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Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome

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Key words
breath testing, carbohydrates, dietary therapy, FODMAPs, gastrointestinal symptoms, irritable bowel syndrome.

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Conflicts of interest: S.J.S has published cookbooks directed towards issues of dietary fructan restrictions, fructose malabsorption and celiac disease. She has also published shopping guides for low FODMAPs and low fructose and fructan foods.

Abstract

Background and Aim: Reduction of short-chain poorly absorbed carbohydrates (FODMAPs) in the diet reduces symptoms of irritable bowel syndrome (IBS). In the present study, we aimed to compare the patterns of breath hydrogen and methane and symptoms produced in response to diets that differed only in FODMAP content.

Methods: Fifteen healthy subjects and 15 with IBS (Rome III criteria) undertook a single-blind, crossover intervention trial involving consuming provided diets that were either low (9 g/day) or high (50 g/day) in FODMAPs for 2 days. Food and gastrointestinal symptom diaries were kept and breath samples collected hourly over 14 h on day 2 of each diet.

Results: Higher levels of breath hydrogen were produced over the entire day with the high FODMAP diet for healthy volunteers (181 ± 77 ppm.14 h *vs* 43 ± 18; mean ± SD $P < 0.0001$) and patients with IBS (242 ± 79 *vs* 62 ± 23; $P < 0.0001$), who had higher levels during each dietary period than the controls ($P < 0.05$). Breath methane, produced by 10 subjects within each group, was reduced with the high FODMAP intake in healthy subjects (47 ± 29 *vs* 109 ± 77; $P = 0.043$), but was not different in patients with IBS (126 ± 153 *vs* 86 ± 72). Gastrointestinal symptoms and lethargy were significantly induced by the high FODMAP diet in patients with IBS, while only increased flatus production was reported by healthy volunteers.

Conclusions: Dietary FODMAPs induce prolonged hydrogen production in the intestine that is greater in IBS, influence the amount of methane produced, and induce gastrointestinal and systemic symptoms experienced by patients with IBS. The results offer mechanisms underlying the efficacy of the low FODMAP diet in IBS.

Introduction

Irritable bowel syndrome (IBS) is the most common disorder seen in gastroenterological practice, affecting approximately 15% of the population.[1] This condition is characterized by abdominal pain, bloating, wind, distension and altered bowel habit but with no abnormal pathology.[2] It is often stated that diet has a major role in triggering symptoms. Dietary factors such as citrus fruits, cereals, dairy foods, some fiber, caffeine and alcohol have all been implicated[3] but dietary trials have produced mixed results and in general have offered little guidance for the management of IBS.

Recent work has identified a collection of short-chain carbohydrates that are poorly absorbed in the small intestine, FODMAPs (Fermentable Oligo- Di- and Mono-saccharides And Polyols)[4–6] as important triggers of functional gut symptoms. Open studies have suggested that three out of four patients with IBS will respond well symptomatically to restriction of FODMAP intake,[7] and a randomized placebo-controlled rechallenge trial confirmed that the benefit was likely to be due to reduction of FODMAP intake.[8] Breath hydrogen testing helps identify which specific sugars behave as FODMAPs in the individual.[9]

It has been hypothesized that FODMAPs trigger gastrointestinal symptoms in people with visceral hypersensitivity or abnormal motility responses[10,11] largely by inducing luminal distension via a combination of osmotic effects and gas production related to their rapid fermentation by bacteria in the small and proximal large intestine.[6] Indeed, a recent study in ileostomates showed that a diet high in FODMAPs increased the volume of liquid and fermentable load likely to be delivered to the proximal colon as postulated.[12] The fate of the fermentable load is, however, less clearly defined. Fermentation will generate the gases hydrogen and carbon dioxide, but the rate and time course at which that occurs in response to FODMAPs, and the fate of the hydrogen liberated are not known. Hydrogen can diffuse in to the circulation to be excreted via the lungs, may be used to form methane by methanogens, and may be incorporated into volatile end-products such as acetate or sulfides.[13,14] The amount of luminal distension induced will therefore depend at least in part on the disposal mechanisms of hydrogen atoms liberated during fermentation.

The aim of the present study was to examine the effects of diets that varied in their FODMAP content on two of the disposal mechanisms, the production of hydrogen and methane, in terms of the relative amounts and time course of production and in the relation to the induction of functional symptoms. Since FODMAPs induce symptoms more readily in patients with IBS than in those without functional gut symptoms, the effects on disposal mechanisms were compared in these groups to examine the hypothesis that the FODMAPs potentially induce more distension in patients with IBS.

Methods

Subjects

Two groups of fifteen subjects were studied. Fifteen healthy volunteers were recruited by advertising at Deakin University. All had no gastrointestinal symptoms and believed themselves to be healthy. Fifteen patients with IBS fulfilling Rome III criteria[15] were recruited at the Functional Gut Disorders Clinic of Box Hill Hospital. The patients had no medically significant co-morbidities. All subjects were at least 18 years old, not pregnant and had not taken probiotic supplements or antibiotics for at least 8 weeks prior to the study. None had undergone prior dietary education regarding their IBS. No subjects reported gastrointestinal symptoms following consumption of milk. The protocol was approved by the Eastern Health Research and Ethics Committee and the Deakin University Human Ethics and Research Committee.

Study design

A randomized, single-blinded, crossover intervention trial was carried out. During 7 days of baseline assessment, participants completed a 7-day food diary, a daily questionnaire regarding gastrointestinal symptoms, and daily questions on their physical activity. They were then randomized according to a computer-generated table to receive either a low FODMAP (LFD) or a high FODMAP (HFD) diet containing 9 g and 50 g FODMAPs, respectively, for 2 days. In terms of FODMAP content the subjects were blinded to the nature of the diet being consumed. All food was provided to the subjects. There was a 7-day washout period before subjects crossed over to the alternate diet to ensure the symptom level prior to commencing the second diet was similar to that prior to the first dietary period. Subjects recorded food and fluid consumed during the study. Breath samples were collected hourly for 14 h on the second day of each dietary period, commencing prior to breakfast (i.e. one fasting sample). The gastrointestinal symptom questionnaire was completed each evening and physical activity was documented daily. In order to minimize variables that might affect breath hydrogen production, subjects were also asked to maintain good oral hygiene during the breath testing phase by brushing their teeth before taking their first breath sample and to refrain from smoking and vigorous physical activity.[16,17]

Dietary interventions

The quantity of food provided for each diet was determined by the energy requirements of the subjects as calculated by the Schofield equations and according to their respective age, gender, weight and activity level. The two diets were matched for content of total energy, total starch, protein and fat. Indigestible long-chain carbohydrates-total dietary fiber and resistant starch (RS) were also kept constant across treatment periods. As no comprehensive food composition tables exist for RS, estimates of RS composition of foods were carried out using a combination of published information[18] and direct measurement using a previously validated RS assay.[19] As the low FODMAP diet was lower in RS than the high FODMAP diet, wheat muffins containing high amylose maize (high in RS) were added to balance the RS content. An example of the test diets provided on day 2 of the study is shown in Table 1. All food used was purchased from the local supermarket with the exception of the 355 mL can of soda that was sweetened with high fructose corn syrup (imported from the USA) and was obtained from a specialty supermarket.

Samples of food and drinks used in the study were separately analyzed for their content of fructose, glucose, lactose, sugar polyols (sorbitol and mannitol), galacto-oligosaccharides (GOS, raffinose and stachyose) by high performance liquid chromatography (HPLC) as previously described.[20] Total fructan content was measured using an enzymatically-based assay kit (Megazyme International Ireland Ltd, Wicklow, Ireland), as per the manufacturer's instructions.[21] Results from laboratory analysis were added to the Foodworks database (Foodworks Professional 2007, Xyris Software, Highgate Hill, QLD, Australia) to enable the complete assessment of the macronutrient and FODMAP dietary intake during the study.

Breath sample collection

Breath samples were collected every hour for 14 h into 250 mL sample holding bags (Quintron Instrument Co., Milwaukee, Wisconsin). The first sample of the day was a fasting sample and taken prior to breakfast. Samples were then taken hourly for a total of 14 h. All of the supplied food was to be consumed within the 14-h time period. The exact time each subject consumed their meals varied slightly between individuals but was kept constant within each individual during the two dietary periods (i.e. each person was their own control in the crossover design). Breath samples were analyzed for hydrogen and methane within 24 h using a Quintron Microlyzer Model DP Plus (Quintron Instrument Co., Milwaukee, WI, USA). Total breath gas production over the 14-h period was then calculated from the graphed area-under-the-curve (AUC) using the trapezium rule and expressed in parts per million over 14 h (ppm.14 h). A subject was considered to produce hydrogen or methane if the AUC was more than 10 ppm.14 h during at least one of the dietary periods.

Assessment of gastrointestinal symptoms

All subjects were asked to complete the gastrointestinal symptom questionnaire at the same time in the evening of each day. The

Table 1 Examples of the low and high FODMAP diets (9 MJ/day)

Meal	Low FODMAP diet	High FODMAP diet
Breakfast	3/4 cup rice flakes	2 Weet-bix
	1/2 cup lactose-free milk	1/2 cup low fat milk
	1 slice of corn/rice bread	1 slice rye bread
	1 tsp margarine	1 tsp margarine
	1 tsp vegemite	1 tsp honey
	Orange cordial 100 mL	200 mL apple juice
	Tea/coffee with lactose-free milk	Tea/coffee with milk
Morning tea	1 orange	1 pear
	Tea/coffee with lactose-free milk	Tea/coffee with milk
Lunch	130 g rice/corn pasta with bolognaise sauce†	140 g durum wheat pasta with bolognaise sauce†
	355 ml can lemonade sweetened with sucrose	355 mL can soda sweetened with high fructose corn syrup
Afternoon tea	1 mandarin	1 apple
	Tea/coffee with lactose-free milk	Tea/coffee with milk
Dinner	Salmon patties	Vegetable patties‡
	1 slice cheddar cheese	4 lettuce leaves
	4 lettuce leaves	3 Spanish onion rings
	2 slices tomato	35 g cottage cheese
	4 slices cucumber	
Supper and snacks	Hot drinking chocolate with lactose-free milk.	Ecco (caro) with low fat milk.
	Chocolate wheat muffins§	Chocolate wheat muffins§
	Two pellets of sucrose-containing chewing gum	Two pellets of sorbitol-containing chewing gum

†Low FODMAP bolognaise sauce made without using onion, garlic or mushroom, high FODMAP bolognaise sauce made including onion, garlic mushroom and also a small quantity of Jerusalem artichokes were added. ‡High FODMAP vegetable patties contain canned chickpeas, onion and garlic. §Low FODMAP muffins had high amylose maize starch added to correct for differences in resistant starch (RS) content between the two diets. High FODMAP wheat muffins contained low amylose (waxy) maize.

questionnaire comprised five categories for general gastrointestinal symptoms (abdominal pain/discomfort, abdominal bloating/distension, wind, nausea, heartburn and lethargy). Bowel function was noted but not analyzed due to the heterogeneity of bowel habits across the subjects. The symptoms were rated using a Likert scale 0 to 3, where 0 = none, 1 = mild, 2 = moderate and 3 = severe. A composite score for abdominal symptoms of IBS was calculated by adding the scores for abdominal pain, bloating and wind.

Statistical analysis

Statistical analysis of all data was done using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Outliers, no more than one per outcome variable, were removed. Comparisons between diets for nutrient composition, breath hydrogen and methane production and physical activity levels were made using a Student's or paired or unpaired samples *t*-test, whereas results relating to changes in gastrointestinal symptoms used the Wilcoxon signed rank test for categorical variables. Proportions were compared using Fisher's exact test. A *P*-value of 0.05 or less was considered statistically significant.

Results

Subject details and compliance

Fifteen healthy subjects were studied, median age was 23 (range 22–68 years) and nine were female. Their body mass index was 22.4 (19.7–30.4) kg/m^2. Fifteen patients with IBS were also studied, median 41 (22–59) years and 13 were female. Their body mass index was 21.6 (18.7–35.2) kg/m^2. Predominant bowel habits for patients with IBS were diarrhea in four, constipation in seven, mixed in two and unclassified in two. All participants were hydrogen-producers, but 10 (67%) healthy subjects and 11 (73%) patients with IBS produced methane. There were no significant differences between the two groups for any index.

All subjects completed the study, consumed the diet as requested, and kept levels of physical activity the same during both test dietary periods. During the two test dietary periods, actual dietary intake was assessed from the food diaries. The composition of the diets consumed is shown in Table 2. The two test diets were similar for total energy, protein and starch, but fat intake was significantly lower during the HFD dietary period for both healthy and IBS. Potentially fermentable indigestible long-chain carbohydrates—dietary fiber and resistant starch—were kept constant and did not differ significantly across the two dietary periods. As planned, total FODMAP intake varied significantly between the two test diets being 48–50 g/day for the HFD compared with 8–9 g/day for the LFD.

Breath hydrogen production

All subjects were hydrogen-producers. The profiles of breath hydrogen production over 14 h on day 2 of each dietary period for both healthy volunteers and IBS patients are shown in Figure 1. By allowing subjects to consume the diet and collect breath samples over the day, levels of breath hydrogen tended to rise over the day.

Table 2 Composition of dietary intake by healthy subjects and patients with irritable bowel syndrome (mean ± SEM)

Dietary component		Healthy			Irritable bowel syndrome		
		Low FODMAP	High FODMAP	*P*-value	Low FODMAP	High FODMAP	*P*-value
Total energy (kJ)		7839 ± 258	8124 ± 197	0.093	7976 ± 352	8178 ± 419	0.603
Total protein (g)		78 ± 3	74 ± 2	0.018	82 ± 4	73 ± 44	0.054
Total fat (g)		62 ± 2	53 ± 2	$P < 0.0001$	71 ± 3	54 ± 34	$P < 0.0001$
Total starch (g)		119 ± 4	128 ± 4	0.018	132 ± 54	140 ± 84	0.388
Dietary fiber (g)		27 ± 0.8	28 ± 0.8	0.154	27 ± 1.0	26 ± 1.3	0.142
Resistant starch (g)		6.9 ± 0.3	6.6 ± 0.3	0.100	6.3 ± 0.4	5.6 ± 0.3	0.096
Monosaccharides	Glucose (g)	22.1 ± 0.8	40.9 ± 1.5	<0.0001	18.7 ± 1.0	42.8 ± 3.3	<0.0001
	Fructose (g)	18.7 ± 0.7	55.4 ± 1.6	<0.0001	15.5 ± 1.0	61.7 ± 4.6	<0.0001
	Excess fructose (g)	*0*	*14.5 ± 1.2*	<0.0001	*0*	*18.9 ± 2.0*	<0.0001
Disaccharides	*Lactose (g)*	*4.4 ± 0.4*	*13.7 ± 0.6*	<0.0001	*5.3 ± 0.7*	*16.2 ± 0.9*	<0.0001
Sugar polyols	*Sorbitol (g)*	*0*	*5.4 ± 0.3*	<0.0001	*0*	*5.1 ± 0.3*	<0.0001
	Mannitol (g)	*0*	*0.1 ± 0.01*	<0.0001	*0.01 ± 0.01*	*0.1 ± 0.02*	<0.0001
Oligosaccharides	*Fructans (g)*	*2.5 ± 0.1*	*12.5 ± 0.9*	<0.0001	*2.4 ± 0.2*	*7.9 ± 0.6*	<0.0001
	GOS (g)	*1.4 ± 0.1*	*1.8 ± 0.1*	0.0003	*1.6 ± 0.9*	*2.0 ± 0.1*	0.0300
Total FODMAPs† *(g)*		*8.3 ± 0.4*	*48.1 ± 2.2*	<0.0001	*9.3 ± 0.7*	*50.2 ± 2.7*	<0.0001

Dietary fiber was calculated using Foodworks dietary software which is based on the Australian Food composition tables. Resistant starch was calculated using published[18] or by direct analysis as described.[19] FODMAP carbohydrates are shown in italics. †Total FODMAPs = excess fructose + lactose + sorbitol + mannitol + fructans + galacto-oligosaccharides (GOS). Foods were analyzed directly as described in the methods. Results from laboratory analysis were added to the Foodworks database.

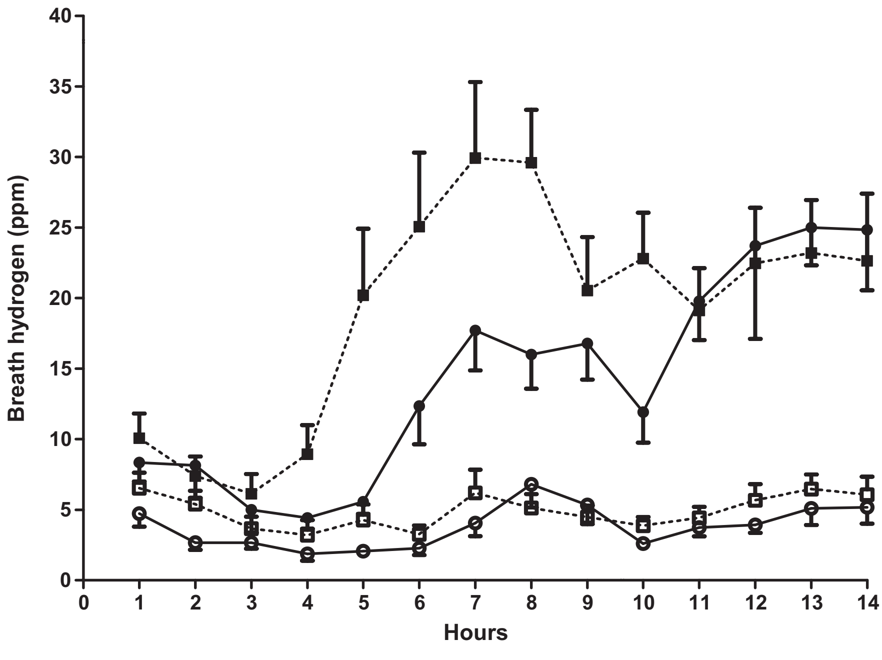

Figure 1 Profiles of breath hydrogen ($n = 15$ (irritable bowel syndrome [IBS]) and $n = 14$ (healthy controls), mean ± SEM) production over 14 h of each dietary period in healthy subjects and patients with IBS on high FODMAP diets (HFD) and low FODMAP diets (LFD). Total breath hydrogen was significantly greater on the HFD diet in both groups ($P < 0.0001$, paired *t*-test test). Patients with IBS produced significantly more breath hydrogen over the 14-h period than healthy controls during both the HFD ($P = 0.039$, unpaired *t*-test) and LFD ($P = 0.025$). One outlier from the healthy control group for breath hydrogen was removed (86ppm.14h [LFD] and 400ppm.14h [HFD]). –●–, Healthy—HFD; –○–, Healthy—LFD; ··■··, IBS—HFD; ··□··, IBS—LFD.

The AUC for breath hydrogen was significantly higher during the high FODMAP diet than the low FODMAP diet for both healthy volunteers (LFD, 43 ± 18 *vs* HFD, 181 ± 77 ppm.14 h; $P < 0.0001$; paired *t*-test) and patients with IBS (62 ± 23 *vs* 242 ± 79 ppm.14 h; $P < 0.0001$) (Fig. 1). Patients with IBS produced more hydrogen gas (AUC) than healthy controls during both the low FODMAP ($P = 0.025$, unpaired *t*-test) and high FODMAP ($P = 0.039$) dietary periods (Fig. 1). Individual results are also shown in Figure 2.

Breath methane production

Ten of the 15 subjects in each group were considered methane-producers. The patterns of breath methane (AUC) over the 14 h are shown in Figure 3. For healthy volunteers, there was significantly less breath methane produced during the HFD (47 ± 29 ppm.14 h) compared with that during the LFD (109 ± 77 ppm.14 h; $P = 0.043$) (Fig. 4). In contrast, patients with IBS had no change in breath methane with the HFD (126 ± 153 ppm.14 h) compared

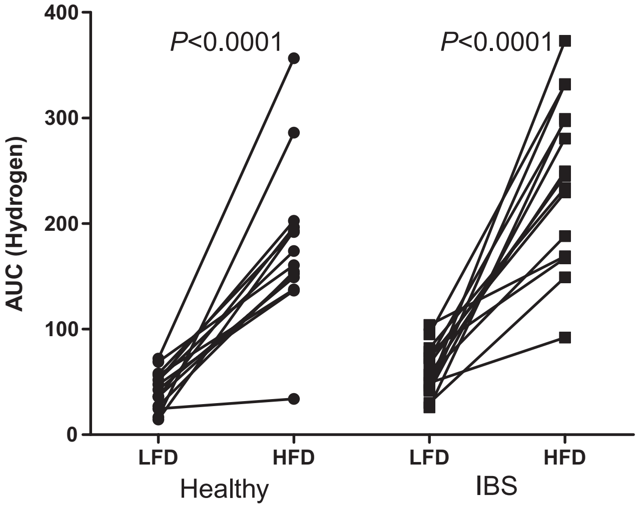

Figure 2 Individual responses in breath hydrogen ($n = 15$ (irritable bowel syndrome [IBS]), $n = 14$ (healthy) shown as area-under-the-curve) to low and high FODMAP diets in healthy subjects and patients with IBS. Total breath hydrogen was significantly greater on the high FODMAP diet in both groups ($P < 0.0001$, paired *t*-test test). Outlier was removed.

with that on the LFD (86 ± 72 ppm.14 h; $P = 0.280$). There was no significant difference in methane gas production between patients with IBS and healthy controls during either the LFD ($P = 0.499$) and HFD ($P = 0.125$) dietary periods.

Gastrointestinal symptoms

Since the effects of the diets on symptoms were similar at the end of the first and second days of the dietary periods, only day 2 results are shown. Symptom scores during the low and high FODMAPs diet for healthy subjects and patients with IBS were assessed according to a self-rating Likert scale where 0 = no symptoms, 1 = slight, 2 = moderate, 3 = severe are shown in Table 3. In patients with IBS all symptoms were significantly worse with the HFD when considered individually (Table 3). In the healthy subjects, the only symptom to change significantly was an increase in the passage of flatus (Table 3). A composite IBS symptom score that included the most commonly reported IBS gastrointestinal symptoms (abdominal pain, bloating and wind) was significantly higher for IBS patients during the HFD (median 6; range 2–9) than during the LFD (2; 0–7; $P = 0.002$). In healthy volunteers, the composite score was also higher during the HFD (3; 0–5 *vs* 1; 0–4; $P = 0.014$), but this was due to the increased flatus passed.

In the IBS group, upper gastrointestinal symptoms and lethargy increased during the HFD (Table 3). There was no association of the pattern of hydrogen and methane production with the induction of symptoms (data not shown).

Discussion

Luminal distension is a major stimulus for the induction of gastrointestinal symptoms associated with IBS. The predominant way that diet can potentially alter the volume of contents within the

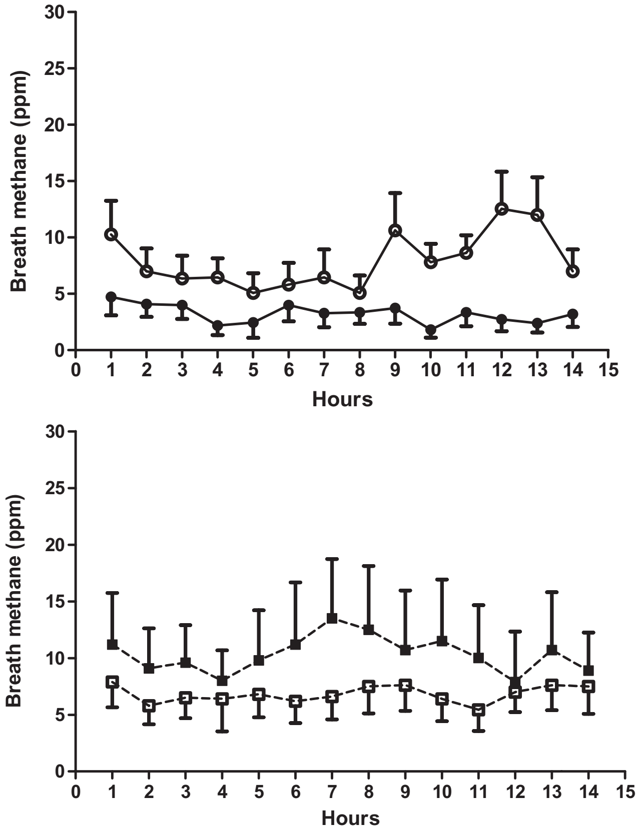

Figure 3 Profiles of breath methane ($n = 10$, mean ± SEM) production over 14 h of each dietary period in healthy subjects and patients with irritable bowel syndrome (IBS) on low FODMAP diets (LFD) and high FODMAP diets (HFD). For healthy controls only total breath methane was lower during the HFD than the LFD ($P = 0.044$). Data from non-methane producers were not included and data from one outlier was removed. —●—, Healthy—HFD; —○—, Healthy—LFD; ··■··, IBS—HFD; ··□··, IBS—LFD.

intestinal lumen is via intraluminal gas production. The present study has demonstrated that dietary manipulation of poorly absorbed short-chain carbohydrates (FODMAPs) can impact on the total amount of gastrointestinal gas production and the spectrum of gas produced (hydrogen *vs* methane) in healthy individuals and in hydrogen production in patients with IBS. It can induce gastrointestinal symptoms and systemic symptoms predominantly in those with IBS.

The two test diets used were matched for all carbohydrate substrates except FODMAPs that potentially would be available for bacterial fermentation in the distal small and large intestine. Thus, contents of resistant starch and non-starch polysaccharide were similar, but the amount of oligosaccharides, fructose, lactose and polyols differed by approximately 40 g. Furthermore, all food consumed was provided to the participants and their adherence to the dietary protocol was high. Thus, it was anticipated that the pattern of gas production in response to the two test diets would reflect the effects of the FODMAP content of the food consumed. While there was less fat consumed during the high FODMAP diet by both healthy and IBS subjects, it is unlikely that this would have

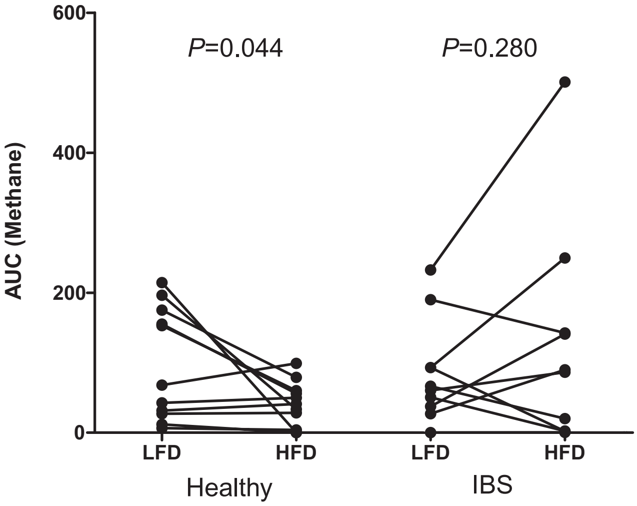

Figure 4 Individual responses in breath methane ($n = 10$) shown as area-under-the-curve to low and high FODMAP diets in healthy subjects and patients with irritable bowel syndrome (IBS). Total breath methane was significantly less in the healthy subjects on a high FODMAP diet ($P = 0.044$, paired *t*-test), but no differences were observed for the patients with IBS. Non-methane producers not included. One outlier from the healthy control group for breath methane was removed (318 ppm.14 h [LFD] and 256 ppm.14 h [HFD]).

contributed to the observed increase in gas or symptoms. Indeed, higher (not lower) fat intake has been associated with functional gastrointestinal disorders[22] and with impaired gas clearance and induction of symptoms.[10] The HFD (low fat, high FODMAP) was associated with considerably greater gas production than that associated with the LFD (higher fat, low FODMAP), and the gas was produced over the entire 14-h period of observation.

Subjects with IBS produced more hydrogen gas than healthy controls during both the low and high FODMAP dietary periods. Breath hydrogen output was fourfold greater during the HFD. Paradoxically, methane output did not increase during the HFD, despite greater hydrogen production. Indeed, its output significantly fell in the healthy volunteers. These observations imply that hydrogen produced with a high FODMAP load will occupy a relatively greater space than that produced when the FODMAP load is low, since four liters of hydrogen are used to produce one liter of methane.[23] Conversely, reducing FODMAP intake is associated with a relative shift towards methane production in healthy subjects and therefore lower luminal gas volumes in those with methanogenic bacteria.

Mechanisms underlying this 'switch' away from methane production in association with a high luminal FODMAP load in healthy volunteers have not been defined. This change in methane production in healthy controls may be as a result of change in the functional capabilities of the methanogenic organisms. For example, there is some evidence that under more acidic conditions, the activity of some methanogens, such as Clostridia,[24] is reduced. A high FODMAP load will lead to greater production of short-chain fatty acids and subsequent acidification of the lumen may then inhibit methanogenic activity. Also, any osmotic effect associated with the HFD[12] could result in faster transit through the colon, which may inhibit methanogenesis, since purging can reduce methane production.[25]

Why this switch was not observed in some patients with IBS also requires examination. It presumably relates to the balance or dysbiosis of the colonic microbiota compared with the eubiosis in healthy subjects. There is some evidence for differences in the spectrum of bacteria and their functional capabilities in patients with IBS.[26] Also, in patients with IBS, bacteria (including methanogens), tend to be located more diffusely along the gastrointestinal tract (i.e. small intestinal bacterial overgrowth, SIBO).[27] The lack of switch away from methanogenesis in the presence of luminal FODMAPs might be another reflection of such functional and locational abnormalities in colonic microbiota associated with IBS.

Methane may have more functional significance beyond its volume. Methanogenesis has been strongly associated with constipation.[28–30] Six of the seven constipated patients with IBS in the present study were methane-producers. There is circumstantial evidence that methanogenesis is associated with slower colonic transit and direct methane perfusion into the distal small bowel of dogs slows intestinal transit.[31] The higher methane production associated with the LFD might therefore contribute to a tendency to slow transit and increase the rate of constipation, while a reduction of total methane production might shorten transit time, and benefit IBS subjects with established constipation or at increased risk from developing a period of constipation. The time course of the present study was too short to gauge the effect of the dietary changes on bowel function, but this aspect warrants further investigation to evaluate its clinical significance.

The significance of these observations and implications to patients with IBS are unclear since the overall effect of altering FODMAP intake did not change the methane production. The patients with IBS were heterogeneous in their predominant bowel pattern and only 10 patients were methane-producers. Larger cohorts of more homogeneous patients with IBS will need to be studied in order to know whether the effects of FODMAPs on methanogenesis observed in the more homogeneous population of healthy subjects are relevant to those with functional gut symptoms. It is clear, however, that changes in methanogenesis could not be implicated in the genesis of symptoms overall in this small cohort.

The effects of the diets on symptoms were interesting in three respects. First, the symptoms developed quickly being evident over the first day of the HFD in patients with IBS. Since they were blinded to the nature of the diet, this finding supports the concept that FODMAPs presented in a food matrix are a trigger for gastrointestinal symptoms as they are when presented in pure form as a liquid.[8] Second, the diets did induce some symptoms in the healthy, non-IBS subjects, but this almost exclusively manifested as the passage of excessive amounts of wind. Third, the IBS patients, and not healthy subjects, also had an increase in upper gastrointestinal symptoms (heartburn and nausea) and systemic symptoms (lethargy). Gastro-esophageal reflux has been demonstrated to increase with the ingestion of FODMAPs (fructans and lactulose) by ill-understood mechanisms.[32] The present findings support the notion that these effects may be of clinical significance when therapy of upper gut functional symptoms is being chosen. Lethargy was induced by the HFD in patients with IBS. Fatigue is

Table 3 Symptom scores during the low and high FODMAPs diet for healthy subjects and patients with irritable bowel syndrome (IBS) during day 2 according to self-rating Likert scale where 0 = no symptoms, 1 = slight, 2 = moderate, 3 = severe

Symptom(s)	Group	Number of subjects with symptom score (Likert scale)								*P*-value
		Low FODMAP diet				High FODMAP diet				
		0	1	2	3	0	1	2	3	
Abdominal pain/discomfort	Healthy	10	5	–	–	6	8	1	–	0.145
	IBS	6	8	1	–	2	4	7	2	0.006
Abdominal bloating	Healthy	10	5	–	–	8	7	–	–	0.484
	IBS	6	6	3	–	1	3	6	5	0.002
Excessive flatus	Healthy	9	5	1	–	1	6	5	3	0.007
	IBS	6	7	1	1	0	2	7	6	0.002
Nausea	Healthy	13	3	–	–	12	3	–	–	0.773
	IBS	12	3	–	–	7	5	2	1	0.010
Heartburn	Healthy	13	3	–	–	14	1	–	–	0.424
	IBS	10	5	–	–	6	6	2	1	0.025
Tiredness/lethargy	Healthy	11	4	–	–	10	3	2	–	0.454
	IBS	9	5	1	–	4	7	1	3	0.012

frequently described by patients with IBS. A fructose-reduced diet in young women with fructose malabsorption and mild depressive symptoms improved mood,[33,34] putatively by changing serum tryptophan levels (the precursor to serotonin).[35] The effect of a high FODMAP diet on fatigue has not, however, been formally studied.

In conclusion, this single-blind, crossover short-term interventional study of altering the FODMAP content of food has shown that the ingestion of FODMAPs in the diet leads to prolonged hydrogen production in the intestine in healthy volunteers and patients with IBS in whom gastrointestinal and systemic symptoms were induced. Furthermore, the amount of hydrogen produced was greater in the patients with IBS. FODMAPs influenced the amount of methane produced in healthy volunteers, offering another potential mechanism by which the low FODMAP diet might alter gastrointestinal function. However, consistent effects on methanogenesis were not observed in this small and heterogeneous cohort of patients with IBS, indicating that changes in methane production were pathogenically responsible for the symptoms. The influence of FODMAP ingestion on methanogenesis over the longer term and in a larger cohort of patient with IBS warrants further investigation.

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