International Journal of Food Microbiology 290 (2019) 237–246

Contents lists available at ScienceDirect

International Journal of Food Microbiology

journal homepage: www.elsevier.com/locate/ijfoodmicro

Gluten-free and low-FODMAP sourdoughs for patients with coeliac disease and irritable bowel syndrome: A clinical perspective

J.G. Muir*, J.E. Varney, M. Ajamian, P.R. Gibson

Department of Gastroenterology, Central Clinical School, Level 6-The Alfred Centre, 99 Commercial Road, Monash University, Melbourne 3004, Australia

A B S T R A C T

Wheat- and gluten-containing products are often blamed for triggering a wide range of gastrointestinal symptoms, and this has fueled demand for gluten-free products worldwide. The best studied 'gluten intolerance' is coeliac disease, an auto-immune disease that affects the small intestine. Coeliac disease occurs in 1% of the population and requires strict, life-long avoidance of gluten-containing foods as the only medical treatment. There is a larger group of individuals (around 10–15% of the population) who report a wide-range of gastrointestinal symptoms that respond well to a 'gluten-free diet', but who do not have coeliac disease – so called 'non-coeliac gluten sensitivity (NCGS)'. The team at Monash University has identified other factors in gluten-containing foods that may be responsible for symptoms in this group of individuals with so-called, NCGS. We have evidence that certain poorly absorbed short chain carbohydrates (called FODMAPs) present in many gluten-containing food products, induce symptoms of abdominal pain, bloating, wind and altered bowel habit (associated with irritable bowel syndrome, IBS). Our research has shown that FODMAPs, and not gluten, triggered symptoms in NCGS. Going forward, there are great opportunities for the food industry to develop low FODMAP products for this group, as choice of grain variety and type of food processing technique can greatly reduce the FODMAP levels in foods. The use of sourdough cultures in bread making has been shown to reduce the quantities of FODMAPs (mostly fructan), resulting in bread products that are well tolerated by patients with IBS. Greater interaction between biomedical- and food-scientists will improve understanding about the clinical problems many consumers face, and lead to the development of food products that are better tolerated by this group.

1. Wheat and gluten avoidance

Avoidance of wheat and gluten-containing food products is a worldwide phenomenon. These products have been linked to a wide range of conditions including skin problems, fatigue (Hadjivassiliou et al., 2002), migraine (Hadjivassiliou et al., 2002), obesity (Dickey and Kearney, 2006) and autism (Lucarelli et al., 1995). Indeed, the common belief that wheat- and gluten-containing foods are responsible for a wide range of health problems has led to a soaring demand for specialised, wheat- and gluten-free food products. Bread is a staple food and a major source of dietary wheat and gluten. Food technology provides important techniques and approaches to the production of bread-based products that are better tolerated. However, to ensure that specialty food products void of the correct component are developed, a greater understanding of the clinical problem and the true dietary culprits is needed.

1.1. The clinical problem: coeliac disease

The best-studied gluten intolerance is coeliac disease, an auto-immune condition that affects the small intestine and is generally found in around 1% of the population (Dickey and Kearney, 2006; Hadjivassiliou et al., 2002). Coeliac disease is triggered in genetically susceptible individuals and the expression of this disease is dependent on the presence of genes that express human leukocyte antigen (HLA) DQ2 and DQ8 haplotypes (HLA-DQ2 and/or -DQ8 being expressed in 99.4% of patients with coeliac disease) (Lucarelli et al., 1995).

Dietary gluten unequivocally causes this disease via an immune response to specific peptides within the gliadin part of the gluten protein (Anderson et al., 2000). These toxic peptide sequences have been defined (Anderson et al., 2000; Henderson et al., 2007), the genetic susceptibility loci identified and the pathological processes well described. Deamidation of these gliadin epitopes by tissue transglutaminase (tTG) enables them to be presented with high affinity to T-cells in genetically susceptible individuals (HLA-DQ2 or -DQ8 positive) (Sollid et al., 1989). This process initiates a cascade of events resulting in mucosal inflammation, small intestinal villous atrophy (Marsh, 1992), increased intestinal permeability (Cobden et al., 1980) and malabsorption of macro and micronutrients (Green and Jabri, 2003). These events contribute to gut symptoms and long term complications, including small bowel cancer, osteoporosis, fatigue, susceptibility to other autoimmune disease (such as thyroid disease and diabetes), joint pain, infertility and chronic ill health (Fig. 1) (Haines et al., 2008).

The only available treatment for coeliac disease is life-long strict avoidance of gluten-containing foods (including wheat, rye and barley). While the average daily gluten intake in a Western diet is 10–20 g

* Corresponding author.
E-mail address: Jane.Muir@monash.edu (J.G. Muir).

https://doi.org/10.1016/j.ijfoodmicro.2018.10.016
Received 23 July 2018; Received in revised form 15 October 2018; Accepted 22 October 2018
Available online 24 October 2018
0168-1605/

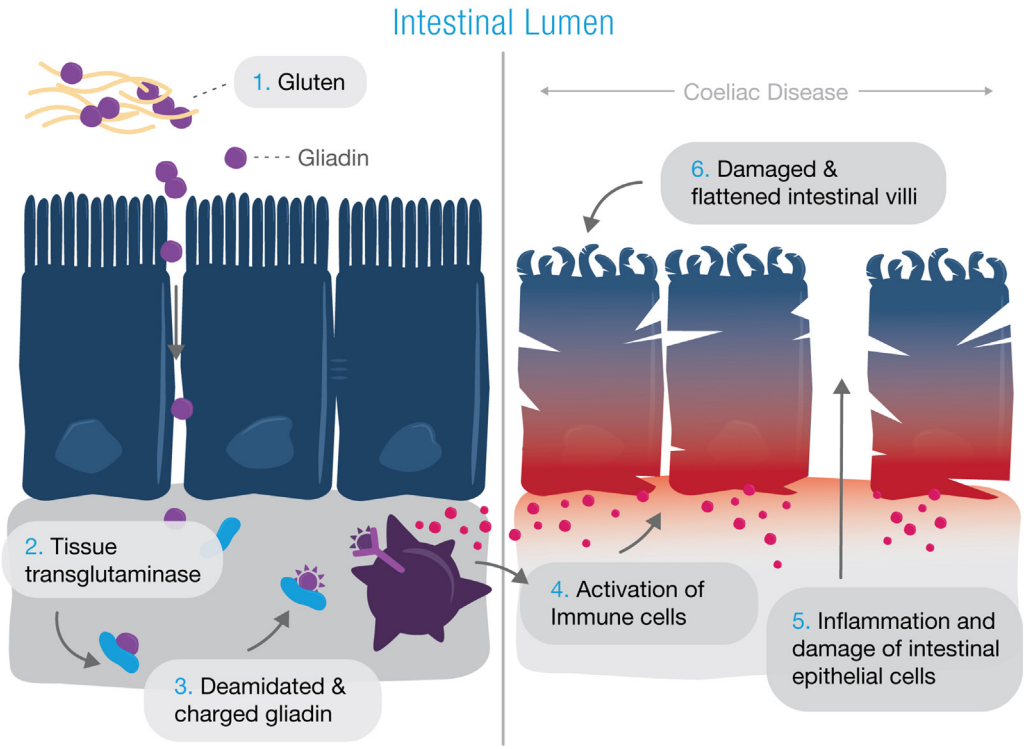

Fig. 1. Role of gluten in coeliac disease.

(equivalent to 2–5 slices of wheat-bread) (van Overbeek et al., 1997), in people with coeliac disease, 50 mg (equivalent to 1/100th of one slice of wheat-bread) is the minimum quantity of gluten needed to induce damage to the lining of the small intestine (Catassi et al., 2007).

1.2. Non-coeliac gluten/wheat sensitivity

There is another group of individuals who report gastrointestinal and extra-intestinal symptoms that are triggered by gluten/wheat consumption, but who do not have the clinical markers of coeliac disease or wheat protein allergy (conditions with well-established pathogenic mechanisms, epidemiology, diagnostic markers and treatment (Markowitz et al., 2000)). Gastrointestinal symptoms characteristically seen in this group include bloating, abdominal pain/discomfort and altered bowel habit, while the extra-intestinal symptoms include headache, anxiety, foggy mind, numbness, skin rash, dermatitis, fatigue and weakness (Volta et al., 2017). However, considerable controversy surrounds this diagnosis, with a lack of high quality evidence to verify its very existence, an absence of diagnostic markers or criteria, and a lack of understanding regarding the mechanisms that contribute to symptoms.

The validity of NCGS as a diagnosis was questioned in cross-sectional survey of 147 patients with self-reported NCGS. While 75% of participants reported improved gastrointestinal symptoms on a gluten free diet, it was also observed that in the majority, coeliac disease had not been adequately excluded (62%); that many experienced uncontrolled symptoms despite gluten restriction (24%), or that they were not actually following a gluten free diet (27%) (Biesiekierski et al., 2014). These findings typify a common scenario in clinical practice, whereby patients present with a self-diagnosis of gluten intolerance without adequate exclusion of coeliac disease or other gastrointestinal disorders and, in many cases, experience ongoing symptoms despite strict adherence to a gluten-free diet.

1.3. Clinical problem - irritable bowel syndrome (IBS)

There is large group of individuals in our community with a condition known as irritable bowel syndrome (IBS). IBS is the most common gastrointestinal disorder seen by specialist gastroenterologists and is characterised by both abdominal pain and abnormal bowel habit (either diarrhoea, constipation, or a mixture of both). Other common symptoms include bloating, distension, excessive gas and urgency to defecate. While the condition does not affect life expectancy, symptoms associated with IBS can have a profound effect on quality of life (QOL) (Hungin et al., 2003). This impact on QOL was highlighted in a large survey of people with IBS, which revealed that one quarter would be willing to relinquish 15 years of their remaining life to attain perfect health (Drossman et al., 2009).

Worldwide, IBS is thought to affect around 11% of the population, although rates vary considerably depending on the population studied and the diagnostic tools used, ranging from 1.1 to 45% (Lovell and Ford, 2012). The condition is more common in women than men and more common in younger people (aged < 50 years) (Lovell and Ford, 2012). Importantly, IBS is undiagnosed in the majority of cases, leading many to self-diagnose their condition (with incorrect diagnoses such as NCGS), and/or seek alternative therapies that lack evidence to support their efficacy (such as a gluten- or wheat-free diet).

2. The phenomenon of gluten/wheat avoidance

Gluten-free and wheat-free diets have grown in popularity worldwide, particularly among people without a confirmed allergy or intolerance to these food components. For instance, in the US it is estimated that 20% of consumers avoid gluten, compared to < 1% with coeliac disease (Kim et al., 2016). Similarly in Australia, a survey revealed that while only 1.2% of the sample had formally diagnosed coeliac disease, 7.3% avoided wheat, even though only 5.7% of wheat avoiders had a medically diagnosed allergy or intolerance that required them to do so.

This trend of gluten avoidance among people without coeliac disease may be driven by a marketing- and media-fueled perception that

gluten free foods are healthier; increased availability of gluten free foods; the phenomenon of NCGS; and perceived symptomatic improvements on a gluten- and/or wheat-free diet. These improvements may be incorrectly attributed to gluten, with a number of other components reduced or removed on a gluten- and/or wheat-free diet, including amylase-trypsin inhibitors (ATIs), wheat germ lectins, galacto-oligosaccharides (GOS) and fructans.

2.1. Components of wheat that may trigger gastrointestinal symptoms

2.1.1. ATIs and wheat-germ lectin

ATIs and wheat-germ lectin are small glycoproteins that may activate the immune system at very small concentrations and theoretically, may induce gastrointestinal symptoms and inflammation. However, there is little, if any human data to support a link between these proteins and IBS-like symptoms (Junker et al., 2012).

2.1.2. Gluten

Gluten is the protein that has attracted the most attention in terms of its role in inducing functional gastrointestinal symptoms. Gluten is the primary storage protein found in the germ of wheat grains, rye, oats and barley. It is a complex mixture of hundreds of related but distinct proteins, but the main proteins present are gliadin and glutenin. Similar proteins to the gliadin found in wheat exist as secalin in rye, hordein in barley and avenins in oats, but collectively are referred to as 'gluten'. Derivatives of these grains, such as triticale, malt, spelt and kamut also contain gluten (Biesiekierski, 2017). The gluten found in all of these grains is capable of triggering the immune-mediated disorder, coeliac disease.

A number of mechanisms have been proposed to explain how gluten may trigger gastrointestinal symptoms in the absence of coeliac disease. For instance, in vitro and animal studies suggest that gluten may induce low-grade intestinal inflammation and gluten challenges have yielded independent changes in neuromotor function and the microbiota (Volta et al., 2016). However, findings from these pre-clinical models have not been replicated in human clinical trials (Biesiekierski et al., 2013; Di Sabatino et al., 2015; Elli et al., 2016; Zanini et al., 2015). Furthermore, while individuals with IBS commonly report that a gluten free diet relieves gastrointestinal symptoms, and numerous studies have revealed symptomatic improvements on a gluten-free diet (Barmeyer et al., 2017; Vazquez-Roque et al., 2013; Wahnschaffe et al., 2007), most failed to answer the question of whether it is the removal of gluten, or other components of gluten containing foods (such as the fructans and GOS in wheat, rye, oats and barley) that is responsible symptomatic improvements.

2.1.3. Fructans/GOS

Strong evidence suggests that the oligosaccharide component (fructans in particular, but also GOS) of grain and cereal foods triggers gastrointestinal symptoms in people with IBS (and probably, in many of those with so-called, NCGS).

Fructans are made up of fructose units with a single D-glucosyl unit at the end. Fructans made up of 2–9 fructose units are generally referred to as fructooligosaccharides (FOS) or oligofructose, while longer chains (> 10 fructose units) are referred to as inulin. Galactooligosaccharides (GOS) are present in foods primarily as raffinose and stachyose. Raffinose is comprised of one fructose, one glucose and one galactose molecule, while stachyose is raffinose with an additional galactose molecule.

Fructans and GOS are not digested in the small intestine, being almost entirely delivered to the large intestine where they are rapidly fermented by resident bacteria. While smaller doses of fructans and GOS are generally well tolerated by healthy individuals, higher doses can cause gastrointestinal symptoms such as flatulence, bloating and abdominal pain. These symptoms occur due to their osmotic effect in the small intestine and to the additional gas formation that occurs with the fermentation of these carbohydrates. Importantly, they are experienced at lower doses in people with functional gastrointestinal disorders (such as IBS) than in healthy people.

2.1.4. FODMAPs

Fructans and GOS are members of a group of short-chain carbohydrates, collectively termed FODMAPs. FODMAP is an acronym that stands for Fermentable Oligo- Di- Mono-saccharides And Polyols. FODMAPs are present naturally in many foods and include lactose (milk), free fructose (pears, apples), fructans (rye, wheat, onions), GOS (legumes), and sugar polyols - sorbitol and mannitol (stone fruits, some vegetables, fermented foods). The FODMAPs present in bread include fructans, GOS and mannitol (in sourdough).

FODMAPs comprise fructose and polyols that are slowly absorbed in the small intestine with the potential for some to reach the large intestine; lactose that cannot be digested in many who have low levels of lactase in the small intestine, and oligosaccharides that cannot be digested (as above). Being small molecules, they attract water the lumen of the small intestine. FODMAPs that pass undigested into the large intestine are rapidly fermented by gut bacteria, producing gas. Increased in water and gas in the intestine causes the intestinal wall to stretch. If visceral hypersensitivity (increased sensitivity to intestinal wall stretching) is present, as it is in many people with IBS, pain and other symptoms (including diarrhoea, bloating and/or distension) may be experienced (Fig. 2).

2.1.5. The FODMAP, fructan, may be responsible for symptoms, not gluten

Historically, there has been considerable confusion among patients, health professionals and researchers about the role of gluten versus oligosaccharides in triggering gastrointestinal symptoms (Table 1) (De Giorgio et al., 2015). This confusion is in part due to the co-existence of these components in grain and cereal foods. Gluten-containing grain and cereal products tend to be high in oligosaccharides (wheat- and rye-products), while gluten-free grains (such as rice- and oat-based products), tend to be low in oligosaccharides (Figs. 3 and 4). These patterns might explain the symptomatic benefit that people report on a gluten-free diet, which may be wrongly attributed to the removal of gluten and more accurately attributed to a reduction in oligosaccharide (particularly fructan) intake.

Studies in this area have fueled the confusion about the role of gluten as a trigger of functional gastrointestinal symptoms. For instance, some studies have:

- failed to adequately exclude coeliac disease (Molina-Infante et al., 2015; Wahnschaffe et al., 2001)
- used wheat challenges, thus failing to separate the effects of gluten from fructans (Biesiekierski et al., 2011a)
- failed to take account of strong nocebo responses in reaction to gluten challenges (as seen in re-challenge studies). Nocebo responses are symptoms that occur due to negative expectations about exposure to a particular substance, not due to the substance per se.

The notion that the removal of dietary FODMAPs (not gluten) results in symptomatic improvement in people with so called, NCGS, was highlighted in a placebo-controlled, crossover re-challenge study in 37 participants with self-reported NCGS and IBS. While the study found that all participants experienced improvements in gastrointestinal symptoms on the initial low FODMAP diet, no independent, gluten-specific effects were observed, suggesting that FODMAPs, not gluten, are the trigger of gastrointestinal symptoms in this population (Biesiekierski et al., 2013).

Findings from a very recent study support this observation. Using blinded gluten, fructan and placebo challenges in people without coeliac disease, but with self-reported gluten sensitivity, this study found no gluten specific effects (when compared to placebo and fructan challenges). It also showed that fructan challenges induced greater

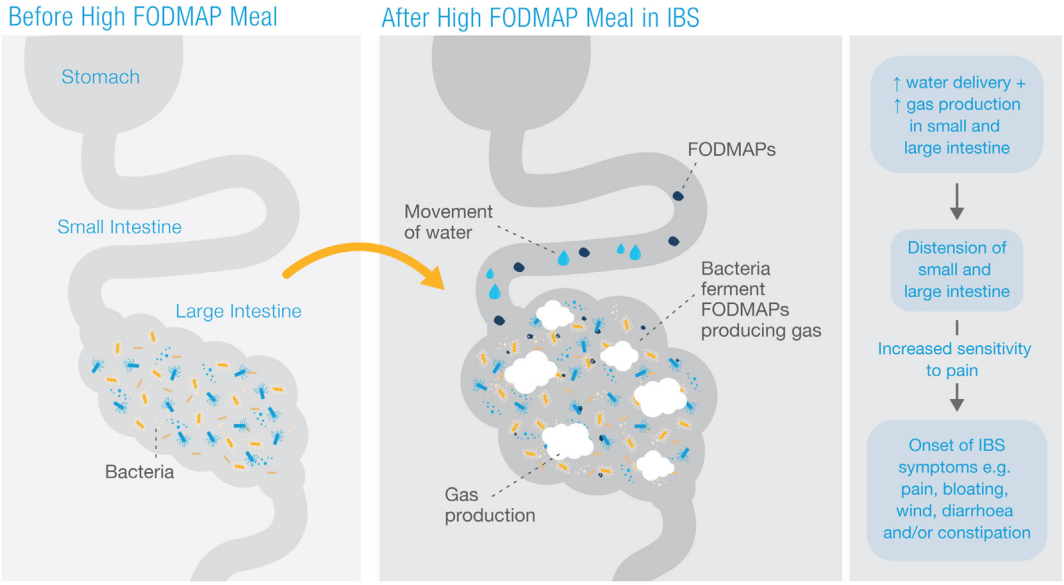

Fig. 2. Role of FODMAPs in triggering symptoms of IBS.

Table 1
The role of gluten and wheat-containing breads in the dietary management of coeliac disease versus IBS.

	Coeliac disease	Irritable bowel syndrome
Tolerate gluten	No	Yes
	• Require no detectable gluten or < 20 ppm.	
Tolerate wheat based-breads		
- At typical serve (2 slices)	No	No
- At reduced serve (½–1 slice)	No	Yes
	• 50 mg (equivalent to 1/100th of one slice of wheat bread) is the minimum quantity of gluten needed to induce damage.	• The levels of FODMAPs, mostly indigestible oligosaccharides (e.g. fructans) at < 0.30 g/serve. The response is very dose dependent and the majority of people with IBS can tolerate ½–1 slice of many wheat-containing breads.
Tolerate gluten-free breads	Yes	Yes
		• Due to the lower FODMAP (mostly fructan) content of gluten-free breads and not the lower gluten content.
Tolerate wheat-containing sourdough breads?		
- At a typical serve (2 slices)	No	Yes
	• Require no detectable gluten or < 20 ppm	• Use of sourdough processing to lower the FODMAP (fructan) has great potential, however must ensure that the sourdough bread is low FODMAP. Final products must be tested for FODMAP levels as not all sourdoughs breads are low in FODMAPs. • It is not appropriate or necessary to aim for zero FODMAP containing sourdough breads. This is because as some FODMAPs (fructans, GOS) are prebiotic (encourage the growth of potential beneficial bacteria) and so it is not desirable to overly restrict this carbohydrate in the diet.
Is this a diet for life?	Yes	No
	• Require a strict gluten-free diet for life	• There are 3 phases to the low FODMAP diet. Phase 1 – FODMAP Restriction for 2–6 weeks and is followed by Phase 2 - Re-challenge phase and finally Phase 3 - Personalised FODMAP diet.
Tolerate high FODMAP foods	Yes as long as gluten-free.	Some FODMAPs may be tolerated
	• Many people with coeliac disease can tolerate higher FODMAP containing foods (provided these are also gluten-free). It is not necessary for these individuals to restrict FODMAPs unless they have concurrent IBS.	• During Phase 1 – FODMAP restriction, all high FODMAP containing foods are restricted. During the following Phases 2 and 3 it may be identified that some FODMAPs can be well tolerate even at high doses and so do not need to be restricted. This varies greatly from individual to individual.

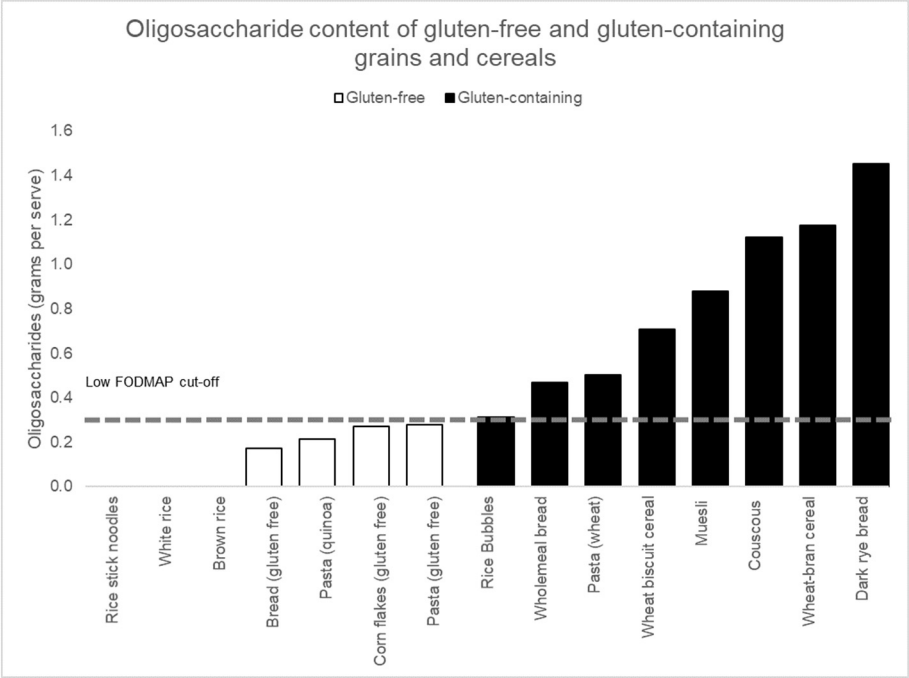

Fig. 3. Oligosaccharide content of gluten free and gluten containing grains and cereals.

symptom response than gluten challenges, suggesting that fructans are the more likely triggers of gastrointestinal symptoms in this population (Skodje et al., n.d.).

Another study assessed symptom responses to double-blind, placebo controlled gluten challenges in people with NCGS (n = 20). This study revealed that the majority of participants (80%) could not differentiate between gluten and placebo challenges. Furthermore, in the minority of participants who could correctly make this distinction (20%), there was no difference in symptom severity following placebo and gluten challenges. These findings led authors to conclude that 1) there were no gluten-specific symptom responses in this group with so-called NCGS, and that 2) participants who correctly identified the gluten challenge as the cause for their symptoms may have done-so by chance (Dale et al., 2018).

Given the considerable overlap between symptoms of NCGS/WS and IBS, and the problems associated with diagnosing this condition, it is likely that NCGS is over-diagnosed in research studies and clinical practice. The majority of patients diagnosed with this condition may have simply exhibited strong nocebo responses to gluten challenges, or may rather suffer from a functional gastrointestinal disorder that makes them sensitive to dietary factors that co-exist with gluten, such as FODMAPs. A minority might have undiagnosed coeliac disease.

3. Low FODMAP diet

FODMAPs are found in a wide range of foods including:

- Excess fructose in fruit/fruit products (e.g., mango, apple, pear, dried fruit, fruit juice), and syrups (e.g., honey, agave syrup, high fructose corn syrup)
- Lactose in dairy products (e.g., milk, yoghurt, ice cream, soft cheeses)
- Fructans in wheat and rye products (e.g. breads, cereals, pasta, noodles, biscuits); and vegetables (e.g., onion, garlic, leek, artichoke)
- GOS in pulses (e.g. baked beans, red kidney beans), nuts (e.g.

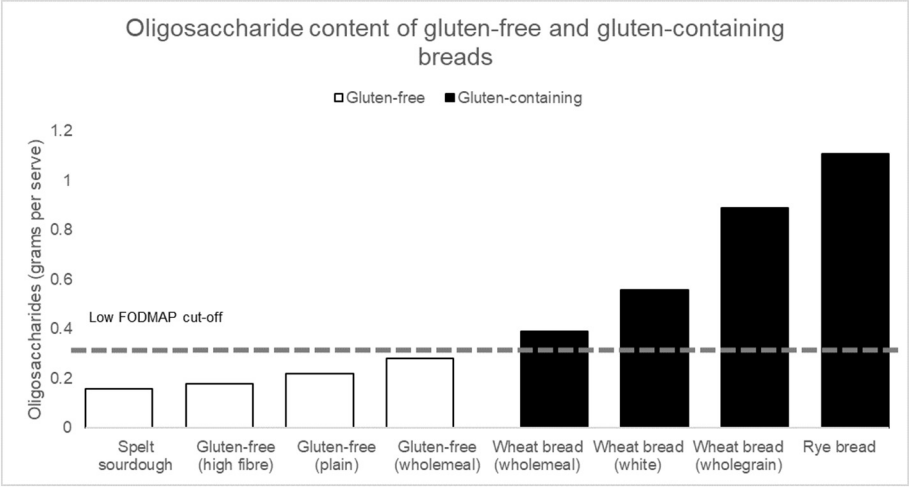

Fig. 4. Oligosaccharide content of gluten free and gluten containing breads.

cashews, pistachios), and vegetables (e.g., frozen peas)
- Sorbitol in fruit (e.g., apples, pears, avocado, many stone fruit), and some artificially sweetened products (e.g., gums, lollies)
- Mannitol in vegetables (e.g., cauliflower, mushrooms and snow peas) and some sourdough breads.

There is stronger evidence supporting the efficacy of a low FODMAP diet for the management of IBS than for any other diet therapy in IBS. At least 10 RCTs, by groups all over the world have now shown that a low FODMAP diet is effective in 50 to 80% of patients, improving overall functional symptoms, symptom severity and quality of life, when compared to a habitual, Western diet (Bohn et al., 2015; Eswaran et al., 2016; Halmos et al., 2014; Harvie et al., 2013; Hustoft et al., 2017; McIntosh et al., 2016; Pedersen et al., 2014; Peters et al., 2016; Staudacher et al., n.d.; Staudacher et al., 2012).

The most important and influential of these studies was an RCT in 30 participants with IBS and 8 healthy controls. All food was provided to participants, the FODMAP content of which was either 'low' or 'normal' (based on a typical Australian diet). Participants consumed either diet and then swapped to the alternate diet. Neither subjects nor investigators knew which diet they were consuming until the study was finished. The study showed impressive effects; 70% of IBS participants experienced symptom improvement on the low FODMAP diet and symptoms were reduced by half. Changes were not observed in healthy subjects (Halmos et al., 2014).

This evidence is now reflected in clinical guidelines that recommend a low FODMAP diet as the first treatment choice for patients with IBS (Drossman, 2016) and the diet is now considered part of standard dietetic practice (Whelan et al., 2018).

3.1. Low FODMAP diet explained

The development of the low FODMAP diet required both extensive information about the FODMAP composition of food, and the formation of cut-off values to classify individual serves of food as low, moderate or high in FODMAPs. These cut-off values were developed by the team at Monash University and have been published (Varney et al., 2017). Monash has tested the reliability of these FODMAP cut-off values in a number of dietary studies (Barrett et al., 2010; Halmos et al., 2014; Ong et al., 2010). In these studies, FODMAP intake in the low FODMAP arm was limited to 0.5 g total FODMAPs (excluding lactose) per sitting. This was found to be generally well tolerated.

The FODMAPs of most relevance to grain and cereal foods are fructans and, to lesser extents, GOS (found in barley, rye, wheat and oats), excess fructose (sometimes added during bread making or a bi-product of fermentation) and mannitol (a bi-product of fermentation in sourdough bread). The cut-off values for these FODMAPs are as follows: excess fructose < 0.15 g per serve, oligosaccharides < 0.3 g per serve (in core grain products such as breads and cereals and also nuts and seeds) and < 0.2 g per serve in fruits, vegetables and all other products, and sorbitol or mannitol < 0.2 g per serve.

Table 2 provides an example of foods classified low and high in FODMAPs based on these cut off values. For more detailed information about the FODMAP composition of food, please refer to the Monash University Low FODMAP Diet™ App.

3.2. Implementation of the low FODMAP diet: how it is done

A low FODMAP diet aims to reduce symptoms of medically diagnosed IBS. Ensuring IBS is accurately diagnosed prior to commencement of this diet is important, as a number of other condition share similar symptoms with IBS, and these should be ruled out to avoid misdiagnosis or delayed diagnosis. It is recommended that patients wishing to implement the diet engage the support of a dietitian. Optimal results are achieved using a dietitian who is trained in this area, and 2 appointments are usually required.

Table 2
Foods classified as low and high in FODMAPs at a single serve based on Monash FODMAP cut-off values.

	Food	High FODMAP	Low FODMAP
Fructans	Bread	Wholegrain wheat bread	2 slices spelt sourdough bread
		Rye bread	2 slices gluten free bread
			1 slice oat sourdough bread
	Cereal	Muesli containing wheat	Oats (1/4 cup)
		Whole wheat grain biscuit	Quinoa flakes (1 cup)
			Corn flakes (1/2 cup)
	Pasta	Wheat pasta	Gluten free pasta (1 cup)
			Quinoa pasta (1 cup)
	Biscuits	Rye crispbread	Rice cakes – plain (2 rice cakes)
GOS		Baked beans	Chickpeas, canned (1/4 cup)
		Four bean mix	
		Lentils	Lentils, canned (1/2 cup)
		Red kidney beans	
			Lima beans, boiled (1/4 cup)
Sorbitol		Pear	Orange
		Corn	Banana
		Apples	Grapes
		Nectarine	Kiwi fruit, green
Mannitol		Peach	Strawberries
		Watermelon	Cantaloupe
		Celery	Capsicum, green
		Sweet potato	Potato
Excess fructose		Asparagus	Beans, green
		Artichoke	Aubergine/eggplant
		Sugar snap peas	Carrot
		Apple	Rhubarb
		Pear	Raspberries
		Watermelon	Pineapple
Lactose	Dairy products	Cows' milk	Lactose free milk
		Custard	Yoghurt (small amounts)
		Evaporated milk	
		Ice cream	Soy milk (soy protein)
			Whipped cream

There are 3 phases in a low FODMAP diet.

- Phase 1 – FODMAP intake is restricted for 2–6 weeks. High FODMAP foods are substituted with low FODMAP alternatives. If symptoms improve, phase 2 is commenced. If symptoms do not improve, FODMAPs should be reintroduced into the diet and other therapeutic approaches should be considered.
- Phase 2 – Low FODMAP diet is continued. Food challenges are used to identify to which FODMAPs the patient is sensitive, and to which they are not.
- Phase 3 – Well tolerated FODMAPs are reintroduced into the diet. Only poorly tolerated FODMAPs are restricted. To ensure nutritional adequacy, patients should aim for a minimally restrictive diet.

3.3. Impact of the low FODMAP diet on dietary fibre intake

Adhering to a low FODMAP diet can limit the variety and quantity of grain- and cereal-products available for an individual to consume. This has implications for dietary fibre intake, as FODMAPs and fibre tend to co-exist in food and many low FODMAP products currently available (including many gluten-free products) tend to be low in dietary fibre.

In Australia and Europe, we recommend a dietary fibre intake of around 30 g per day. However, most people (including those with IBS) consume considerably less dietary fibre than this, with average daily intake in Australia estimated to be around 21 g. Dietitians have an

important role in assisting individuals to adapt their diet and introduce foods that are low in FODMAPs, but high in fibre (e.g., kiwifruit, oranges, strawberries, potato, carrot, eggplant, oat bran, rice ban and brown rice). Food industry also has an important role to play in providing quality products that are low in FODMAPs, but good sources of dietary fibre.

Dietary fibres differ greatly in their actions in the gut. For example, some fibres are very effective at encouraging optimal bowel function via laxation; some fibres are fermented to produce short chain fatty acids (SCFA) (particularly acetate, propionate, and butyrate) and gas (CO_2, H_2, CH_4); while others can have prebiotic actons (i.e., selectively stimulate growth of colonic bacteria with putative health benefits) (Eswaran et al., 2013).

Because of the potential to influence the 'ecology' of the gut microbiota (in terms of quality, types, activity, quantity and diversity), there is worldwide interest in exploring prebiotic fibres. The best-studied prebiotic fibres are fructans and GOS (Gibson et al., 2017). Both are considered FODMAPs and are restricted on a low FODMAP diet. Our own dietary studies have shown that varying FODMAP levels in the diet can indeed impact certain colonic bacteria (Halmos et al., 2014). Hence, it is important to emphasise that this is not a FODMAP-free diet, and that a strict low FODMAP diet should not be followed over the longer-term. The 3-phases of the Low FODMAP diet program encourage the re-introduction of as much prebiotic fibres such as fructans and GOS into the diet as can be tolerated.

4. Use of sourdoughs in patients with IBS and coeliac disease

4.1. Gluten and FODMAPs exist in food together

As noted above, analysis of gluten-free and gluten-containing grain and cereal products has revealed that gluten and fructans tend to co-exist in food. Consequently, 'gluten-free' foods are often lower in FODMAPs (Figs. 3 and 4). Laboratory analysis of a range of different gluten-free breads demonstrated that these were lower in FODMAPs than breads made from wheat and rye (Fig. 4). This type of comparison revealed that sourdough bread products made using spelt wheat were lower in total FODMAPs, particularly fructans (Fig. 4).

4.2. Use of sourdough breads in patients with IBS

The low FODMAP content of gluten-free breads, grains and cereals may explain why patients with IBS and NCGS can tolerate gluten-free breads and grain products. This results in a smaller load of rapidly fermented, indigestible carbohydrates being delivered to the large intestine and thus fewer gastrointestinal symptoms. However, sourdough processing can also lower the FODMAP level of bread. This observation has inspired the interest of our team regarding the role of sourdough processing in improving the tolerability of wheat-containing bread products. Our research studies (such as that from Halmos et al. exploring the role of the low FODMAP diet in controlling the gastrointestinal symptoms associated with IBS) have all utilised low FODMAP sourdough spelt breads (Halmos et al., 2014).

The sourdough process has the potential to lower the quantity of FODMAPs, mostly the indigestible oligosaccharides (fructans and raffinose) to levels that will be well tolerated by most individuals with IBS. The key mechanism behind the success of the sourdough is that the sourdough culture (particularly yeasts) can degrade the fructans during the fermentation process (Nilsson et al., 1987; Struyf et al., 2017; Verspreet et al., 2013).

Conditions including proofing time, temperature, CO_2 levels and types of organisms used in the sourdough are all important to consider and may have a major impact on the levels of FODMAPs in the final product. One of the key modifiable factors relevant to reducing FODMAP content in sourdough bread is proofing time. As shown in Fig. 5, when the same spelt dough is exposed to increasing proofing times, the level of fructans can be greatly reduced and to below the 'cut-off' line for fructans (Fig. 5). The importance of proofing time has also been demonstrated by Ziegler and coworkers where proofing times of 4.5 h were capable of reducing FODMAP content (fructans and raffinose) by up to 90% for a whole-grain wheat bread and 77% for a spelt bread (Ziegler et al., 2016). Interestingly, the shorter proofing time of 1 h showed an increase in fructose (as a result of the breakdown of fructans to fructose). Fructose in excess of glucose is a FODMAP and potential trigger for gastrointestinal symptoms. However, by extending the proofing time to 4.5 h, the levels of fructose in the final product were negligible (Ziegler et al., 2016), again demonstrating the need for the longer proofing periods.

Choice of organisms to use in the culture is also important. For example, the combination of an inulinase-secreting yeast, *Kluyveromyces marxianus*, combined with *Saccharomyces cerevisiae* in wheat dough could lower the fructans in dough made from whole wheat flour (Struyf et al., 2017). Combining different micro-organisms may be key to produce a final bread product with optimal quality (e.g., optimal loaf volume) while also being low in FODMAPs.

The choice of grain species and variety may also assist with the design of products that are lower in FODMAP content. The FODMAP content of a number of different wheat species and varieties (including modern wheat and more ancient wheat varieties) were recently compared (Ziegler et al., 2016). Einkorn contained the higher levels of FODMAPs, with Emmer the lowest (einkorn > bread wheat > spelt > durum > emmer) (Ziegler et al., 2016). The combination of grain choice that is naturally lower in FODMAPs plus sourdough processing will increase the likelihood of producing a product that is low in FODMAPs.

The sourdough process, however, may provide a powerful technique for producing low FODMAP bread products from some high fructan-containing grains. For example, rye is one of the highest fructan-containing grains (Biesiekierski et al., 2011b), but treatment via a carefully selected sourdough was able to produce a rye bread product that is lower in FODMAP content (Laatikainen et al., 2016). Moreover, when used in a dietary study with IBS participants, it was shown that this low FODMAP rye bread product improved symptoms and reduced gas when compared to standard rye bread (Laatikainen et al., 2016).

4.2.1. Are we ready to use low FODMAP sourdough breads in IBS?

There is growing acceptance of the low FODMAP diet strategy as an evidence-based diet therapy for the management of IBS. As a consequence, the low FODMAP diet strategy is being adopted worldwide – for example, it has been recommended in the latest NICE guidelines (Hookway et al., 2015). The use of sourdough to reduce the FODMAP content of bread to assist this group of patients manage their IBS is ready for implementation, and indeed there are a number of manufactures in Australia and Europe providing low FODMAP sourdough breads to satisfy demand from this group of consumers. It should be emphasised, however, that levels of fructans in sourdough breads need to be reduced (to levels that will be tolerated) but not eliminated. This is important because, as noted above, FODMAPs (fructans and GOS in particular), are prebiotic encouraging the growth of so called 'beneficial' bacteria in the gut. For this reason, we recommend that FODMAPs only needed to be restricted to the level that provides symptom relief, without completely removing these carbohydrates from the diet.

4.3. Use of sourdough to generate gluten-free wheat sourdough breads in patients with coeliac disease

Sourdough techniques are also being explored in relation to preparing gluten-free, wheat-based baked products. Sourdough fermentation cultures contain a cocktail of enzymes (including proteases) as well as an acidic environment that can hydrolyze proteins as well as carbohydrates. Traditional sourdough culture methods have been shown to degrade the gluten in wheat. Indeed, there is evidence to suggest that it

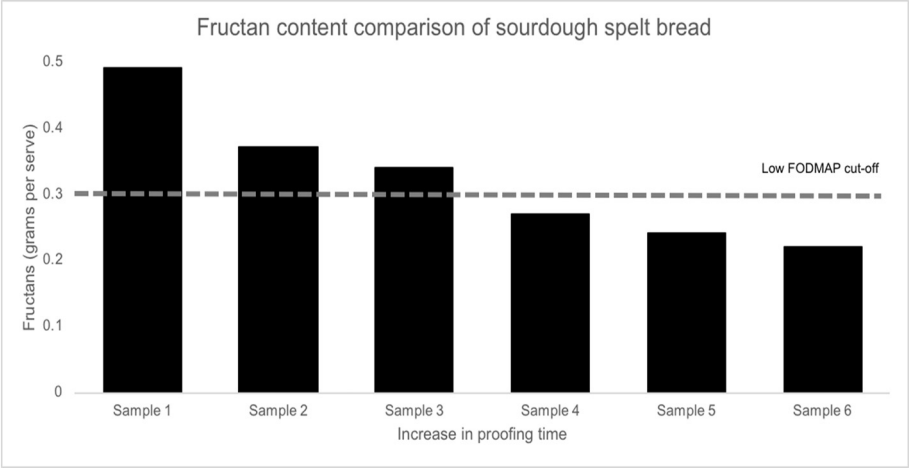

Fig. 5. Effect of sourdough processing on fructan content of breads.

is possible to select for a specific sourdough (e.g., LAB *Lactobacillus casei* strain) that is capable of degrading the toxic 33-mer peptide (considered the most immunogenic peptide responsible for triggering the cascade of events that result in coeliac disease) (Alvarez-Sieiro et al., 2016). Not all in vitro studies, however, confirm this type of result (Engström et al., 2015) suggesting that this effect is strain-specific and thereby very dependent on the sourdough microorganisms used (Engström et al., 2015).

Two clinical studies utilising this approach have been undertaken in young people with coeliac disease (Di Cagno et al., 2010; Mandile et al., 2017). A combination of selected LAB together with fungal protease (Di Cagno et al., 2010; Mandile et al., 2017) was used to ferment and degrade wheat flour gluten. Incorporation of this degraded wheat flour into baked wheat products was shown to abolish the T cell response to gluten in a short-term study (3 days) (Mandile et al., 2017) and did not appear to stimulate immune responses or clinical symptoms in coeliac patients over a longer term (60 days) (Di Cagno et al., 2010). None of these studies, however, have assessed the impact of this technique has on the FODMAP component (i.e., fructan) of the final product.

Can sourdough methods, therefore, be used to produce 'safe' wheat-products for people with coeliac disease? Clearly this approach must reliably degrade gluten to < 10 ppm in order to be suitable for CD, and larger studies in individuals with coeliac disease involving other centers are required. It is also noteworthy that degrading gluten in wheat flour using sourdough fermentation would negatively impact the quality of flour for baking purposes. For example, the degraded gluten will no longer have the characteristic viscoelastic properties of gluten, which are important for optimal bread loaf volume and quality. Moreover, individuals with CD may be reluctant to purchase and consume wheat-based products.

5. Summary and conclusions

Consumers are making food choices based on the 'effects' (real or perceived) that certain foods are having on them. Gastrointestinal symptoms are a common complaint in relation to wheat-based products. There are two major health-related issues responsible for fueling the demand for wheat- and gluten-free foods worldwide. The best studied and understood disease that requires a strict gluten-free diet (as the only medical treatment) is coeliac disease (affecting around 1% of the population). The other clinical problem that is fueling the biggest demand (up to 10–15% of the population) is most likely related to gastrointestinal symptoms associated with IBS. Some individuals strongly identify that their gastrointestinal symptoms are triggered by gluten when the latest evidence suggests that the real culprits are other components of wheat, namely fructans (mostly) and GOS. Fructans and GOS belong to a new and emerging category of short-chain carbohydrates called FODMAPs that are poorly absorbed and rapidly fermented in the large intestine. There is now a strong evidence base to support the notion that FODMAPs trigger gastrointestinal symptoms and the low FODMAP diet is increasingly being used as first line therapy to control the gastrointestinal symptoms associated with IBS.

There is an important distinction to be made between 'gluten-free' and 'low FODMAP'. Unlike gluten-free for coeliac disease, which requires strict and life-long removal of gluten from the diet, the low FODMAP diet strategy involves 3 phases - restriction, re-challenge and personalisation (taking around 3–4 months to complete the program). This diet only requires that FODMAPs are lowered to levels that are tolerated, but does not require the complete removal of FODMAPs. The use of fructanase producing micro-organisms associated with LAB and yeasts as part of the sourdough process have enormous potential to provide quality bread products that will be well tolerated by this large group of consumers with IBS (10–15% of the population) – as well as providing a good source of dietary fibre.

Clearly, a deeper understanding of the science and clinical problems associated with consumer demands is essential in ensuring that new products are developed based on facts rather than pseudoscience and the demands of the latest diet fad.

Declaration of personal interests

The authors work in a department that financially benefits from the sales of a digital application and booklets on the low FODMAP diet. They have published an educational/recipe book on diet. Funds raised contribute to research of the Department of Gastroenterology and to the University. The authors receive no personal remuneration.

References

Alvarez-Sieiro, P., Montalban-Lopez, M., Mu, D., Kuipers, O.P., 2016. Bacteriocins of lactic acid bacteria: extending the family. Appl. Microbiol. Biotechnol. 100, 2939–2951.

Anderson, R.P., Degano, P., Godkin, A.J., Jewell, D.P., Hill, A.V., 2000. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. Nat. Med. 6, 337–342.

Barmeyer, C., Schumann, M., Meyer, T., Zielinski, C., Zuberbier, T., Siegmund, B., Schulzke, J.D., Daum, S., Ullrich, R., 2017. Long-term response to gluten-free diet as evidence for non-celiac wheat sensitivity in one third of patients with diarrhea-dominant and mixed-type irritable bowel syndrome. Int. J. Color. Dis. 32, 29–39.

Barrett, J.S., Gearry, R.B., Muir, J.G., Irving, P.M., Rose, R., Rosella, O., Haines, M.L., Shepherd, S.J., Gibson, P.R., 2010. Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. Aliment. Pharmacol. Ther. 31, 874–882.

Biesiekierski, J.R., 2017. What is gluten? J. Gastroenterol. Hepatol. 32 (Suppl. 1), 78–81.

Biesiekierski, J.R., Newnham, E.D., Irving, P.M., Barrett, J.S., Haines, M., Doecke, J.D., Shepherd, S.J., Muir, J.G., Gibson, P.R., 2011a. Gluten causes gastrointestinal

symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am. J. Gastroenterol. 106, 508–514 (quiz 515).
Biesiekierski, J.R., Rosella, O., Rose, R., Liels, K., Barrett, J.S., Shepherd, S.J., Gibson, P.R., Muir, J.G., 2011b. Quantification of fructans, galacto-oligosacharides and other short-chain carbohydrates in processed grains and cereals. J. Hum. Nutr. Diet. 24, 154–176.
Biesiekierski, J.R., Peters, S.L., Newnham, E.D., Rosella, O., Muir, J.G., Gibson, P.R., 2013. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology 145, 320–328.e3.
Biesiekierski, J.R., Newnham, E.D., Shepherd, S.J., Muir, J.G., Gibson, P.R., 2014. Characterization of adults with a self-diagnosis of nonceliac gluten sensitivity. Nutr. Clin. Pract. 29, 504–509.
Bohn, L., Storsrud, S., Liljebo, T., Collin, L., Lindfors, P., Tornblom, H., Simren, M., 2015. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology 149, 1399–1407.e2.
Catassi, C., Fabiani, E., Iacono, G., D'Agate, C., Francavilla, R., Biagi, F., Volta, U., Accomando, S., Picarelli, A., De Vitis, I., Pianelli, G., Gesuita, R., Carle, F., Mandolesi, A., Bearzi, I., Fasano, A., 2007. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. Am. J. Clin. Nutr. 85, 160–166.
Cobden, I., Rothwell, J., Axon, A.T., 1980. Intestinal permeability and screening tests for coeliac disease. Gut 21, 512–518.
Dale, H.F., Hatlebakk, J.G., Hovdenak, N., Ystad, S.O., Lied, G.A., 2018. The effect of a controlled gluten challenge in a group of patients with suspected non-coeliac gluten sensitivity: a randomized, double-blind placebo-controlled challenge. Neurogastroenterol. Motil. 30 (8), e13332.
De Giorgio, R., Volta, U., Gibson, P.R., 2015. Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction? Gut 65, 169–178.
Di Cagno, R., Barbato, M., Di Camillo, C., Rizzello, C.G., De Angelis, M., Giuliani, G., De Vincenzi, M., Gobbetti, M., Cucchiara, S., 2010. Gluten-free sourdough wheat baked goods appear safe for young celiac patients: a pilot study. J. Pediatr. Gastroenterol. Nutr. 51, 777–783.
Di Sabatino, A., Volta, U., Salvatore, C., Biancheri, P., Caio, G., De Giorgio, R., Di Stefano, M., Corazza, G.R., 2015. Small amounts of gluten in subjects with suspected non-celiac gluten sensitivity: a randomized, double-blind, placebo-controlled, cross-over trial. Clin. Gastroenterol. Hepatol. 13, 1604–1612.e3.
Dickey, W., Kearney, N., 2006. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. Am. J. Gastroenterol. 101, 2356–2359.
Drossman, D.A., 2016. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology 150, 1262–1279.
Drossman, D.A., Morris, C.B., Schneck, S., Hu, Y.J., Norton, N.J., Norton, W.F., Weinland, S.R., Dalton, C., Leserman, J., Bangdiwala, S.I., 2009. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J. Clin. Gastroenterol. 43, 541–550.
Elli, L., Tomba, C., Branchi, F., Roncoroni, L., Lombardo, V., Bardella, M.T., Ferretti, F., Conte, D., Valiante, F., Fini, L., Forti, E., Cannizzaro, R., Maiero, S., Londoni, C., Lauri, A., Fornaciari, G., Lenoci, N., Spagnuolo, R., Basilisco, G., Somalvico, F., Borgatta, B., Leandro, G., Segato, S., Barisani, D., Morreale, G., Buscarini, E., 2016. Evidence for the presence of non-celiac gluten sensitivity in patients with functional gastrointestinal symptoms: results from a multicenter randomized double-blind placebo-controlled gluten challenge. Nutrients 8, 84.
Engström, N., Sandberg, A.-S., Scheers, N., 2015. Sourdough fermentation of wheat flour does not prevent the interaction of transglutaminase 2 with α(2)-gliadin or gluten. Nutrients 7, 2134–2144.
Eswaran, S., Muir, J., Chey, W.D., 2013. Fiber and functional gastrointestinal disorders. Am. J. Gastroenterol. 108, 718–727.
Eswaran, S.L., Chey, W.D., Han-Markey, T., Ball, S., Jackson, K., 2016. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am. J. Gastroenterol. 111 (12), 1824–1832.
Gibson, G.R., Scott, K.P., Rastall, R.A.et.al., 2017. Dietary prebiotics: current status and new definition. Food Sci. Technol. Bull. Funct. Foods 7, 1.
Green, P.H., Jabri, B., 2003. Coeliac disease. Lancet 362, 383–391.
Hadjivassiliou, M., Grünewald, R.A., Davies-Jones, G.A.B., 2002. Gluten sensitivity as a neurological illness. J. Neurol. Neurosurg. Psychiatry 72, 560–563.
Haines, M.L., Anderson, R.P., Gibson, P.R., 2008. Systematic review: the evidence base for long-term management of coeliac disease. Aliment. Pharmacol. Ther. 28, 1042–1066.
Halmos, E.P., Power, V.A., Shepherd, S.J., Gibson, P.R., Muir, J.G., 2014. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 146, 67–75.e5.
Harvie, R., Schultz, M., Chisholm, A., 2013. A Reduction in FODMAP Intake Correlates Strongly With a Reduction in IBS Symptoms-The FIBS Study.
Henderson, K.N., Tye-Din, J.A., Reid, H.H., Chen, Z., Borg, N.A., Beissbarth, T., Tatham, A., Mannering, S.I., Purcell, A.W., Dudek, N.L., van Heel, D.A., McCluskey, J., Rossjohn, J., Anderson, R.P., 2007. A structural and immunological basis for the role of human leukocyte antigen DQ8 in celiac disease. Immunity 27, 23–34.
Hookway, C., Buckner, S., Crosland, P., Longson, D., 2015. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. BMJ 350, h701.
Hungin, A.P., Whorwell, P.J., Tack, J., Mearin, F., 2003. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment. Pharmacol. Ther. 17, 643–650.
Hustoft, T.N., Hausken, T., Ystad, S.O., Valeur, J., Brokstad, K., Hatlebakk, J.G., Lied, G.A., 2017. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterol. Motil. 29.
Junker, Y., Zeissig, S., Kim, S.J., Barisani, D., Wieser, H., Leffler, D.A., Zevallos, V., Libermann, T.A., Dillon, S., Freitag, T.L., Kelly, C.P., Schuppan, D., 2012. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J. Exp. Med. 209, 2395–2408.
Kim, H.S., Patel, K.G., Orosz, E., Kothari, N., Demyen, M.F., Pyrsopoulos, N., Ahlawat, S.K., 2016. Time trends in the prevalence of celiac disease and gluten-free diet in the US population: results from the National Health and Nutrition Examination Surveys 2009–2014. JAMA Intern. Med. 176, 1716–1717.
Laatikainen, R., Koskenpato, J., Hongisto, S.M., Loponen, J., Poussa, T., Hillilä, M., Korpela, R., 2016. Randomised clinical trial: low-FODMAP rye bread vs. regular rye bread to relieve the symptoms of irritable bowel syndrome. Aliment. Pharmacol. Ther. 44, 460–470.
Lovell, R.M., Ford, A.C., 2012. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin. Gastroenterol. Hepatol. 10, 712–721.e4.
Lucarelli, S., Frediani, T., Zingoni, A.M., Ferruzzi, F., Giardini, O., Quintieri, F., Barbato, M., D'Eufemia, P., Cardi, E., 1995. Food allergy and infantile autism. Panminerva Med. 37, 137–141.
Mandile, R., Picascia, S., Parrella, C., Camarca, A., Gobbetti, M., Greco, L., Troncone, R., Gianfrani, C., Auricchio, R., 2017. Lack of immunogenicity of hydrolysed wheat flour in patients with coeliac disease after a short-term oral challenge. Aliment. Pharmacol. Ther. 46, 440–446.
Markowitz, M.A., Jhingran, P., Asgharian, A., Harris, W.A., Brod, M., Wentz, A.L., Gordon, S.H., Carter, E., 2000. IBS prevalence: results from a community based patient registry based on the Rome II criteria. Am. J. Gastroenterol. 95, 2634.
Marsh, M.N., 1992. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 102, 330–354.
McIntosh, K., Reed, D.E., Schneider, T., Dang, F., Keshteli, A.H., De Palma, G., Madsen, K., Bercik, P., Vanner, S., 2016. FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial. Gut 66, 1241–1251.
Molina-Infante, J., Santolaria, S., Sanders, D.S., Fernandez-Banares, F., 2015. Systematic review: noncoeliac gluten sensitivity. Aliment. Pharmacol. Ther. 41, 807–820.
Nilsson, U., Öste, R., Jägerstad, M., 1987. Cereal fructans: hydrolysis by yeast invertase, in vitro and during fermentation. J. Cereal Sci. 6, 53–60.
Ong, D.K., Mitchell, S.B., Barrett, J.S., Shepherd, S.J., Irving, P.M., Biesiekierski, J.R., Smith, S., Gibson, P.R., Muir, J.G., 2010. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J. Gastroenterol. Hepatol. 25, 1366–1373.
Pedersen, N., Andersen, N.N., Vegh, Z., Jensen, L., Ankersen, D.V., Felding, M., Simonsen, M.H., Burisch, J., Munkholm, P., 2014. Ehealth: low FODMAP diet vs *Lactobacillus rhamnosus* GG in irritable bowel syndrome. World J. Gastroenterol. 20, 16215–16226.
Peters, S.L., Yao, C.K., Philpott, H., Yelland, G.W., Muir, J.G., Gibson, P.R., 2016. Randomised clinical trial: the efficacy of gut-directed hypnotherapy is similar to that of the low FODMAP diet for the treatment of irritable bowel syndrome. Aliment. Pharmacol. Ther. 44, 447–459.
Skodje, G.I., Sarna, V.K., Minelle, I.H., Rolfsen, K.L., Muir, J.G., Gibson, P.R., Veierød, M.B., Henriksen, C., Lundin, K.E.A., 2018. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. Gastroenterology 154, 529–539.
Sollid, L.M., Markussen, G., Ek, J., Gjerde, H., Vartdal, F., Thorsby, E., 1989. Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. J. Exp. Med. 169, 345–350.
Staudacher, H.M., Lomer, M.C., Anderson, J.L., Barrett, J.S., Muir, J.G., Irving, P.M., Whelan, K., 2012. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J. Nutr. 142, 1510–1518.
Staudacher, H.M., Lomer, M., Louis, P., Farquharson, F., Lindsay, J.O., Irving, P.M., Whelan, K., 2017. 1133 the low FODMAP diet reduces symptoms in irritable bowel syndrome compared with placebo diet and the microbiota alterations may be prevented by probiotic co-administration: a 2 × 2 factorial randomized controlled trial. Gastroenterology 150 S230.
Struyf, N., Laurent, J., Verspreet, J., Verstrepen, K.J., Courtin, C.M., 2017. *Saccharomyces cerevisiae* and *Kluyveromyces marxianus* cocultures allow reduction of fermentable oligo-, di-, and monosaccharides and polyols levels in whole wheat bread. J. Agric. Food Chem. 65, 8704–8713.
van Overbeek, F.M., Uil-Dieterman, I.G., Mol, I.W., Kohler-Brands, L., Heymans, H.S., Mulder, C.J., 1997. The daily gluten intake in relatives of patients with coeliac disease compared with that of the general Dutch population. Eur. J. Gastroenterol. Hepatol. 9, 1097–1099.
Varney, J., Barrett, J., Scarlata, K., Catsos, P., Gibson, P.R., Muir, J.G., 2017. FODMAPs: food composition, defining cutoff values and international application. J. Gastroenterol. Hepatol. 32 (Suppl. 1), 53–61.
Vazquez-Roque, M.I., Camilleri, M., Smyrk, T., Murray, J.A., Marietta, E., O'Neill, J., Carlson, P., Lamsam, J., Janzow, D., Eckert, D., Burton, D., Zinsmeister, A.R., 2013. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Gastroenterology 144, 903–911.e3.
Verspreet, J., Hemdane, S., Dornez, E., Cuyvers, S., Delcour, J.A., Courtin, C.M., 2013. Maximizing the concentrations of wheat grain fructans in bread by exploring strategies to prevent their yeast (*Saccharomyces cerevisiae*)-mediated degradation. J. Agric. Food Chem. 61, 1397–1404.
Volta, U., Pinto-Sanchez, M.I., Boschetti, E., Caio, G., De Giorgio, R., Verdu, E.F., 2016. Dietary triggers in irritable bowel syndrome: is there a role for gluten? J. Neurogastroenterol. Motil. 22, 547–557.
Volta, U., Caio, G., Karunaratne, T.B., Alaedini, A., De Giorgio, R., 2017. Non-coeliac

gluten/wheat sensitivity: advances in knowledge and relevant questions. Expert Rev. Gastroenterol. Hepatol. 11, 9–18.
Wahnschaffe, U., Ullrich, R., Riecken, E.O., Schulzke, J.D., 2001. Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. Gastroenterology 121, 1329–1338.
Wahnschaffe, U., Schulzke, J.D., Zeitz, M., Ullrich, R., 2007. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Clin. Gastroenterol. Hepatol. 5, 844–850 (quiz 769).
Whelan, K., Martin, L.D., Staudacher, H.M., Lomer, M.C.E., 2018. The low FODMAP diet in the management of irritable bowel syndrome: an evidence-based review of FODMAP restriction, reintroduction and personalisation in clinical practice. J. Hum. Nutr. Diet. 31 (2), 239–255.
Zanini, B., Basche, R., Ferraresi, A., Ricci, C., Lanzarotto, F., Marullo, M., Villanacci, V., Hidalgo, A., Lanzini, A., 2015. Randomised clinical study: gluten challenge induces symptom recurrence in only a minority of patients who meet clinical criteria for non-coeliac gluten sensitivity. Aliment. Pharmacol. Ther. 42, 968–976.
Ziegler, J.U., Steiner, D., Longin, C.F.H., Würschum, T., Schweiggert, R.M., Carle, R., 2016. Wheat and the irritable bowel syndrome – FODMAP levels of modern and ancient species and their retention during bread making. J. Funct. Foods 25, 257–266.