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Predictors of response to a low-FODMAP diet in patients with functional gastrointestinal disorders and lactose or fructose intolerance

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SUMMARY

Background
Diets low in fermentable sugars (low-FODMAP diets) are increasingly adopted by patients with functional gastrointestinal disorders (FGID), but outcome predictors are unclear.

Aim
To identify factors predictive of an efficacious response to a low-FODMAP diet in FGID patients with fructose or lactose intolerance thereby gaining insights into underlying mechanisms.

Methods
Fructose and lactose breath tests were performed in FGID patients to determine intolerance (positive symptom score) and malabsorption (increased hydrogen or methane concentrations). Patients with fructose or lactose intolerance consumed a low-FODMAP diet and global adequate symptom relief was assessed after 6–8 weeks and correlated with pre-diet clinical symptoms and breath test results.

Results
A total of 81% of 584 patients completing the low-FODMAP diet achieved adequate relief, without significant differences between FGID subgroups or types of intolerance. Univariate analysis yielded predictive factors in fructose intolerance (chronic diarrhoea and pruritus, peak methane concentrations and fullness during breath tests) and lactose intolerance (peak hydrogen and methane concentrations and flatulence during breath tests). Using multivariate analysis, symptom relief was independently and positively predicted in fructose intolerance by chronic diarrhoea [odds ratio (95% confidence intervals): 2.62 (1.31–5.27), $P = 0.007$] and peak breath methane concentrations [1.53 (1.02–2.29), $P = 0.042$], and negatively predicted by chronic nausea [0.33 (0.16–0.67), $P = 0.002$]. No independent predictive factors emerged for lactose intolerance.

Conclusions
Adequate global symptom relief was achieved with a low-FODMAP diet in a large majority of functional gastrointestinal disorders patients with fructose or lactose intolerance. Independent predictors of a satisfactory dietary outcome were only seen in fructose intolerant patients, and were indicative of changes in intestinal host or microbiome metabolism.

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INTRODUCTION

Intolerances to food are claimed by a majority of patients with Functional Gastrointestinal Disorders (FGID), such as Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD).[1] Numerous publications have investigated the role of allergies and intolerances in FGID, with a wide range of conclusions.[1–8] Recently, attention has focused on short-chain fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) as a potential cause of the symptoms characteristic of FGID, such as bloating, abdominal fullness and pain, altered stool patterns and consistency and nausea.[9–17] Higher quality studies are demonstrating the effectiveness of reducing FODMAPs in patients with Irritable Bowel Syndrome (IBS), achieving adequate symptom relief in 60–80% of patients (for recent reviews, see[18–20]).

At present, it is unclear which patients will benefit from a dietary manipulation of FODMAPs. The selection criteria for the recommendation of a low-FODMAP diet in patients with FGID have evolved over time, in accordance with hypotheses regarding pathogenesis. The main proposed mechanism of action of the low-FODMAP diet has been a reduction in small intestinal malabsorption of osmotically active short-chain carbohydrates, resulting in diminished intestinal water content and downstream effects on colonic fermentation and gas production.[11] Recently, other factors, such as alterations in the gut microbiome, immune responses and sensation have been recognised as potentially relevant, but their exact role in symptom response has yet to be fully elucidated.[15, 21, 22]Consequently, the selection criteria for the low-FODMAP diet have also evolved from patients with malabsorption demonstrated by breath tests, to patients with symptoms provoked by high doses of sugars, to practically all IBS patients without further testing.[11, 15, 21–24]

Despite the rising popularity of the low-FODMAP diet, certain limitations must be emphasised. The implementation of the formal low-FODMAP diet is cumbersome, necessitating a multi-week elimination of fermentable carbohydrates and a subsequent staggered re-introduction of specific classes of carbohydrates for personalised fine-tuning of the diet. Few long-term follow-up reports exist, but a retrospective, postal-follow-up study showed substantially reduced and sporadic dietary compliance, albeit with reasonable symptom relief.[25] Furthermore, the consequences of the downstream long-term effects of the diet on the microbiome and fermentation metabolites are unknown. Factors relating to patient demographics, microbiome composition and metabolism, and to the subtype of IBS may be associated with the response to a low-FODMAP diet, but no large-scale studies of response predictors have been published, to the best of our knowledge.[15, 23, 26] The ability to predict responders to the low-FODMAP diet would not only allow rationalisation of resources and improved clinical care, but also provide insights regarding possible disease mechanisms.

We hypothesised that the chronic clinical symptoms, as well as the type of symptoms provoked during breath testing, but not the breath gas results, would be associated with the efficacy of the low-FODMAP diet. Consequently, we studied the predictive value of clinical symptoms and breath test results on the outcome of a low-FODMAP diet in a large cohort of patients with FGID and fructose or lactose intolerance in a single referral centre.

PATIENTS, MATERIALS AND METHODS

All successive patients referred to our gastroenterology practice by general practitioners between January 2008 and December 2011 with FGID and with either fructose or lactose intolerance (as defined below) and referred for specialist low-FODMAP dietary advice were eligible for inclusion in this longitudinal, observational study. FGID was defined according to the Rome III criteria.[27] Exclusion criteria were evidence of organic disease, as assessed by haematology and biochemistry blood testing, and stool testing for calprotectin and pancreas elastase. Coeliac disease was excluded by tissue anti-transglutaminase antibodies or duodenal biopsies. Upper and lower endoscopies with biopsies were required in patients older than 40 years or in patients with diarrhoea or faecal blood. Parasite and bacterial stool cultures and abdominal ultrasound were performed if clinically indicated. One consultant gastroenterologist (CWS) performed all the medical and dietary history taking and examinations. The dietary history included two sections: an open question requesting a listing of avoided and poorly tolerated foods and then a specific list of the main fructose-, fructo-oligosaccharide-, galacto-oligosaccharide-, lactose- and sorbitol-containing foods, as well as 10 common food allergies in Europe (cow's milk, chicken eggs, peanuts, tree nuts, wheat, soy, fish, shellfish, carrots, apples).[28–30]

In addition, skin rashes, urticaria, rhinitis, headache, urgency to defaecate and changes in stool consistency related to mealtimes were documented. Patients completed a standardised questionnaire, which included the specific questions for classification of GI symptoms into FGID groups according to the Rome III criteria, and additional questions regarding allergies, childhood and family history,

central nervous, musculoskeletal and cardiovascular system symptoms and the use of polyol-containing sweets and chewing gum.[15] Diarrhoea was defined as loose (mushy) or watery stools occurring in at least 75% of stools in the past 3 months.[27] Constipation was defined as lumpy or hard stools in at least 75% of defaecations or fewer than three defecations per week in the previous 3 months.[27] The study was performed in accordance with the Helsinki Declaration. Ethics Committee approval was not required by Swiss regulation at the time of initiation of the study.

Breath test protocol

Only FGID patients with fructose or lactose intolerance were included in the study. Fructose and lactose intolerances were assessed by standardised breath testing performed by the same technician in our practice. No antibiotics, colonoscopy or laxatives were permitted within 14 days and a specific low-saccharide diet was adhered to 1 day before the tests. Patients arrived for testing in the morning after fasting overnight and without having smoked, chewed gum or performed vigorous exercise for at least 4 h. Chlorhexidine mouthwash was used and teeth were brushed before testing. The breath tests were performed in randomised sequence on two separate occasions at least 6 days apart. Breath samples were collected in sealed glass tubes (Quintron Instruments, Milwaukee, WI, USA) before and hourly for 5 h after ingestion of lactose 50 g or fructose 35 g dissolved in 300 mL water. Hydrogen, methane and CO_2 concentrations were measured within 72 h using the Quintron BreathTracker SC (Quintron Instruments, Milwaukee, WI, USA). Hourly breath sampling was performed as validated in previous studies.[15] A distinction was made between malabsorption and intolerance. *Malabsorption was defined* as an increase >20 ppm in hydrogen or >10 ppm in methane levels over baseline twice in succession.[15] *Intolerance was defined* as an increase >2 over baseline in our previously published symptom score index, which is the sum of the intensities (0 = none, 1 = mild, 2 = intense) of abdominal distension or bloating, flatulence, fullness, nausea, diarrhoea, abdominal cramps, borborygmi, and gastro-oesophageal reflux symptoms, scored hourly concurrently with the collection of the breath samples.[15] Additional non-GI symptoms rated, but not part of the symptom index, were tiredness, diminished concentration, headache, myalgia, arthralgia, palpitations, oral aphthoid ulcers and skin rash.

Dietary protocol

All patients shown to be fructose or lactose intolerant by breath testing were referred to the same experienced dietician for a standardised 4-week dietary adaptation based on published low-FODMAP diet guidelines.[11] Patients received individual instruction by the dietician regarding a diet low in fermentable saccharides and polyols, which was maintained for 3–4 weeks. Subsequently, standardised daily re-introduction of defined classes and amounts of fructose-, fructan-, galacto-oligosaccharide- and lactose-containing foods was performed to determine individual tolerability thresholds. Patients were maintained on the level of saccharides and polyols below their threshold of symptoms. Generally, four individual sessions were scheduled with patients and questionnaires regarding abdominal symptoms, bowel and dietary habits were completed before and after the dietary modification. Intensity scoring of gastrointestinal and extra-gastrointestinal symptoms was performed using 10-point Likert scales.

Outcomes

The primary outcome measure was the global adequate relief question: "Have you achieved adequate relief of your usual symptoms with the dietary modification? (yes/no)". Dietary compliance was assessed by direct interview by the dietician 6–8 weeks after initiation of the dietary changes. Compliance was considered adequate if patients confirmed they adhered to the dietary guidelines during at least 50% of the meals consumed, based on the range of dietary compliance in previous studies.[11, 25, 31, 33]

Statistics

All data are presented as means ± s.d. unless otherwise indicated. Student's *t* test and chi squared tests were used to compare clinical and demographical variables between patient subgroups. Factors potentially associated with dietary outcome ($P < 0.10$) in univariate logistic regression models were included in multivariate models. Results were presented as odds ratios (ORs) with 95% confidence intervals after correction for bias (internal validation) using bootstrap-corrected analysis based on 5000 samples. Repeated measures analysis of variance (RM-ANAOVA) was used to compare hydrogen and methane concentration-time profiles between patient subgroups stratified by dietary outcome. A two-tailed $P < 0.05$ was considered statistically significant. The software package STATA version 14.1 (StataCorp LP, College Station, TX, USA) was used for statistical calculations.

RESULTS

During the study period 653 patients with FGID qualified for inclusion in the study on the basis of the

diagnosis of a fructose (n = 430) or lactose (n = 289) intolerance, defined by a positive symptom score during breath testing, and referral to dietary advising. Patient characteristics are shown in Table 1. A total of 584 of these patients (89%) completed their course of dietary advising and modification (see Table 1 for exclusion reasons). There were no significant differences in any demographic or clinical characteristics between patients completing or not completing the dietary programme.

Of all the FGID patients completing the dietary programme, 81% achieved adequate relief. The positive response rate was similar in patients with fructose or lactose intolerances, 83% and 79%, respectively. As there was no difference in outcome with combined intolerances, further analyses were performed for fructose and lactose intolerance, without considering combined intolerances as a separate group. Subgroup analysis of adequate relief outcome for the different Rome III FGID subgroups was performed and yielded no significant group differences (Figure 1), hence, the data from all FGID patients were pooled for further analysis.

Associations between chronic symptoms and outcome of dietary programme

Results of the univariate analysis of the association between chronic gastrointestinal and extra-gastrointestinal symptoms and the outcome of dietary programme are shown in Table 2. In patients with fructose intolerance, adequate relief with the low-FODMAP diet was associated with a clinical history of chronic diarrhoea [odds ratio: 2.62 (1.45–4.74), $P < 0.001$] and pruritus [2.46 (1.11–5.46), $P = 0.027$], while an absence of relief was associated with nausea [0.48 (0.26–0.87), $P < 0.015$]. In patients with lactose intolerance, similar nonsignificant trends in associations were seen, with adequate dietary responses more common in patients with chronic diarrhoea [1.79 (0.91–3.54), $P = 0.092$] and pruritus [2.08 (0.90–4.80), $P = 0.086$].

Associations between breath test results and outcome of dietary programme

The associations between provoked symptoms and exhaled gas concentrations measured during fructose and lactose breath testing and dietary outcome are shown in Tables 3 and 4. With univariate analysis in patients with fructose intolerance, adequate relief with the low-FODMAP diet was associated with abdominal fullness [1.85 (1.05–3.25), $P = 0.03$] and a trend to increased peak concentrations of breath methane [1.40 (0.98–1.99), $P = 0.06$] during breath testing. In lactose intolerant patients, adequate dietary symptom relief was associated with peak hydrogen [1.06 (1.00–1.13), $P = 0.038$] and peak methane [1.41 (1.06–1.89), $P = 0.02$] concentrations. There was a trend to adequate relief being less common in lactose intolerant patients with headache [0.56 (0.29–1.08), $P = 0.083$] or tiredness [0.54

Table 1 | Patient characteristics and exclusion criteria. Data for all functional gastrointestinal disorder patients enrolled and those completing the dietary programme are shown

	All patients N = 653	Patients completing low-FODMAP diet N = 584
Age (years)*	42 ± 16	42 ± 20
Gender:		
Male/female, *n* (%)	160 (25%)/493 (75%)	144 (25%)/440 (75%)
Ethnicity, %:		
Northern European/Southern European/Middle Eastern/Asian/Black	82/15/2/1/0	82/15/1/2/0
Body mass index (kg/m^2)*	24 ± 6	24 ± 7
Waist circumference (cm)*	98 ± 11	98 ± 12
Types of FGID†, %:		
IBS-D/IBS-C/IBS-M/FD/other	22/12/16/32/36	18/10/16/33/46
Patients with fructose/lactose intolerance, *n* (%)‡	430 (66%)/289 (44%)	394 (67%)/259 (44%)
Patients not completing dietary programme:		
Lost to follow-up, *n*	43	N.A.
Discontinuation due to other medical condition, *n*	26	N.A.

FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; FD, functional dyspepsia; N.A., not applicable.

* means ± s.d.

† Overlap between FGID subgroups, therefore sum >100%.

‡ Overlap between both intolerances, therefore sum >100%.

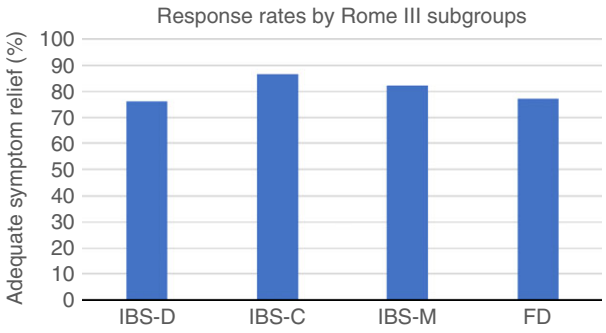

Figure 1 | Adequate relief response rates in percentage of patients with Rome III subtypes: Irritable bowel syndrome predominantly with diarrhoea (IBS-D), Irritable bowel syndrome predominantly with constipation (IBS-C), Irritable bowel syndrome with mixed stool pattern (IBS-M) and Functional dyspepsia (FD). There are no significant differences in response rates between subtypes. IBS and FD may occur in the same patient, hence some group overlap.

(0.28–1.03), $P = 0.062$], The hydrogen and methane concentration-time profiles of fructose and lactose intolerant patients with adequate dietary relief vs. those without adequate relief are shown in Figure 2. There was no significant association between the area-under-the-curve (AUC) of hydrogen or methane gas concentration-time profiles and adequate relief in either fructose or lactose intolerant patients (Tables 3 and 4). Furthermore, the hydrogen and methane concentration-time profiles were comparable between patients with either intolerance with or without adequate relief, albeit with a trend towards greater methane production in fructose intolerant patients responding adequately to the low-FODMAP diet compared to those without an adequate response ($F = 3.22$; $P = 0.074$)(Figure 2a, right panel).

The most common symptoms were similar during fructose and lactose breath testing, namely bloating, flatulence, abdominal fullness, borborygmi, headache, tiredness, nausea and abdominal cramps (Tables 3 and 4). There was no significant association between the cumulative number of symptoms experienced during breath testing with either fructose or lactose and the outcome of the dietary programme (Table 5).

Multivariate associations between clinical symptoms, breath test variables and the outcome of dietary adaptation

Multivariate analysis of the clinical symptoms, breath test variables and the outcome of dietary adaptation in fructose intolerance revealed a positive and independent association of adequate dietary relief with chronic diarrhoea [2.62 (1.31–5.27), $P = 0.007$] and with peak methane breath concentrations [1.53 (1.02–2.29), $P = 0.042$], and a negative association with chronic nausea [0.33 (0.16–0.67), $P = 0.002$]. In lactose intolerant patients, there was a trend to an absence of adequate dietary relief with increased tiredness during breath testing [0.49 (0.21–1.13), $P = 0.094$]. No other significant associations were demonstrated (Table 6).

DISCUSSION

In this large monocentric study, the dietician-guided reduction in dietary FODMAPs resulted in a highly effective amelioration of symptoms, with 81% of 584 patients with fructose or lactose intolerance confirming adequate clinical relief of symptoms, irrespective of the type of sugar intolerance and of the subtype of FGID. The very favourable efficacy of the low-FODMAP diet in this study corroborates the results of earlier, smaller studies with mixed groups of mainly IBS patients, often including patients with malabsorption (increased breath gas concentrations) but not necessarily intolerance (provoked symptoms during breath test).[9-17, 20, 32, 33]

Associations between clinical symptoms of FGID and outcome of a low-FODMAP diet

Chronic diarrhoea and pruritus emerged as the univariate predictors of a positive outcome of the low-FODMAP diet, highly significant in FGID patients with fructose intolerance and a consistent trend in patients with lactose intolerance. Nausea, conversely, was a predictor of an inadequate dietary response, which was also significant in fructose intolerance and showed a trend in lactose intolerance. Multivariate analysis confirmed diarrhoea as an independent positive predictor and nausea as a negative predictor of dietary response in fructose intolerance. These individual symptoms are more useful predictors of outcome in fructose intolerance than symptom groupings, such as the Rome III subtypes, which were neither significant outcome predictors, nor did response rates differ across subtypes. Although diarrhoea was shown to be a predictor of a favourable dietary outcome, constipation was not a predictor of an inadequate response, confirming the usefulness of the low-FODMAP diet across all IBS subgroups. There are few large studies assessing the responsiveness of the different IBS subgroups to a low-FODMAP diet, showing mixed results and generally using symptom scores rather than the global symptom response as the primary outcome measure.

Table 2 | Univariate analysis of the associations between clinical symptoms and the outcome of low-FODMAP dietary advising in patients with functional gastrointestinal (GI) disorders and fructose or lactose intolerance. Responders are defined as patients responding positively to the global adequate relief question: "Have you achieved adequate relief of your usual symptoms with the dietary modification? (yes/no)".

Symptoms	Complete data *n* (%)	Responder *n* (%)	Non-responder *n* (%)	OR (95%CI)	*P*-value
Fructose intolerance (*n* = 394)					
GI symptoms					
Bloating	309 (78)	229 (74)	51 (89)	1.17 (0.45–3.02)	0.74
Stomach cramps	300 (76)	199 (81)	46 (81)	1.08 (0.52–2.25)	0.83
Diarrhoea	295 (75)	166 (69)	26 (46)	2.62 (1.45–4.74)	0.001
Nausea	302 (77)	106 (43)	33 (61)	0.48 (0.26–0.87)	0.015
Constipation	304 (77)	115 (46)	28 (52)	0.79 (0.44–1.43)	0.44
Acid reflux	306 (78)	122 (49)	26 (47)	1.05 (0.59–1.89)	0.86
CNS symptoms					
Depressive mood	294 (75)	82 (35)	14 (25)	1.62 (0.84–3.14)	0.15
Problems concentrating	302 (77)	105 (43)	23 (42)	1.03 (0.57–1.86)	0.93
Tiredness	306 (78)	187 (75)	37 (67)	1.42 (0.75–2.67)	0.27
Musculoskeletal symptoms					
Myalgia	301 (76)	69 (28)	20 (36)	0.68 (0.37–1.26)	0.22
Joint pain	304 (77)	75 (30)	19 (35)	0.82 (0.44–1.52)	0.52
Other symptoms					
Skin rash	308 (78)	74 (30)	15 (26)	1.21 (0.63–2.30)	0.57
Pruritus	297 (75)	70 (29)	8 (14)	2.46 (1.11–5.46)	0.027
Irregular heart beat	300 (76)	62 (25)	12 (23)	1.15 (0.57–2.32)	0.71
Aphthoid oral ulcers	298 (76)	55 (23)	14 (26)	0.83 (0.42–1.64)	0.59
Lactose intolerance (*n* = 259)					
GI symptoms					
Bloating	202 (78)	162 (92)	40 (91)	1.08 (0.34–3.43)	0.90
Stomach cramps	216 (83)	147 (85)	37 (86)	0.92 (0.35–2.39)	0.86
Diarrhoea	213 (72)	106 (62)	20 (48)	1.79 (0.91–3.54)	0.092
Nausea	216 (83)	77 (45)	25 (58)	0.58 (0.29–1.14)	0.11
Constipation	215 (83)	82 (47)	22 (55)	0.72 (0.36–1.44)	0.35
Acid reflux	214 (83)	82 (47)	19 (48)	0.99 (0.50–1.96)	0.97
CNS symptoms	207 (80)	63 (38)	13 (30)	1.44 (0.70–2.97)	0.32
Depressive mood	215 (83)	82 (47)	20 (49)	0.94 (0.47–1.85)	0.85
Problems concentrating	218 (84)	135 (76)	33 (80)	0.78 (0.33–1.82)	0.56
Tiredness	218 (84)	135 (76)	33 (80)	0.78 (0.33–1.82)	
Musculoskeletal symptoms					
Myalgia	212 (82)	57 (34)	15 (35)	0.95 (0.47–1.92)	0.89
Joint pain	212 (82)	57 (34)	16 (38)	0.82 (0.40–1.65)	0.58
Other symptoms					
Skin rash	218 (84)	55 (32)	9 (20)	1.80 (0.81–4.00)	0.15
Pruritus	208 (80)	56 (34)	8 (20)	2.08 (0.90–4.80)	0.086
Irregular heart beat	211 (81)	43 (25)	10 (24)	1.05 (0.48–2.32)	0.91
Aphthoid oral ulcers	210 (81)	39 (23)	11 (27)	0.82 (0.38–1.78)	0.61

GI, gastrointestinal; CNS, central nervous system; OR, odds ratio; CI, confidence intervals.

A lesser response of constipated IBS patients has been reported in several, but not all studies.[15, 32, 34] The association between a beneficial response in patients with diarrhoea and the low-FODMAP diet may either be via a direct influence on malabsorption or an indirect effect on fermentation processes. Fermentable sugars and downstream fermentation products can influence gastrointestinal motility and physiology via various pathways, including changes in sensing and sensation, absorption and secretion, immune responses, motility and muscle tone, and gut hormone regulation (e.g. PYY, GLP-1, GLP-2) and a low-FODMAP diet may either directly or indirectly modify these responses, although this remains to be confirmed.[35–38] The association of a positive dietary outcome with malabsorption, as reflected in abnormal breath tests, is discussed further below.

Table 3 | Univariate analysis of fructose breath test results and associations with the effect of a low-FODMAP diet in patients with functional gastrointestinal disorders and fructose intolerance (n = 394). Responders are defined as patients responding positively to the global adequate relief question: "Have you achieved adequate relief of your usual symptoms with the dietary modification? (yes/no)".

Breath test variables	Complete data *n* (%)	Responder *n* (%)	Non-responder *n* (%)	OR (95% CI)	*P*-value
Hydrogen (H^+)					
Malabsorption *n* (%)*	394 (100)	219 (68)	49 (67)	1.05 (0.61–1.81)	0.86
Peak concentration (ppm)	394 (100)	42 ± 41	38 ± 32	1.03 (0.96–1.11)	0.43
Time to peak ppm (min)	394 (100)	113 ± 67	102 ± 72	1.03 (0.99–1.07)	0.20
AUC	394 (100)	86 ± 89	87 ± 79	1.00 (0.97–1.03)	0.94
Methane ($CH4^+$)					
Malabsorption *n* (%)†	354 (90)	126 (43)	22 (34)	1.47 (0.83–2.58)	0.18
Peak concentration (ppm)	354 (90)	12 ± 16	9 ± 7	1.40 (0.98–1.99)	0.061
Time to peak ppm (min)	354 (90)	112 ± 67	102 ± 70	1.02 (0.98–1.07)	0.27
AUC	354 (90)	33 ± 30	35 ± 25	0.97 (0.89–1.07)	0.58
GI symptoms during test					
Bloating	362 (92)	226 (76)	51 (78)	0.87 (0.46–1.67)	0.68
Wind/Gas	362 (92)	207 (70)	51 (78)	0.63 (0.33–1.20)	0.16
Fullness	362 (92)	222 (75)	40 (62)	1.85 (1.05–3.25)	0.033
Stomach cramps	362 (92)	168 (57)	30 (46)	1.52 (0.89–2.60)	0.13
Diarrhoea	361 (92)	126 (43)	21 (32)	1.55 (0.88–2.74)	0.13
Nausea	357 (91)	135 (46)	28 (43)	1.14 (0.66–1.95)	0.64
Borborygmi	354 (90)	195 (67)	38 (59)	1.40 (0.81–2.45)	0.23
Acid reflux	350 (89)	129 (45)	27 (42)	1.13 (0.65–1.95)	0.67
CNS symptoms during test					
Headache	351 (89)	126 (44)	33 (52)	0.74 (0.43–1.27)	0.27
Problems concentrating	353 (90)	96 (33)	26 (40)	0.73 (0.42–1.27)	0.26
Tiredness	354 (90)	138 (48)	28 (44)	1.17 (0.68–2.01)	0.58
Musculoskeletal symptoms during test					
Myalgia	353 (90)	35 (12)	3 (5)	2.80 (0.83–9.41)	0.096
Joint pain	353 (90)	27 (9)	5 (8)	1.22 (0.45–3.29)	0.70
Other symptoms during test					
Skin rash	353 (90)	11 (4)	0 (0)	N.A.	0.11
Irregular heart beat	353 (90)	14 (5)	4 (6)	0.76 (0.24–2.40)	0.65
Aphtoid oral ulcers	353 (90)	8 (3)	2 (3)	0.88 (0.18–4.26)	0.88

AUC, area-under-the-curve over 5 h; CI, confidence intervals; CNS, central nervous system; GI, gastrointestinal; N.A., not applicable; OR, odds ratio.

* Defined as peak >20 ppm.

† Defined as peak >10 ppm.

Nausea has in a large previous study been shown to respond poorly to FODMAP manipulation, although other studies have shown contradictory responses.[32, 33] Nausea may be more related to upper GI pathophysiology and therefore be less amenable to changes in the intestinal microbiome and fermentation products. However, it should be noted, that patients with functional dyspepsia had similar symptom relief as IBS patients with a low-FODMAP diet in a large previous study, implying useful effects of the reduction in fermentable sugars in a FGID classically thought to originate in the upper GI tract.[15, 39] Some of the divergent results between studies can be related to different inclusion and exclusion criteria, such as specific exclusion of lactose intolerance or allergies, as well as differences in pre-study probiotic use and in the nonstandardised diet itself.[34]

Pruritus was not an independent outcome predictor and is not a classic component of FODMAP intolerances. However, pruritus is often present when intolerances and allergies overlap, such as in fruit allergies, oral allergy syndromes or histamine intolerance. In these cases, exclusion or reduction in FODMAPs will also reduce exposure to foods precipitating fruit allergy or histamine intolerance and thereby coincidentally relieve pruritus and further symptoms. Interestingly, histamine production and mast cell activation are altered in IBS

Table 4 | Univariate analysis of lactose breath test results and associations with the effect of a low-FODMAP diet in patients with functional gastrointestinal disorders and lactose intolerance (n = 259). Responders are defined as patients responding positively to the global adequate relief question: "Have you achieved adequate relief of your usual symptoms with the dietary modification? (yes/no)".

Breath test variable	Complete data *n* (%)	Responder *n* (%)	Non-responder *n* (%)	OR (95% CI)	*P*-value
Hydrogen (H^+)					
Malabsorption *n* (%) *	259 (100)	114 (55)	23 (44)	1.55 (0.84–2.85)	0.16
Peak concentration (ppm)	259 (100)	56 ± 64	36 ± 46	1.06 (1.00–1.13)	0.038
Time to peak ppm (min)	258 (100)	189 ± 98	168 ± 105	1.02 (0.99–1.05)	0.18
AUC	259 (100)	68 ± 117	83 ± 121	0.99 (0.97–1.01)	0.42
Methane ($CH4^+$)					
Malabsorption *n* (%) †	243 (94)	88 (45)	14 (30)	1.92 (0.97–3.81)	0.062
Peak concentration (ppm)	243 (94)	14 ± 15	9 ± 10	1.41 (1.06–1.89)	0.020
Time to peak ppm (min)	243 (94)	183 ± 95	174 ± 106	1.00 (0.98–1.04)	0.57
AUC	243 (94)	31 ± 67	36 ± 35	0.99 (0.95–1.03)	0.64
GI symptoms during test					
Bloating	245 (95)	154 (78)	42 (88)	0.51 (0.20–1.28)	0.15
Wind/Gas	245 (95)	142 (72)	40 (83)	0.52 (0.22–1.17)	0.11
Fullness	245 (95)	149 (76)	38 (79)	0.82 (0.38–1.76)	0.61
Stomach cramps	245 (95)	113 (57)	28 (58)	0.96 (0.51–1.82)	0.90
Diarrhoea	245 (95)	73 (37)	14 (29)	1.43 (0.72–2.84)	0.31
Nausea	244 (94)	112 (57)	22 (47)	1.50 (0.79–2.84)	0.22
Borborygmi	243 (94)	137 (70)	28 (60)	1.58 (0.82–3.04)	0.18
Acid reflux	241 (93)	75 (38)	14 (30)	1.43 (0.72–2.85)	0.31
CNS symptoms during test					
Headache	241 (93)	95 (49)	29 (63)	0.56 (0.29–1.08)	0.083
Problems concentrating	243 (94)	69 (35)	12 (26)	1.58 (0.77–3.25)	0.21
Tiredness	243 (94)	91 (46)	29 (62)	0.54 (0.28–1.03)	0.062
Musculoskeletal symptoms during test					
Myalgia	243 (94)	28 (14)	6 (13)	1.14 (0.44–2.93)	0.79
Joint pain	243 (94)	22 (11)	4 (9)	1.36 (0.45–4.15)	0.59
Other symptoms during test					
Skin rash	243 (94)	8 (4)	0 (0)	N.A.	0.16
Irregular heart beat	243 (94)	12 (6)	4 (9)	0.70 (0.22–2.28)	0.56
Aphtoid oral ulcers	243 (94)	3 (2)	1 (2)	0.72 (0.07–7.03)	0.77

AUC, area-under-the-curve over 5 h; CI, confidence intervals; CNS, central nervous system; GI, gastrointestinal; N.A., not applicable; OR, odds ratio.

* Defined as peak >20 ppm.

† Defined as peak >10 ppm.

and a low-FODMAP diet reduced urinary histamine release in a recent study.[40] Further investigation of the role of histamine and biogenic amines in FGID and the response to dietary and microbiome manipulation are clearly of interest as a possible contributing mechanisms.

Associations between symptoms and gas concentrations during breath testing and outcome of a low-FODMAP diet

Some symptoms provoked during breath testing were predictive of an adequate response to the low-FODMAP diet by univariate analysis. In the fructose intolerant group, abdominal fullness was significantly associated with an adequate response. In lactose intolerant, there was a marginally nonsignificant positive association between an adequate dietary response and greater flatulence and a negative association with central nervous system effects, such as tiredness and headache. However, none of the symptoms provoked during breath testing were associated with dietary outcome in the multivariate analysis, and, as such, these symptoms could not be used to independently predict the effect of dietary intervention in our cohort.

Peak breath methane concentrations above the threshold of 10 ppm were associated with adequate dietary relief in fructose intolerance by both uni- (trend) and multivariate (significant) analyses, indicating an independent association between methane production during

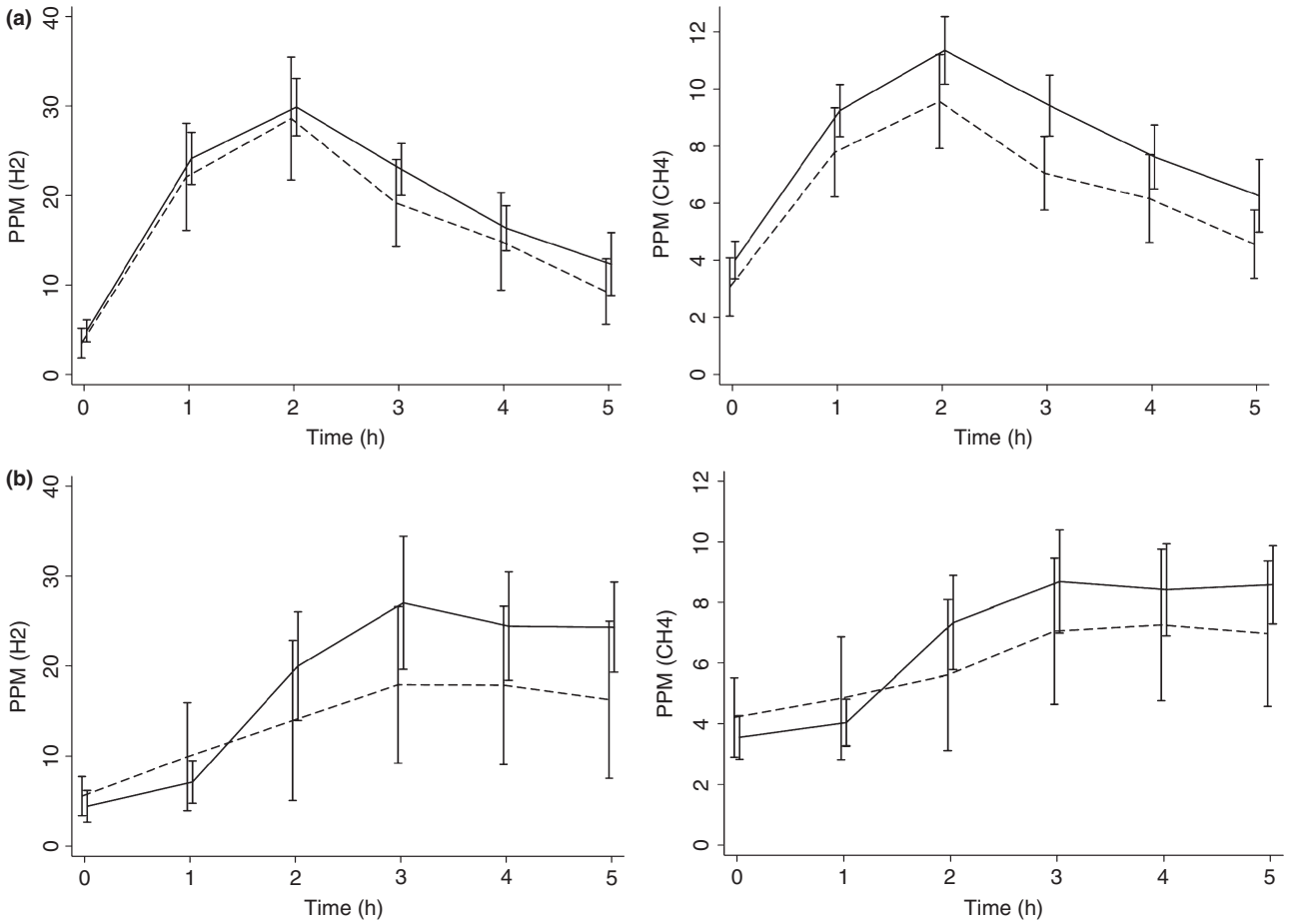

Figure 2 | H_2- (left panel) and CH_4- (right panel) breath concentrations (mean and 95% confidence intervals) in patients with (a) fructose and (b) lactose intolerance with (solid line) or without (dashed line) adequate symptom relief with a low-FODMAP diet.

Table 5 | Number of gastrointestinal (GI) symptoms during fructose and lactose breath tests and associations with the effect of a low-FODMAP diet in patients with functional GI disorders and fructose intolerance (n = 394) or lactose intolerance (n = 259). Patients with adequate symptom relief are defined as responders. Sum of percentages may not equal 100 due to rounding

Number of GI symptoms during breath testing	Responders, *n* (%)	Non-responders, *n* (%)	OR (95% CI)	*P*-value
Fructose intolerance (n = 394)				
1–2	18 (6)	4 (5)	1.00	
3–5	197 (61)	52 (71)	0.84 (0.27–2.59)	0.76
6–8	106 (33)	17 (23)	1.39 (0.42–4.59)	0.59
Lactose intolerance (n = 259)				
1–2	47 (23)	15 (29)	1.00	
3–5	101 (49)	27 (52)	1.19 (0.58–2.45)	0.63
6–8	59 (29)	10 (19)	1.88 (0.78–4.57)	0.16

OR, odds ratio; CI, confidence intervals.

fructose breath testing and dietary outcome. In lactose intolerant patients, peak hydrogen and peak methane concentrations were significantly predictive of a positive dietary outcome in the univariate analysis. However, none of the gas results in lactose intolerance were independently associated with outcome, as shown by the

Table 6 | Multivariate analysis of clinical symptoms and breath test variables and their association with adequate symptomatic relief during a low-FODMAP diet in patients with functional gastrointestinal disorders and fructose (n = 394) or lactose (n = 259) intolerance

	Multivariate analysis*	
Test variable	OR (95% CI)	P-value
Fructose intolerance (n = 394)		
Clinical symptoms		
Diarrhoea	2.62 (1.31–5.27)	0.007
Pruritus	2.14 (0.82–5.59)	0.12
Nausea	0.33 (0.16–0.67)	0.002
During breath tests		
Peak CH_4 concentration ppm†	1.53 (1.02–2.29)	0.042
Fullness	1.19 (0.54–2.62)	0.66
Myalgia	1.69 (0.44–6.56)	0.45
Lactose intolerance (n = 259)		
Clinical symptoms		
Diarrhoea	1.55 (0.71–3.37)	0.27
Pruritus	2.13 (0.84–5.43)	0.11
During breath tests		
Peak CH_4 concentration ppm†	2.73 (0.80–9.29)	0.11
Peak H_2 concentration ppm†	0.86 (0.68–1.09)	0.20
Headache	0.65 (0.28–1.54)	0.33
Tiredness	0.49 (0.21–1.13)	0.094

* Parameters potentially associated with study outcome in univariate analysis ($P < 0.1$) were included in the multivariate model; 95% confidence intervals (CI) and P-values were calculated using bootstrap-corrected analysis.

† The odds ratios (OR) are based on changes of 10 ppm.

absence of significant effects in the multivariate analysis. The association of peak methane levels and abdominal fullness during fructose breath testing with an adequate response to the low-FODMAP diet indicates sensitivity to rapid intestinal distension, possibly due to an osmotic effect with subsequent methanogenic fermentation by intestinal flora of fructose, could be a trigger of symptoms in FGID patients with fructose intolerance. A rapid increase in small bowel diameter and water content (small bowel gas content was not assessed), as well as colonic gas content after fructose ingestion has recently been shown by MRI in healthy individuals[41] Similar mechanisms may be relevant in lactose intolerance, although there are differences to fructose intolerance. In lactose intolerant FGID patients, a positive outcome of the reduction in fermentable saccharides was associated with greater flatulence and peak breath hydrogen as well as methane gas concentrations during breath testing. It is known and also evident from this study, that the peak localisation of metabolism is more distal and the time to peak gas metabolite concentrations more delayed for lactose than for fructose.[15, 42, 43] This difference in time to peak metabolism and absorption between fructose and lactose may explain the positive predictive association of dietary outcome with fullness (a more proximal intestinal symptom) with fructose intolerance and flatulence (a more distal intestinal symptom) with lactose intolerance. Association of outcome with peak gas concentrations, rather than concentration-time profiles, indicates maximum changes in intestinal distension to be more important for symptoms than total gas load or degree of malabsorption and fermentation.[44] Visceral hypersensitivity due to either peripheral sensitisation or altered endogenous sensory modulation will pre-dispose to increased symptoms with distension and may be triggered by chemosensitivity to a fermentation product.[45, 46] The resident intestinal microbiome is therefore likely to be an important determinant in FODMAP-related symptoms and the outcome of a low-FODMAP diet and a recent small study in children demonstrated a baseline microbiome with greater saccharolytic capacity was associated with a beneficial symptomatic response to a 48 h reduction in FODMAPs.[26] A reduction in fermentation using the low-FODMAP diet probably addresses one of the important causative mechanisms. Whether the fermentation is due to an altered microbiome composition, activity or distribution is not addressed by the present study, nor do appropriate tools currently exist to accurately answer these issues.

As evident from the discussion above, responses to fructose and lactose differed and the predictive associations between the clinical symptoms of diarrhoea, pruritus and nausea were stronger in fructose intolerance than in lactose intolerance. Although overall dietary outcome is excellent across all groups of FGID, the results indicate a more selective responsiveness to FODMAP reduction in fructose intolerance. This may be due to a different intestinal microbiome composition or activity, or other physiological mechanisms, such as absorption or metabolite generation, between the two intolerances. Differences in the fermentation of the monosaccharide, fructose, and the disaccharide, lactose, have been shown and the resident microbiome will be influenced by the type of malabsorbed sugar.[47] There is indirect evidence for this in the significant positive association of outcome with peak methane production in fructose intolerance,

but with both peak methane and hydrogen concentrations in lactose intolerance.

Methodological considerations

The outcome of treatment studies in FGID is currently assessed by global relief scales, related quality of life measures or by specific symptoms or groups of symptoms.[19, 48] In this study, we chose the global relief assessment as the broadest main outcome measure, as changes in specific symptoms incompletely assess the impact of treatment in FGID or changes in quality of life.[49] The study objective, therefore, was not to evaluate predictors of responsiveness of individual GI and non-GI symptoms to a low-FODMAP diet, which may have yielded different patterns. It is well known, that patient satisfaction with treatment in IBS is not linearly related to relief of individual symptoms and even multicomponent assessments of symptom severity are problematic and highly individualistic.[49–51] It should be noted that the Rome III and FDA global outcome question versions include a reference to IBS symptoms or abdominal pain and discomfort. The outcome question we used in this study referred to all symptoms, as the FODMAP diet is likely to influences non-GI symptoms. The lack of validation of this change can be considered a study limitation.

The selection of patients for inclusion differs between studies and has changed over time, with earlier studies selecting malabsorbers based on breath gas threshold concentrations and often not considering induced symptoms, while subsequent studies have generally accrued patients with symptoms during breath testing, that is, with intolerances. Responses may differ between studies based on the patient selection criteria, although in a previous large study, we showed responses to a low-FODMAP diet to be similar in patients with fructose or lactose intolerance with or without malabsorption.[15] In this study, only patients with lactose or fructose intolerance were included, signifying that all patients per definition had gastrointestinal symptoms during breath testing. We therefore emphasise, that this study assessed the clinical predictive value of the type of symptom, rather than the existence of any symptom during breath testing, on dietary outcome. The inclusion of FGID patients without intolerances may have resulted in a different predictive pattern.

Further limitations of this and all studies investigating FGID are the probable lumping together of heterogeneous patient groups according to phenotype, the uncertainties and inaccuracies of the breath test technique, the difficulty of documenting dietary composition over extended time periods and the absence of clear-cut control cohorts. It is also recognised that IBS symptom vary considerably over time and that the responsiveness to a more protracted low-FODMAP diet may consequently also show increased variability.

CONCLUSIONS

In conclusion, a low-FODMAP diet achieves adequate symptom relief in a large majority of patients with FGID and fructose or lactose intolerance. Predictors of a satisfactory dietary outcome were chronic diarrhoea and elevated breath methane concentrations during breath testing in patients with fructose intolerance. There were no independent response predictors in lactose intolerance. This difference between intolerances may reflect underlying factors related to fermentation, microbiome metabolism or composition. Due to the heterogeneous nature of FGID patients and the beneficial effect in a large majority, it is likely a low-FODMAP diet modulates a broad spectrum of underlying disease mechanisms.

AUTHORSHIP

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LINKED CONTENT

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