Dietary Treatments in IBS

Progress, possibilities and patient preference



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Irritable bowel syndrome (IBS) has been defined by NICE as: *'...a chronic, relapsing and often life-long disorder, characterised by the presence of abdominal pain/discomfort associated with a change in bowel habit together with constipation or diarrhoea, or both, and the sensation of abdominal distension."* [1]

Background

The prevalence of IBS globally has been estimated to be between 10% and 20%.[2] Aproximately 50% of patients with gastrointestinal complaints seen in general practice have IBS and this prevalence is increasing.[3] Patients with IBS have a significantly lower quality of life and the economic and societal costs associated with IBS are also considerable. In the UK, annual mean healthcare expenditure has been estimated at £383.20 per patient.[4-6]

Diagnosis is determined on clinical features alone, using the Rome III criteria, which is considered the most sensitive and is routinely used in primary care.[7] IBS is commonly categorised by the most predominant presenting symptom: diarrhoea (IBS-D), constipation (IBS-C), mixed (IBS-M) or unspecified (IBS-U).

Currently, the medical treatment of IBS is considered suboptimal and its physiopathology is poorly understood.[8] It is thought that IBS results from abnormalities of the 'gut-brain axis' and these could be both peripheral and central in nature (see **Table One**).[9]

Nutrition appears to play an important role in exacerbating IBS, with estimates of up to 80% of patients having postprandial symptomology, and 15-20% reporting specific food intolerances.[10-12] The British Dietetic Association (BDA) has recently produced revised clinical guidelines that summarise the nutritional treatment options in IBS.[13]

Over the last 10 years, research has largely focused on the role of two common components of the western diet, specifically, fermentable oligo-, di-, mono- saccharides and polyols or FODMAPs and (perhaps more controversially) gluten in relation to the induction of IBS symptoms. This article looks at the current evidence base around these two treatment modalities and proposed directions for future research.

The low FODMAP approach in IBS

In the early 1980s, many observational studies were beginning to clarify the negative effects of poorly absorbed short chain carbohydrates on gastrointestinal function.[14-17] This led to the 'FODMAP hypothesis', suggesting these carbohydrates as a potential environmental risk factor in the development of Crohn's disease, due to their effect on the ileocolonic microbiome: *"Even if FODMAPs do not prove to be aetiologically relevant as proposed in this hypothesis (Crohn's disease), they might provide a ready target for improving symptoms and for reducing the current reliance on drug therapy."*[18]

This led to further research examining the role of FODMAPs in IBS symptomology. A retrospective audit evaluating the effect of a low-fructose/fructan diet demonstrated symptomatic relief in 74% of participants' IBS symptoms.[19] Since then, several randomised control trials (RCTs) (summarised in **Table Two**) have demonstrated the efficacy of the low FODMAP diet (LFD) and probable mechanisms (see **Figure 1**). A recent meta-analysis of six RCTs showed adherence to a LFD leads to a significant decrease in IBS severity scores (odds ratio 0.44; 95% confidence interval 0.25 to 0.76).[20, 21]

However, this complex diet requires delivery by an experienced dietitian to help ensure both success and overall nutritional adequacy, a point emphasised by both the BDA and NICE.[1, 13, 22]

A significant reduction in iron and calcium intakes during a four-week trial (elimination phase of the LFD) has been reported, with over half of the participants not meeting dietary reference values for these micronutrients.[23] Whilst mean intakes were similar to that of the general population, further studies are required in patients with a 'liberalised' FODMAP diet, to determine the long-term nutritional adequacy of the approach.[24]

Given the increasing public awareness of the LFD, it is possible many patients are self-treating without an appropriate reintroduction phase under the guidance of a specialist dietitian. This is of concern considering the LFD alters the colonic microbiota. A significant reduction in bifidobacteria after four weeks of a LFD has been observed.[25] Furthermore, a recent Australian trial showed that FODMAP restriction was associated with a higher faecal pH and a significant reduction in colonic bacterial groups with known health benefits when compared to the typical Australian diet.[26] Both studies suggest further trials are required to assess the long-term effects of FODMAP reduction on the microbiome.

Adherence is another predictor of response in the LFD that warrants further investigation. Dietetic guidance and supportive written (or digital) information are essential. However, even with these aspects in place the initial exclusion and reintroduction phases can be difficult to follow – as highlighted by a patient in an article in this publication last year by Delaney.[27]

Given the responsibility placed on patients, clarifying who is most likely to respond and benefit from a LFD is important. For example, two recent clinical guidelines and a meta-analysis have suggested that FODMAP reduction is of limited benefit in patients with IBS-C.[13, 28, 29] Additionally, a recent RCT that included patients with both IBS-C and IBS-D showed that the, perhaps more simple, standard first line dietary advice was of similar efficacy to FODMAP reduction.[30]

Whilst there is recognition of the symptom improvement achieved in patients following the LFD, questions remain as to its long-term effect on nutritional adequacy, the microbiome and its efficacy in relation to other dietary and non-dietary treatments. In addition, the increasing adoption of this approach, and the specialist dietetic time involved, necessitates the development of new and novel models of delivery.[31] This presents an opportunity for dietitians to lead in the development of robust RCTs that address these issues but which can only be achieved with an efficient partnership between patients, dietitians and gastroenterologists.[32]

IBS and non-coeliac gluten sensitivity

The concept of patients presenting with a sensitivity to gluten outside of a diagnosis of coeliac disease is not new; in fact a case report published in the British Medical Journal in 1978 clearly describes such a scenario.[33] Move forward 30 years and the concept is not only receiving renewed medical scrutiny, but has become a popular notion within the minds of the general public, as evidenced by the increase in popularity of the gluten-free diet (GFD) and simultaneous drop in the trends of 'low carb' and 'fat free' diets.[34]

For many individuals following a GFD, it is a lifestyle choice that requires no medical attention. However, the question arises as to whether it is only people with the diagnostic features of coeliac disease (CD) that need to remove gluten from their diet, or if there is a spectrum of gluten-related disorders? An expert consensus paper, in 2011, recognised the need for an updated classification in this area and identified a new clinical entity 'non-coeliac gluten sensitivity (NCGS)', defined as: *"gluten-related symptoms without evidence of coeliac disease or IgE mediated wheat allergy."*[34] Although seen by some as a controversial 'self-reported' diagnosis, recent studies are beginning to help clarify a potential diagnostic pathway, its pathogenesis and the role of the GFD in the treatment of NCGS.[35]

Epidemiological studies have suggested a prevalence range from 0.6-13%.[36-38] Parallel to IBS, NCGS affects more young women (F:M ratio >3:1), who present with both intestinal and extra intestinal symptoms after gluten exposure that last from hours to a few days.

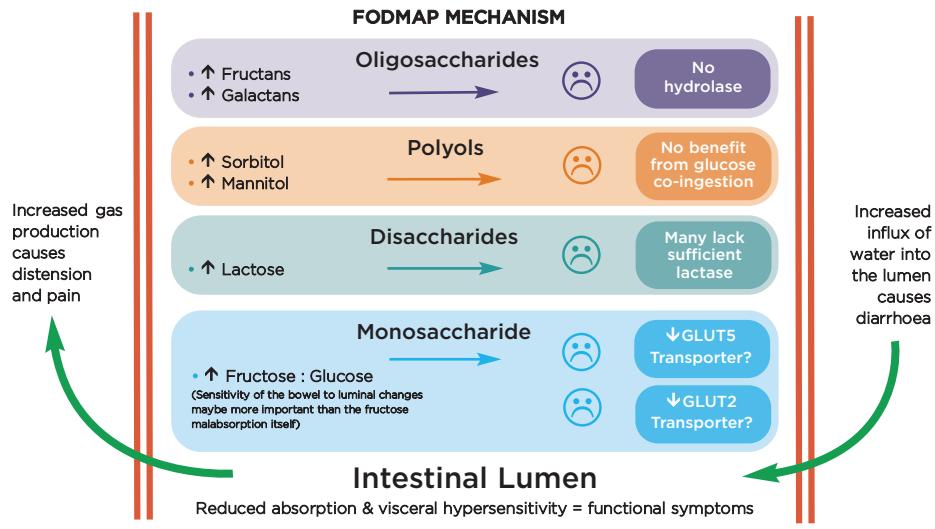
Central to the diagnosis of NCGS is the exclusion of both 'classical' and potential CD. The former presenting with villous atrophy, positive serological antibodies and HLA DQ2/8 genetic phenotypes, where as the latter may present with positive serology and genetics but no intestinal damage, these patients can be said to be 'in the waiting room for coeliac disease' but eventually will require a GFD.[39] Once CD is rejected, double-blind placebo-controlled (DBPC) gluten rechallenges have been seen as the gold standard of diagnosis but are difficult to perform in routine clinical practice.[40] However, antigliadin antibodies (AGAs) in the absence of coeliac-specific serology, in patients with characteristic symptoms, have been shown to be potential non-specific, diagnostic markers.[41] Additionally, in the future, new endoscopic techniques using confocal lasers that can detect food associated changes in the intestinal mucosa of patients with IBS might prove to be a major development in diagnosing NCGS.[42]

Unlike coeliac disease, which results from an adaptive immune response, NCGS may involve an innate reaction to gluten, leading to a rapid mucosal inflammatory response.[43, 44]

Table One: Physiopathological Elements of IBS[9]

Peripheral	Central
Gut dismotility	Aberrant CNS representation of gut events
Visceral hypersensitivity	Aberrant stress responses
Mucosal inflammation	Hypothalamic-pituitary axis disturbances
Intestinal microbiota	
Impaired epithelial barrier	

Figure 1: FODMAPs and Symptom Induction in IBS



Indeed, a recent study comparing patients with NCGS and CD showed that specific IgM AGAs were only elevated in the NCGS cohort demonstrating a systemic (rather than autoimmune) activation and gut epithelial cell damage.[45] Figure 2 presents a model of how gluten-related disorders and FODMAP intolerances may interrelate.

Despite this ongoing research, controversies remain as to the primary causal agent in NCGS. Wheat contains a number of compounds, apart from gluten, that could produce a symptomatic response; perhaps the most obvious of these are FODMAPS, specifically fructans. One trial showed that individuals with self-reported NCGS already on a GFD further benefited when placed on a low FODMAP diet and found no specific or dose-dependent effect of gluten.[46] However, the participants reported very high visual analogue scale ratings of their symptoms when they were already on a GFD, which is unlikely to be representative of the NCGS population. Furthermore, this study's DBPC design, where all participants cycled through high-dose, low-dose or no gluten control diets, could have produced an anticipatory nocebo response.[47] It is also interesting to note that all the participants returned to a GFD at the end of the trial as they subjectively described 'feeling better'.[48]

Research into the GFD in the treatment of IBS-D (summarised in Table Three) has demonstrated that it reduced patient symptomatology and improved quality of life. A recent double-blinded trial with 72 patients with IBS-D who were well controlled on a GFD were randomised to either six weeks of 50 g of gluten-containing powder/day (n=35) or gluten-free powder/day (n=37). There was a significant symptom deterioration in 74.3% of the gluten-containing group, compared to 16.2% of those receiving gluten-free powder.[49]

Our own group conducted a pragmatic prospective study of 41 patients with IBS-D. All participants were placed on a six-week GFD following advice by a dietitian, at the six-week follow-up the GFD had significantly reduced IBS Symptom Severity Scores in 71% (n=29) of the cohort and the mean total IBS Symptom Severity Score decreased from 286 to 131 points (see Figure 3). These patients were reviewed again at 18 months and 21 patients who were still on a GFD had maintained symptom reductions, and demonstrated similar anthropometric and biochemical features compared with baseline.[50]

The exact role of gluten in IBS and NGCS still remains unclear and further well-designed trials need to be conducted to offer further clarification. Furthermore, several studies have shown a GFD can cause a reduction of lacto and bifidobacteria gut bacteria, as well as potentially being lower in a number of nutrients, such as calcium, iron, folate and fibre, than a gluten-containing diet.[51-56] Nevertheless, some of aforementioned studies have suggested a GFD represents a simpler dietary modality for improving symptomology in IBS patients.[49, 50, 60-76]

Summary and comments

Undoubtedly, the low FODMAP diet is an important tool in the range of strategies that dietitians can use to improve the quality of life in patients with this distressing condition. However, a number of questions remain around the long-term consequences of the diet, which cohort of patients benefit the most and how best to deliver it.

Non-coeliac gluten sensitivity is still an emergent condition and further studies are required to clarify if gluten or another component of wheat (or other grains) is the causative agent. A gluten-free diet, after meticulous exclusion of coeliac disease and a discussion with both the gastroenterologists and patients, has been shown to be an intervention capable of providing sustainable symptomatic relief in patients with IBS-D type symptoms.

Of course, the evolving evidence is what will, ultimately, guide our practice. As dietitians, we are uniquely placed to lead and support the development of research in this area, elucidating which dietary intervention will provide the most benefit for each individual patient referred to us. Eminent Gastroenterologist, Professor Peter Green, summarises: *"Irritable bowel syndrome may prove to be a heterogeneous group of conditions that respond to a range of dietary strategies. It is likely that one size does not fit all."*[57]

Figure 2: Gluten Sensitivity and IBS Crossover

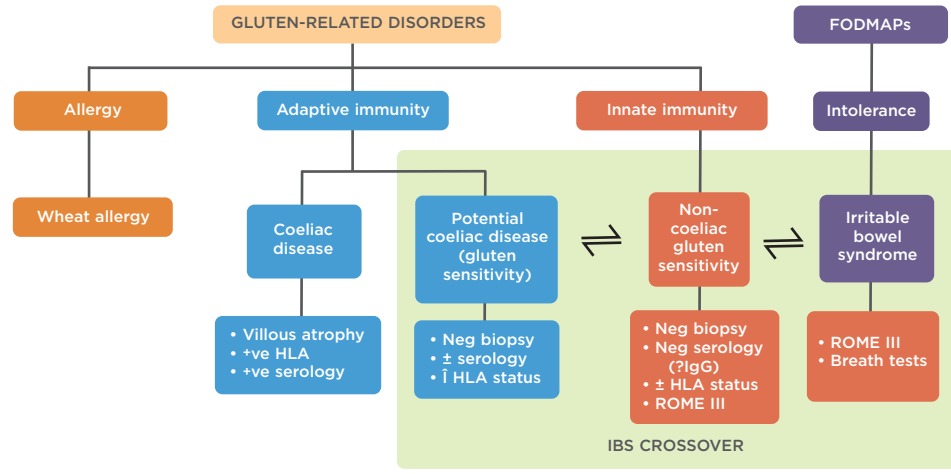


Figure 3: Effect of Gluten-free Diet on IBS-D Symptoms

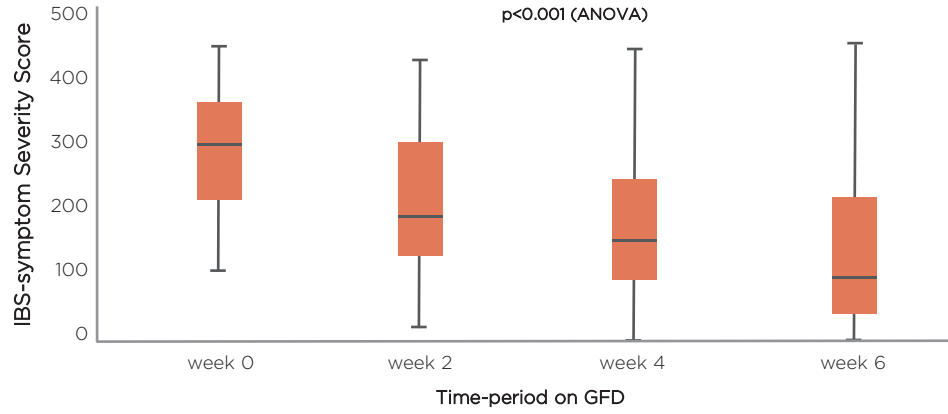


Table Two: Summary of Studies Examining the Role of FODMAPs in IBS

Lead Author	Country	Year	Patients	Outcome
Shepherd[19]	Australia	2006	62 patients with IBS (based on Rome II criteria)	LFD. 74% exhibited a positive response
Shepherd[58]	Australia	2008	25 patients with IBS (based on Rome II criteria)	Randomised placebo controlled re-challenge. Dietary restriction of fructose and/or fructans responsible for symptomatic improvement
Ong[59]	Australia	2010	15 patients with IBS (based on Rome III criteria); 15 'healthy' controls	Randomised crossover single blind. High FODMAP foods increase symptoms in IBS patients *vs.* controls
Biesiekierski[60]	Australia	2011	34 patients with IBS (self-reported gluten sensitive)	Significant reduction in overall symptoms in GFD group
Staudacher[61]	UK	2012	82 patients with IBS (based on NICE criteria)	LFD *vs.* Standard advice. 76% response *vs.* 54% standard
Staudacher[61]	UK	2012	41 patients with IBS (recruited from gastroenterology outpatient clinics)	Randomised to LFD or habitual diet. 68% response *vs.* habitual diet 23% response
Ostgaard[63]	Norway	2012	79 patients with IBS (based on Rome III criteria)	Significant improvement in quality of life and reduction IBS symptoms
Biesiekierski[46]	Australia	2013	37 patients with NCGWS on GFD	Patients responded to reduction in FODMAPs during run-in but no difference between GFD and gluten-containing arms
De Roest[64]	New Zealand	2013	90 patients with IBS (based on breath tests)	72% satisfied with symptom improvement
Mazzawi[65]	Norway	2013	46 patients with IBS (based on Rome III criteria)	17 patients completed study reduced total IBS symptoms and improved quality-of-life.
Wilder-Smith[66]	Switzerland	2013	312 patients with a functional GI disorder	Of the 76% who completed adequate relief in 93%
Pedersen[67]	Denmark	2014	19 with patients IBS (based on Rome III criteria)	Significant improvement in IBS quality-of-life scores
Halmos[68]	Australia	2014	30 patients with IBS (based on Rome III criteria)	50% reduction in symptoms
Böhn[30]	Sweden	2015	75 patients with IBS (based on Rome III criteria)	67 completed with equal response to FODMAP diet (50%) *vs.* traditional dietary advice (46%)
Marsh[20]		2016	Meta-analysis of 6 RCTs & 16 non-randomised trials	Demonstrated significant reductions in IBS symptom severity scores and significant improvements in IBS quality-of-life scores. IBS SSS* OR 0.44 (CI 0.25–0.76) IBS-QOL** OR 1.84 (CI 1.12–3.03)

IBS SSS* = IBS symptoms severity score. IBS QOL** = IBS Quality of Life Score

Table Three: Summary of Studies Examining the Role of Gluten and Wheat in IBS

Lead Author	Country	Year	Patients	Outcome
Wahnschaffe[69]	Germany	2001	102 IBS-D without CD	Stool frequency significantly improved in patients with HLA DQ2/DQ8+ve
Wahnschaffe[70]	Germany	2007	145 IBS-D without CD	HLA-DQ2 predicted response to GFD
Biesiekierski[60]	Australia	2010	34 NCGWS	Significant reduction in overall symptoms in GFD group
Carroccio[71]	Italy	2012	920 patients with IBS	70 patients wheat-sensitive and 206 food sensitivities
Vazquez-Roque[72]	USA	2012	45 patients with IBS-D	Increased intestinal permeability in patients receiving gluten
Vazquez-Roque[73]	USA	2013	45 patients with IBS-D	Reduction in stool frequency in patients on GFD
Biesiekierski[46]	Australia	2013	37 NCGWS on GFD	Patients responded to reduction in FODMAPs during run-in but no difference between GFD and gluten-containing arms
Aziz[50]	UK	2015	40 patients with IBS-D	70% had reduced symptomology with GFD for 6 weeks
Di Sabatino[74]	Italy	2015	59 self-reported NCGWS	4 g of gluten per day for 1 week increased overall clinical symptoms compared with placebo in (P = 0.034)
Shahbazkhani[49]	Iran	2015	72 patients with IBS (based on Rome III criteria)	Worsening of intestinal symptoms with gluten compared to placebo
Zanini[75]	Italy	2015	35 NCGWS on a GFD	Given either and containing or gluten-free flour. 34% symptomatic with gluten-containing flour, 49% symptomatic with gluten-free flour, 17% no response
Zanwar[76]	India	2016	60 patients with IBS (based on Rome III criteria)	GFD for 4 weeks. Significant reduction in visual analogue scales (VAS) of symptomology

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