

RESEARCH PAPER

Dietary sorbitol and mannitol: food content and distinct absorption patterns between healthy individuals and patients with irritable bowel syndrome

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Keywords

hydrogen breath tests, intestinal absorption, irritable bowel syndrome, mannitol, polyols, sorbitol malabsorption.

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How to cite this article

Yao C.K., Tan H.-L., van Langenberg D.R., Barrett J.S., Rose R., Liels K., Gibson P.R. & Muir J.G. (2014) Dietary sorbitol and mannitol: food content and distinct absorption patterns between healthy individuals and patients with irritable bowel syndrome. *J Hum Nutr Diet.* **27** (Suppl. 2), 263–275
doi:10.1111/jhn.12144

Abstract

Background: Sorbitol and mannitol are naturally-occurring polyol isomers. Although poor absorption and induction of gastrointestinal symptoms by sorbitol are known, the properties of mannitol are poorly described. We aimed to expand data on food composition of these polyols, and to compare their absorptive capacities and symptom induction in patients with irritable bowel syndrome (IBS) and healthy individuals.

Methods: Food samples were analysed for sorbitol and mannitol content. The degree of absorption measured by breath hydrogen production and gastrointestinal symptoms (visual analogue scales) was evaluated in a randomised, double-blinded, placebo-controlled study in 21 healthy and 20 IBS subjects after challenges with 10 g of sorbitol, mannitol or glucose.

Results: Certain fruits and sugar-free gum contained sorbitol, whereas mannitol content was higher in certain vegetables. Similar proportions of patients with IBS (40%) and healthy subjects (33%) completely absorbed sorbitol, although more so with IBS absorbed mannitol (80% versus 43%; $P = 0.02$). Breath hydrogen production was similar in both groups after lactulose but was reduced in patients with IBS after both polyols. No difference in mean (SEM) hydrogen production was found in healthy controls after sorbitol [area-under-the-curve: 2766 (591) ppm 4 h⁻¹] or mannitol [2062 (468) ppm 4 h⁻¹] but, in patients with IBS, this was greater after sorbitol [1136 (204) ppm 4 h⁻¹] than mannitol [404 (154) ppm 4 h⁻¹; $P = 0.002$]. Overall gastrointestinal symptoms increased significantly after both polyols in patients with IBS only, although they were independent of malabsorption of either of the polyols.

Conclusions: Increased and discordant absorption of mannitol and sorbitol occurs in patients with IBS compared to that in healthy controls. Polyols induced gastrointestinal symptoms in patients with IBS independently of their absorptive patterns, suggesting that the dietary restriction of polyols may be efficacious.

Introduction

Sorbitol and mannitol are polyols frequently used as sugar substitutes by the food industry to produce 'low-calorie' products (Zumbe *et al.*, 2001). It is less commonly known that both polyols are also present naturally in a wide variety

of food. Recently published food composition data by our group indicated that sorbitol tends to be more common in fruits, whereas mannitol is found more commonly in vegetables (Muir *et al.*, 2009). Both polyols appear to have primary roles in these plants as energy reserves and as osmoregulatory agents (Lewis & Smith, 1967).

Sorbitol and mannitol are six-carbon polyol isomers with a similar molecular weight and size, differing only in the orientation of one of their hydroxyl group (Le & Mulderrig, 2001; see Figure S1). They appear to be partly absorbed via passive diffusion across the small intestinal epithelium (Beaugerie *et al.*, 1990; Krugliak *et al.*, 1994). Breath hydrogen studies indicate a high prevalence of sorbitol malabsorption in healthy adults, where 71% show malabsorption after consumption of 10 g of sorbitol and 20% report gastrointestinal symptoms of bloating, flatulence and abdominal pain (Hyams, 1983). Some studies have extrapolated these findings to the absorption of mannitol, and have assumed that a similar proportion of mannitol is absorbed; however, this has not been compared directly (Wursch *et al.*, 1989; Le & Mulderrig, 2001).

Short-chain carbohydrates called FODMAPs (Fermentable, Oligo-, Di-, Monosaccharide and Polyols) that are slowly or poorly absorbed in the small intestine increase luminal water content of the small and large intestine by virtue of their osmotic effect (Barrett *et al.*, 2010; Marciari *et al.*, 2010) and are rapidly fermented by intestinal bacteria, resulting in increased gas production (Ong *et al.*, 2010). The resultant luminal distension has been hypothesised to trigger abdominal symptoms in patients with functional bowel disorders because of the visceral hypersensitivity and dysmotility that characterises such patients (Chey *et al.*, 2001; Agrawal *et al.*, 2008). Because sorbitol and mannitol are also poorly or slowly absorbed in the small intestine and readily fermented by bacteria, it is assumed that they will also induce symptoms in a similar way. However, it is not well established whether the malabsorption of sorbitol with or without fructose and, subsequently, the induction of symptoms occurs to a greater extent in patients with irritable bowel syndrome (IBS) compared to controls because one study attributes a clear difference (Fernandez-Banares *et al.*, 1993) and another does not (Nelis *et al.*, 1990). Regardless of the inconsistent findings, it is appropriate to restrict the intake of sorbitol and mannitol-rich foods in symptomatic individuals. However, knowledge of the sorbitol and mannitol content in foods is limited and needs to be expanded to prevent unnecessary restrictions.

It was hypothesised that, first, as isomeric molecules, sorbitol and mannitol are absorbed similarly in the small intestine of healthy subjects and patients with IBS; second, both would induce gastrointestinal symptoms predominantly in patients with IBS; and third, symptom induction would be associated with the malabsorption of the polyol. The present study therefore aimed to address the knowledge gaps by quantifying the content of sorbitol and mannitol naturally-occurring in various foods and also to address the hypothesis by examining patterns of absorptive

capacity of sorbitol and mannitol in patients with IBS compared to those in healthy individuals and assessing symptomatic responses in relation to patterns of absorption.

Materials and methods

Measurement of sorbitol and mannitol content

A total of 73 foods from several food groups were screened for quantities of sorbitol and mannitol. As previously described in detail by Muir *et al.* (2009), the sampling and processing methods of the foods complied with the guidelines of Food Standards Australia New Zealand. Triplicates of the extracts from food samples were analysed for sorbitol and mannitol content using high-performance liquid chromatography (HPLC) with an evaporative light scattering detector (ELSD) analytical technique. Sugar standards, HPLC apparatus (consisting of ELSD Waters 2424, HPLC pump Waters 515, Waters auto sampler 717 plus and Waters column heater; Waters Corp, Milford, MA, USA) and chromatographic procedure were performed as described in Muir *et al.* (2009). Samples were reanalysed if any of the triplicate measurement values differed by >5% from the mean of other samples (Muir *et al.*, 2009). The relative SD for using HPLC measurement technique has previously been calculated for sorbitol (3.76%) and mannitol (2.85%) (Muir *et al.*, 2009). Food composition of sorbitol and mannitol were constructed using standard serving sizes and weights from FOODWORKS, version 6 (Xyris Software Australia Pty Ltd, Highgate Hill, Australia).

Subjects

Patients with IBS and no other co-existing gastrointestinal disorders were recruited from an outpatient breath testing centre at Box Hill Hospital (Box Hill, Victoria, Australia). Healthy participants with no previous history of gastrointestinal illness or symptoms were also recruited through advertisements in Box Hill Hospital. All participants were aged ≥ 18 years and not pregnant. None of them had been treated with antibiotics in the previous 6 weeks, or pre- or probiotics in the 2 weeks leading up to the study. The intake of nonsteroidal anti-inflammatory drugs and alcohol was recorded. During screening, a detailed history was obtained to confirm that IBS patients met the Rome III diagnostic criteria (Longstreth *et al.*, 2006). Written informed consent was obtained from all participants prior to commencing the study. The study protocol was approved by the Eastern Health Research and Ethics Committee.

Experimental design

Prior to entering the study, all subjects were initially challenged with 15 g of lactulose (15% w/v) for 2 h to ensure

that they produced adequate breath hydrogen, denoted as a rise in breath hydrogen ≥ 10 ppm in two consecutive breath samples (Bate *et al.*, 2010). Subjects who had a rise in breath methane ≥ 15 ppm from baseline were classified as 'methane producers'. This was followed by a routine breath hydrogen test with 35 g of fructose (17% w/v) to determine the presence of fructose malabsorption.

The effects of a single dose (10 g) of sorbitol, mannitol or glucose (as placebo) were investigated using a randomised, double-blinded, placebo-controlled, cross-over design. Randomisation of the test sequence was performed with a computer-generated list of random numbers and the sequence was kept by an independent investigator. The dose of 10 g was chosen to reflect a realistic but high intake of the individual polyol that is achievable through the diet (Muir *et al.*, 2009; Barrett & Gibson, 2010) and is also not likely to induce osmotic diarrhoea in healthy individuals (Hyams, 1983). The sugars were given as a colourless solution in 100 mL of water (10% w/v), made up in identical unmarked containers to ensure blinding of both participants and researchers. The absorption of these sugars was then determined through breath hydrogen testing. Each sugar challenge was followed by a washout period of 1–7 days before crossing over to the next sugar challenge to allow symptoms (if any) to return to baseline prior to re-challenge.

Breath hydrogen testing

Breath hydrogen testing was performed as previously outlined in detail (Ong *et al.*, 2010). Briefly, participants were provided with a diet low in fibre and poorly-absorbed short-chain carbohydrates for 24 h. After an 8-h fast, a baseline breath sample was taken before ingesting the sugar solution. Thereafter, breath samples were collected at 15-min intervals into collection bags (Quintron Instrument Co., Milwaukee, WI, USA) for 4 h. Subjects were instructed to refrain from smoking and strenuous exercise during the test to minimise potential confounding of these variables on breath hydrogen responses (Thompson *et al.*, 1985). Breath hydrogen and methane concentrations were analysed immediately using a gas chromatograph (Microlyzer Model DP Plus; Quintron Instrument Co., Milwaukee, WI, USA).

A rise in breath hydrogen concentrations ≥ 10 ppm above baseline in two consecutive breath samples was used to define malabsorption. Total breath hydrogen and methane production for lactulose and test sugars were estimated using the trapezoid rule to approximate the area-under-the-curve (AUC) against time (ppm h^{-1}) for each sugar (Kotler *et al.*, 1982). The degree of sugar malabsorption was semi-quantitatively determined relative to AUC after ingestion of 15 g of lactulose (a non-absorbable

carbohydrate) (Rumessen *et al.*, 1990). Responses were arbitrarily categorised as marked (61–100%), moderate (31–60%), low (6–30%) or no (0–5%) malabsorption. Oro-caecal transit time (OCTT), defined as the time (min) from sugar ingestion of first breath hydrogen rise ≥ 10 ppm in two consecutive samples, was measured for lactulose (Bate *et al.*, 2010).

Assessment of gastrointestinal symptoms

Gastrointestinal symptoms were assessed by completing bowel symptom questionnaires before and 4 h after sugar ingestion. Symptoms were rated on 100-mm visual analogue scales (VAS) according to severity from 0 (no symptoms) to 100 mm (worst it has been) for overall gastrointestinal symptoms, abdominal pain/discomfort, bloating, wind, as previously applied (Francis *et al.*, 1997). A composite score for abdominal symptoms was calculated by combining scores for abdominal pain, bloating and wind. Scores were corrected for the baseline level of symptoms.

Statistical analysis

Because a per-protocol analysis was planned, only participants who completed all three interventions were included in the final analysis. Primary end-points were the proportion of individuals with malabsorption and their breath hydrogen response to the sugar challenges. Secondary end-points included gastrointestinal symptom response to polyol ingestion, the correlation of breath hydrogen-producing ability and OCTT for lactulose with polyol absorption/malabsorption, and the proportion of individuals with concomitant fructose and polyol malabsorption. A sample size of 20 participants in each group was required to detect a 30% change in breath hydrogen response to the polyol challenges, with a power of 80%. $P \leq 0.05$ (two-tailed) was considered statistically significant.

The frequency of sugar malabsorption was compared using Fisher's exact or a chi-squared test. Comparisons between subject groups were performed with unpaired *t*-tests and the Mann-Whitney *U*-test for nonparametric data. Comparisons between sugar challenges were also analysed using paired *t*-tests and the nonparametric Wilcoxon signed-rank tests, respectively. Correlations were performed using Pearson's and Spearman's correlation for nonparametric data. Effect sizes (eta squared statistic, r^2) were calculated and expressed as the mean difference (MD) and 95% confidence interval (CI). Results are expressed as the mean (SEM) for parametric data, median [interquartile range (IQR)] for nonparametric and discontinuous variables, and proportions as percentages (95% CI). Statistical tests for data analysis were computed using spss, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

The composition of sorbitol and mannitol in a range of foods is listed in Table 1. Of 73 foods analysed, sorbitol was detected in 12, namely in fruits and sugar-free chewing gum. Sorbitol content (per average portion eaten) was the highest in prunes > dried apricot > dried pear > sugar-free chewing gum > plum > apricot > apple juice > dried apple > wasabi > cherries > coconut milk > dried coconut. Mannitol was present in seven foods and these were predominantly vegetables, six of which contained moderate amounts when a standard portion size is consumed. Celery contained the highest amount (per average portion eaten) of mannitol, followed by butternut pumpkin > pomegranate > celeriac. Neither sorbitol, nor mannitol was detected in nuts and legumes.

Subject characteristics

Forty-one participants completed all sugar challenge tests. This included 20 subjects with IBS and 21 healthy controls. Eleven IBS subjects were constipation-predominant, seven were diarrhoea-predominant and two had alternating bowel habits. Table 2 compares the baseline characteristics between the two groups. No differences in characteristics were observed.

Gastrointestinal symptoms

Severity of gastrointestinal symptoms for healthy and IBS subjects as scored by the VAS after all three sugar challenges are shown in Fig. 1. In the healthy controls, overall symptoms were generally minimal compared to IBS subjects (sorbitol, $P = 0.02$; mannitol, $P = 0.004$) with no differences in scores across both polyols compared to glucose (not significant, Wilcoxon signed-rank test) and composite score (not significant). For patients with IBS, the development of symptoms after the ingestion of glucose was uncommon and very mild (Fig 1). Compared to glucose, significantly greater overall gastrointestinal symptoms developed after sorbitol ($P = 0.05$) and mannitol ($P = 0.02$). Other symptoms were more frequent after the polyols, although the composite scores did not reach statistical significance compared to those after glucose ($P = 0.12$). There were no differences in the development of symptoms after sorbitol compared to those after mannitol (not significant).

Breath responses to lactulose

There were no differences in mean breath hydrogen produced after lactulose between patients with IBS [1334 (282) ppm 2 h^{-1}] and controls [1412 (250) ppm

2 h^{-1} ; $P = 0.84$; unpaired t -test]. In the six healthy controls and six patients with IBS who were classified as 'methane-producers', breath methane production after lactulose was similar between controls [805 (206) ppm 2 h^{-1}] and IBS patients [897 (359) ppm 2 h^{-1} ; $P = 0.85$, unpaired t -test].

Frequency of polyol malabsorption

The proportion of patients with IBS and healthy controls with sugar malabsorption is shown in Fig. 2. Malabsorption of sorbitol occurred at a similar frequency in both groups ($P = 0.67$; Fisher's exact test). By contrast, mannitol malabsorption occurred less frequently in IBS patients compared to controls ($P = 0.02$). No subject malabsorbed glucose. As shown in Fig. 3, a greater proportion of patients with IBS were classed as having a low degree or no malabsorption of mannitol compared to healthy controls ($P = 0.02$; chi-squared). By contrast, no difference was observed between the two subject groups for sorbitol ($P = 0.24$). No differences were observed across IBS subtypes according to bowel habits (data not shown).

Fructose malabsorption occurred in 63% of patients with IBS and 42% of controls. Its frequency was not associated with having malabsorption of both polyols, one of the polyols or none in patients with IBS (16% versus 21% versus 26%, respectively; $P = 0.84$) or in healthy controls (21% versus 11% versus 11%; $P = 0.21$).

Relationship between oro-caecal transit time and polyol malabsorption

Median (range) OCTT in patients with IBS was 105 (75–135) min, which was significantly longer than 75 (45–120) min observed in healthy controls ($P = 0.03$, Mann–Whitney U -test). However, no correlations were found in the whole group between median OCTT and total AUC (sorbitol: $r = -0.20$, $P = 0.22$; mannitol: $r = -0.28$, not significant) for either sorbitol or mannitol.

Breath hydrogen production

Breath hydrogen profiles over 4 h after the ingestion of sorbitol, mannitol and glucose for the 27 subjects who malabsorbed sorbitol and/or mannitol are shown in Fig. 4. In healthy controls, total breath hydrogen production after sorbitol [2766 (591) ppm 4 h^{-1}] and mannitol [2062 (468) ppm 4 h^{-1}] were similar ($P = 0.07$, paired t -test) (Fig. 4a), whereas that after glucose was markedly less [211 (113) ppm 4 h^{-1} ; $P = 0.01$ for both]. The mean (95% CI) difference in AUC between sorbitol and glucose was 3452 (2064–4839) ppm 4 h^{-1} . Similarly,

Table 1 Content of sorbitol and mannitol in various food groups shown as grams per 100 g edible portion and grams per serving

Food			Sorbitol			Mannitol		
			Present study	Published data	USDA	Present study	Published data	USDA
Vegetables	Artichoke hearts	g/100 g	0			0		
		g/1 cup (204 g)	0			0		
	Carrot	g/100 g			0		0	0.2
		g/1 cup (116 g)			0		0	0.2
	Celeriac	g/100 g	0			0.1		
		g/1 celeriac (72 g)	0			0.1		
	Celery	g/100 g	0		0	1.5		0.2
		g/1 cup (127 g)	0		0	1.9		0.2
	Leek	g/100 g	0			0		
		g/1 leek (83 g)	0			0		
	Lettuce, rocket	g/100 g	0			0		
		g/1 cup (35 g)	0			0		
	Sugar snap peas	g/100 g	0			0		
		g/1 cup (120 g)	0			0		
	Pumpkin, butternut	g/100 g	0			0.4		
		g/1 cup (120 g)	0			0.5		
	Parsnip	g/100 g	0			0		
		g/1 cup (124 g)	0			0		
	Tomatoes, sundried	g/100 g	0			0		
		g/1 TB (7 g)	0			0		
	Radish	g/100 g	0		0	0		0.1
		g/1 radish (20 g)	0		0	0		0.0
	Seaweed	g/100 g	0			Trace		
		g/0.25 cup (40 g)	0			Trace		
	Water chestnuts	g/100 g	0			0		
		g/1 cup (120 g)	0			0		
	Asparagus	g/100 g		0*			0.1*	
		g/4 spears (60 g)		0			0.1	
	Bok choy	g/100 g		0.2*			0*	
		g/1 cup (85 g)		0.2			0	
	Brussel sprouts	g/100 g		0.2*			0*	
		g/1 cup (164 g)		0.3			0	
	Broccoli	g/100 g		0.4*			0*	
		g/1 cup (94 g)		0.4			0	
	Cabbage, common	g/100 g		0.2*			0*	
		g/1 cup (94 g)		0.2			0	
	Capsicum, green	g/100 g		0.4*			0*	
		g/1 cup (102 g)		0.4			0	
	Cauliflower	g/100 g		0*			2.6*	
		g/1 cup (132 g)		0			3.4	
	Corn, sweet	g/100 g		0.5*			0*	
		g/1 cob (85 g)		0.4			0	
	Cucumber	g/100 g		0*	0		0*	0.1
		g/1 cup (128 g)		0	0		0	0.1
	Mushrooms	g/100 g		0.1*			2.6*	
		g/1 cup (74 g)		0.1			1.9	
	Snow peas	g/100 g		0*			1.2*	
		g/10 pods (33 g)		0			0.4	
	Sweet potato	g/100 g		0*			0.3*	
		g/1 cup (140 g)		0			0.4	
Legumes	Beans, continental	g/100 g	0			0		
		g/0.5 cup (90 g)	0			0		
	Baked beans	g/100 g	0			0		
		g/0.5 cup (90 g)	0			0		

Table 1 (Continued)

Food	Amount according to serving sizes	Sorbitol			Mannitol		
		Present study	Published data	USDA	Present study	Published data	USDA
Fruits	Lima beans	g/100 g	0 [†]			0.1 [†]	
		g/0.5 cup (90 g)	0			0.1	
	Plum	g/100 g	2.4	0.6	0		0
		g/1 fruit (66 g)	1.6	0.4	0		0
	Apple	g/100 g	1.2*	0.3		0*	0
		g/1 fruit (165 g)	1.9	0.5		0	0
	Apricot	g/100 g	1.2	0.8	0		0
		g/1 fruit (112 g)	1.3	0.9	0		0
	Blackberries	g/100 g	4.1*			0*	
		g/10 berries (50 g)	2.1			0	
	Boysenberries	g/100 g	0		0		
		g/10 berries (80 g)	0		0		
	Carambola	g/100 g	0		0		
		g/1 fruit (116 g)	0		0		
	Cherries	g/100 g	0.7	1.0–2.1	0		0
		g/5 cherries (35 g)	0.3	0.3–0.7	0		0
	Grapes	g/100 g	0*	0.1		0*	0
		g/10 grapes (40 g)	0	0.0		0	0
	Longon	g/100 g	0.7*			0*	
		g/5 fruits (15 g)	0.1			0	
	Nectarine	g/100 g	1.0*	0.6		0*	0
		g/1 fruit (151 g)	1.5	0.9		0	0
	Peach	g/100 g	0.9*	0.2		0.5*	0
		g/1 fruit (145 g)	1.3	0.3		0.7	0
	Figs	g/100 g	0		0		
		g/1 fruit (50 g)	0		0		
	Pear	g/100 g	2.3*	2.3		0*	0
		g/1 fruit (166 g)	3.8	3.8		0	0
	Pomegranate	g/100 g	Trace		0.3		
		g/1 fruit (76 g)	Trace		0.2		
	Rhubarb	g/100 g	0		0		
		g/1 stalk (104 g)	0		0		
	Strawberries	g/100 g	0		0		
		g/5 berries (60 g)	0		0		
	Tamarillo	g/100 g	0		0		
		g/1 fruit (44 g)	0		0		
	Dried apple	g/100 g	1.9		0		
		g/0.5 cup (45 g)	0.9		0		
	Dried apricot	g/100 g	6.0		0		
		g/0.5 cup (67 g)	4.1		0		
	Dried, shredded coconut	g/100 g	0.6		0		
		g/0.5 cup (37 g)	0.2		0		
	Dried pear	g/100 g	8.1		0		
		g/6 pieces (27 g)	2.2		0		
	Prunes	g/100 g	10.8	12.0	0		0.0
		g/0.25 cup (80 g)	8.7	9.6	0		0.0
Grains and cereals	Pumpkin bread	g/100 g	0		0		
		g/1 slice (50 g)	0		0		
	Spelt bread, organic	g/100 g	0		0		
		g/2 slices (52 g)	0		0		

Table 1 (Continued)

Food	Amount according to serving sizes	Sorbitol			Mannitol		
		Present study	Published data	USDA	Present study	Published data	USDA
Raisin toast	g/100 g	0			0		
	g/1 slice (75 g)	0			0		
Naan bread	g/100 g	0			0		
	g/1 piece (46 g)	0			0		
Oat bran	g/100 g	0			0		
	g/1 cup (137 g)	0			0		
Wheat bran, processed	g/100 g	0			0		
	g/1 cup (63 g)	0			0		
Wheat bran, unprocessed	g/100 g	0			0		
	g/1 cup (63 g)	0			0		
Basmati rice	g/100 g	0			0		
	g/1 cup (137 g)	0			0		
Polenta/cornmeal	g/100 g	0			0		
	g/1 cup (254 g)	0			0		
Nuts	Almonds	0			0		
	g/10 nuts (12 g)	0			0		
Cashew	g/100 g	0			0		
	g/10 nuts (12 g)	0			0		
Peanuts	g/100 g	0			0		
	g/10 nuts (12 g)	0			0		
Beverages	Apple juice	0.5		1.0	0		0
	g/1 cup (250 mL)	1.1		2.1	0		0
Orange juice	g/100 g	0			0		
	g/1 cup (250 mL)	0			0		
Coconut milk	g/100 g	0.1			0		
	g/1 cup (250 mL)	0.3			0		
Beer	g/100 g	0			0		
	g/1 can (375 mL)	0			0		
Gin	g/100 g	0			0		
	g/30 mL	0			0		
Rum	g/100 g	0			0		
	g/30 mL	0			0		
Vodka	g/100 g	0			0		
	g/30 mL	0			0		
Whiskey	g/100 g	0			0		
	g/30 mL	0			0		
Wine, red	g/100 g	0			0		
	g/100 mL	0			0		
Wine, white	g/100 g	0			0		
	g/100 mL	0			0		
Other food products	'Sugarless' chewing gum	41.9			0		
	g/2 gum strips (4 g)	1.7			0		
	Horseradish sauce (wasabi)	11.1			0.3		
	g/1 tsp (5 g)	0.6			0.0		

Average serving sizes were obtained from FOODWORKS, version 6 (Xyris Software Australia Pty Ltd).

Shaded boxes indicate: not analysed or no data available.

Comparisons were made with previously published composition data taken from Muir *et al.* (2009)* and Biesiekierski *et al.* (2011)[†], as well as the USDA Nutrition Composition Database (US Department of Agriculture Agricultural Research Service, 2011).

Table 2 Baseline characteristics of irritable bowel syndrome (IBS) subjects and healthy controls

	IBS patients (<i>n</i> = 20)	Healthy controls (<i>n</i> = 21)	<i>P</i> -value
Ratio of men: women, <i>n</i>	5 : 15	3 : 18	0.45 [†]
Age (years)*	34 (27–47)	25 (22–48)	0.10 [‡]
Alcohol intake (g day ⁻¹)*	3 (0–7)	1 (0–2)	0.22 [‡]
Regular NSAID use [<i>n</i> (%)]	5 (25)	1 (5)	0.18 [†]

NSAID, nonsteroidal anti-inflammatory drug.

*Values are expressed as the median (interquartile range).

[†]Fisher's exact test; [‡]Mann–Whitney *U*-test.

the mean (95% CI) difference between AUC mannitol and AUC glucose was 2519 (1410–3628) ppm 4 h⁻¹. A strongly positive correlation between the hydrogen production after sorbitol and mannitol ingestion was also demonstrated ($r = 0.78$, $P < 0.0001$; Pearson's correlation).

Conversely, the patterns of breath hydrogen production differed between sorbitol and mannitol in the patients with IBS (Fig. 4b). Total breath hydrogen production after mannitol [601 (228) ppm 4 h⁻¹] was significantly lower than that for sorbitol [1629 (210); $P = 0.003$, paired *t*-test], although it was significantly higher in comparison than that after glucose [102 (42) ppm 4 h⁻¹; $P \leq 0.05$]. The mean (95% CI) difference in AUC between mannitol and glucose was 499 (–10.2–1008) ($r^2 = 0.29$). The mean (95% CI) difference was also substantial between AUC after sorbitol and that after glucose [1526 (1048–2004) ppm 4 h⁻¹, $r^2 = 0.82$]. Consistently, no correlation was found between hydrogen production in response to sorbitol or mannitol ($r = 0.42$, $P = 0.07$). Within this same cohort of malabsorbers, total breath

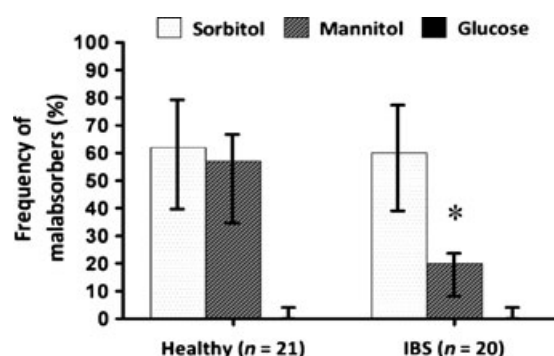


Figure 2 Proportion (%) of subjects with malabsorption of sorbitol or mannitol in patients with irritable bowel syndrome (IBS) (*n* = 20) and healthy controls (*n* = 21). Bars represent 95% confidence intervals. *Significantly different ($P = 0.02$) compared to healthy controls.

hydrogen production was significantly lower in the IBS group compared to that in the healthy controls after sorbitol ($P = 0.02$, unpaired *t*-test) and mannitol ($P = 0.003$) but not after lactulose ($P = 0.68$).

Breath methane production

In methane-producers, methane production was similar between challenges with sorbitol and mannitol in both healthy controls [$n = 6$; AUC sorbitol: 595 (155) ppm 4 h⁻¹ versus. mannitol: 476 (147) ppm 4 h⁻¹; $P = 0.56$, paired *t*-tests] and IBS patients [$n = 6$; sorbitol: 538 (210) ppm 4 h⁻¹ versus mannitol: 231 (76) ppm 4 h⁻¹; $P = 0.09$].

Relationship between polyol malabsorption and gastrointestinal symptoms

Polyol-associated overall abdominal symptoms appeared to be independent of the absorptive pattern of the

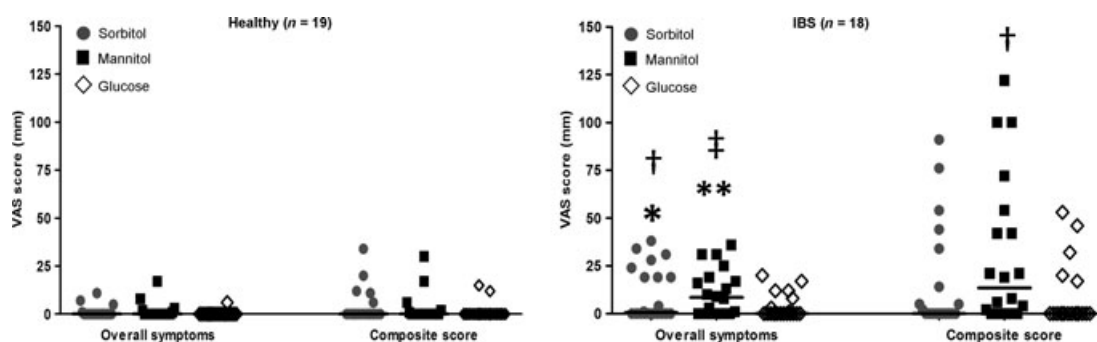


Figure 1 Comparison of 4-h overall gastrointestinal symptoms and composite scores of abdominal pain, wind and bloating, assessed by the visual analogue scale (VAS) (Montalto *et al.*), after sorbitol, mannitol and glucose challenges in healthy (*n* = 18) and irritable bowel syndrome (IBS) subjects (*n* = 20). Horizontal lines represent median VAS scores. Significant differences are shown: * $P = 0.05$ for overall symptoms after sorbitol and ** $P \leq 0.03$ for overall symptoms after mannitol compared to glucose (Wilcoxon sign-ranked test). Significant results for IBS patients compared to healthy controls are shown: [†] $P < 0.01$ and [‡] $P < 0.02$.

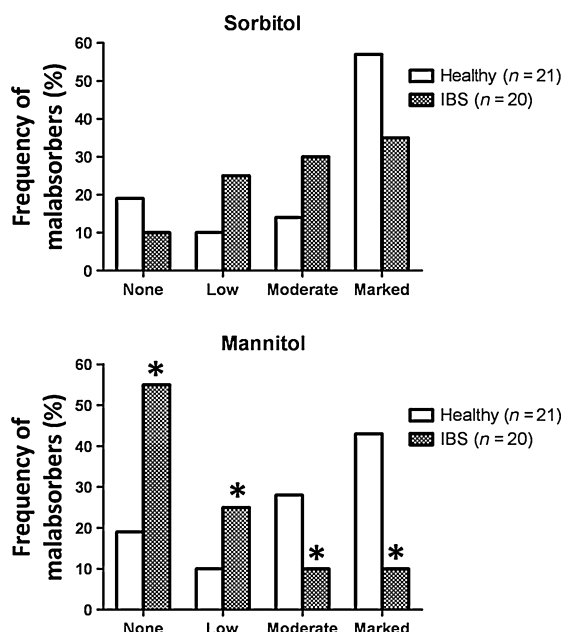


Figure 3 Frequency (%) of subjects in the different categories of polyol malabsorption estimated using semi-quantitative analyses between patients with irritable bowel syndrome (IBS) ($n = 20$) and healthy controls ($n = 21$). *Statistically significant differences between the proportion of patients with mannitol malabsorption and that in the healthy controls within each category ($P = 0.02$).

polyols. Thus, three of 12 versus five of eight ($P = 0.17$, Fisher's exact) with or without malabsorption of sorbitol, respectively, and three of four versus five of 16 ($P = 0.25$) of mannitol developed abdominal symptoms. Figure 5 shows the association of overall abdominal symptom scores with the semi-quantitative classification of extent of malabsorption in patients with IBS. No significant associations were found between the extent of malabsorption and symptom scores for either mannitol ($r = -0.07$, $P = 0.97$, Spearman's correlation) or sorbitol ($r = -0.15$, $P = 0.55$).

Discussion

As 6-carbon isomers that are absorbed by passive diffusion across the intestinal barrier, sorbitol and mannitol might be anticipated to show similar absorption patterns in any individual. Indeed, in agreement with a previous study (Wursch *et al.*, 1989), the absorption patterns in healthy volunteers were similar; approximately 40% completely absorbed each polyol and the patterns were concordant in almost all of them. By contrast, the findings in a demographically-matched population of patients with IBS were very different. First, double the proportion (80%) completely absorbed mannitol. Second, the absorption patterns were discordant in that three out of five

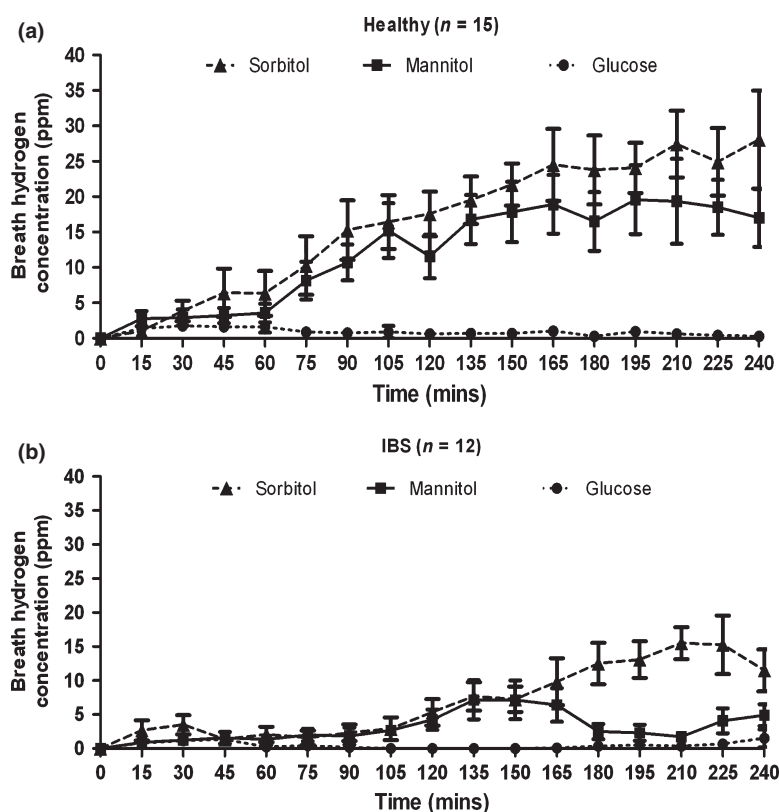


Figure 4 Breath hydrogen response over 4 h to the ingestion of sorbitol, mannitol and glucose in (a) healthy ($n = 15$) and (b) irritable bowel syndrome (IBS) subjects ($n = 12$) with sorbitol and/or mannitol malabsorption. Values are plotted as the mean (SEM).

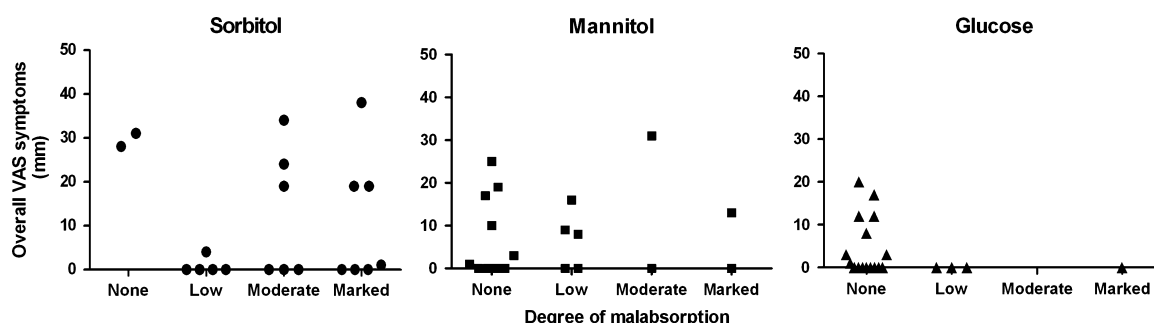


Figure 5 Severity of overall gastrointestinal symptoms according to visual analogue scale (VAS) in relation to the degree of malabsorption for sorbitol, mannitol and glucose in patients with irritable bowel syndrome (IBS) ($n = 20$). No correlation was observed for sorbitol (Spearman's $r = -0.15$, $P = 0.55$) or mannitol ($r = -0.07$, $P = 0.97$).

patients had different patterns of absorption for mannitol and sorbitol. Third, the ability to absorb both sorbitol and mannitol is enhanced in patients with IBS, as shown by lower total hydrogen production in those with malabsorption, despite similar hydrogen production to lactulose. Finally, both polyols appeared to trigger symptoms independently of its absorption pattern.

Previously, studies using breath hydrogen (Wursch *et al.*, 1989) or recovery in ileostomy effluent (Saunders & Wiggins, 1981; Beaugerie *et al.*, 1997) have consistently demonstrated at least partial absorption of sorbitol and mannitol, with estimates suggesting that an average of 26% and 40% of 10-g doses of sorbitol and mannitol, respectively, are absorbed. The present study has similarly found evidence for substantial absorption of both polyols in healthy and IBS subjects. What has not been reported previously is that the degree of absorption of sorbitol and mannitol was at least two-fold greater from the small intestine in patients with IBS than in healthy controls, as shown by a significantly lower hydrogen production. This observation was not a reflection of different functional capabilities of the intestinal microbiota in the two groups because their hydrogen-producing capacity was similar after lactulose and there was no evidence of diversion of gas production towards a methane pathway, as we previously observed in when a low FODMAP diet is consumed (Ong *et al.*, 2010). The reason for the differences must lie in the physiology of the intestine. It might reflect slower oro-caecal transit, as defined by the first rise of breath hydrogen after lactulose (Madsen *et al.*, 2006). For molecules that are slowly and passively absorbed, this would give more time for absorption to occur. Alternatively, the differences in absorption patterns between healthy and IBS subjects might reflect epithelial abnormalities, which have been reported in some subgroups of patients with IBS (Marshall *et al.*, 2004; Dunlop *et al.*, 2006). Further enquiry is warranted to provide an explanation for these observations.

Perhaps the most intriguing observation was the discordance between sorbitol and mannitol absorption in patients with IBS but not in healthy controls. As shown by the 4-h hydrogen production, mannitol absorption was almost three-fold greater than that of sorbitol, a finding that has not been observed previously. This is unlikely to be artefactual because breath hydrogen tests have good reproducibility (Welsh *et al.*, 1981; Barillas-Mury & Solomons, 1987) and the order of testing was randomised. Two reasons for the discordance are possible. First, bacterial fermentation of mannitol may have different kinetics to those for sorbitol in the IBS group. Sorbitol has slower and more complex bacterial fermentation than rapidly fermentable sugars such as lactose and fructose (Mishkin *et al.*, 1997; Clausen *et al.*, 1998). In support of this, the pattern of hydrogen production after mannitol over the 4-h period was different to that for sorbitol in IBS patients. A comparison of the kinetics of fermentation of sorbitol and mannitol has not been reported. Another likely explanation, however, is that, despite the structural similarities that exist between the two polyols, the different orientation of the hydroxyl position in each polyol may result in dissimilarities in polyol–water interactions (Grigera, 1988) and, subsequently, their passage across the intestinal barrier. In water, mannitol adopts a planar configuration that attracts more water molecules and may enhance its permeation via water-filled intracellular pores (Grigera, 1988). It is also possible that the unstirred water layer, suggested to regulate osmotic gradients for the passive uptake of water-soluble molecules (Barry & Diamond, 1984), is a key player in differentiating permeation rate between sorbitol and mannitol. This unstirred water layer has also been shown to be altered in disease. Strocchi *et al.* (1996) demonstrated that patients with coeliac disease were shown to have increased jejunal unstirred water layer thickness compared to healthy controls, reducing nutrient absorption. Alterations in this layer in patients with IBS have yet to be examined but may potentially

explain the discordance in sorbitol and mannitol absorption.

As reported previously (Fernandez-Banares *et al.*, 1993), an increase in abdominal symptoms was induced by sorbitol and mannitol over the duration of the breath testing in patients with IBS but not in healthy controls. However, the induction of symptoms for both polyols was independent of whether the polyol was malabsorbed and fermented. Over this short duration, another mechanism other than fermentation-driven gaseous distension of the intestine must underlie symptom exacerbation. Fluid distension of the small intestine is proposed because the slowly-absorbed polyols can exert an osmotic effect around most of the small intestine, as elegantly shown by magnetic resonance methodology (Marciani *et al.*, 2010). Hence, the implication for dietary therapy is that these polyols can trigger symptoms whether they enter the large bowel to be subsequently fermented or not, as a result of their slow rate of absorption and osmotically-mediated distension of the small intestine. Breath testing to assess polyol absorption, as is frequently performed for fructose and lactose, may not then be clinically useful or relevant. Alternatively, mannitol and sorbitol absorption might directly affect the function of the enteric nervous system via local osmolytic effects or the involvement of inflammatory mediators. Perhaps mast cell-histamine release, suggested as an explanation for anaphylactoid reactions to mannitol in several case reports (Findlay *et al.*, 1983; Eggleston *et al.*, 1987; Hegde & Venkatesh, 2004), may be involved.

Such an effect on symptom induction reinforces attention to those polyols in the design of dietary therapy to alleviate IBS symptoms. Thus, sorbitol and mannitol are appropriately included in the class of poorly absorbed short-chain carbohydrates, termed FODMAPs, for which an accumulating evidence-base is now available as major dietary triggers of functional gut symptoms (Gibson & Shepherd, 2010). The principles of the low FODMAP diet indicate that individual FODMAPs have additive effects on symptoms and should not be considered separately but rather together in dietary interventions. The results of the present study suggest not only that both sorbitol and mannitol should be restricted in patients with IBS, but also that this decision should be independent of the demonstration of their malabsorption via breath hydrogen testing. Whether acute challenges with sorbitol and mannitol serve as a better guide of gastrointestinal tolerance for patients who may benefit from such restrictions, as recently suggested for fructose (Wilder-Smith *et al.*, 2013), would require further study.

Food composition data from the present study reinforce previously published data showing that the intake of up to 10 g day⁻¹ from foods with naturally-occurring

polyols can be achieved in patients with IBS. Fruits, particularly in their dried forms such as prunes and dried pears, are concentrated sources of sorbitol that may be the major problem FODMAP, instead of the much-maligned fructose in such sources. Existing food composition data indicating that certain vegetables are relatively rich sources of mannitol were confirmed. Amounts approaching 10 g day⁻¹ mannitol can be derived from large intake of these vegetables, particularly celery, cauliflower, mushrooms and snow peas. However, it may not require such a dose when consumed in combination with sorbitol or other FODMAPs, as discussed above. In comparison with published data from the USDA, the quantities of sorbitol in these fruits were quite similar to those reported in the present study, whereas there were some variations with respect to the mannitol content of food. These differences can be explained by several factors, including seasonal and climate variations, fruit or vegetable varieties analysed, as well as differences in the quantification methodologies used (Makinen & Soderling, 1980; Wrolstad & Shallenberger, 1981).

Conclusions The present randomised, double-blinded, placebo-controlled cross-over study has demonstrated distinct differences in the small intestinal handling of sorbitol and mannitol between healthy and IBS individuals. By contrast to healthy subjects who appear to absorb both polyols to an almost similar extent, patients with IBS not only have a greater ability to absorb both polyols, but also absorb mannitol more readily than sorbitol. The mechanisms by which such differences occur require clarification. Despite superior absorption, both sorbitol and mannitol specifically induced abdominal symptoms, suggesting that mechanism(s) other than (or additional to) their fermentation are involved. Such observations suggest that the dietary restriction of these polyols should be included in dietary restriction of FODMAPs for patients with IBS, irrespective of their ability to absorb them according to breath hydrogen results. Comprehensive food knowledge on polyol content not only eases the design of such dietary therapy, but also provides prebiotic food sources for asymptomatic individuals. Additionally, the role of xylitol and other commonly-used polyols in the food industry (Zumbe *et al.*, 2001) as dietary triggers in IBS also warrants further study because evidence from the healthy population cannot be extrapolated to this patient population.

Acknowledgments

We would also like to thank all laboratory research staff and breath testing staff at Box Hill Hospital for the help and technical support received.

Conflict of interests, source of funding and authorship

The authors declare that there are no conflicts of interest.

No external funding was received for the present study. JGM, JSB and PRG designed the study. KL and RR conducted the food analysis. CKY, HLT and DRVL carried out the clinical study. CKY analysed and interpreted study data. CKY, JGM, JSB, DRVL and PRG drafted and revised the manuscript for publication. All authors approved the final manuscript submitted for publication.

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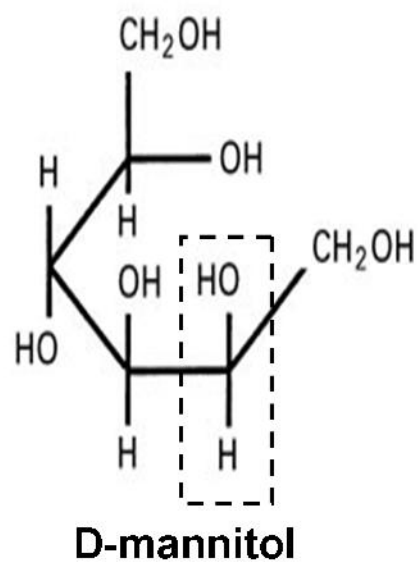
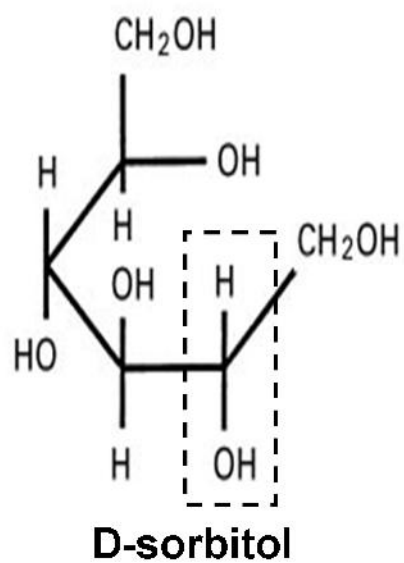
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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Isomeric configuration of sorbitol and mannitol. Dotted boxes highlight the orientation of their hydroxyl group.



Supplementary Figure 1 Isomeric configuration of sorbitol and mannitol. Dotted boxes highlight the orientation of their hydroxyl group.