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The low FODMAP diet: recent advances in understanding its mechanisms and efficacy in irritable bowel syndrome

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Abbreviations

DP	degree of polymerisation
FODMAPs	fermentable oligosaccharides, disaccharides, monosaccharides and polyols
GI	gastrointestinal
GOS	galacto-oligosaccharides
IBS	irritable bowel syndrome
IBS-SSS	irritable bowel syndrome Symptom Severity Scale
MRI	magnetic resonance imaging
NSP	non-starch polysaccharides
RCT	randomised controlled trial
SCFA	short-chain fatty acid

Abstract

There is an intensifying interest in the interaction between diet and the functional gastrointestinal symptoms experienced in irritable bowel syndrome (IBS). Recent studies have used magnetic resonance imaging to demonstrate that short-chain fermentable carbohydrates increase small intestinal water volume and colonic gas production that, in those with visceral hypersensitivity, induces functional gastrointestinal symptoms. Dietary restriction of short-chain fermentable carbohydrates (the low FODMAP diet) is now increasingly utilised in the clinical setting. Initial research evaluating the efficacy of the low FODMAP diet was limited by retrospective study design and lack of comparator groups, but more recently well-designed clinical trials have been published. There are currently at least 10 randomised controlled trials or randomised comparative trials showing the low FODMAP diet leads to clinical response in 50-80% of IBS patients, in particular with improvements in bloating, flatulence, diarrhoea and global symptoms. However, in conjunction with the beneficial clinical impact, recent studies have also demonstrated that the low FODMAP diet leads to profound changes in the microbiota and metabolome, the duration and clinical relevance of which are as yet unknown. This review aims to present recent advances in the understanding of the mechanisms by which the low FODMAP diet impacts on symptoms in IBS, recent evidence for its efficacy, current findings regarding the consequences of the diet on the microbiome, and recommendations for areas for future research.

Key words: irritable bowel syndrome, intestinal microbiology, colonic microflora, diet

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic gastrointestinal (GI) disorder characterised by recurrent abdominal pain related to defaecation or a change in bowel habit.(1) It is a common condition worldwide, with a meta-analysis of 260,960 people across America, Asia, Europe and Africa reporting a pooled prevalence of 14% in females and 9% in males.(2) The Rome IV criteria identify four IBS subtypes based on predominant stool form (1), with diarrhoea predominant IBS (IBS-D) generally reported as being the most common (40-60% of all IBS).(3, 4) The pathophysiology of IBS is complex and multifactorial; visceral hypersensitivity, altered brain-gut signalling, immune dysregulation, the microbiota and psychosocial factors are recognised as important. Subtypes of IBS may differ in their pathophysiology, highlighting the importance of subtyping patients for targeting treatment.

Although there is no impact of IBS on mortality, it is likely that the morbidity associated with its chronic nature and the high incidence of GI and extra-intestinal comorbidities, such as anxiety and depression,(5) contribute to its negative impact on health-related quality of life (HRQOL).(6, 7) IBS results in considerable healthcare utilisation, with 30% of consultations in primary care relating to gastroenterology,(8) up to 60% of referrals to gastroenterology in secondary care (9) being due to IBS, and annual national healthcare costs related to IBS totalling £45-200 million in the United Kingdom (10) and $1.66 billion in the United States.(11) Despite the burden of IBS to both patients and the healthcare system, there is a lack of effective pharmacological treatments available, with a technical review reporting high quality of evidence for only one of nine pharmacological treatments.(12) Furthermore, pharmacological therapy for IBS usually targets only one symptom, which may necessitate polypharmacy in patients with IBS, many of whom report multiple symptoms.

THE ROLE OF DIET IN THE MANAGEMENT OF IBS

Numerous studies show the majority of patients with IBS (70-89%) report specific foods exacerbate symptoms and consequently many patients limit or exclude some food items.(13, 14) There is a lack of evidence regarding the underlying mechanisms by which food provokes symptoms in IBS, which has limited the development of validated diagnostic tests to identify specific food triggers. First line dietary advice in IBS usually focuses on modification of dietary fibre intake and restriction of potential triggers such as caffeine, alcohol and fat (15). Two recent meta-analyses identified between 14 (16) and 22 (17) randomised controlled trials (RCTs) of dietary fibre, and reported moderate quality evidence for fibre supplementation in IBS, with greater global symptom improvement compared with placebo, in particular for soluble fibre. In contrast, evidence for the effect of caffeine, alcohol and fat have only been reported in cross-sectional studies,(13, 18, 19) and no RCTs investigating the effect of their lone restriction have been performed.(15)

Regarding exclusion diets, the effect of gluten restriction in IBS is unclear. Evidence from uncontrolled studies (20,21) and a controlled trial (22) suggests a gluten-free diet leads to symptomatic benefit in patients with diarrhoea-predominant IBS with HLA-DQ2 or HLA-DQ-8 genotype. A short-term double-blind placebo-controlled crossover trial that controlled for background diet, however, failed to show any benefit (23). Further clarification of the role of gluten restriction in managing IBS symptoms is required. Historic trials involving multiple food restrictions followed by reintroduction suggest individual foods (e.g. milk, wheat) exacerbate symptoms,(24, 25) but most trials are uncontrolled and the mechanism by which individual foods induced symptoms was not identified. More recently, food hypersensitivity has been demonstrated in response to oral challenge with specific foods (soya, milk, wheat, yeast), the first fascinating real-time demonstration that food antigens might lead to immune activation and altered permeability of the intestinal mucosa.(26) Prospective controlled trials that challenge with specific food antigens followed by customised dietary exclusion are required to corroborate these findings.

Dietary modification of the GI microbiota through probiotics or prebiotics presents another potential approach for the management of IBS. Although the extent and quality of evidence for prebiotic supplementation in IBS to date is limited, there is some evidence for the efficacy of probiotic supplementation (27), with up to nine systematic reviews of 35 RCTs indicating small, but statistically significant, effects for some strains.(28) Rigorous trials of individual probiotic strains are required to delineate the most effective probiotic strains for particular symptoms.

Dietary restriction of short-chain fermentable carbohydrates or fermentable oligosaccharides, disaccharides, monosaccharides and polyols (low FODMAP diet) is a relative newcomer to dietary management in IBS. Over the past 10 years the magnitude of evidence for the mechanisms and clinical efficacy of the low FODMAP diet has surpassed any other dietary intervention for IBS, except for probiotics.(29) Although initial research was limited in study design, there has been a recent surge in well-designed clinical trials published. The aim of this review is to provide a critical review of the mechanisms by which short-chain fermentable carbohydrates impact on symptoms in IBS, the evidence for the efficacy of the low FODMAP diet, and the unintended consequences of the diet, as well as provide recommendations for areas for future research.

THE LOW FODMAP DIET

Carbohydrates are an important component of the human diet and consist of a range of molecules with diverse chemical and physical structures and consequently varied physiological and functional properties. Digestibility of carbohydrates varies due to the absence of (or reduced production of)

hydrolase enzymes for their digestion; such non-digestible carbohydrates include non-starch polysaccharides (NSP), resistant starch oligosaccharides and some polyols.(30) In addition, some disaccharides and monosaccharides are not completely absorbed in the small intestine. The degree of carbohydrate digestion and absorption is further influenced by the presence of disease (e.g. malabsorption disorders), inter-individual variation, and in some cases, transit time and the dose consumed.(30)

Up to 40 g/d of undigested and/or unabsorbed carbohydrate enters the colon.(31) Long-chain polysaccharides contribute to a substantial proportion of this indigestible dietary carbohydrate, and include plant cell wall NSP (e.g. cellulose, hemicelluloses and pectin), psyllium and resistant starch. Along with these long chain carbohydrates, smaller quantities of protein and fat also enter the colon from exogenous (dietary) and endogenous sources (e.g. red blood cells, sloughed epithelial cells), although their fate is less well studied than carbohydrates.(31) On entering the colon, carbohydrates with a high number of monomers (degree of polymerisation, DP>10 e.g. inulin) are fermented more slowly and produce a lower volume of gas than carbohydrates with fewer monomers (DP<10, e.g. oligofructose).(32)

It has long been acknowledged that ingestion of specific carbohydrates (e.g. fructose, lactose) can lead to exacerbation of GI symptoms in IBS.(33, 34) Furthermore, short-chain fermentable carbohydrates (FODMAPs) have been shown to induce symptoms in patients with IBS in a blinded re-challenge trial.(35) In contrast, the low FODMAP diet involves the restriction of multiple fermentable oligosaccharides (fructans, galacto-oligosaccharides), disaccharides (lactose), monosaccharides (fructose when in excess of glucose) and polyols (e.g. sorbitol, mannitol). The chemical nature, key dietary sources and dietary intake of these carbohydrates in patients with IBS are reviewed elsewhere.(29)

Clinical implementation of the low FODMAP diet involves in-depth dietary advice on FODMAP restriction followed by dietary exclusion of FODMAPs for 4-8 weeks in order to test for response to the diet. Where symptomatic response has been achieved, these carbohydrates are then reintroduced into the diet individually to tolerance whilst monitoring symptoms, with the ultimate aim of achieving a diverse and nutritionally adequate diet alongside long-term symptom control.

Mechanisms of action of the low FODMAP diet
A key limitation of most exclusion diets for IBS is a lack of identification of the specific mechanisms by which the food components induce symptoms.(24, 25) However, there is an expanding evidence base for the mechanisms of the effects of FODMAPs on GI function (Figure 1).

Small intestinal water

One of the two most established mechanisms by which FODMAPs are proposed to provoke symptoms in IBS is the augmentation of small intestinal water, which has been clearly demonstrated by both ileostomy recovery and magnetic resonance imaging (MRI) studies (Table 1, Figure 1). One randomised, single-blind, crossover feeding study in 10 ileostomates showed effluent water increased by 20% after a 4-day very high FODMAP diet (112 g/d) compared with a with very low FODMAP diet (6 g/d).(36) An even more pronounced effect on small intestinal water has been demonstrated in response to acute challenges using MRI. Healthy individuals exhibited a 4-fold higher small intestinal water volume 60 minutes after consumption of a 17.5 g mannitol solution compared with an equimolar glucose solution.(37) The same magnitude of effect was seen 60 minutes after administration of 40 g fructose, (38, 39) and this was partially resolved through contemporaneous ingestion of 40 g glucose, (38) thought to be due to enhanced co-transport of fructose and glucose via the GLUT-2 transporter. Conversely, inulin (a high DP fructan), had no effect on small intestinal water in healthy individuals (38) or in patients with IBS.(39) Further study is needed on the effect on small intestinal water of smaller DP fructans that are more representative of those found in the diet. In addition, the effects of other oligosaccharides (e.g. galacto-oligosaccharides, GOS), the disaccharide lactose, and other polyols (e.g. sorbitol) on small intestinal water are unknown.

The impact of increased small intestinal water on functional gastrointestinal symptoms in IBS is unclear. Firstly, the increase in luminal water may induce abdominal pain and bloating in those with visceral hypersensitivity, although recent research failed to demonstrate a correlation between peak small intestinal water and symptom exacerbation in IBS following blinded challenge with fructose (n=11) or inulin (n=13), perhaps related to the relatively small additional luminal volume (<100 ml).(39) Secondly, the additional small intestinal water has been hypothesised to contribute to loose stool and diarrhoea, however, the maximal colonic water volume tolerated, albeit in healthy volunteers (40), has been shown to be much greater than the additional water induced by these FODMAPs.

Colonic gas production

The availability of non-digested and/or non-absorbed short-chain carbohydrates for colonic fermentation leads to accumulation of colonic gas including hydrogen and methane (Figure 1). This is likely to lead to luminal distension, and therefore provocation of symptoms in IBS, specifically in those with visceral hypersensitivity. Table 1 summarises studies that have investigated the effect of FODMAPs on fermentation. A controlled, crossover feeding study demonstrated that a high FODMAP diet (50 g/d) led to a marked increase in 14-hour breath hydrogen production after two

days compared with a low FODMAP diet (<10 g/d) in 15 patients with IBS and 15 healthy individuals,(41) which was paralleled by higher symptoms scores in those with IBS. Furthermore, a recent crossover study in IBS

Table 1:

Studies investigating the effect of FODMAPs (or FODMAP restriction) on small intestinal water content and colonic gas production

Reference	Study design	Participants	Intervention	Outcome measures	Findings
Small intestinal water content					
(36)	Randomised crossover (single blind)	Ileostomates n=10	4-day HFD (112 g/d) 4-day LFD (6 g/d)	Effluent weight Effluent water content	Greater effluent weight (HFD 409 g vs LFD 504 g; p=0.01) Greater water content HFD vs LFD (mean difference 58 ml; p=0.013)
(37)	Randomised crossover (single blind)	Healthy n=11	17.5 g glucose (control) 17.5 g mannitol	SBWC using MRI	Greater SBWC at 40 minutes (mannitol 381ml vs glucose 47 ml; p<0.001)
(38)	Randomised crossover (single blind)	Healthy n=16	40 g glucose (control) 40 g fructose 40 g inulin 40 g fructose + 40g glucose	SBWC using MRI	Greater SBWC fructose (67 ml/min) vs glucose (36 l/min; p<0.005) No difference fructose + glucose vs fructose (mean difference 16 l/min) No difference inulin (33 l/min) vs glucose (36 l/min; p>005)
(39)	Randomised crossover (double blind)	IBS n=29 Healthy n=29	40 g glucose (control) 40 g fructose 40 g inulin	SBWC using MRI	Greater change in SBWC fructose (73 ml) vs glucose (21 ml; p<0.005) Similar patterns in SBWC between IBS and healthy
Colonic gas production					
(38)	Randomised crossover (single blind)	Healthy n=16	40 g glucose (control) 40 g fructose 40 g inulin 40 g fructose + 40g glucose	Breath H_2 over 400min Colonic gas using MRI	Greater H_2 production inulin (18000 ppm/min) vs glucose (3009 ppm/min; p<0.0001) Greater colonic gas inulin (33 l/min) vs glucose (19 l/min; p<0.05)
(39)	Randomised crossover (double blind)	Healthy n=29 IBS n=29	40 g glucose (control) 40 g fructose 40 g inulin	Breath H_2 over 300 min Colonic gas using MRI	Greater change H_2 production inulin (34 ppm) vs glucose (-2 ppm; p<0.005) Greater change colonic gas inulin (23 au) vs glucose (5 au; p<0.005) Similar patterns H_2 production and colonic gas IBS and healthy
(41)	Randomised crossover (single blind)	IBS n=15 Healthy n=15	2-day HFD (50 g/d) 2-day LFD (9 g/d)	Breath H_2 14 hours on day 2	Greater H_2 production (HFD 242 ppm vs LFD 62ppm; p<0001) in IBS Greater H_2 production (HFD 181 ppm vs LFD 43 ppm; p<0.001) in healthy

HFD, high FODMAP diet; LFD, low FODMAP diet; SBWC, small bowel water content; MRI, magnetic resonance imaging; H_2, hydrogen

showed that a 3-week low FODMAP diet (unknown total FODMAP dose) reduced 5-hour breath hydrogen following a lactulose challenge compared with a high FODMAP diet (unknown total FODMAP dose),(42) suggesting the low FODMAP diet leads to a shift in colonic fermentation patternindependent of acute fermentable carbohydrate intake (i.e. lactulose challenge), which is likely mediated by an alteration in microbiota composition.

Quantification of the effect of fermentable carbohydrates on colonic fermentation has been elegantly demonstrated by MRI. For example, inulin challenge (40 g/d) leads to an approximate two-fold greater colonic volume at four hours compared with glucose in healthy individuals and patients with IBS.(38, 39) It is also clear that there are distinct patterns of gas production elicited by individual FODMAPs. Specifically, inulin leads to a later and overall almost double the total gas production compared with fructose according to hydrogen breath testing in healthy individuals.(38) This is likely due to differences in degree of absorption of individual carbohydrates and differences in GI transit time that leads to variable availability for fermentation in the proximal colon. Fermentation rates also vary between carbohydrates of different molecular geometry.(32)

However, this recent research using MRI to investigate symptom induction in IBS challenges the assumption that people with IBS have elevated response to FODMAP ingestion (in terms of colonic gas production) compared with healthy controls, as both breath hydrogen production and colonic volume kinetics were almost identical in patients compared with healthy individuals.(39) Interestingly, this research also questions the extent to which increased colonic gas is responsible for symptoms induction in IBS. Patients with IBS who developed symptoms on FODMAP challenge did not, in fact, have greater colonic volume than those that do not report symptoms, suggesting that visceral hypersensitivity to luminal distension, rather than increased luminal distension *per se*, is key to symptom provocation during colonic fermentation.(39) However, these associations were only measured in a limited subgroup of 12 patients and therefore replication of this work in a larger sample is required to verify these findings. Importantly, measurement of visceral hypersensitivity (e.g. by barostat) is also required to confirm its role in the causality of symptom provocation in response to FODMAP administration.

Other proposed mechanisms

There is preliminary evidence of mechanisms by which FODMAPs might induce symptoms in IBS, beyond small intestinal water volume and colonic fermentation. Firstly, some FODMAPs increase GI motility. Small intestinal transit time is decreased following ingestion of a 30 g fructose-sorbitol mixture in healthy individuals,(43) which further reduces opportunity for small intestinal absorption and increases availability for colonic fermentation. However, the evidence for the effect of a low

FODMAP diet on transit time *per se* is lacking. One crossover RCT demonstrated no effect of a 3-week low FODMAP diet on whole gut transit time compared with a standard diet in patients with IBS.(44) This is surprising considering the aforementioned effects of FODMAPs on small intestinal water, however this study included both constipation and diarrhoea-predominant IBS subtypes, which may have masked potential differences between specific subtypes. The effect of FODMAP restriction on transit time, whilst controlling for fibre intake and other dietary factors that stimulate motility, requires clarification in large studies of specific IBS subtypes.

Secondly, there is now data to suggest that adherence to a low FODMAP diet is accompanied by changes in the GI microbiota and its metabolic output . The effect of a 3-week low FODMAP diet was compared with a high FODMAP diet (actual intakes unknown) in 37 patients with all IBS subtypes in a recent parallel design RCT.(42) A higher abundance of the hydrogen-utilising genus *Adlercreutzia* was reported in the low FODMAP group compared with the high FODMAP group. This may have contributed to the reduction in symptoms and the diminished hydrogen response to lactulose challenge. Metabolomic analysis of urine was able to discriminate the low FODMAP and high FODMAP groups based on three key urinary metabolites including histamine, a modulator of inflammation and immune function. Several associations were also found between abundance of various taxa, the metabolome and clinical symptoms, suggesting that the observed diet-induced changes in the microbiota and metabolome may be in part responsible for clinical outcomes.

A major limitation of this study was the absence of dietary composition assessment and therefore only an arbitrary assessment of dietary adherence. However, this is the first evidence to suggest that reducing the availability of fermentable substrate in the colon impacts the metabolomic output of the microbiota, which may plausibly be involved in the generation of GI symptoms. Taxonomic correlations with clinical and metabolic markers are important in contributing to our understanding of the mechanisms and/or potential detrimental effects of the low FODMAP diet, but causality is more difficult to ascertain and longitudinal follow up studies are needed to determine if diet-induced microbiota shifts lead to change in long-term health outcomes.

The low FODMAP diet may also reduce production of short-chain fatty acids (SCFAs). This is important, as there may be a higher stool concentration of SCFAs in IBS and an association with IBS symptomatology,(45) with an animal study demonstrating SCFAs induce visceral hypersensitivity.(46) Reducing luminal SCFAs could present another pathway by which the low FODMAP diet has its effect, although this has yet to be extensively studied, and findings are inconsistent. Reduction in total stool SCFAs,(47,49) acetate (47, 48) and butyrate (47, 49) have been

demonstrated in some studies in IBS, although no differences in SCFA between the low FODMAP diet and controls were reported in two small RCTs.(44,50)

Reduction in stool SCFA concentration in patients on a low FODMAP diet is likely the result of reduced availability of fermentable substrate and shifts in the abundance of taxa involved in SCFA production and/or cross-feeding reactions.(51) The potential effect of diet-induced alteration in SCFAs, especially butyrate, on various factors including epithelial barrier function, risk of colorectal cancer is of significance particularly if dietary restriction is prolonged. However, current evidence regarding the effect of the low FODMAP diet on SCFA is limited by conflicting findings between studies,(44,48,49,50) small patient numbers, differences in study design and SCFA quantification methodology. Furthermore, stool SCFA concentration is not an accurate measure of *in vivo* SCFA production due to the effect of colonic transit time on SCFA absorption (52) and stool volume on SCFA dilution (53), and thus variations across IBS subtypes.(52) Importantly, without assessment of SCFA concentration at the major site of production in the ascending colon, which requires technically demanding and invasive techniques,(54) it will be difficult to confirm the interaction between the low FODMAP diet, SCFA production and symptom provocation in IBS.

Finally, others have suggested alternative mechanisms by which a low FODMAP diet improves symptoms. One RCT of patients provided low FODMAP advice in combination with other dietary advice (n=13) reported normalisation of colonic serotonin cell density after 3-9 months.(55) It was suggested that this may have mediated symptom improvement by modulating transit time and visceral sensitivity. Furthermore, normalisation of stool lipopolysaccharide to levels comparable with healthy controls has been demonstrated in patients reporting a symptomatic response to a low FODMAP diet.(56) A series of animal and *in vitro* studies using the stool supernatant of these patients showed beneficial effects on visceral sensitivity and colonic mucosal integrity.

These latter human studies are limited by very small patient numbers and/or substantial attrition rate,(55, 56) and the absence of the assessment of dietary composition or dietary control during the intervention period.(55, 56) Crucially, it is unknown whether these findings are causal or merely epiphenomena. However, they present preliminary findings suggesting that the low FODMAP diet may have effects over and above reducing luminal distension, through effecting changes in epithelial integrity and inflammatory processes that have been implicated in IBS symptomatology.(57) Much research is required in this area, including *in vitro* studies that aim to identify discrete effects of individual FODMAPs on intestinal physiology, larger studies of homogenous IBS cohorts that identify key microbiome and metabolomic effects linked with response to the low FODMAP diet, and how these changes alter gut function.

Efficacy of the low FODMAP diet

Short-term clinical endpoints

The last decade has seen publication of numerous trials of the efficacy of the low FODMAP diet in reducing IBS symptoms. Publication of two recent systematic reviews, albeit with different conclusions, confirms the growing interest in the area.(58, 59) Many studies of the low FODMAP diet in IBS are limited due to their retrospective design,(60-63) lack of control or comparator groups,(64-66) and where these existed a lack of randomisation,(58) the use of low FODMAP diet in conjunction with other dietary advice,(67, 68) and the widespread lack of dietary assessment to confirm adherence. However some well-designed RCTs have been undertaken, with promising findings, many which have only recently been published, and only these will be reviewed in detail here.

At least 10 RCTs have been undertaken investigating the efficacy of a low FODMAP diet in adults with IBS (Table 2). Five studies were unblinded and involved patients being randomised to low FODMAP dietary advice from a dietitian for 4-6 weeks, with all five studies reporting improvements in functional GI symptoms using various symptom scoring tools (60,68,69,71,72) as well as improvement in quality of life.(69, 72) There are inevitable limitations with unblinded intervention studies, particularly in a disorder with a reportedly high placebo response.(73)

However, recently two blinded placebo-controlled studies have been performed evaluating the effect of the low FODMAP diet on IBS symptoms. In the first, a 21-day crossover feeding study that compared the low FODMAP diet with a "typical diet", showed the low FODMAP diet led to an improvement in overall GI symptoms, and resulted in a response (defined as 10 mm reduction on a visual analogue scale) in 70% of patients (response in "typical diet" group not reported).(74) An advantage of a feeding study such as this is the ability to carefully control dietary intake, however controlled feeding does not mimic the real-life challenges experienced by free living individuals undergoing dietary change. Furthermore, the crossover nature of the study carries questions regarding the minimum washout period required between interventions. Furthermore, symptoms worsened during the "typical diet" control, which may have been the result of increased FODMAP intake compared with habitual diet, leading to an artificially greater difference in symptoms between groups. Nevertheless, this was the first placebo- controlled low FODMAP intervention trial and a vital contribution to the current evidence-base for the low FODMAP diet in the management of functional GI symptoms.

The second placebo-controlled RCT used dietary advice in order to evaluate the effect of the low FODMAP diet as it would be used in clinical practice.(48) In total, 104 patients with IBS were

randomised to either low FODMAP dietary advice or to sham (placebo) dietary advice for four weeks, with lower Irritable Bowel Syndrome Severity Scale (IBS-SSS) scores and greater numbers experiencing a response ($\geq$50 point reduction in IBS-SSS) in the low FODMAP group (73%) compared

Table 2:

Randomised trials investigating the clinical efficacy of the low FODMAP diet in adults with IBS

Ref	Study design	Participants	Intervention vs Control/comparator (n)	Duration	Symptom scoring	Findings
Controlled trials						
(48)	Placebo-controlled dietary advice RCT (single blind)	Rome III IBS-D, IBS-M, IBS-U	LFD n=51 Sham diet n=53	4 weeks	AR IBS-SSS IBS-QOL	Primary outcome: No difference in AR (LFD 57% vs control 38%; p=0.051). Secondary outcomes: Lower IBS-SSS score (LFD 173 vs control 224; p=0.001) and greater numbers achieving MCID for IBS-QOL (LFD 51% vs control 26%; p<0.023)
(50)	Dietary advice RCT (unblind)	Rome III IBS with bloating or diarrhoea	LFD n=19 Habitual diet n=22	4 weeks	AR GSRS Bristol Stool Form	Primary outcome: luminal microbiota (see table 3) Secondary outcomes: Greater numbers reporting AR (LFD 68% vs control 23%; p=0.005) Lower bloating, borborygmi, overall symptoms LFD vs control (p<0.05) Greater number of normal stools (LFD 24% vs control 7%; p=0.02)
(69)	Dietary advice RCT (unblind)	Rome III IBS	LFD n=23 Waiting list n=27	3 months	IBS-SSS IBS-QOL	Outcomes: Greater reduction in IBS-SSS (LFD 276 to 129 pts vs control 247 to 204 pts; p<0.01), frequency of pain episodes (p<0.01) Greater increase in IBS-QOL score for LFD vs control (p<0.0001)
(70)	Dietary advice RCT (unblind)	Rome III IBS	LFD n=42 Probiotic n=41 Habitual diet n=40	6 weeks	IBS-SSS IBS-QOL	Primary outcome: Greater reduction in IBS-SSS (LFD -75 pts vs control -32 pts; p<0.01) Secondary outcome: No change in IBS-QOL for all groups
(74)	Placebo-controlled feeding RCT, crossover (single blind)	Rome III IBS	LFD n=27 Typical diet n=27	21 days	100 mm symptom VAS Stool frequency Stool water content	Primary outcome: Lower overall GI symptoms (LFD 23 mm vs control 45 mm; p<0.001). Secondary outcome: Lower stool frequency in IBS-D in LFD vs control
Comparative trials						
(42)	Dietary advice RCT (single blind)	Rome III IBS	LFD n=20 HFD n=20	3 weeks	Responder: ≥50 pt reduction IBS-SSS	Primary outcome: area under the curve for lactulose breath test Secondary outcomes: Greater number of responders (LFD 72% vs HFD 21%; p<0.009) Lower IBS-SSS in LFD vs HFD (p=0.01)
(49)	Dietary advice RCT, crossover (double blind)	Rome III IBS-D, IBS-M	LFD+placebo n=20 LFD+fructans n=20	6 weeks	IBS-SSS 100mm symptom VAS	Outcomes: Lower IBS-SSS (LFD 80% vs control 30%; p=0.014) and severity of nausea/vomiting, belching, flatulence in LFD vs control (p<0.05)
(71)	Dietary advice RCT (unblind)	Rome III IBS-D	LFD=45 Modified NICE guideline n=39	4 weeks	Responder: AR ≥50% of weeks 3,4 Composite pain & stool score	Primary outcome: No difference in numbers of responders (LFD 52% vs control 41%; p=0.31) Secondary outcomes: No difference in those achieving composite score endpoint (LFD 27% vs control 13%; p=0.13) Greater reduction in pain (LFD 51% vs control 23%; p=0.008)

| (72) | Dietary advice RCT (unblind) | Rome III IBS | LFD n=24 Hypnotherapy n=25 Combined LFD and hypnotherapy n=25 | 6 weeks | Responder: ≥20mm VAS improvement in symptoms IBS-QOL | Primary outcome: No difference in numbers of responders (LFD 71% vs hypnotherapy 72% vs combination 72%; p=0.67). Secondary outcomes: Lower symptom severity in LFD and hypnotherapy vs baseline (p<0.05) and higher IBS-QOL scores in all groups compared with baseline (p<0.001) but no differences between groups for symptoms or IBS-QOL |
| (76) | Dietary advice RCT (single blind) | Rome III IBS | LFD n=38 NICE guideline n=37 | 4 weeks | Responder: ≥50 pt reduction IBS-SSS Stool frequency and consistency | Primary outcome: No difference in number of responders (LFD 50% vs control 46%; p=0.72) |

RCT, randomised controlled trial; LFD, Low FODMAP diet; AR, adequate relief; GSRS, Gastrointestinal Symptom Rating Scale; GI, gastrointestinal; FFQ, food frequency questionnaire; IBS-SSS, IBS severity scoring system; IBS-QOL, IBS quality of life questionnaire; LGG, *Lactobacillus rhamnosus* GG; VAS, visual analogue scale; MCID, minimal clinically important difference; HFD, high FODMAP diet; NICE, National institute for Health and Care Excellence; FOS, fructo-oligosaccharide

with sham dietary advice (42%, p=0.005) although adequate relief was reported by similar numbers in the low FODMAP (57%) group compared with sham (38%, p=0.051). This trial presents the first evidence that the low FODMAP diet is superior to placebo when administered as dietary advice.

Five RCTs have compared the low FODMAP diet with active interventions. Two randomised comparative trials have been undertaken comparing low FODMAP dietary advice with standard dietary guidelines for IBS (e.g. small frequent meals, limit caffeine and alcohol, restrict intake of fatty or spicy food).(75) One study randomised 38 patients to low FODMAP advice and 37 to standard dietary advice for 4 weeks with a clinical response (≥50-point reduction in IBS-SSS) reported in 50% in the low FODMAP group and 46% in the standard advice group, with no difference between groups.(76) In the second RCT, although there was no difference in proportion of patients achieving the adequate relief endpoint, there were a greater number of pain responders in the low FODMAP group (51%) compared with standard advice (23%, p=0.008), as well as a greater magnitude of response of multiple individual symptoms (abdominal pain, bloating, stool consistency frequency and urgency).(71) This data on individual symptom response is consistent with previous findings of a non-randomised comparative trial that reported a significant difference in the numbers responding to low FODMAP dietary advice (76%) compared with standard NICE guideline dietary advice (54%).(63) One recent trial also compared the low FODMAP diet with hypnotherapy in IBS.(72) Both interventions improved symptoms, although there was no difference in symptom severity between groups at 6 weeks.

Finally, two RCTs have compared symptom response to the low FODMAP diet with interventions not intended to improve symptoms. The comparator group in one study was a high FODMAP diet (42) and in the other was a low FODMAP diet supplemented with fructo-oligosaccharide (fructans) to achieve a "normal" FODMAP intake.(49) Whilst the primary aim of these studies was not to investigate symptom response, both found the low FODMAP diet led to symptomatic benefit compared with the comparator interventions, both of which were high in fermentable carbohydrates.

In summary, evidence to date suggests 50-80% of patients with IBS report symptomatic benefit on a low FODMAP diet in the short term, and data from comparative trials suggests it is at least as effective as general dietary and lifestyle interventions. Preconceived expectations about a treatment may prime patients to sense and record symptom outcomes differently, and this is a particular problem in IBS where outcomes are subjectively assessed, highly sensitive to participant behaviour, and where placebo effect is considerable (20-40%).(73) Therefore, recent placebo-controlled trials provide robust evidence for its clinical efficacy over placebo, and the first meta-analysis of low FODMAP RCTs reports a greater odds of reduction of abdominal pain (OR 1.81), abdominal bloating

(OR 1.75) and overall GI symptoms (OR 1.81) compared with controls.(59) In line with these findings, national guidelines for the dietary management of IBS in the UK now advise consideration of a low FODMAP diet where basic diet and lifestyle measures (e.g. NICE guideline advice) have been unsuccessful.(17, 75)

Long term clinical endpoints

The majority of clinical trials of the low FODMAP diet evaluate short term clinical endpoints ($\leq$ 12 weeks). The durability of the diet over the longer term is arguably more meaningful given the chronicity of symptoms in IBS, but there is limited data available. This is particularly important given that standard practice is to systematically reintroduce FODMAPs to tolerance once symptoms are controlled. A retrospective study suggests the continued effectiveness of the diet in the longer term. Follow up of patients consuming a FODMAP modified diet suggests clinical benefit in 57-74% of patients at 14-16 months,(62) although the results are likely subject to significant recall bias.

The RCT previously described comparing low FODMAP advice with hypnotherapy examined the long term symptomatic outcomes of patients.(72) Lower severity scores were evident for overall symptoms in 24 patients in the low FODMAP group at six months compared with baseline, with an impressive 82% categorised as responders. However, the improvement in symptoms in patients was not different to 25 patients who had originally been randomised to receive hypnotherapy or combined low FODMAP diet-hypnotherapy treatment (p=0.32). Further high quality long term RCTs are required to clarify the longevity of symptom response in patients who receive low FODMAP dietary advice, especially following reintroduction of FODMAPs to individual tolerance. Furthermore, considering the chronicity of patients' symptoms, the impact of long term dietary manipulation on nutrient intake requires evaluation.

Potential hazards of the low FODMAP diet

Gastrointestinal microbiota

Despite the clinical efficacy of a low FODMAP diet in IBS, some potentially unfavourable consequences have been reported. In particular, the low FODMAP diet leads to a considerable reduction in intake of prebiotic fructans and GOS,(50, 76) and therefore a sizeable reduction in substrate available for colonic fermentation. Significant dietary restriction will alter the composition and functioning of the GI microbiota. Six studies, including a number already reviewed in the clinical section, have investigated the effect of the low FODMAP diet on the gut microbiota in IBS (Table 3).

Two studies, undertaken by our group, have investigated the effect of a 4-week low FODMAP diet on stool microbiota in patients with IBS. Using fluorescence *in situ* hybridisation, the first demonstrated

that a 50% reduction in FODMAP intake led to a marked six-fold reduction in relative abundance of Bifidobacteria compared with controls who maintained their habitual diet.(50) There were no

Table 3:

Studies investigating the effect of the low FODMAP diet on the microbiota and microbiota metabolites

Reference	Study design	Participants	Duration	Microbiota		Microbiota metabolite	
				Method	**Findings**	**Method**	**Findings**
(42)	Dietary advice RCT (single blind)	Rome III IBS LFD n=19 HFD n=18	3 weeks	16S rRNA sequencing (Illumina)	Microbiota: Increased richness of Actinobacteria, Firmicutes, Clostridiales in LFD vs HFD No difference in α-diversity or β-diversity after LFD vs baseline but higher richness in LFD vs HFD Increased abundance of Clostridiales family XIII *Incertae sedis* spp. and *Porphyromonas* spp. in LFD vs baseline Decreased abundance of Propionibacteriaceae, Bifidobacteria in LFD vs baseline	MS	No difference in urinary metabolomic profile at baseline in LFD vs HFD but separation after intervention Three metabolites (histamine, p-hydroxybenzoic acid and azelaic acid) discriminated groups Metabolite concentrations correlated with abundance of various taxa
(44)	Feeding RCT, crossover (single blind)	Rome III IBS and healthy LFD vs typical diet IBS n=27 Healthy n=6	3 weeks	qPCR	Lower absolute abundance of Bifidobacteria, *F. prausnitzii*, Clostridium Cluster IV in LFD vs typical diet and baseline Lower relative abundance *A. muciniphila* in LFD vs typical diet Lower total bacteria in LFD vs baseline Greater diversity Clostridium Cluster XIV in LFD vs typical diet and baseline	GLC	No difference in total or individual stool SCFAs in LFD vs typical and baseline
(47)	Dietary advice uncontrolled trial (unblind)	Rome III IBS n=63	4-week	-	-	GLC	Lower total stool SCFAs, acetate, butyrate vs baseline
(48)	Dietary advice RCT (single blind)	Rome III IBS LFD n=51 Sham n=53	4 weeks	qPCR	Lower abundance of Bifidobacteria in LFD vs sham	GLC	Lower stool acetate concentration in LFD vs control
(50)	Dietary advice RCT (unblind)	Rome III IBS LFD n=19 Habitual diet n=22	4 weeks	FISH	Lower absolute and relative abundance of Bifidobacteria in LFD vs habitual No difference in total abundance of other groups e.g. *F. prausnitzii*	GLC	No difference in total or individual stool SCFAs in LFD vs habitual
(77)	Dietary advice uncontrolled trial (unblind)	Paediatric Rome III n=12	1 week	454 pyrosequencing	No difference in α-diversity after LFD No changes in distribution of taxa	UPLC/MS GC/MS	A number of stool metabolites (L-urobilin) associated with response to LFD

RCT, randomised controlled trial; low FODMAP diet; HFD, high FODMAP diet; MS, mass spectrometry; FISH, fluorescence *in situ* hybridisation; GLC, gas liquid chromatography; SCFA, short chain fatty acid; qPCR, quantitative polymerase chain reaction; UPLC/MS, ultra-performance liquid chromatography tandem mass spectroscopy; GC/MS, gas chromatography mass spectroscopy
All differences reported are significant (p<0.05)

differences in total bacteria or other bacterial groups such as Lactobacillus or *Faecalibacterium prausnitzii,* or fermentation byproducts such as stool SCFA concentration or pH between groups. These findings were corroborated in a recent large, placebo-controlled RCT where low FODMAP dietary advice led to reduction in Bifidobacteria concentration using quantitative polymerase chain reaction.(48)

The third study was the previously described 3-week feeding study that used quantitative polymerase chain reaction to show lower absolute Bifidobacteria concentration, *F. prausnitzii* and Clostridium Cluster IV accompanied by a substantially lower total bacterial load of 47% during the low FODMAP diet compared with habitual diet.(44) Diversity of Clostridium Cluster XIV was greater after low FODMAP intervention compared with habitual diet, which was postulated to be due to species adaptation to altered substrate availability. This was a crossover study, and therefore the potential of carryover effects cannot be ruled out and the 80% reduction in FODMAP intake, which was achieved through total food provision, is unlikely to be reflective of the reductions achieved in dietary advice in routine practice.

In addition to these studies, two others have evaluated microbiota composition in response to FODMAP restriction in IBS using metagenomic sequencing methods.(42, 77) Deep analysis of microbiota composition and structure revealed no change in α-diversity (number of operational taxonomic units [OTU] i.e. number of species) in children after a 1-week low FODMAP diet in a small uncontrolled study.(77) Furthermore, the previously described 3-week study that reported low FODMAP-induced metabolomic alterations in adults demonstrated no effect on α-diversity or β-diversity (differences in species composition between samples at baseline and follow-up) compared with baseline.(42) In the latter study, the abundance of several taxa increased (Clostridiales XIII *Incertae sedis* spp. and *Porphyromonas* spp.) and decreased (Propionibacteriaceae, Bifidobacteria) in the low FODMAP group.

Whether quantitative analysis of the microbiota could be harnessed as a predictor of response to the low FODMAP diet is an exciting proposition, and has been evaluated in a limited number of studies. In one study, increased baseline abundance of taxa such as Bacteroides, *Ruminococcaceae* and *F. prausnizii* predicted response to a 2-day low FODMAP diet in children, where response was based on pain frequency.(78) This was a crossover feeding study, however, and symptom response occurred in only 24% of patients, but it did suggest patients with a higher abundance of saccharolytic microbiota may benefit the most from a reduction in dietary fermentable substrates. No such association has been demonstrated in adult patients,(44) and more data is required from large parallel-arm trials.

Clearly, there is still much to understand regarding the impact of the low FODMAP diet on the GI microbiota. Whether the effect of the low FODMAP diet on the specific bacterial groups (e.g. Bifidobacteria) or overall microbiota community has identifiable downstream effects on their metabolic output or has detrimental effects on colonic health is unknown. Furthermore, it is not yet known whether the mucosal compartment is affected, whether there is a definitive effect on SCFA concentration and luminal pH in the proximal colon, or if there is a critical time point at which microbiota alterations might have functional consequences and whether these changes alter short or long-term health outcomes. The vast majority of studies thus far are descriptive observations of the microbiome and metabolome in clinical trials of the low FODMAP diet. *In vitro* studies will be important in guiding investigations of low FODMAP-induced alterations in the microbiome and its output in humans. Reintroduction of FODMAPs to tolerance may attenuate some of these changes, and studies of FODMAP restriction combined with probiotic or prebiotic supplementation are underway.

Nutrient intake

Most patients with IBS meet nutrient requirements,(14, 79) and their nutrient intake does not differ from that of healthy controls.(80) The clinical effectiveness of a therapeutic diet must always be weighed against the impact it has on maintaining appropriate nutrient intake, as well as the difficulties of following the diet. In relation to macronutrients, three dietary advice studies have reported that the low FODMAP diet leads to a lower total carbohydrate intake compared with habitual diet,(50, 71,76) although the effect sizes are small and result in carbohydrate intakes reflect those of healthy individuals (150-200 g/d).(81) One study previously mentioned reports a considerable reduction in energy intake in patients following low FODMAP advice,(76) which may be of concern particularly if the diet is followed in the longer term. However, the same change was seen in patients following standard IBS advice, and therefore it is unlikely this effect is specific to the low FODMAP diet, and may instead be due to dietary vigilance.

The 4-week study evaluating the effect of low FODMAP dietary advice compared with controls following habitual diet is the only RCT to date that has examined micronutrient intake.(50) Iron intake was not different to controls, suggesting that iron-rich foods restricted on the low FODMAP diet (e.g. iron-fortified cereal, pulses, nuts) were adequately substituted when advice was given by a registered dietitian. However, a lower calcium intake was reported (600 mg/d in the low FODMAP group vs 730 mg/d in controls, p=0.016), and it is likely that this was due to restriction of lactose-containing dairy products with insufficient replacement of high calcium alternatives. Measurement error due to lack of low lactose food composition data may also be a contributing factor. Nevertheless, further larger studies are required to confirm whether the intake of calcium and/or other

micronutrients is compromised when patients with IBS follow a low FODMAP diet. Importantly, evaluation of nutrient intake and dietary diversification at sequential periods following FODMAP reintroduction will be important to establish whether the low FODMAP diet poses any nutritional risk in IBS in the long term.

FUTURE PERSPECTIVES

Future research on the low FODMAP diet must move away from simply assessing clinical responses. Careful characterisation of patients in clinical trials and clarification of mechanisms of action will help in the identification of phenotypes most likely to respond, which is important when considering a diet that is complex to implement. Long term follow-up of patients who have liberalised their diet require further formal evaluation. The low FODMAP diet co-administered with a microbiota-targeted therapy may be a novel approach to inducing clinical response whilst preventing a detrimental impact on the microbiota and metabolome. Future research must also focus on the use of the diet in other clinical conditions characterised by functional GI symptoms. For example, preliminary research shows the low FODMAP diet results in reduction in functional gut symptoms in co-existent inflammatory bowel disease (IBD),[64] but microbiota composition shifts also occur [82], including alterations in the abundance of species already reduced in IBD e.g. *Akkermansia muciniphila* [83] and *F. prausnitzii*.[84] A bottom-up approach (limited restriction of high FODMAP foods at the outset) may be more appropriate in these patients.[85] In addition, studies that compare the low FODMAP diet with single sugar exclusion (e.g. fructose, lactose) would enable understanding of whether the effects of the diet are due to restriction of all FODMAPs or just individual sugars. Whether a long term low FODMAP diet is appropriate in specific disease states requires clarification. Future work will need to acknowledge that microbiota and metabolomic response to dietary intervention is highly individually variable, and evaluating these differences may be important in informing whether subsets of patients are more likely to respond clinically.

Methods of implementation of the diet are also important areas for future work. The rapid rise in evidence for the efficacy of the diet has increased demand for clinical services. Preliminary data suggests low FODMAP group education by a dietitian is just as effective as 1:1 education, [61] and this may represent a more practical method for treating large patient numbers, although long term effectiveness and nutritional consequences of this approach requires evaluation.

The strength of future evidence will rely on precise implementation of the low FODMAP diet using established published food composition data (86-88) and measurement of adherence by careful measurement of dietary intake. Studies should be suitably powered and apply validated instruments to measure clinical outcomes. Evaluation of the impact on the microbiota and metabolome will always

be constrained by confounding factors, but effort must be made to control for certain variables if possible (e.g. stress, concurrent medications), including dietary components known to have considerable effects on microbiota composition (e.g. fibre, polyphenols).

CONCLUSION

Convincing evidence exists for the clinical efficacy of the low FODMAP diet in IBS, which represents a therapeutic milestone for a condition that has historically been difficult to treat by either medical or dietary means. There is mounting evidence of the profound effect of the low FODMAP diet on the microbiota and its metabolites, but further research is necessary to clarify the duration, nature and implications of this in the short and long term. Interventions used in conjunction with the low FODMAP diet to prevent potentially deleterious impacts on the microbiota may become key dual prophylactic and co-therapeutic measures. Furthermore, predicting response to the diet will assist in optimising management of patients with IBS, and limit unnecessary dietary restriction in those less likely to respond.

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Figure 1: Mechanisms of the effects of FODMAPs on gastrointestinal function.

Some short-chain fermentable carbohydrates are absorbed. For example, fructose is absorbed via GLUT2 or GLUT5 and lactose is absorbed if hydrolysed by lactase. Unabsorbed fructose, polyols and lactose lead to increased small intestinal water. Unabsorbed carbohydrates, including fructans and GOS, are fermented in the colon leading to gas production. The resulting luminal distension leads to functional gastrointestinal symptoms in those with visceral hypersensitivity and IBS.