose and the highly efficient uptake and absorption of fructose and glucose when presented as sucrose to the apical membrane, where it is readily hydrolysed by sucrase activity to its constituents.³⁰ This mechanism is highly adaptive to wide variations of luminal glucose concentrations, ensures efficient hexose absorption, at least when glucose is present in the mix, and protect distal regions of the intestine from the presence of hexoses.³¹

Factors influencing the absorption of free fructose and sucrose

From the current understanding of the physiology of fructose absorption presented above, there is potential for the efficiency of fructose absorption to be influenced by alterations in the functional capability of GLUT5. While GLUT5 is polymorphic, genotype-phenotype correlations have yet to be made.³² The expression of the GLUT5 gene has a diurnal variation³³ and is influenced by several factors as outlined in Table 2. Most notably, dietary fructose and sucrose can induce greater expression of the GLUT5 transporter^{33, 34} and presumably of its functional capacity.

A second way of altering the ability to absorb free fructose is to modulate the ability of small intestinal epithelial cells to insert GLUT2 into the apical membrane in response to luminal dietary sugars and the rapidity by which they do that. Co-ingestion of glucose or galactose considerably enhances fructose absorption and this appears to occur via the apical GLUT2 mechanism (see above). Animal studies have indicated that this mechanism can be primed or

Table 2. Factors that potentially alter fructose uptake by small intestinal epithelial cells

Mechanism	Promoting uptake	Inhibiting uptake
Altering GLUT5 expression	Luminal fructose, sucrose ^{33, 34, 95} Diabetes ⁹⁶	Absence of luminal fructose ^{33, 34}
Alteration of the insertion of GLUT2 into apical membrane	High glycaemic index diet ⁹⁵ Luminal glucose, galactose, sucrose, fructose ⁹⁵ Metformin ⁹⁷ Diabetes ⁹⁸ Glucagon-like peptide 2 ⁹⁹	Low glycaemic index diet ⁹⁵ Inhibition of cellular calcium entry ²⁶ Stress ¹⁰⁰ Glucocorticosteroids ¹⁰⁰
Not determined	Co-ingestion of amino acids ³⁵ Corticosteroids (topical and systemic) ³⁶	Tumour necrosis factor- α ³⁷

suppressed under the influence of several conditions and specific factors. These are shown in Table 2. Whether such mechanisms operate in the human small intestine awaits investigation.

Other factors have been shown to alter fructose absorption without a satisfactory mechanism having been identified (Table 2). These include the elevation of fructose uptake induced by co-ingestion of amino acids³⁵ or by the use of systemic or topical corticosteroids.³⁶ Exposure to tumour necrosis factor- α in a rabbit model reduced fructose absorption,³⁷ suggesting a link between inflammation and the ability to absorb fructose.

Sucrose malabsorption is associated with sucrase-isomaltase deficiency, a very rare congenital condition except in Greenland.³⁸ It will not be considered any further in this review.

Absorption of fructans

The fate of fructans is different to that of free fructose and sucrose. Long-chain fructans, i.e. those with a high degree of polymerization (DP) – can be broken by sheer stress forces that potentially occur in the process of chewing and gut motility. Thus, fructans with a high DP may become low DP (short-chain) fructans.³⁹ However, such a process, while likely to occur, has not been examined *in vivo*. Because the small intestine lacks hydrolases capable of breaking fructose–fructose bonds, fructans cannot be broken into monosaccharide units. Hence, they cannot be transported across the epithelium and are malabsorbed. Formal examination of this has confirmed that about 90% of ingested fructans can be recovered from small intestinal output in subjects with an ileostomy.^{40, 41}

Consequences of malabsorbed fructose

Delivery of free fructose and fructans to the lumen of the distal small intestine and proximal large bowel may have potential clinical sequelae of importance and these might occur for any of several reasons.

Osmotic load

Being small molecules, fructose, and to a lesser extent FOS, will exert an osmotic effect and deliver more water with it to the distal small intestine and colon.⁴² Increasing the liquidity of luminal contents can affect gut motility, such as hastening transit. This effect is

utilized by laxatives such as lactulose, sorbitol and polyethylene glycol.

Substrate for bacterial fermentation

Fructose and fructans are fermented by bacteria, yielding short-chain fatty acids (SCFA) and the gases, hydrogen, carbon dioxide and, in some, methane.⁴³ Observations *in vitro* using faecal slurries and *in vivo* using breath hydrogen testing indicate that fructose and fructans are rapidly fermented by bacteria.⁴⁴ It is probable, therefore, that such substrates are totally fermented in the very proximal large bowel and possibly distal small intestine, and that subsequent rapid gas formation might distend the lumen locally before the gas is absorbed or further metabolized. SCFA alter the pH of colonic contents, provide an energy substrate for the colonic epithelium, influence sodium and water exchange, and stimulate colonic motility.

Gastrointestinal motility

Malabsorption of a mixture of fructose (25 g) and sorbitol (5 g) accelerates small bowel transit.⁴⁵ While the precise mechanism of this effect is unknown, there is evidence that the products of bacterial fermentation may activate feedback pathways that regulate gut motility.⁴⁶ For example, in healthy subjects, ingestion of lactulose and infusion of SCFA directly into the caecum produced dose-dependent relaxation of the proximal stomach.⁴⁷ Also, intraluminal infusion of a mixture of SCFA into the proximal colon increased colonic peristalsis in rats leading to faster colonic transit.⁴⁸ This effect of fermentation products on gut motility may help to explain the altered bowel habit frequently reported in patients with IBS.

Prebiotic effect

Fructose and fructans may promote the growth of selective bacterial populations, especially bifidobacteria.¹ This prebiotic effect has been postulated to carry several health benefits including improved calcium absorption with positive effects on bone turnover,⁴⁹ improvement in lipid profiles⁵⁰ and fasting glycaemia,⁵¹ protection against colorectal carcinogenesis,⁵² and therapeutic benefits in patients with Crohn's disease.⁵³ Enthusiasm about such broad-ranging benefits has to date far outweighed solid evidence of actual benefit.

Promotion of mucosal biofilm

Some bacteria also utilize fructose to synthesize fructans as bacterial adherence factors. This is a major mechanism by which cariogenic bacteria adhere to the smooth enamel of teeth.⁵⁴ Whether this applies to bacteria in the small or large intestine has not been ascertained, but dietary fructans increase the total number of bacteria adherent to the mucosa in the colon.^{55, 56} While such effects are generally interpreted as health-promoting in the colon, it may well not be the case. Fructan ingestion in rats has been associated with elevated epithelial proliferation and excessive mucin release (suggesting epithelial injury and irritation),⁵⁵ and with increased mucus production, epithelial permeability and susceptibility to experimental salmonella colitis.⁵⁷ Furthermore, ingestion of arabinoxylans, likely to contain xylo-oligosaccharides, also induces epithelial injury and increased susceptibility to carcinogens.⁵⁸ FOS also promotes apoptosis of colonic epithelial cells in a model of acute DNA injury,⁵⁹ an effect that might be beneficial in the prevention of neoplasia but detrimental in a patient with colitis.⁶⁰ Few data exist in humans, except that mucus production is increased by the ingestion of fructans.⁶¹ Fructose malabsorption and fructan intake might then lead to the expansion of the mucosal biofilm in the distal small intestine. This potentially has detrimental effects, both by virtue of luminal fermentation and subsequent distension, and by mucosal injury as observed in the colon. Indeed, some evidence does suggest distal small intestinal bacterial overgrowth is present and responsible for many symptoms in a proportion of patients with IBS,⁶²⁻⁶⁵ and that this may be associated with fructose malabsorption.⁶⁶

Gastro-oesophageal reflux

FOS ingestion induced greater gastro-oesophageal reflux and more heartburn than did placebo in a human study.⁶⁷ This observation is consistent with the association found between reflux disease and symptoms of IBS. Altering dietary intake of fructans has yet to be evaluated as a therapy for reflux disease.

Depression

Fructose malabsorption has been associated with depression in young women with mood improvement following restriction of free fructose intake.^{68, 69} The

mechanisms of these effects are poorly understood, but may involve low circulating levels of tryptophan, the precursor of serotonin.⁷⁰ Such association is also consistent with the frequency of fatigue and lethargy in IBS.

Clinical significance of fructose malabsorption

The contribution of fructose malabsorption to the development of gastrointestinal symptoms was first recognized in 1978⁷¹ when four patients with fructose malabsorption confirmed on breath hydrogen tests, had symptoms improved with removal of the offending sugar from their diet. As this landmark paper, the role of fructose malabsorption in the genesis of symptoms in patients with IBS has received considerable, though sporadic, attention. Incomplete absorption of free fructose induces dose-dependent gastrointestinal symptoms that mimic those of IBS in a high proportion of patients with functional gut disorders and in healthy subjects where the symptoms are generally less severe and less frequent in their occurrence (see Table 3 and discussion below). Ingestion of fructans is likewise associated with dose-dependent gastrointestinal symptoms as shown in multiple studies in which they have been added to the diet (reviewed by Cummings and MacFarlane⁷²). However, the malabsorption of free fructose has not been widely accepted as a major contributor to symptoms of IBS and rates only a peripheral mention in most scholarly reviews on the management approach to patients with IBS. A contribution of dietary fructans to the symptomatology has had limited attention.⁷³

While it is easy to dismiss fructose malabsorption as irrelevant in the majority of patients, theoretical considerations and observations outlined above are compelling. There are several reasons that might contribute to the lowly place treatment of fructose malabsorption has in the hierarchy of therapies for patients with IBS, and these are considered below.

Uncertainties regarding the diagnosis of fructose malabsorption

Hydrogen breath tests have become a key tool in identifying those who malabsorb short-chain carbohydrates and have been the subject of recent detailed reviews.^{74, 75} The principle of the test lies in unabsorbed ingested carbohydrate reaching and being fermented by intestinal bacteria which generate hydrogen

Table 3. Reported studies of the absorption of fructose in healthy subjects and in patients with FGDs as shown by breath hydrogen testing using a variety of methodologies

Subjects	Fructose		Induction of symptoms		Breath sampling regimen				Non-hydrogen producer (%)	Country	Reference		
	Number	Male	Dose	Concentration (%)	FM positive (%)	FM positive vs. FM negative (%)	Correlation with breath H ₂ peak	Frequency (min)				Duration (h)	Cut-off (ppm)
Healthy	16	8	50 g 50 g	10 20	38 71	83 vs. 40	No	30	4	>20	Checked before entry	US	101
Healthy	10	7	50 g 37.5 g 25 g	10	80 70 50	38 vs. 0 Very mild symptoms 6 vs. 5	NR	15–30	3–4	>20	Checked before entry	Denmark	83
Healthy	103	31	50 g 25 g	10	58 11		Yes	15	0.75–2.25	>20	NT	Australia	30
Healthy children	114	59	1 g/kg 2 g/kg	20	44 100	5 overall 21 overall	No	30	2.5	>20	NT	Holland	77
Healthy	34	12	25 g	NR	38	46 vs. NR	No	30	2	>20	7	Germany	102
Healthy	32	17	50 g 25 g	20 10	81 19	NR		15	6	>20	Checked before entry	Greece	103
FGD	197	92	50 g	33	76	NR		30	5	>20 or 3 consecutive rise >3	NT	US	87
FGD	25	2	25 g	10	54	92 vs. 42	NR	15–30	4	>10	4	Denmark	82
FGD	239	NR	25 g	NR	44	NR	Yes	30	4	>20	NT	Israel	89
FGD	183	50	50 g	33	73	75 vs. NR	NR	30	5	>20 or consecutive rise >3	4	US	104
FGD + healthy children	520	162	25 g 2 g/kg	10 20	39 70 80	43 vs. NR 83 vs. NR 88 vs. NR		15–30	3	>10	NT	Canada	84
FGD vs. healthy	6	NR	25 g 2 g/kg	10 20	53 71	NR 13 vs. 0	NR	30	2.5	>10	NT	Holland	78
FGD vs. healthy	25	5	25 g	10	52	Score 1	NR	15	3	>20	NT	Spain	79
	12	6			42	(0–5) vs. NR Score 0 (0–1) vs. NR							

FM, fructose malabsorption; NR, not reported; NT, not tested; FGD, functional gut disorder.

(or methane in those who have methagens in their colonic microbiota). Unfortunately, up to 28% of humans utilize hydrogen efficiently in other ways and/or have a predominance of bacteria that do not produce hydrogen, in whom breath responses for hydrogen are not observed (so-called 'non-hydrogen producers'). A positive breath hydrogen response following fructose ingestion indicates that bacteria are able to ferment the fructose prior to its absorption. This may be due to all or any of the following scenarios – inefficient fructose absorptive mechanisms, rapidity of small bowel transit leaving insufficient time to enable absorption, or excessive bacteria in the small intestine where fructose would 'normally' be absorbed.

Many studies have evaluated the absorption of varying doses and concentrations of fructose in both healthy subjects and subjects with abdominal symptoms. They are shown in detail in Table 3. The heterogeneity of methodologies used and the patient populations studied is evident. This illustrates that, despite the simplicity of the principles, the conduct and interpretation of breath hydrogen testing is problematic. There are several issues of concern.

•*The cut-off value for breath hydrogen concentration:* There is no consensus on what defines a significant rise in breath hydrogen and widely differing values have been used. Whilst a cut-off of a rise of 20 ppm of breath hydrogen over baseline has been used by the majority, a cut-off of 10 ppm has not adversely affected the interpretation.⁷⁶ Other authors⁹ have shown adequate sensitivity and specificity when the cut-off of 6 ppm is used (but the time scale of 6 hours has significant practical implications), and one group used three consecutive readings of a rise of 3 ppm as evidence of malabsorption. The type of device used significantly alters the absolute value obtained. For some, the hydrogen concentration is corrected for alveolar carbon dioxide content and for others it is not. This can significantly alter the absolute value for hydrogen concentration. Such issues have seldom been considered in publications.

•*Role of symptoms:* The importance of the induction of symptoms on the interpretation of the breath test is not clear. Symptoms do not appear to correlate with the degree of hydrogen production,^{77, 78} but this is not surprising because symptoms are not the direct result of the malabsorption but reflect the net response of the gut-brain axis to the malabsorbed carbohydrate. In studies where patients with IBS-like symptoms and

healthy subjects have been compared within the same study, the symptoms generated during the breath testing have been more frequent and severe in patients with IBS-like symptoms than in healthy subjects.⁷⁸⁻⁸¹ Symptoms have been induced by fructose in a variable proportion of apparently healthy subjects (up to 46%), but they are more likely to occur in subjects with, rather than without fructose malabsorption (see Table 3). What is not clear is whether the absence of symptoms following the provocation by fructose (or other sugar) gives any indication as to the role of that sugar in the genesis of the patient's symptoms. Some authors have interpreted the lack of symptom induction as excluding fructose malabsorption as a role player in an individual's IBS picture.⁸² This may represent a gross overinterpretation of the results.

•*The ingested dose and concentration of fructose:* These differ across studies (Table 3). The higher the dose and the concentration, the greater is the chance of a significant rise in breath hydrogen being recorded. The question therefore arises – What dose should be used when evaluating for possible fructose malabsorption? A dose of 25 g at a concentration of 10% more closely approaches daily intake, in the paediatric population a dose of 1 g/kg has been considered as appropriate,⁷⁷ and one key manufacturer of breath testing equipment recommends the dose of 1 g/kg regardless of the age or weight of the patient. There is no consensus, but the choice of dose should depend on how the results of the test are to be used. For example, if the test is to be used to guide dietary intervention strategies, then the dose that discriminates those who will benefit from free fructose restriction to those who will not is the one to use. If the test is used to identify subjects with severely restricted fructose absorptive capacity, lower doses should be used.

•*Reproducibility of the breath test result:* There are limited data on test-retest performance characteristics of fructose breath hydrogen tests. This is an important aspect if the test will direct the therapeutic approach to be taken. In a study of 10 healthy volunteers, seven of eight had repeated breath hydrogen peaks >20 ppm after 50 g fructose.⁸³ Repeated testing in seven healthy subjects with positive breath tests showed the same qualitative finding after 50 g fructose, but the peak breath hydrogen was moderately reproducible, reflecting the limitations of the breath testing methodology for quantitative measurement.³⁰ The qualitative reproducibility of breath hydrogen testing following lower

doses of fructose that are commonly used in routine practice (25–35 g) is generally assumed but has received little attention.

DEFINING WHAT IS NORMAL

As quantitative population studies have not been performed, it not known whether there are distinct populations of low and high absorbers. Fructose malabsorption and symptom induction during the test appear to be similar in men and women.^{30, 81, 84} Ethnicity does not seem to be a variable⁸⁴ but geographical factors may (see Table 3). Fructose malabsorption might be more common in children under 9 years of age⁷⁸ but less common with advancing age,⁸⁴ although the latter was not found in a smaller study of an adult population.³⁰ As shown in Tables 3 and 4, the prevalence of fructose or fructose-sorbitol malabsorption (see below) in the healthy population appears to be similar that in populations with functional gut disorders.^{79, 80, 82, 83} The main difference between the symptomatic and asymptomatic populations has been the frequency of inducing symptoms (as discussed above), suggesting that the sensitivity of the bowel to the change in luminal conditions induced by fructose malabsorption is the key difference rather than the malabsorption itself. In other words, the vast majority of data indicate that fructose malabsorption is not abnormal, and its presence cannot be regarded as a 'condition' or 'illness'. If restriction of free fructose intake does offer symptomatic control in patients with IBS, identification of patients with fructose malabsorption by breath hydrogen testing provides an opportunity to rationally introduce dietary modification with the goal of achieving better symptom control.

Expanding the concepts

The consideration of fructose malabsorption in isolation has been challenged by the demonstration that the polyol, sorbitol, when ingested with fructose has at least additive and possibly synergistic effects in terms of breath hydrogen production and symptom generation (see Table 4). Sorbitol is poorly absorbed from the small intestine, as demonstrated by a dose as low at 5 g giving a positive breath hydrogen response in more than 50% of subjects tested (see Table 4). The basis for the more than additive effects has not been determined but, despite structural similarities with fructose, sorbitol absorption is not facilitated by

glucose.^{44, 85} Additive symptomatic effects have also been observed for fructans and lactose in hypolactasic subjects.⁸⁶

There are several species of fermentable, poorly absorbed short-chain carbohydrates in the diet. As there is no summary descriptor for these, the acronym, FODMAPs has been formed, to collectively represent this disparate group of molecules. Those identified include fructose, and lactose in subjects where these are malabsorbed, polyols (such as sorbitol, xylitol) that are generally poorly absorbed, and fructans and galactans (galacto-oligosaccharides, such as raffinose and stacchiose) in all subjects as these are always poorly absorbed. All FODMAPs share both osmotic effects in the colon and rapid fermentability by bacteria. It is likely that these effects will be additive when combinations of FODMAPs are delivered to the colon as might be anticipated to occur following the ingestion of food, as seen for fructose-sorbitol and fructan-lactose combinations. It makes sense then that, if dietary intervention were planned to reduce these events, FODMAPs should be considered as a whole and not as individual items as has been the general trend in the past. For example, if a patient with IBS was found to have fructose and lactose malabsorption on breath hydrogen testing, dietary restriction should involve attention to free fructose and lactose intake, as well as the additional restriction of fructans, galactans and polyols. If a patient returned a positive test for lactose but not for fructose, the diet should lead to restriction of lactose, fructans, galactans and polyols, and so on. While this approach has been very successful in an open observational study,⁷³ it has not been compared with more restricted approaches.

Evidence for the efficacy of dietary intervention

While there is clear evidence that FODMAPs induce gastrointestinal symptoms in provocation tests, the critical clinical issue is whether the withdrawal of FODMAPs from the diet will specifically reduce symptoms in patients with IBS or whether improvements seen represent no more than a placebo effect. In the absence of high quality evidence, this issue cannot be resolved. Evidence has been confined to observational studies where substantial and durable symptomatic improvements have been reported across patients with a wide variety of functional gut symptoms. The quality of the data has in some studies been further compromised by poor definition of the diet that was applied,

Subjects illness	N	Sugar sucrose	Glucose	Fructose	Sorbitol	Breath test positive (%)	Reference
Healthy	7				5	57	105
					10	71	
					20	86	
FGD*	73			25		31	81
				25	5	42	
Healthy	87			25		47	
				25	5	59	
FGD	15			20 g	3.5	33	80
				25 g	5	58	
Healthy	24			20 g	3.5	60	
				25 g	5	75	
FGD	25			25	0	52	79
					5	68	
				25	5	92	
Healthy	12			25		42	
					5	50	
				25	5	83	
Healthy	34			25 g		38	102
					25	84	
FGD	520			25		53	84
					5	58	
Healthy	32			25		19	103
				50		81	
					10	59	
					20	84	
FGD	239			25		44	89
				25	5	73	
Healthy	16			50		38	101
		50				0	
Healthy + FGD	7		2 g/kg	2 g/kg		100	78
						14	
Healthy	10			50		80	83
		50				0	
			50	50		0	
			25	50		30	
			12.5	50		70	
FGD	25			25		54	82
	13†			25	5	>additive response	
					5	62	
		50				0	
Healthy	103			50		58	30
	14	50				0	
	15		25	25		0	

* FGD, functional gut disorder.

† Only subjects with fructose malabsorption were tested.

Table 4. Comparison of mal-absorption patterns with sugars alone or in combination

leaving the reader to ponder what is meant by a 'fructose-free' diet.

The first report comprised successful dietary-mediated reduction of diarrhoea in four patients with fructose malabsorption.⁷¹ In a 1 week crossover trial,

fructose restriction led to improvement of symptoms in 73% of subjects.⁷⁹ The importance of adherence to the dietary regimen was highlighted by Johlin *et al.*⁸⁷ in achieving symptomatic improvement in patients with a variety of functional gut complaints, not only

those where diarrhoea was the predominant symptom. In 50 randomly selected subjects with fructose malabsorption from that study, the durability of dietary intervention was indicated by continuing symptomatic benefit in 58% after 3 years on the diet. Efficacy of the dietary manipulation was further supported by two patients being able to cease long-term opiate therapy for abdominal pain, and by the significant reduction from 75% to 26% of compliant patients meeting Rome I criteria for IBS at the end of follow-up. Other symptoms linked with fructose malabsorption, particularly mood and depression, have also been improved in patients following a 'fructose-free' diet. Thus, a 4-week exclusion diet in fructose malabsorbers has been shown to improve mood and depressive symptoms.⁶⁹

A recent study for the first time defined the 'sugar-free' diet that was applied to patients with abdominal bloating but no bowel disturbance.⁸⁸ The diet eliminated all foods containing free fructose and/or sorbitol, and lactose if lactose malabsorption was demonstrated. Twenty-six of 36 patients who had sugar malabsorption (20 with fructose malabsorption and six with isolated lactose malabsorption) were educated in the dietary restriction. Symptomatic benefit was reported by 81% at 1 month and 67% after 12 months with 50% reporting symptom resolution. Unfortunately, those without positive breath hydrogen tests were not offered the diet.

The FODMAP approach to dietary intervention, specifically extending restriction to include oligosaccharide FODMAPs, especially fructans, has recently been applied in patients with IBS.⁷³ A well defined and carefully described dietary approach that involved several strategies including restricting the intake of free fructose and fructans was evaluated in 62 consecutive patients with IBS and fructose but not lactose malabsorption. Evaluation of the patients by a structured telephonic interview 2–40 (median 14) months later showed that three of four patients had a marked and sustained response of all abdominal symptoms to the dietary change. Patients judged adherent to the diet on specific criteria (77% of the group) did significantly better than those who were not. An important feature of this retrospective analysis was the high adherence rate (presumably related to the ongoing efficacy of the diet) which compared favourably with previous rates reported between 26%⁸⁹ and 56%.⁸⁷ The durability and high rate of symptomatic benefit across patients with both diarrhoea- or constipation-predominant IBS were encouraging. Apart from one preliminary positive

report,⁹⁰ there are few data on the symptomatic response of patients without fructose or lactose malabsorption to a FODMAP-restricted diet. However, these promising findings must be interpreted in the context of the known limitations associated with retrospective analysis and lack of a control group.

The definitive way of providing high level evidence for a therapeutic intervention is via a randomized, placebo-controlled trial. Because dietary intervention is a complex process that involves individualizing the approach according to tastes and eating habits, the treatment arms cannot be delivered without active human involvement. The delivery of placebo dietary advice is fraught with difficulties including designing a placebo diet that will not in itself improve or worsen the condition; the dietician selling the advice with identical enthusiasm and body language as for the active diet; effective blinding of the placebo to the patients as they are often well versed in other dietary approaches, and of ensuring adherence to the diet. The only way truly of achieving the level of proof needed is to provide 100% of the food for treated groups for the entire trial period, a major undertaking that presents considerable resource issues. This is especially the case as placebo responses are usually high in interventional studies in patients with IBS, necessitating large sample sizes to achieve appropriate power.

Fructose malabsorption and small intestinal bacterial overgrowth

Theoretical considerations and limited data have intriguingly suggested that fructose malabsorption and small intestinal bacterial overgrowth might have a bidirectional cause-effect relationship, as outlined in Figure 2a. On the one hand, fructose might promote the survival of bacteria in the distal small intestine as a ready metabolic substrate (a 'fast food') and by providing substrate for the synthesis of fructans as adherence factors (as discussed earlier). While there is currently no direct evidence supporting or dismissing that these events are occurring in the distal small intestine, removal of all potential metabolic substrates for bacteria by feeding patients an elemental diet resulted in loss of features of small intestinal bacterial overgrowth together with improvement of IBS symptoms (Figure 2b).⁶⁴ On the other hand, antibiotic therapy in patients with presumed small intestinal bacterial overgrowth abolished fructose malabsorption in a high proportion of patients with concomitant

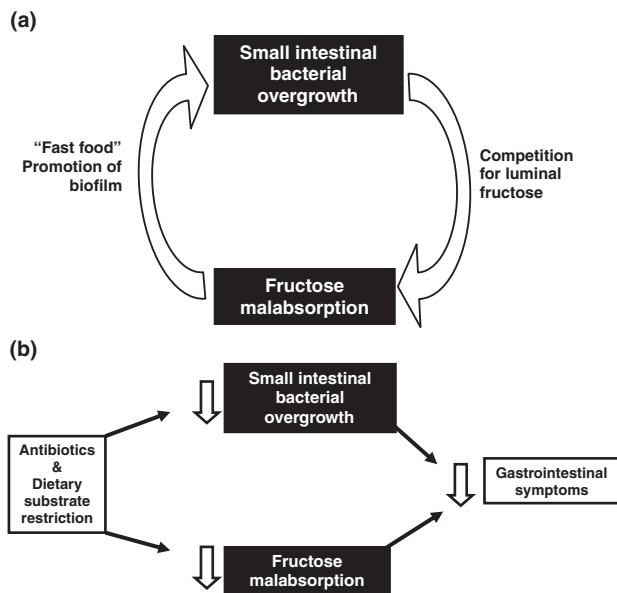


Figure 2. Fructose malabsorption and small bacterial overgrowth. (a) The hypothetical interdependent relationship between fructose malabsorption and distal small bacterial overgrowth. (b) Circumstantial evidence for this relationship. Evidence (outlined in the text) shows that antibiotics and dietary substrate restriction reduce both fructose malabsorption and small intestinal bacterial overgrowth, and are associated with a reduction of gastrointestinal symptoms in patients with irritable bowel syndrome.

symptom reduction (Figure 2b).⁶⁶ Antibiotics have been shown to alleviate gut symptoms in patients with small intestinal bacterial overgrowth in a randomized-controlled trial⁶³ and in a retrospective series.⁶⁵ Whether the FODMAP-restricted diet is therapeutic in both reducing symptoms and reducing bacterial populations in the distal small intestine remains unexplored. One impediment to progress in this area is the uncertainty of the actual diagnosis of small intestinal bacterial overgrowth as it depends upon interpretation of breath hydrogen tests, which itself has been inconsistent.^{74, 75}

Expanding the target patient population

The benefits of evaluating patients with IBS for fructose and lactose malabsorption and their subsequent dietary intervention are emerging. There is no reason, however, why the target population for this approach needs to be restricted to those with IBS. In patients with inflammatory bowel disease, IBS is thought to be commonly present (though this is difficult to objec-

tively evaluate) and the ability of the large bowel to handle excessive fluid loads may be reduced. A preliminary report has indicated that application of the FODMAP approach and dietary intervention in patients with Crohn's disease has had symptomatic benefit in a high proportion.⁹¹ Likewise, reducing FODMAP intake may lead to improved pouch function in patients with an ileo-anal pouch anastomosis.⁹² One reason that patients with coeliac disease fail to improve IBS-like symptoms despite adherence to a gluten-free diet is fructose malabsorption.⁹³ A FODMAP-restricted diet may potentially have efficacy in this situation.

Other unresolved issues

There are many other issues that require further study. FODMAPs may potentially play a role in other gastrointestinal diseases. The adverse effect of supplemental FOS on gastro-oesophageal reflux and its symptoms⁶⁷ suggests a role for dietary FODMAPs in the pathogenesis of gastro-oesophageal reflux disease and the potential for reduction in their intake in its therapy. FODMAPs have been recently hypothesized to play a role in the pathogenesis of Crohn's disease and have been speculatively linked to the increased prevalence of Crohn's disease in Western countries.²¹ While evidence to support such a contention is limited, it does warrant serious consideration because such factor is amenable to preventive measures.

CONCLUSION

The concept of fructose malabsorption has been generally poorly understood in the gastroenterological community, perhaps to a large extent due to its being considered an illness or abnormality, and due to the lack of awareness of dietary fructans in the genesis of symptoms. In the setting of IBS affecting up to 15% of the community and of the lack of effective therapy, the potential importance of malabsorbed fructose in the genesis of symptoms cannot be underplayed. The apparent increase in the intake of fructose and fructans in the community may compound this problem. It is proposed that a more expansive view be taken, where the vision is not restricted to fructose or sorbitol or lactose in isolation, but rather to all poorly absorbed short-chain carbohydrates and polyols. Continuing observational experience and, hopefully, randomized-controlled trials are needed to address the true place of these issues in clinical medicine.

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