Low FODMAP diet efficacy in IBS patients—what is the evidence and what else do we need to know?

Tim Kortlever, Clarice Hebblethwaite, Julie Leeper, Leigh O'Brien, Chris Mulder, Richard B Gearry

ABSTRACT

Irritable Bowel Syndrome (IBS) is a common and significant health problem which may be treatable with dietary interventions. Here we aim to explain the principles of the low Fermentable Oligo-, Di-, Monosaccharides and Polyol diet, and discuss both the limitations and opportunities of the diet in those with IBS, a common cause of presentation to primary and secondary care in New Zealand.

Background

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterised by abdominal pain, altered bowel habits (diarrhoea or constipation) and bloating. The Rome III criteria are the current standard test for the diagnosis of IBS being validated and used frequently (Figure 1). In industrialised countries, IBS is one of the most common gastrointestinal disorders presenting to general practitioners (GPs). IBS prevalence in New Zealand is 10–18%, with a higher prevalence in women. The highest rates of IBS are seen in those less than 50 years of age. Data on the distribution of IBS among different ethnic and age groups in New Zealand are not available.

While not requiring major medical or surgical interventions, the impact of IBS on quality of life is significant. Health-related quality of life is reduced in IBS patients who present to doctors, more so than controls and to similar levels as individuals with diabetes, end stage renal failure and gastroesophageal reflux disease. Furthermore, comorbidities such as anxiety and depression are more common in IBS patients. The impact on daily activities is significant and it is estimated that the yearly direct costs of IBS may range up to NZ$1,000 (or around US$750) per patient. Indirect costs, such as absence from work and impaired productivity, are more difficult to calculate but have been acknowledged as substantial.

Figure 1: Diagnosis of Irritable Bowel syndrome is based on the following criteria:

- A patient must have recurrent abdominal pain or discomfort for at least three days/month in the last three months with symptom onset at least six months prior to diagnosis
- Abdominal pain or discomfort must be associated with at least two of the following:
  1. Improvement with defaecation
  2. Onset associated with change in frequency in stool
  3. Onset associated with change in form (appearance) of stool
Although the pathophysiology of IBS is unclear, a number of putative mechanisms have been identified. These include visceral hypersensitivity, brain-gut axis dysregulation, altered gastrointestinal microbiota, increased gut mucosal immune activity and the direct action of specific food chemicals. Visceral hypersensitivity has received significant attention. Functional MRI brain studies, for example, support the importance of this mechanism. However, without a clear understanding of IBS aetiology and pathogenesis, a symptom-based approach has been adopted to palliate symptoms. Current therapeutic options include pharmaceuticals (eg antidepressants, antispasmodics, laxative agents or 5-HT3 receptor antagonists), fibre supplements, regular exercise, probiotics, psychological and dietary therapy. Often simple pharmacotherapy may be safe and effective but many treatments only achieve partial relief and may have serious adverse effects. For example, laxatives improve stool frequency and consistency in patients with constipation-predominant IBS, but do not have an effect on abdominal pain or bloating. Furthermore, antidepressants may improve abdominal pain, but may have side effects and are, therefore, not suitable for all IBS patients.

Over the past decade, a new dietary therapy has emerged with convincing results in multiple clinical trials. In studies from a range of populations, up to three-quarters of IBS patients experience symptom improvement when adhering to a diet low in Fermentable Oligo-, Di-, Mono-saccharides and Polyols (FODMAPs). Key symptoms such as abdominal pain, bloating, stool frequency and flatulence improve significantly in most IBS patients adherent to this diet. Restricting certain short-chain carbohydrates from the diet involves guidance from skilled dietitians to ensure that the diet is nutritionally adequate and balanced, and presented in a practical way.

Here we aim to explain the principles of the low FODMAP diet and to discuss both the limitations and opportunities of the diet in those with IBS, a common cause of presentation to primary and secondary care in New Zealand.

The low FODMAP diet
Origin and mechanisms
Up to 84% of patients with IBS attribute specific foods as triggers of their abdominal symptoms. Up to 70% of all patients believe that incompletely absorbed carbohydrates may be associated with their GI symptoms. This view is supported by observations of symptom improvement after dietary exclusion of solitary short-chain carbohydrates such as: fructose, lactose, fructans and sorbitol. A number of these carbohydrates even share an additive effect, increasing the severity of symptoms when ingested together. In the last decade, a restriction diet that incorporates these and other carbohydrates, the low FODMAP diet, has been developed.

The key characteristics shared by foods that are restricted in the low FODMAP diet are, firstly, that they are osmotically active. Secondly, they are malabsorbed due to the absence (relative or absolute) of specific hydrolases to effectively digest them or due to an absorption rate that is slower than intestinal transit time. Consequently, these molecules remain in the small intestine, attracting water into the gastrointestinal tract via osmosis (Figure 2A). FODMAPs then pass into the colon where they are fermented by the colonic microbiota. FODMAP fermentation releases gases (primarily hydrogen, carbon dioxide and in some cases methane) and short-chain fatty acids (Figure 2B).

Small intestinal water accumulation following high FODMAP consumption has been confirmed by imaging and experimental studies. In one study, twelve ileostomates consumed a low and high FODMAP diet in a randomised, single-blinded cross-over study. Effluent weight, dry weight and volume increased by approximately 20% on the high FODMAP diet. A MRI study by Murray et al found an increase in small bowel water content (SBWC) after ingestion of large amounts of fructose. The addition of glucose lessened the increase in SBWC via co-transport of glucose and fructose.

The fermentation of FODMAPs by intestinal microbiota has been studied by Ong...
et al, who found that both IBS patients and healthy subjects produced more breath hydrogen while consuming a high rather than low FODMAP diet. In addition, breath hydrogen levels of IBS patients were significantly higher than that of healthy subjects, suggesting differences in the microbiota composition and metabolism, as described previously.

Increased small intestinal water delivery and colonic fermentation leads to luminal distension and a more liquid effluent. In IBS patients (who have visceral hypersensitivity) this may trigger symptoms such as abdominal pain and bloating, diarrhoea and wind. Constipation while digesting osmotically active carbohydrates may be explained by a slower transit time due to the production of methane gas in some individuals.

Principles of the low FODMAP diet

A diet low in FODMAPs minimises foods with a high content of fermentable short-chain carbohydrates. These include fructose (in excess of glucose), lactose, fructans, galacto-oligosaccharides and polyols. As the name suggests, the low FODMAP diet does not eliminate FODMAPs completely, but rather reduces gastrointestinal FODMAP concentration to an extent where symptoms are controlled. This threshold is, however, variable between individuals. Therefore, dietitians will advise a significant reduction in FODMAP containing foods with a subsequent re-introduction of specific FODMAPs until a symptom threshold is reached.

While there is no ability for most FODMAPs to be absorbed in the small intestine, lactose and fructose can be transported across the intestinal barrier in some individuals. Absorption of lactose, the natural sugar in milk and other dairy products, depends on the persistence of lactase enzymes in the brush border of the small intestinal mucosa. Lactase non-persistence is common after weaning in the majority of the global population. However, high lactase levels may persist to adulthood in some populations, especially those of Northern European descent. In those with lactase non-persistence and IBS, lactose acts as a FODMAP leading to significant gastrointestinal symptoms.

Fructose may be absorbed in one of two ways. Fructose is generally absorbed slowly via the low capacity GLUT5 transporter. However, this mechanism may be overwhelmed when there are larger quantities of fructose ingested over a short period (eg by drinking a glass of orange juice). Alternatively, when fructose and glucose are ingested simultaneously in

**Figure 2:** The effects of FODMAPs in the small (A) and large intestine (B). Subsequent luminal distension caused by an increased luminal volume may trigger symptoms in patients with visceral hypersensitivity, including: abdominal pain or discomfort, diarrhoea, constipation and bloating.
Table 1: Summary of the key studies of low FODMAP diet efficacy. IBS = Irritable Bowel Syndrome, LFD = low FODMAP diet, HFD = high FODMAP diet, NCGS = non-coeliac gluten sensitivity, LGG = Lactobacillus rhamnosus GG, GI = gastrointestinal.

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<td>Shepherd et al (2008)</td>
<td>Australia</td>
<td>IBS patients with Fructose Malabsorption (n=25)</td>
<td>Randomised, double-blind, quadruple arm, controlled rechallenge trial</td>
<td>2 week treatment arms with fructose, fructans, mix and glucose drinks each, whilst adherent to the LFD at all times</td>
<td>Symptoms were adequately controlled in the glucose drink arm (86%), but significantly worsened during each of the other arms: % of patients experiencing adequately controlled symptoms was 30%, 23% and 21% for the fructose, fructans and mixture drinks respectively.</td>
<td>All food was provided to the participants, cohort consisted only of patients who had a marked response to the LFD diet prior to recruitment.</td>
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<td>Ong et al (2010)</td>
<td>Australia</td>
<td>IBS patients (n=15) healthy subjects (n=15)</td>
<td>Randomised, single-blinded, controlled crossover trial</td>
<td>2 days HFD 2 days LFD (7 day washout period)</td>
<td>In IBS patients all symptoms (Abdominal pain, bloating, flatus, nausea, heartburn and tiredness) were significantly worse when adherent to the HFD. Healthy subject only had a significant increase in flatus with the HFD.</td>
<td>Short dietary window, all food was provided to the participants.</td>
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<td>Staudacher et al (2011)</td>
<td>UK</td>
<td>IBS patients on standard IBS diet (n=39), IBS patients on LFD (n=42)</td>
<td>Prospective, controlled</td>
<td>2–6 months</td>
<td>Significantly more patients in the LFD group reported improvement in bloating, abdominal pain, nausea, energy levels and flatulence. Improvement in composite symptom score was greater in LFD than in the standard group (86% vs. 49%). More patients in the LFD group were satisfied with their symptom response (76% vs. 54% in the group standard group).</td>
<td>Standard dietary advice and LFD overlapped, adherence was not objectively measured, no control group.</td>
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<td>De Roest et al (2013)</td>
<td>New Zealand</td>
<td>IBS patients (n=90)</td>
<td>Prospective, uncontrolled</td>
<td>Mean 15.7 months</td>
<td>Key symptoms improved with the LFD. Most patients (72.1%) reported satisfaction with their symptoms. Most patients (75.6%) also were found adherent to the diet, which was associated with greater symptom improvement.</td>
<td>Variable follow-up duration, adherence was not objectively measured.</td>
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<td>Halmos et al (2014)</td>
<td>Australia</td>
<td>IBS patients (n=30), Healthy subjects (n=8)</td>
<td>Randomised, single-blinded, controlled crossover trial</td>
<td>21 days LFD 21 days Australian diet (21 day wash-out period)</td>
<td>Patients with IBS had lower overall symptoms scores while on LFD compared to the typical Australian diet and baseline. Symptoms were unaltered in the control group for both diets. A majority of IBS patients (70%) had an improvement in overall gastrointestinal symptoms that was considered clinically significant.</td>
<td>All food was provided to the participants.</td>
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<td>Pedersen et al (2014)</td>
<td>Denmark</td>
<td>IBS patients on LFD (n=42), LGG (n=41) and normal Danish diet (n=40), all supplemented with a web-based monitoring programme.</td>
<td>Randomised, unblinded, controlled trial</td>
<td>6 weeks</td>
<td>Significant improvement in symptom score of patients on the LFD compared to patients on the normal Danish diet and to baseline. The average symptom score was reduced more in patients who used both IBS medication and were in the LFD group.</td>
<td>Study was unblinded, intended control group (normal Danish diet) had significant improvement too (possible bias), adherence was not measured.</td>
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<td>Bohn et al (2015)</td>
<td>Sweden</td>
<td>IBS patients on standard IBS dietary advice (n=37), IBS patients on LFD (n=38)</td>
<td>Randomised, single-blinded trial</td>
<td>4 weeks</td>
<td>Symptom score in both diets reduced significantly compared to baseline. No difference was observed in symptom score reduction between the two diets. The proportion of patients having a clinically significant response was similar in both diets.</td>
<td>Standard IBS dietary advice and LFD overlapped, use of probiotics, lactose-reduced diet and IBS medication was allowed in both groups.</td>
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<td>Chumpitaz et al (2015)</td>
<td>US</td>
<td>IBS patients aged 7–17 years (n=33)</td>
<td>Randomised, double-blind, crossover trial</td>
<td>2 days LFD 2 days typical American childhood diet (5 day washout period)</td>
<td>Patients had fewer daily abdominal pain episodes and a lower composite GI score in the LFD arm compared to the typical American childhood diet arm. However, composite GI score was not significantly different compared to baseline in any of the two diets, and pain severity decreased evenly in both diets.</td>
<td>Limited duration of intervention, all food was provided to the participants.</td>
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equimolar quantities (eg kiwifruit), a more efficient co-transporter, GLUT2, is upregulated, facilitating the absorption of glucose and fructose simultaneously. The total capacity of both GLUT5 and GLUT2 are variable, hence fructose malabsorption can be considered as a physiological feature in healthy people and IBS patients alike.

The three other restricted carbohydrates are fructans, galacto-oligosaccharides and polyols. Fructans, polymers of fructose molecules, are found in wheat, onions, garlic and other foods such as legumes. Galacto-oligosaccharides are also found in onions and legumes, and in a number of vegetables. The human gut is unable to hydrolyse fructans and galacto-oligosaccharides, leading to non-absorption and subsequent delivery to the colon where they are readily fermented. Polyols are found in fruits such as apples, apricots and watermelon, and in avocado, mushrooms and cauliflower. In addition, a specific polyol, sorbitol, is frequently used as alternative sweetener. Absorption of these carbohydrates occurs mainly in the jejunum and is variable between individuals. When the amount of polyol in the diet exceeds the absorptive capacity, the non-absorbed carbohydrate will be osmotically active in the small intestine and fermented in the colon leading to symptoms in IBS patients with visceral hypersensitivity.

Implementation
In current clinical practice, the low FODMAP diet is taught by dietitians trained in the delivery of the low FODMAP diet in a 30-minute to one-hour session. Food diaries and sometimes breath testing are undertaken before the session to personalise the diet to the patient's specific circumstances. After 4–6 weeks on a low FODMAP diet, a follow-up session is important. If symptoms are controlled, the dietitian and patient can both work towards reintroduction of restricted food items to a tolerated level. This ensures that the patient's diet is as complete and unrestricted as possible, reducing the risk of long term nutritional deficiencies (eg calcium, dietary fibre, B vitamins).

In studies of free-living individuals, low FODMAP diet adherence rates have been high (approximately 70%), and adherence has been strongly associated with efficacy. While up to 60% of those adhering to the diet find it easy to follow, some patients report less positively on taste, cost, maintaining the diet while eating away from home and the effort needed to incorporate the diet into their lives.

Efficacy
Table 1 describes the key studies that have been published concerning the low FODMAP diet in the management of IBS symptoms. Whole diet intervention studies are difficult to design, perform and remain blinded. As such, it is difficult to compare the methodology of randomised placebo controlled drug trials with those of whole foods or diets where it is near impossible to blind participants to the intervention and placebo. This was noted in recent systematic reviews where the quality of studies in the FODMAP field was noted to be poor. A number of criticisms have been raised against the quality of many of the low FODMAP dietary intervention studies, including small number in the studies, the lack of a control group, the short duration of follow-up and that many studies have come from the same investigators. However, interventions of a whole diet are notoriously difficult to perform. The ideal study would blind participants and investigators to the diet, the participants would have the entire diet provided to them and the study would continue for years. Clearly the practicalities of adequately addressing any of these issues are very difficult to manage and have not been addressed in other whole-diet studies to our knowledge.

However, across a range of retrospective and prospective intervention studies, there has been a consistent effect demonstrated, supporting the use of low FODMAP diet in those with IBS. Nearly all studies found that 70–80% of IBS patients improved while on the low FODMAP diet, usually within 1–4 weeks. Furthermore, the low FODMAP diet was favoured over usual IBS dietary interventions, local dietary habits and/or subject's baseline diet. These findings are supported by the studies that underpin the mechanism of action of low FODMAP diet described earlier. Finally, data suggests a prolonged response to low FODMAP diet in those who remain adherent.
Potential limitations and health-related drawbacks

So are there potential problems with a low FODMAP diet? Oligosaccharides are also prebiotics, which are a useful energy source to saccharolytic and probiotic bacteria in the gut (eg Lactobacillus and Bifidobacterium). Some of these genera have demonstrated in animal studies health-promoting effects on the host by influencing both the innate and adaptive immune system, the composition of the microbiota (preventing dominance of harmful species), and reducing the risk of developing colorectal cancer.27 Moreover, the products of FODMAP fermentation, short-chain fatty acids (SCFA) suppress pathogens and increase the absorption of minerals by acidifying luminal pH, modulate energy homeostasis and support apoptosis.

The low FODMAP diet eliminates the major source of dietary prebiotics, thus the source of energy for saccharolytic bacteria. This has a marked effect on the microbiota as was demonstrated in studies were the total abundance of major groups of bacteria decreased after a period of low FODMAP consumption.28,29 Most notably among these were Bifidobacteria and other butyrate-producing species, which both have been widely described for their anticarcinogenic and anti-inflammatory effects. The relative decrease in the proportion of these bacteria may predispose to long-term adverse effects that have not been studied or demonstrated. Reassuringly, the few studies in this area have found that SCFA concentration and pH remain largely unchanged and had conflicting results on the change in Bifidobacterium after the institution of a low FODMAP diet.

Finally, there are no data investigating the long-term impact of low FODMAP diet on the GI microbiota, or after the reintroduction of high FODMAP foods. Given that the intestinal microbiota reacts rapidly to dietary changes,20 adequate reintroduction of FODMAP foods could abolish any potential detrimental effects of the initial diet. Such re-introduction should be done in a slow stepwise manner, to determine whether there may be threshold effects whereby smaller quantities of FODMAP containing foods can be safely included without triggering symptoms. In conclusion, the short-term use of the low FODMAP diet is widely considered as a safe treatment, provided that patients alleviate their level of restriction after satisfactory symptom control and do not commence the diet when asymptomatic.

Future developments

Individualising dietary advice

Approximately a quarter of patients trialling the low FODMAP diet do not experience an improvement in symptoms. This could be partly due to poor adherence, but may reflect IBS pathogenic mechanisms independent of FODMAP triggers. A method of predicting the outcome of dietary intervention could prevent unnecessary treatment, reducing costs and potential risks.

With this in mind, Chumpatzi et al have attempted to discover if microbiome patterns can predict outcome and compared metagenome in responders and non-responders.25 Responders had higher concentrations of bacteria with high saccharolytic metabolic capacity (thus were more able to ferment carbohydrates) and also had more markers of FODMAP-specific carbohydrate metabolism, than non-responders. Interestingly, microbial diversity was not significantly different between the two groups.

While the field of nutritional genomics has led to the prediction of individual postprandial blood sugar response, enabling important individual lifestyle adjustments that reduce the risk of developing type II diabetes mellitus,31 there has been less progress in the field of IBS. Once again, this may be a fertile area for developing personalised medicine solutions for people with functional gastrointestinal disorders.

Streamlining dietary information delivery

At this point in time, the most evidence for the efficacy and safety of low FODMAP diet for the management of IBS symptoms is when it is delivered by a dietitian with expertise and training in its implementation in a one-to-one interview. However, this approach is also costly. Different methods of dietary advice delivery may benefit the availability and economic impact of
the low FODMAP diet. A recent study by Whigham et al found considerable cost savings and a similar clinical efficacy in a programme that facilitated group treatment for eligible patients, for example.32 Traditional one-to-one sessions were still needed for patients with atypical symptoms and other nutritional and medical concerns in this study. Another alternative could be an online-based treatment platform, potentially in collaboration with GPs, since a number of studies have reported that patients generally find any written information about the diet they receive easy to understand.9,10 Similar to group treatment, this approach may be suitable for providing low FODMAP advice to patients with typical symptoms of IBS and without any nutritional or medical concerns.

However, research on the nutritional safety and efficacy of these ways of dietary advice is needed before such measures are implemented. Besides, one-to-one dietary consultation has clear benefits that are not found in the methods described earlier. Firstly, specialist dietitians are able to ensure they are delivering correct information based on the current status of testing for FODMAPs in foods. Over the years, FODMAP content measuring has been intensified and refined and has forced adjustments in the diet. Some foods that were initially tested as high in FODMAPs have subsequently been re-evaluated and allowed back into the diet, others on the other hand have been re-listed as FODMAP rich foods. This has led to a variety of information available both in print and online that can appear to be conflicting as regards to certain foods and their safe threshold. Furthermore, some sources of information have misinterpreted the FODMAP tables and incorrectly limited certain foods when they have never been classified as high FODMAP (eg coconut milk and coconut cream).

The one-to-one approach also has the benefit of personalising the diet to the individual patient, increasing the chance of adherence and efficacy while reducing the chance of adverse effects due to prolonged low FODMAP diet without the re-introduction of FODMAP containing foods or poor nutritional quality. A dietitian can also take into consideration the bowel function and in the case of constipation, monitor this carefully when on a low FODMAP diet. It is possible constipation can worsen in some cases due to the lowering of fibre and loss of stimulant effect of osmotically active FODMAPs. Further modifications can be made to the diet with inclusion of suitable fibre or alternative supplements to benefit the bowel frequency without increasing the burden of bloating or flatulence.

**Conclusion**

Up to three-quarters of IBS patients experience symptom improvement on the low FODMAP diet. Although it comprises considerable changes, the diet appears safe as long as reintroduction of higher FODMAP foods (to a tolerated) level is part of the diet plan. The current method of dietitian-guided intervention in combination with written resources delivers high adherence among patients. However, exploring the possibilities of group, online or GP-based treatment in patients in formalised studies is warranted. Research should also concentrate on the effects of low FODMAP diet on quality of life, changes in tolerance and sensitivity towards certain foods after dietary intervention, and long-term nutritional and microbiotal health. Finally, the development of predictory tools that enable dietitians to tailor the low FODMAP diet based on individuals’ microbiota or genetics could increase efficacy and reduce unnecessary treatment. However, despite an interesting and promising outlook for the low FODMAP diet in IBS patients, it is important to realise that the solution for IBS might be beyond FODMAPs alone and that future treatments may be more potent in reducing symptoms.
Competing interests:
Clarice Hebblethwaite, Julie Leeper and Leigh O’Brien are professional and registered dietitians who give dietary advice to patients with IBS in a private clinic on a regular basis. Richard B Gearry is a Consultant Gastroenterologist with a research and clinical interest in luminal gastroenterology including IBS. He is a director of Digestive Health Services Ltd, a private clinic specialising in gastrointestinal diagnostics.

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