Mechanisms and efficacy of dietary FODMAP restriction in IBS

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Abstract | IBS is a debilitating condition that markedly affects quality of life. The chronic nature, high prevalence and associated comorbidities contribute to the considerable economic burden of IBS. The pathophysiology of IBS is not completely understood and evidence to guide management is variable. Interest in dietary intervention continues to grow rapidly. Ileostomy and MRI studies have demonstrated that some fermentable carbohydrates increase ileal luminal water content and breath hydrogen testing studies have demonstrated that some carbohydrates also increase colonic hydrogen production. The effects of fermentable carbohydrates on gastrointestinal symptoms have also been well described in blinded, controlled trials. Dietary restriction of fermentable carbohydrates (popularly termed the 'low FODMAP diet') has received considerable attention. An emerging body of research now demonstrates the efficacy of fermentable carbohydrate restriction in IBS; however, limitations still exist with this approach owing to a limited number of randomized trials, in part due to the fundamental difficulty of placebo control in dietary trials. Evidence also indicates that the diet can influence the gut microbiota and nutrient intake. Fermentable carbohydrate restriction in people with IBS is promising, but the effects on gastrointestinal health require further investigation.

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Introduction

Much attention has been focused on the dietary management of gastrointestinal symptoms in IBS. Some fermentable carbohydrates have been shown to increase ileal luminal water content or colonic hydrogen (H_2) production, processes that might elicit gastrointestinal symptoms in IBS. Although restriction of individual carbohydrates (such as fructose or lactose) has been used for many years, broader restriction of several short-chain fermentable carbohydrates—popularly termed the 'low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet'—has been of clinical and research interest. Dietary trials are fraught with methodological difficulties,[1] such as the problems of incorporating a placebo, and therefore randomized, placebo-controlled trials of dietary interventions are challenging. This Review aims to critically and comprehensively evaluate the literature regarding the mechanisms underlying fermentable carbohydrate restriction, critique the available evidence regarding its efficacy and discuss the strengths and limitations of the diet and its clinical application in IBS.

Irritable bowel syndrome

IBS affects ~11% of individuals in the Americas, Europe, Asia Pacific and Africa, with marked variation according to geographical location (21% in South America versus 7% in southeast Asia, for example).[2] Diagnosis of IBS relies on the presence of chronic gastrointestinal symptoms with absence of alarm features suggestive of organic disease.[3] The condition is characterized by abdominal pain or discomfort associated with disordered defecation or a change in bowel habit.[3] IBS is most prevalent in young adult women[4] and those with a low income.[5,6] IBS can also co-exist with other gastrointestinal disorders.[7]

IBS has a considerable effect on quality of life. People with IBS spend more days in bed, miss more work days and have more consultations with their primary care physician than those without the condition.[8] Indeed, some components of quality of life, such as role limitations and social functioning, are worse in IBS than in other chronic diseases including GERD and diabetes,[9] highlighting the profound effect of gastrointestinal symptoms on health. The chronic nature of IBS, its high prevalence and its associated comorbidities contribute to a considerable economic burden on health-care services (in 2000, the total annual cost of IBS in the USA was US$1.7 billion).[10,11]

The pathogenesis of IBS is multifactorial and includes altered gastrointestinal motility,[12] increased gastrointestinal fermentation,[13] abnormal gas transit,[14] visceral hypersensitivity[15] and brain–gut axis dysregulation.[16] Genetic predisposition[17,18] and psychosocial aspects (for example, hypervigilance)[19–22] are also recognized as important factors. Dysbiosis of the gut microbiota has also been implicated in its pathogenesis.[23] Reduced numbers of bifidobacteria[24–28] and lactobacilli[26,28] in the lumen, reduced numbers of bifidobacteria in the mucosa,[29,30] and lower diversity in both the lumen,[31,32,33] and mucosa[31] have been reported in patients with IBS compared with healthy individuals.

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The authors declare no competing interests.

Key points

- The underlying pathophysiology of IBS is complex and the efficacy of medical treatment is variable
- Prebiotic carbohydrates selectively increase numbers of specific bacteria (for example, bifidobacteria) that could influence gastrointestinal health
- Short-chain fermentable carbohydrates (termed FODMAPs) are known to induce gastrointestinal symptoms and do so through their effects on luminal water handling and colonic gas production
- Evidence suggests fermentable carbohydrate restriction (low FODMAP diet) is effective for IBS symptoms; however, data are limited to uncontrolled or retrospective studies, one controlled trial and three randomized, controlled trials
- Further randomized trials are required to confirm the efficacy of fermentable carbohydrate restriction in IBS management and to further examine the effects on the gut microbiota and dietary quality
- Placebo-controlled trials are difficult to undertake in studies of dietary advice

Treatment of IBS and other common functional bowel disorders, such as functional bloating, have historically been symptom-directed (for example, bulking agents, antispasmodic agents) or centrally acting (for example, antidepressants, cognitive–behavioural therapy). Unfortunately, the efficacy of these treatments is variable. Interest in therapeutic options to modulate the gut microbiota using probiotics, prebiotics[34] and antibiotics is growing.[35] Clinical guidelines of the treatment of IBS are developed from systematic reviews and meta-analyses that include data from clinical trials, some of which are hindered by small sample size and inconsistent end points.[36] Furthermore, symptom heterogeneity of study participants and publication bias are common in systematic reviews and meta-analyses of the IBS literature.[36]

Dietary management of IBS

Many patients believe that their IBS symptoms are diet-related[37,38] and therefore seek information about the effect of diet on their symptoms.[39] As a result, the majority of patients self-limit consumption of perceived culprit foods,[37,39] increasing the risk of nutritional inadequacy. Despite this potential risk, there is inconsistent evidence that nutrient intake is compromised in IBS, although many studies do not compare intakes with national dietary guidelines and the quality of studies varies.[38,40–42] The lack of clarity of the underlying mechanisms by which food provokes symptoms in IBS has limited the development of validated diagnostic tests to identify specific food triggers.

Evidence supporting the effect of dietary intervention on IBS symptoms has been of limited quality. Outcomes of studies addressing the usefulness of altering dietary fibre intake (non-starch polysaccharides) are inconsistent and numerous meta-analyses and systematic reviews on this topic are reviewed elsewhere.[43,44] Associations between IBS symptoms and intake of caffeine,[37,45] alcohol[37,46] and fat[38,45] have been reported in cross-sectional studies; however, no randomized controlled trials (RCTs) investigating the effect of their restriction have been performed. Interest in gluten restriction in IBS has also increased.[47,48] Nevertheless, interest in dietary approaches for the management of IBS continues to grow amongst both clinicians and patients, and is now focused on the restriction of short-chain fermentable carbohydrates.

Fermentable short-chain carbohydrates

Dietary carbohydrates can be classified into sugars, oligosaccharides and polysaccharides based on their degree of polymerisation (DP).[49] A discrete group of carbohydrates are described as 'fermentable' owing to their availability for fermentation in the colon, which is either due to the absence, or reduced concentration, of suitable hydrolase enzymes for digestion (for example, lactase deficiency), or in the case of monosaccharides because of incomplete absorption in the small intestine.

Fructans

The inulin-type fructans are a major dietary source of fermentable carbohydrates. They are either linear or branched fructose oligosaccharides that include inulin, (DP 2–60), oligofructose (DP 2–8) and fructo-oligosaccharides (<10 DP).[50] Minimal digestion of fructans occurs in the small intestine[51] due to the absence of enzymes in the human gastrointestinal tract that are able to digest the β-(2–1) fructosyl–fructose glycosidic bonds.

Fructans are present as storage carbohydrates in plants.[52–55] Most dietary fructans are obtained from wheat and onion,[54,56] which are fairly low in fructans but are consumed in large quantities. Commercial fructans derived from sucrose or chicory root are increasingly added to pre-prepared foods due to their textural and sensory properties and potential health benefits, including their low-energy content.[57] Fructans are also prebiotic, as they are "non-digestible, fermentable compounds that lead to selective stimulation of growth and/or activity of one or a limited number of microbial genera/species in the gut microbiota that confer health benefits to the host".[58] Average inulin intake in healthy people is highest in mainland Europe (estimated at 6 g per day), and lower in the UK (4 g per day)[56] and the USA (2.6 g per day).[59] Fructan intake in patients with IBS has not been extensively investigated, although in one UK study intake was reported to be 3.6 g per day.[60]

Galacto-oligosaccharides

Galacto-oligosaccharides (GOS) consist of galactose monomers (DP <10) with a terminal glucose unit. Humans lack an α-galactosidase enzyme, leading to the availability of GOS for colonic fermentation and its prebiotic effect.[61] Food composition data for GOS is less well documented than for fructans, but common sources include human milk, pulses, legumes and some grains, nuts and seeds.[62,63] Commercially, GOS can be produced via β-galactosidase enzymatic treatment of lactose, and is commonly added to infant formula, dairy products and beverages.[61,64] The dietary intake of GOS in patients with IBS is 2 g per day,[60] but has not been reported in healthy individuals.

Disaccharides and monosaccharides

Lactose and fructose are disaccharides and monosaccharides, respectively, which are incompletely absorbed in some people, and are therefore available for colonic fermentation. Lactose is a disaccharide of glucose and galactose, digestion of which consists of hydrolysis by lactase. However, up to 70% of humans exhibit hypolactasia,

which results in lactose malabsorption.[65] The prevalence of lactose malabsorption in patients with IBS is in the range of 18–82%,[66–68] but is not higher than in the general population.[66,68] Moreover, diagnosis of lactose malabsorption using lactose challenge and H_2 breath testing is not clinically meaningful unless lactose consumption exacerbates gastrointestinal symptoms, which is termed lactose intolerance. Naturally present in mammalian milk (for example, cow, goat and ewe's milk), lactose is also added to commercial foods such as breads, cakes and slimming products,[69] and average intakes in a healthy population in Sweden are reported as 12 g per day[70] and in patients with IBS in the UK as 7 g per day.[60]

Fructose is a 6-carbon monosaccharide that is dose-dependently and variably absorbed.[71] Fructose absorption can occur through a number of routes of facilitated transport. The most widely researched are through the fructose-specific GLUT5 transporter and the GLUT2 transporter on the apical membrane of the intestinal epithelium,[71] the latter involving a process of glucose:fructose co-transport. A third transporter (GLUT7) has also been identified, but it is unlikely to be a major candidate owing to its distal location in the ileum.[71] Considerable debate exists about the distribution and role of these transporters in fructose absorption. Clinical trials confirm that a fructose:glucose ratio of 1:1 is optimal for fructose absorption to occur.[72,73] Studies vary considerably in methodology; however, consumption of a 35 g dose of fructose alone is incompletely absorbed in 30–60% of healthy people and a similar proportion of those with IBS.[68,74] The major contributors to fructose intake have only been reported in the US population, these being fruit, fruit products and products sweetened with high-fructose sweeteners. Average intake in the USA has been reported as 41 g per day,[75] whereas a much lower intake was reported in patients with IBS from the UK (17 g per day).[60]

Polyols

Polyols are sugar alcohols such as sorbitol and mannitol. Their absorption is passive, variable between individuals and is affected both by molecular size and organic disease.[76] Passive absorption is greater in the proximal small intestine, where the jejunal paracellular space is larger, than in the ileum.[77] Collectively, studies demonstrate that between 60–70% of healthy people and those with IBS incompletely absorb a 10 g dose of sorbitol.[78,79] Absorption of mannitol is greater than for sorbitol in patients with IBS,[79] a finding that was hypothesized to be due either to its differing hydroxyl position or to luminal factors affecting its water solubility and therefore availability for paracellular absorption. Fruit and vegetables are natural sources of sorbitol and mannitol. Sugar-free chewing gum is a major source, containing at least 10 times the amount of sorbitol per gram compared with many fruits and vegetables.[79] Polyol intakes are not well documented, but have been reported as <1 g per day in one IBS study.[60]

Polysaccharides

Some longer-chain polysaccharides escape digestion and are fermented to various extents by the gut microbiota, including plant cell wall non-starch polysaccharides (for example cellulose, hemicelluloses or pectin), psyllium and resistant starches.[80–84] These carbohydrates fulfill the definition of dietary fibre, but have a greater DP, are fermented more slowly and produce less gas than the short-chain carbohydrates described earlier.[85] Intake of such longer-chain polysaccharides is therefore not restricted during a low FODMAP diet. Small quantities of protein and fat enter the colon from exogenous (dietary) and endogenous sources (for example, red blood cells, sloughed epithelial cells); however, their effect on fermentation and metabolic by-products is less well studied.[86]

Gastrointestinal effects

The effect of short-chain fermentable carbohydrates on gastrointestinal function has been the subject of research for >30 years. Up to 40 g per day of unabsorbed carbohydrate enters the colon in those consuming a Western diet.[86] Favourable effects of prebiotic fermentable carbohydrates (such as fructans and GOS) include increasing stool bulk, enhancing calcium absorption and modulating immune function, as well as selective stimulation of some microbial groups such as bifidobacteria.[58] Fermentation of short-chain fermentable carbohydrates results in the production of short-chain fatty acids (acetate, propionate and butyrate), and gas (H_2; carbon dioxide, CO_2; methane, CH_4) and contributes to growth and functioning of the gut microbiota. The numerous beneficial effects of short-chain fatty acids both locally and systemically are extensively reviewed elsewhere.[87]

Induction of functional symptoms

Despite their desirable health effects, ingestion of short-chain fermentable carbohydrates can trigger undesirable gastrointestinal symptoms, such as abdominal pain, flatulence and diarrhoea. Symptom induction after ingestion of fructans, GOS and polyols has been widely demonstrated in many uncontrolled,[78,88–90] and an increasing number of controlled,[91,92,93] trials. Furthermore, an unblinded study, using individuals with excessive flatulence, found that when challenged with a 3-day high fermentable carbohydrate 'flatulogenic' diet (high in fructans, GOS and polyols) the frequency and volume of flatulence and other gastrointestinal symptoms increased compared with baseline.[94] Other longer-term work supports this data; supplementation of 10–20 g per day of fructans for up to 12 weeks induced gastrointestinal symptoms in healthy people and those with functional bowel disorders.[95–98]

The gastrointestinal effects of lactose and fructose have also been recognized for many years[99,100] and double-blind challenge studies now support these historical observations. Challenges of 25–50 g fructose in solution induce gastrointestinal symptoms in healthy individuals[101,102] and those with IBS,[92] and 20–50 g lactose induces symptoms in those with lactose malabsorption when given as milk[103] or as pure lactose in solution.[104,105] Data on the tolerance to individual fermentable carbohydrates in food form is limited. Food is a complex matrix of macronutrients, fermentable carbohydrates, non-starch polysaccharides and other components, and proving

Table 1 | Studies of the mechanisms underlying the effects of fermentable carbohydrates on gastrointestinal symptoms

Reference	Study design	Participants	Intervention	Outcome measures	Findings
Ong *et al.* (2010)[112]	Randomized, single-blind, crossover	IBS ($n=15$) Healthy ($n=15$)	2-day high FODMAP diet (50 g per day) 2-day low FODMAP diet (9 g per day)	Hourly H_2 profile for 14 h on day 2	Higher H_2 production in high vs low FODMAP diet in both patients with IBS (242 ppm vs 62 ppm; $P<0.001$) and controls (181 ppm vs 43 ppm; $P<0.001$)
Barrett *et al.* (2010)[109]	Randomized, single-blind, crossover	IBD with ileostomy ($n=12$)	4-day high FODMAP diet 4-day low FODMAP diet	Effluent weight Effluent water content	Higher effluent weight on high vs low FODMAP diet (409 g vs 504 g; $P=0.01$) Higher water content on high vs low FODMAP diet (20% increase; $P=0.013$)
Marciani *et al.* (2010)[110]	Randomized, single-blind, crossover	Healthy ($n=11$)	17.5 g mannitol solution 17.5 g glucose solution	Small bowel water content using MRI	Higher small bowel water content after mannitol vs glucose at 40 min (381 ml vs 47 ml; $P<0.001$)
Murray *et al.* (2013)[111]	Randomized, single-blind, crossover	Healthy ($n=17$)	40 g fructose solution 40 g glucose solution 40 g inulin solution 40 g fructose + 40 g glucose solution	Small bowel water content using MRI	Higher small bowel water content following fructose (median 0–5 h area under curve = 67 l/min) vs glucose (36 l/min), which was reduced following combined fructose–glucose (46 l/min) Inulin fructans did not affect small bowel water (33 l/min), but increased colonic H_2 production

Abbreviations: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; H_2, hydrogen.

that an individual constituent is the cause of symptoms is inevitably problematic.

Other observations have been made with regard to the nature of the gastrointestinal effect of these carbohydrates. The effect on gastrointestinal symptoms seems to be dose-dependent;[91,92] intake of several fermentable carbohydrates at a time is additive.[88,92] Gastrointestinal symptoms might also be affected by the duration of exposure to fermentable carbohydrates, with adaptation occurring over time, resulting in symptom resolution with continued intake. This finding was demonstrated in a 12-week supplementation study of 20 g fructo-oligosaccharides in patients with IBS in whom stool frequency initially increased (compared with individuals taking placebo) but then normalized after 8 weeks.[97] A crossover study in healthy people with lactose malabsorption who were fed either 0.6–1.0 g/kg lactose or dextrose (control) for 10 days and then challenged with 0.35 g/kg lactose also demonstrated this resolution in symptoms; flatulence was markedly lower during the challenge after the lactose feeding period than with the dextrose control.[106]

Mechanisms of symptom induction

Short-chain fermentable carbohydrates might exacerbate IBS symptoms through various mechanisms, such as increasing small intestinal water volume, colonic gas production and intestinal motility (Table 1). Firstly, fermentable carbohydrates are osmotically active; ileostomy recovery studies revealed that a diet high in sucrose (by nature high in fructose),[107] polyols[108] and total fermentable carbohydrates[109] caused up to a twofold increase in total effluent wet weight resulting from increased water content. This finding has been confirmed in studies using MRI to measure small intestinal water volumes following ingestion of some fermentable carbohydrates. Ingestion of 17.5 g mannitol solution in healthy individuals induced a 10-fold higher small intestinal water volume at 40 min than ingestion of an equimolar glucose solution.[110] Likewise, similar results have been demonstrated after 40 g fructose ingestion, with the increase in small intestinal water volume partially resolved through contemporaneous ingestion of 40 g glucose.[111] Some individuals do not completely absorb mannitol and fructose in the small intestine,[68,79] leaving these molecules available for fermentation by the colonic microbiota resulting in increased colonic gas production. However, the effect of mannitol and fructose on small intestinal water volume occurs irrespective of whether or not the carbohydrate is completely absorbed.[110,111] Interestingly, small intestinal water volume did not increase following ingestion of 40 g of inulin (fructans).[111] Increased small intestinal water volume might worsen abdominal pain, and in the absence of adaptive colonic water absorption might result in diarrhoea. Figure 1 describes the pathways by which fermentable carbohydrates might induce symptoms in IBS and other functional bowel disorders.

Secondly, short-chain fermentable carbohydrates increase luminal H_2 and CH_4 production, resulting in luminal distension and pain in those with visceral hypersensitivity. Measurement of H_2 or CH_4 in expired air is often used as a surrogate measure of fermentative colonic gas production. Several breath testing studies demonstrate that gas production increases between 0–5 h after ingestion of various doses of individual fermentable carbohydrates both in healthy individuals and in patients with IBS. A controlled, crossover feeding study has demonstrated that the combined intake of different short-chain fermentable carbohydrates markedly elevated breath H_2 production compared with a standard diet in patients with IBS and healthy individuals.[112] In addition, different carbohydrates elicit distinct H_2 responses. A randomized placebo-controlled trial demonstrated that total H_2 production over 5 h is greater after a 40 g fructan solution than with ingestion of a 40 g fructose solution.[111] H_2 production occurred

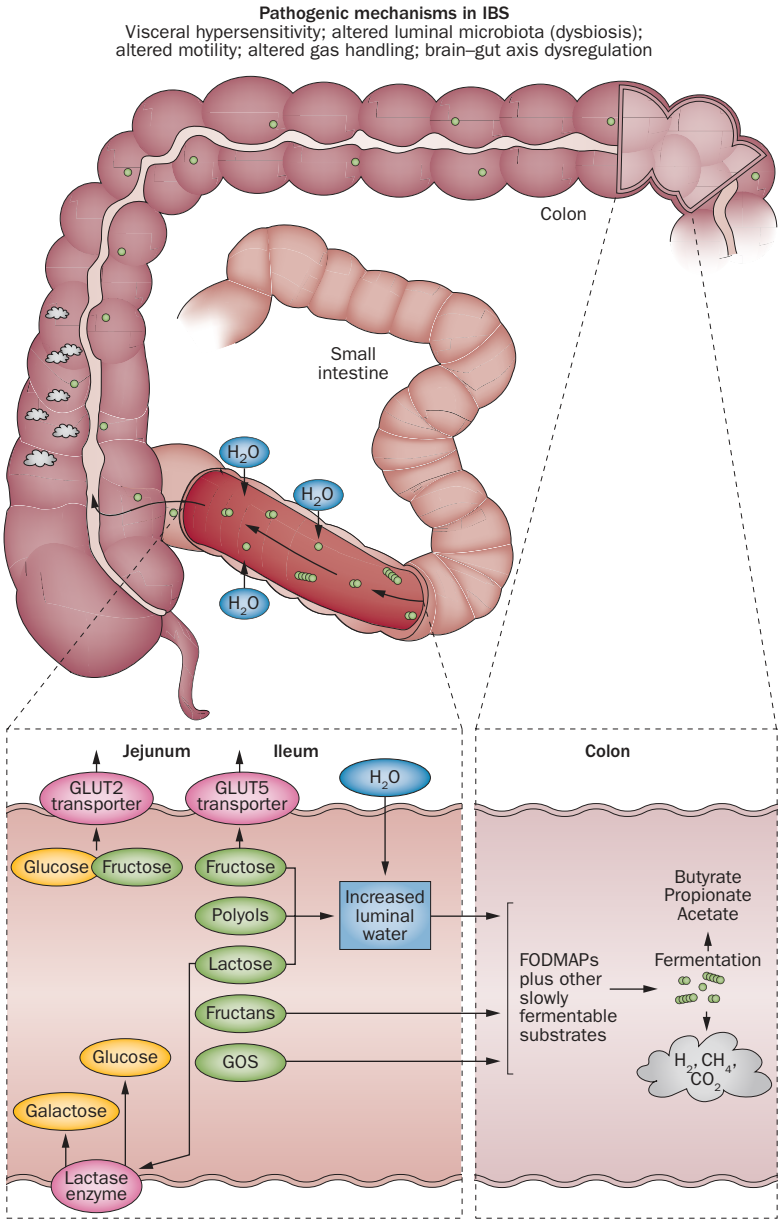

Figure 1 | Mechanisms by which short-chain fermentable carbohydrates might induce symptoms in IBS. Some short-chain fermentable carbohydrates are absorbed. For example, fructose can be absorbed via GLUT2 or GLUT5 transporters and lactose can be absorbed if hydrolysed by lactase. Unabsorbed fructose, polyols and lactose lead to osmotic shifts in the ileum. Unabsorbed fermentable carbohydrates are fermented in the colon leading to luminal gas production. In the setting of visceral hypersensitivity and altered colonic functioning the resulting luminal distension leads to symptom exacerbation. Abbreviations: CH_4, methane, CO_2, carbon dioxide; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GOS, galacto-oligosaccharides; H_2, hydrogen; H_2O, water.

later and remained elevated for longer after fructans ingestion, whereas H_2 peaked earlier and returned to baseline more quickly following fructose ingestion.[111]

A large study demonstrated the importance of colonic gas production in conjunction with visceral hypersensitivity. Total gas production after lactose ingestion was associated with gastrointestinal symptoms in 277 people with IBS, but not in 64 healthy individuals, and symptoms were associated with the presence of rectal sensitivity.[105] The degree of symptom induction can depend on inter-individual variability and the volume and rate of gas production. In the context of carbohydrate fermentation, the volume and rate of gas production is related to the molecular geometry of the carbohydrate and its DP.[85] Interestingly, there can also be a shift towards H_2 production rather than CH_4 on consumption of fermentable carbohydrates, at least in healthy individuals.[112] Methanogenesis involves the metabolism of H_2 by methanogenic bacteria, which ultimately leads to a reduction in gas volume of up to 75%, and might be of importance in our understanding of the gastrointestinal effects of these carbohydrates.[112] More research is required to reproduce these data, to investigate the patterns of gas production caused by other fermentable carbohydrates and to determine the relevance of these different responses in the context of IBS.

Fermentable carbohydrates also have an effect on motility. A scintigraphy study has demonstrated that fructose–sorbitol ingestion reduced orocecal transit time by just over 3 h in healthy people.[113] No difference in gastric emptying time was observed, indicating the difference was due to decreased small intestinal transit time.[113] The relevance of this finding to data suggesting jejunal immune dysregulation in patients with IBS and diarrhoea[114] is unknown.

Thus, short-chain fermentable carbohydrates increase small intestinal water volume, small intestinal motility and colonic gas production. Dietary restriction of fermentable carbohydrates might, therefore, be effective in managing IBS symptoms. Limiting luminal distension through reducing gas production and osmotic load would reduce sensory afferent input from the enteric nervous system. Furthermore, the additive effect of these carbohydrates would suggest that collective restriction might improve symptoms more than restriction of one or two individual carbohydrates.

Clinical efficacy

Collective dietary restriction of the short-chain fermentable carbohydrates described earlier has been termed a diet low in FODMAPs, and has been the focus of much clinical and research attention over the past 5 years. Dietary intervention involves consultation with a specialist dietician who advises on a 4–8-week exclusion of foods high in fermentable carbohydrates, based on comprehensive food composition data.[52,53,62,79] This advice is followed by symptom evaluation and graded reintroduction of such foods to investigate tolerance. The approach is gaining widespread acceptance through primary, secondary and tertiary centres as a treatment for IBS. A number of clinical studies have investigated the efficacy of fermentable carbohydrate restriction in IBS (Table 2). However, many of the studies are limited in design, being retrospective and/or uncontrolled. However, some RCTs have been undertaken with promising findings.

Retrospective and uncontrolled trials

Three retrospective studies evaluating the effectiveness of fermentable carbohydrate restriction have

Table 2 | Studies investigating the effectiveness of fermentable carbohydrate restriction on IBS symptoms

Reference	Study design	Participants	Duration	Symptom scoring	Findings
Shepherd *et al.* (2006)[115]	Retrospective, uncontrolled	IBS with fructose malabsorption (*n*=62)	14 months (median)	Unvalidated symptom scoring tool (–10 to +10 scale)	85% of adherent patients had symptom improvement for all symptoms
Gearry *et al.* (2009)[116]	Retrospective, uncontrolled	IBD with functional gastrointestinal symptoms (*n*=72)	17 months (median)	Unvalidated symptom scoring tool (–10 to +10 scale)	56% of all patients had symptom improvement in overall symptoms
Østgaard *et al.* (2012)[117]	Retrospective, case control	IBS, guided advice (*n*=43) IBS, unguided (*n*=36) Healthy (*n*=35)	Not reported	Birmingham IBS symptom score IBS-QoL	65% of participants completed the study Substantial reduction in pain in guided vs unguided, but not for total score, constipation or diarrhoea Marked improvement in QoL in guided vs unguided
De Roest *et al.* (2013)[119]	Prospective, uncontrolled	IBS (*n*=90)	16 months (mean)	GI Symptom Rating Scale	Improvement in pain, bloating, nausea, flatulence, range of stool output measures 72% satisfied with overall IBS symptoms
Mazzawi *et al.* (2013)[118]	Prospective, uncontrolled	IBS (*n*=46)	4 months (median)	Birmingham IBS symptom score IBS-QoL	37% of participants completed the study Total symptoms, pain and diarrhoea improved Marked improvement in QoL
Wilder-Smith *et al.* (2013)[67]	Prospective, uncontrolled	IBS (*n*=212) Other functional gastrointestinal disorder (*n*=1,160)	6–8 weeks	Unvalidated symptom scoring tool (1 to 10 scale)	Symptom relief in 90% and 94% of those considered 'intolerant' of fructose and lactose, respectively
Staudacher *et al.* (2011)[120]	Non-RCT (dietary advice)	IBS, low FODMAP (*n*=43) IBS, standard advice (*n*=39)	2–6 months	Unvalidated questionnaire (7-point scale 'substantially worse' to 'substantially improved')	Greater proportion of the intervention group satisfied with symptom response (76%) vs controls (54%) Greater proportion of the intervention group reported improvement in composite symptom score (86%) vs controls (49%)
Staudacher *et al.* (2012)[60]	RCT (dietary advice)	IBS, habitual diet (*n*=22) IBS, low FODMAP (*n*=19)	4 weeks	'Adequate relief' question GI Symptom Rating Scale Bristol Stool Form Scale	Greater proportion reporting adequate relief following low FODMAP diet (68%) vs control (23%) Reduced symptom score for bloating, borborygmi, urgency and overall symptoms following low FODMAP compared with controls
Ong *et al.* (2010)[112]	Randomized blinded, controlled crossover (feeding study)	IBS (*n*=15) Healthy (*n*=15)	4 days	Unvalidated symptom scoring tool (0–3)	Median symptom score lower on low FODMAP diet (2) vs high FODMAP diet (6)
Halmos *et al.* (2013)[121]	Randomized, blinded, controlled crossover (feeding study)	IBS (*n*=33) Healthy (*n*=12)	21 days	Unvalidated symptom scoring tool (100 mm VAS) Stool frequency Stool water content	83% of participants completed the study Lower overall gastrointestinal symptoms on low FODMAP diet (23 mm) vs a typical Australian diet (45 mm) Reduced stool frequency in IBS-D during low FODMAP diet versus Australian diet

Abbreviations: FODMAP, fermentable oligosaccharides, oligosaccharides, disaccharides, monosaccharides and polyols; IBS-D, diarrhoea-predominant IBS; QoL, quality of life; RCT, randomized controlled trial; VAS, visual analogue scale.

been performed. The first undertook a case review of 62 patients with IBS a median of 14 months after the initial dietary consultation for fermentable carbohydrate restriction, with most patients reporting improved symptom scores. Patients with increased adherence to the diet reported the greatest benefit, although, of course, those not experiencing a response are unlikely to continue to adhere. The direction of this relationship is therefore unclear.[115] In the second study, 72 patients with quiescent IBD and concurrent functional symptoms were assessed by telephone interview a median of 17 months after initial dietary advice. Again, more than half of patients reported symptomatic improvement.[116] The third study was a case–control study comparing symptom change in a group of 'guided' patients who received dietary advice, with 'unguided' patients who did not receive advice. Abdominal pain was lower and quality of life was higher in the guided group than in those who were unguided.[117]

Three prospective, uncontrolled studies have been performed to date. Beneficial effects on overall symptoms,[67,118] pain[118,119] diarrhoea,[118,119] bloating[119] and quality of life[118] were demonstrated; however, these studies are limited by lack of controls and variable completion rates (37–76%). Furthermore, two of three studies only presented per protocol analyses.[67,118]

These retrospective and uncontrolled trials provide important data on which to base future research, but are insufficient to support a change in clinical practice. However, four controlled trials have been undertaken investigating the effectiveness of fermentable carbohydrate restriction, three of which were randomized. The first of these was a non-RCT comparing IBS patients receiving fermentable carbohydrate restriction with those receiving standard dietary advice (focusing on fibre or resistant starch intake).[120] Substantially more patients undergoing fermentable carbohydrate restriction reported improvement in overall symptoms as well

as satisfaction with response at a follow-up appointment 2–6 months after initial advice compared with those receiving standard advice. Although this study is the only one to compare fermentable carbohydrate restriction with other dietary interventions, the lack of randomization and the follow-up of only those who returned to the clinic are major limitations.

Randomized controlled trials

Thus far, three RCTs have investigated the effect of fermentable carbohydrate restriction on IBS symptoms, two of which are controlled feeding studies (food provided and carefully controlled) and the other based upon dietary advice in the clinical setting. The first controlled feeding study compared the effect of two 4-day diets differing in fermentable carbohydrate content (50 g versus 9 g per day) and showed composite symptoms were substantially reduced during fermentable carbohydrate restriction.[112] Although symptom response was not the primary outcome measured in this study, it was the first attempt at a placebo-controlled trial, through the use of controlled provision of all food and fluid. The second feeding study was a randomized, controlled, crossover trial that demonstrated a statistically significant reduction in overall symptoms, pain, bloating and flatulence in patients with IBS consuming a fermentable carbohydrate restricted diet compared with a diet reflective of typical Australian intake. Improvement in overall gastrointestinal symptoms, demonstrated by at least a 10 mm reduction on a visual analogue scale, was observed in 70% of participants.[121] Controlled feeding, however, does not mimic the real-life challenges associated with sustaining a restricted diet in free-living individuals.

In one RCT of fermentable carbohydrate restriction in patients with IBS who had bloating and/or diarrhoea, participants were given dietary advice from a specialist dietician, validated methods were used for evaluating symptoms[122] and stool output, and semiquantitative food records were used to carefully assess dietary intake.[60] Adequate relief of symptoms was reported in 68% of patients receiving dietary intervention compared with 23% of control patients with IBS who continued their usual diet. However, the treatment group was not blinded to their intervention, a common problem in dietary intervention trials.

In general, these uncontrolled and controlled trials indicate that, in patients with IBS, the symptoms most responsive to fermentable carbohydrate restriction are bloating, flatulence, abdominal pain, urgency and altered stool output, with up 70% of patients reporting benefit. Indeed, one national guideline for the dietary management of IBS has now advised consideration of fermentable carbohydrate restriction when basic diet and lifestyle measures have been unsuccessful in managing symptoms[123] and other guidelines might follow. Authors of a literature review suggest that the number of patients needed to treat for efficacy is four,[124] although true estimates are not possible owing to limited large datasets. Prospective analysis of the predictors of response has not been performed and evidence for the efficacy of the diet in patients with IBS and constipation is currently limited. Early work points towards a potential role for fermentable carbohydrate restriction in other specific situations, such as in individuals with an ileal pouch or ileorectal anastomosis[125] and in those with diarrhoea receiving enteral feeding.[126]

Limitations

Difficulties of dietary research

Although clinical effectiveness data is accumulating, more high-quality, adequately powered, well-controlled studies are required to confirm the place of fermentable carbohydrate restriction as a therapy for IBS. High-quality studies are imperative, but it must also be acknowledged that in dietary research, double-blind, placebo-controlled trials are fraught with problems. Controlled feeding studies enable diets with a precise composition to be provided in a laboratory setting, but blinding is still problematic because participants might become aware of their group allocation when consuming specific foods, unless these can be masked (for example, disguised in composite dishes). In addition, controlled feeding studies do not reflect 'real life' eating behaviour and it is not known whether the same symptom response would occur when a participant attempts to incorporate the intervention into their habitual diet. By contrast, studies in which participants are given dietary advice better reflects what happens in clinical practice and provides an understanding of the degree of dietary change, and therefore symptom response, that a patient is likely to be able to achieve. However, it is difficult to provide 'control dietary advice' unless a comparator dietary intervention is chosen. Furthermore, blinding of control groups is difficult, unless sham dietary advice is provided. There will always be difficulties with the choice and nature of the control group and the blinding of dietary intervention trials compared with pharmacological trials, and therefore clinicians, researchers and guideline developers must understand the complexity of performing such trials when appraising the quality of such research.

Another difficulty with dietary research is that restriction of one constituent often influences the intake of another. For example, restriction of fructans from wheat inevitably leads to reduced gluten intake. Whether gluten affects symptoms in patients with IBS has been investigated in a double-blind, randomized, placebo-controlled trial. Patients with IBS and self-reported improvement in gastrointestinal symptoms on a gluten-free diet were randomly allocated to either 16 g per day gluten or placebo for 6 weeks.[127] Symptom induction was substantially greater in the gluten arm than in the placebo group, suggesting a role for gluten in inducing IBS symptoms, although no changes to possible biomarkers, such as intestinal permeability or inflammatory markers, were identified. These findings were not replicated, however, in a double-blind crossover gluten challenge study that controlled for intake of fermentable carbohydrates, dairy and natural and added food chemicals (for example, salicylates), which found no effect of gluten challenge on gastrointestinal symptoms in patients with self-reported non-coeliac gluten sensitivity and functional gastrointestinal symptoms.[48] Indeed, baseline symptoms improved during the low fermentable carbohydrate run-in phase, supporting

the role of fermentable carbohydrate restriction in this population.

Effect on dietary intake

Although fermentable carbohydrate restriction seems to improve symptoms in people with IBS, there could be nutritional and microbiological implications. From a nutritional perspective, this diet can be complex to understand and implement. Despite extensive advice (both verbal and written) and education on food label reading, the exclusion of foods across several groups might lead to nutritional inadequacy. The only study to date to carefully measure the effect of dietary advice for fermentable carbohydrate restriction on habitual dietary intake found no difference in micronutrient intake compared with controls except for a lower calcium intake,[60] presumably a result of lower intake of dairy foods. In this study, dietary intervention was administered by an expert dietician. However, there is a complete lack of evidence regarding patients following such restrictive diets with no support, which is a reason for considerable concern.

Effect on gut microbiota

Concerns also exist regarding the effects of restricting prebiotic carbohydrates from the diet on the gut microbiota. A marked reduction in luminal bifidobacteria concentration after a 4-week fermentable carbohydrate restriction diet was demonstrated in patients with IBS.[60] There were no effects on total numbers of bacteria or any other bacterial group measured (such as *Faecalibacterium prausnitzii*). This phenomenon is not new; that dietary carbohydrate restriction has a radical effect on the composition of the gut microbiota,[128–130] even within 24 h,[131] is well known. Indeed, carbohydrates might not just affect saccharolytic bacteria, but could affect others as a result of cross-feeding reactions whereby bacterial products are metabolized by other host bacteria.[86] Multiple putative beneficial effects of bifidobacteria have been reported for humans, including production of short-chain fatty acids and immunomodulation.[132] However, it is not known whether reduction in bifidobacteria is deleterious in the long term, particularly in the setting of dysbiosis. Consideration also needs to be given as to how this finding fits with the preliminary findings that reduced bifidobacteria concentration in patients with IBS is negatively correlated with pain score[25,29] and stool frequency.[29] Furthermore, some evidence exists that low-dose prebiotic supplementation increases proportions of luminal bifidobacteria and improves IBS symptoms (although high doses have also been shown to worsen symptoms).[34] This finding seems to be in direct conflict with an intervention that essentially reduces overall prebiotic intake in the same disease entity. Given the multifactorial aetiology of IBS, the heterogeneity of symptoms and the complex and diverse nature of the gut microbiome, it is not surprising that both interventions might be effective in patient subgroups.

Much is still to be learned regarding the influence of fermentable carbohydrate restriction on the gut microbiota in IBS. Resistant starch, non-starch polysaccharide, polyphenols and oats are not restricted on the low FODMAP diet, and these dietary constituents have been linked with favourable effects on the gut microbiota.[133,134] Furthermore, host factors (for example, baseline gut microbiota composition, transit time, age) and the chemical structure (for example, molecular weight, DP) and physicochemical nature (for example, grain particle size) of fermentable carbohydrates effect how they modify the gut microbiota community.[86] The establishment of a microbiome gene catalogue[135] has enabled analysis of a larger spectrum of microbiota. Whether any 'keystone species',[136] a small number of organisms that seem to have key metabolic functions, are affected will be important in determining the effects on the wider microbiota ecosystem. High-throughput molecular approaches for characterizing the gut microbiota and the use of 'metabolomics' to characterize its metabolic function, will help to shed further light on the interplay between the gut microbiota and diet, and in particular fermentable carbohydrate restriction, and how these affect long-term health. Whether there are any effects on mucosal microbiota is also unknown and should be an important consideration in future research. Concurrent strategies (for example supplemental probiotics) might help to maintain bifidobacteria concentration and have an additive effect on reducing symptoms, although this aspect has yet to be investigated.

Conclusions

Individuals with IBS or other functional bowel disorders have historically been difficult to treat by both medical and dietary means. Widespread progress in the dietary management of IBS has been of major interest and has helped to successfully manage symptoms in patients. However, further work is urgently needed both to confirm clinical efficacy of fermentable carbohydrate restriction in a variety of clinical subgroups and to fully characterize the effect on the gut microbiota and the colonic environment. Whether the effect on luminal bifidobacteria is clinically relevant, preventable, or long lasting, needs to be investigated. The influence on nutrient intake, dietary diversity, which might also affect the gut microbiota,[137] and quality of life also requires further exploration as does the possible economic effects due to reduced physician contact and need for medication. Although further work is required to confirm its place in IBS and functional bowel disorder clinical pathways, fermentable carbohydrate restriction is an important consideration for future national and international IBS guidelines.

Review criteria

A literature search was performed using Medline and Sciverse Scopus using the words: "irritable bowel syndrome", "functional bowel disorders", "diet", "dietary intervention", "fermentable carbohydrates", "FODMAPs" and "gastrointestinal microbiota". Studies investigating the underlying mechanisms and the clinical effectiveness of fermentable carbohydrate restriction in IBS and other functional bowel disorders were included. Randomized controlled trials, nonrandomized controlled trials and uncontrolled trials were included and the limitations in study design were highlighted.

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