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Review article: the aetiology, diagnosis, mechanisms and clinical evidence for food intolerance

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SUMMARY

Background
Food intolerance is non-immunological and is often associated with gastrointestinal symptoms.

Aim
To focus on food intolerance associated with gastrointestinal symptoms and critically appraise the literature in relation to aetiology, diagnosis, mechanisms and clinical evidence.

Methods
A search using the terms and variants of food intolerance, lactose, FODMAP, gluten, food chemicals within Pubmed, Embase and Scopus was carried out and restricted to human studies published in English. Additionally, references from relevant papers were hand searched for other appropriate studies.

Results
Food intolerance affects 15–20% of the population and may be due to pharmacological effects of food components, noncoeliac gluten sensitivity or enzyme and transport defects. There have been significant advances in understanding the scientific basis of gastrointestinal food intolerance due to short-chain fermentable carbohydrates (FODMAPs). The most helpful diagnostic test for food intolerance is food exclusion to achieve symptom improvement followed by gradual food reintroduction. A low FODMAP diet is effective, however, it affects the gastrointestinal microbiota and FODMAP reintroduction to tolerance is part of the management strategy.

Conclusions
There is increasing evidence for using a low FODMAP diet in the management of functional gastrointestinal symptoms where food intolerance is suspected. Exclusion diets should be used for as short a time as possible to induce symptom improvement, and should be followed by gradual food reintroduction to establish individual tolerance. This will increase dietary variety, ensure nutritional adequacy and minimise impact on the gastrointestinal microbiota.

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INTRODUCTION

Food intolerance is non-immunological and may occur in response to pharmacological effects of food or food components, noncoeliac gluten sensitivity or enzyme/transport defects. Food intolerance should not be confused with food hypersensitivity which is an umbrella term used to describe food intolerance and food allergy, the latter being defined as an adverse reaction to food whereby immunoglobulin E (IgE)-mediated or non-IgE-mediated immunological mechanisms have been demonstrated.[1]

Food intolerance is common in the modern world, and depending on data collection methods and definitions, it affects up to 15–20% of the population.[2] Even 20 years ago, 20% of the population reported food intolerance.[3] Most people with food intolerance report gastrointestinal symptoms and in patients with functional gastrointestinal disorders, the most common of which being irritable bowel syndrome (IBS), 50–84% perceive their symptoms are related to food intolerance.[4–6] The most commonly reported food intolerances leading to gastrointestinal symptoms are provided in Table 1.

This review will focus on food intolerance leading to gastrointestinal symptoms such as increased flatulence, abdominal pain, bloating or diarrhoea and will critically appraise the literature in relation to aetiology, diagnosis, mechanisms and clinical evidence. Extra-intestinal symptoms such as migraine, asthma, eczema, malaise will not be reviewed.

SEARCH STRATEGY

A search using the terms and variants of food intolerance, lactose, FODMAP, gluten, food chemicals within Pubmed, Embase and Scopus was carried out and restricted to human studies published in the English language. Additionally, references from relevant papers were hand searched for other appropriate studies.

AETIOLOGY

Pharmacology

There are a number of chemicals present in food with potential pharmacological activity and these include salicylates, vasoactive amines (e.g. histamine), glutamates (e.g. monosodium glutamate) and caffeine. The chemical reactions do not always induce gastrointestinal symptoms, but where they do, the mechanisms are not fully understood but may influence the gastrointestinal neuroendocrine system. These chemicals are widespread in the diet and their dietary sources and possible mechanisms are described in Table 2. Diets avoiding food chemicals are extremely difficult to undertake and limit a wide variety of foods with the potential to lead to multiple nutrient inadequacies. Furthermore, there is no robust clinical evidence that these diets are effective in the management of gastrointestinal symptoms.

Noncoeliac gluten sensitivity

Noncoeliac gluten sensitivity is a relatively new definition to describe gastrointestinal symptoms that occur in response to including gluten in the diet but in the absence of diagnostic features of coeliac disease or wheat allergy.[7, 8] The mechanisms by which gluten causes symptoms are not elucidated and dietary studies using gluten in double-blind placebo controlled food challenge have been inconsistent and unreliable to confirm gluten sensitivity. Noncoeliac gluten sensitivity is not fully understood and has been reviewed elsewhere.[9–11]

Enzyme/transport defects

Lactose is a disaccharide found in mammalian milk that is broken down into its constituent monosaccharides, glucose and galactose, in the brush border of the jejunum by a β-galactosidase enzyme lactase prior to absorption. Lactase is essential during the development of infants before weaning commences, following which,

Table 1 | Prevalence of common food intolerances in functional gastrointestinal disorders[6, 68, 79]

Food group	Food	Percentage of subjects reporting symptoms
Cereal products	Wheat bread	4.8–34.8
Vegetables	Cabbage	9.6–57
	Onion	8.9–56
	Peas/beans	21.4–46
Dairy products	Milk	4.4–41.7
Miscellaneous	Hot spices	25.9–45
	Fatty/deep fried	13.3–44
Drinks	Coffee	26.2–39

Table 2 | Dietary source of food chemicals and their proposed mechanisms for inducing gastrointestinal symptoms

Food chemical	Dietary sources	Proposed mechanism of gastrointestinal symptom provocation
Salicylates	Coffee, tea, green apples, banana, lemon, nectarine, plums, grapes, grapefruit, tomato, carrots, cucumber, peas, herbs and spices[83]	Stimulates mast cells to overproduce leukotriene metabolites[84] which in turn may lead to pro-inflammatory reactions and smooth muscle contraction[85]
Amines (e.g. histamine)	Wine, beer, ripe and mature cheese, cured and processed meat products, tinned fish[86]	Low amine oxidase activity in some individuals limits detoxification of dietary histamine and increased levels of histamine can increase smooth muscle contractions[87]
Glutamates	Tomato, cheese, stock cubes, yeast extract[88]	Unknown but exclusion of dietary additive excitotoxins (including MSG) in IBS resolved >30% of symptoms in 84% of patients[89]
Caffeine	Coffee, tea, chocolate, cola drinks, caffeine drinks	Stimulates central nervous system and increases gastric juice secretion and colonic motor activity possibly via gastrointestinal neuroendocrine hormones (e.g. cholecystokinin, exorphin, gastrin or motilin) but this is unknown[90]

there is a gradual down-regulation in lactase activity which varies depending on ethnicity.[12] Interestingly, a single gene codes for lactase and lactase persistence is an inherited autosomal dominant condition. It occurs frequently in European, South Asian and some African populations and the genetic changes for different populations date back to between 1200 and 23 200 years ago which from archaeological remains is a similar time when domestication of mammals for their milk is thought to have commenced. Evidence suggests that lactase persistence probably evolved as a co-evolutionary process involving both cultural and genetic changes.[13]

Lactase-nonpersistence occurs in approximately 65% of the adult population.[14, 15] It is distinct from congenital alactasia which is extremely rare and potentially fatal with approximately only 40 cases having been reported.[16] In the absence of lactase from birth it is characterised by faltering growth following exposure to mammalian milk.

Lactase-nonpersistence can be secondary and reversible and not due to genetics. It occurs when the jejunal brush border may be affected by gastrointestinal disease (e.g. coeliac disease, Crohn's disease, acute gastroenteritis), thus when the inflammation has resolved lactase production will recommence.

Lactase-nonpersistence results in unabsorbed lactose being present in the lower gastrointestinal tract which can produce two untoward effects. Firstly, the increased osmotic load can increase the bowel water content and secondly, lactose can be readily fermented by the colonic microbiota leading to increased gas production. Both of these effects can lead to symptoms of lactose intolerance in susceptible individuals.

The threshold to tolerance of dietary lactose is dependent on several factors relating to the quantity consumed, gut-transit time, presence of other dietary components within the gastrointestinal lumen, consistency, temperature, the amount of residual lactase expression and diversity of the gastrointestinal microbiota. Symptoms of lactose intolerance generally do not occur until there is less than 50% of lactase activity.[16] Indeed, most people with lactase-nonpersistence can tolerate small amounts of lactose in the diet when it is spread throughout the day[17] and, in total, up to 12–15 g/day.

Fructose is a monosaccharide that is naturally present in fruit and honey and is increasingly being used in the food industry, commonly as high fructose corn syrup.[18]

There is a limit to the absorptive capacity for fructose in the human gut which is determined by a number of different routes of facilitated transport. The GLUT-2 and GLUT-5 transporters are the ones that have been most widely researched; however, little is known about the distribution of these transporters.[19] In a ratio of 1:1, glucose and fructose are co-transported across the apical surface of the intestinal mucosa by GLUT-2 whereas GLUT-5 enables independent fructose absorption through carrier-mediated facilitative diffusion. Other transporters may be involved but either their distal location in the ileum (GLUT-7)[19] suggests it is unlikely to be of great

importance or human studies have not been carried out (GLUT-8).[20]

It has long been known that some fruit can give rise to gastrointestinal symptoms.[21] Free fructose, i.e. fructose in excess of glucose appears to have the strongest effect on whether fructose is malabsorbed. A dose of 50 g fructose was shown to be malabsorbed by 9 out of 17 healthy volunteers using hydrogen production on breath testing, however, when those nine subjects were given a dose of only 25 g fructose only one still demonstrated fructose malabsorption.[22] Furthermore, 25–50 g doses of fructose induce gastrointestinal symptoms in healthy subjects.[23, 24] When fructose is given in combination with glucose, e.g. as sucrose, the capacity for absorption is much improved,[21] however, there is an upper limit for the total fructose load that can be absorbed.

Fructans are short-chain carbohydrates based on linear or branched fructose polymers. Absorption is less than 5% in humans due to lacking enzymes to break down the glycosidic bonds,[25] thus, fructans are available for colonic fermentation by the gastrointestinal microbiota. Fructans include inulin (degree of polymerisation DP; 2–60), oligofructose (DP2–8) and fructo-oligosaccharides (DP < 10)[26] and occur naturally as storage carbohydrates in a variety of cereals (e.g. wheat) and vegetables (e.g. artichoke, garlic, leeks, onion) and are added to food for their prebiotic properties (e.g. fructo-oligosaccharides, inulin, oligofructose). Wheat contains approximately 1% of fructans by weight,[27, 28] however, it contributes over two-thirds of the dietary intake of inulin and oligofructose[29] due to the fact that it is eaten in such high quantities as a dietary staple.

Galacto-oligosaccharides are short-chain carbohydrates of galactose polymers with a glucose terminal end. They are not hydrolysed in the human GI tract due to the lack of an α-galactosidase enzyme so reach the colon intact available for colonic fermentation.[30] Galacto-oligosaccharides include raffinose and stachyose and common dietary sources are human milk, legumes and pulses, some grains, some nuts.[27, 31] It is well established that legumes and pulses increase intestinal gas production leading to gastrointestinal symptoms.[32]

Polyols include sorbitol, mannitol, xylitol and are collectively termed sugar alcohols. They are passively absorbed along the small intestine, the rate at which varies between individuals depending on the molecular size of the polyol, the intestinal pore size, the small intestinal transit time and presence of gastrointestinal disease. It is thought that mannitol is better absorbed than sorbitol, perhaps due to its higher water solubility increasing paracellular absorption and possibly also due to its hydroxyl position, but data are limited.[33] Polyols occur naturally in the diet in some fruit (apricots, peaches, cherries, apples, pears) and vegetables (mushrooms, cauliflower) but are also added as artificial sweeteners to food products (e.g. sugar-free chewing gum) and pharmaceuticals (sugar-free cough syrup). Polyols have been associated with having a laxative effect.[34, 35]

Short-chain fermentable carbohydrates (FODMAPs): Historically, all of the above carbohydrates have been known to induce gastrointestinal symptoms in isolation,[32, 34–36] or combinations of at least two, e.g. fructose-sorbitol[37–41] but have only recently been grouped together as short-chain fermentable carbohydrates or fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs). Although there are differences in the rationale for each type of FODMAP to reach the lower gastrointestinal tract, collectively they have been attributed to increasing functional gastrointestinal symptoms in susceptible individuals, e.g. IBS, and their dietary exclusion as a group has a greater magnitude on symptom improvement than each one in isolation.

DIAGNOSIS

Following a detailed medical history including dietary and lifestyle assessment, with a focus on potential food intolerance, patients with gastrointestinal symptoms will usually undergo clinical investigations in accordance with local/national guidelines. Investigations may include blood and faecal tests, endoscopy and/or radiological imaging to rule out any organic disease. In the absence of organic disease or food allergy, patients will often be diagnosed with a functional gastrointestinal disorder, e.g. IBS or functional dyspepsia. However, there are a limited number of tests that are clinically useful in the identification of specific food intolerance.

Food exclusion, symptom improvement and dietary challenge

The gold standard food intolerance test is food exclusion to achieve symptom improvement followed by gradual food reintroduction and subsequent symptom induction to identify tolerance.[42–44] The gold standard is loosely based on that used in food allergy, however, a reduction, rather than complete exclusion, in the intake of the food or foods in question may be sufficient to induce symptom improvement.

Following a detailed dietary assessment it may be clear that specific dietary components are responsible for gastrointestinal symptoms but more often than not, it is not

that straightforward and an exclusion diet avoiding several dietary components will be required. The most successful of these exclusion diets is a low FODMAP diet (see 'Clinical evidence' section below). Generally once an exclusion diet is implemented, symptoms should resolve within 3–4 weeks. A dietitian experienced in food intolerance is essential to undertake such dietary restrictions. Following this highly restrictive phase of an exclusion diet, excluded foods should be reintroduced under expert guidance using a food challenge process to determine which specific foods are responsible for symptom induction. This will identify the patient's individual tolerance threshold to these foods or dietary components. Many patients who achieve symptom improvement are not keen to reintroduce foods that may trigger symptoms but this is a core component of the diagnostic test to ensure that foods are not being excluded unnecessarily for long periods of time which would have the potential of limiting nutritional adequacy, affecting the gastrointestinal microbial ecosystem and lowering quality of life in terms of social activities with reduced dietary choice.

Breath tests

Hydrogen and/or methane breath testing are useful, non-invasive measurements to assess carbohydrate malabsorption in the gastrointestinal tract. Hydrogen is not produced by humans, so the theory is that any breath hydrogen in expired air is only from fermentation products produced by the gastrointestinal microbiota. For carbohydrate malabsorption, a substrate (typically lactose or fructose) is metabolised by the gastrointestinal microbiota to produce hydrogen which is rapidly absorbed into the bloodstream and then expired via the lungs. Some people have microbiota that appear to produce little or no hydrogen, instead methanogens rapidly utilise hydrogen and carbon dioxide to produce methane which is also measured in expired air. The clinical relevance of whether the gastrointestinal microbiota produce hydrogen and/or methane and at what level is currently unclear and reviewed elsewhere.[45–47]

Lactulose is a synthetic disaccharide of fructose and galactose and is non-absorbable in the gastrointestinal tract and, consequently, is always malabsorbed and available for fermentation by the colonic microbiota. Therefore, a lactulose breath test can be a useful positive control prior to assessment of dietary carbohydrate malabsorption to detect whether a subject produces hydrogen or methane on breath testing within the timescale of a standard breath test protocol (usually 3 h).[48] The lactulose breath test has been inappropriately used in an attempt to identify distal SIBO in patients with IBS-like symptoms. In most of these cases a rapid oro-caecal transit time has probably been misinterpreted as distal SIBO.[46] This has been demonstrated in a study of 25 patients with IBS using serial measurements of breath hydrogen and oro-caecal scintigraphy following ingestion of a test meal containing lactulose and ^{99m}Tc. The study showed that the ^{99m}Tc had already reached the caecum in 88% of patients before breath hydrogen levels reached the threshold for an abnormal result positive for SIBO.[49]

Breath testing protocols for dietary carbohydrate malabsorption vary considerably (Table 3) and can have a profound impact on the results obtained with potential false positives and negatives. Strict breath test protocols generally only permit testing where no antibiotics, colonoscopy preparation, laxatives or probiotics have been allowed in the previous 14 days although there is no universal agreement.[48–54] Twenty-four to 48 h prior to each breath test, a diet low in fermentable carbohydrates should be adhered to, although studies vary in the finer details of the dietary restrictions. An overnight fast prior to commencement of the test is advised. Some protocols, but not all, stipulate teeth must be brushed and an antiseptic mouthwash must be used prior to testing to ensure that oropharyngeal fermentation is not contributing to measurements..[49–54] Baseline measurements for hydrogen and/or methane should be taken prior to testing. The test carbohydrate is consumed as a bolus of 25–50 g and made up with water. Whether a lower amount is more appropriate in paediatrics has not been assessed. The amount of carbohydrate should be at a level considered to be sufficient but not excessive to lead to hydrogen and/or methane production following fermentation by the gastrointestinal microbiota. Protocols generally indicate that a positive result is when there is an increase of at least 10–20 ppm of hydrogen or methane above baseline on two consecutive breath measurements 15–30 min apart for 3–5 h. One study has demonstrated that when only 3 h of measurements are collected instead of 5 h, 16% of positive results for fructose and 23% of positive results for lactose are reported as negative.[54] Some studies indicate that smoking and vigorous exercise should be prohibited during the study to limit confounding variables.[50–54]

In terms of the clinical usefulness of breath tests, when used for identification of lactose and fructose malabsorption, they have variable correlation with intolerance of these carbohydrates. Wilder-Smith *et al.* report lactose and fructose malabsorption in 32% and 45% and intolerance in 51% and 60% of patients with functional

Table 3 | Differing protocols for dietary carbohydrate breath testing

Reference	Lactose dose	Fructose dose	Hydrogen increase	Methane increase	Timing of gas measurements
Nucera 2005[53]	20 g	25 g	>20 ppm over baseline	N/A	Every 30 min for 4 h
Gupta 2007[91]	50 g		>20 ppm over baseline twice in succession	N/A	Every 15 min for 4 h
Babu 2010[50]	25 g		>20 ppm over baseline twice in succession	N/A	Every 15 min for 3 h
Bate 2010[48]	50 g	35 g	>10 ppm over baseline twice in succession	>20 ppm over baseline twice in succession	Every 15 min for 2 h
de Roest 2013[72,75]	50 g	35 g	>10 ppm over baseline twice in succession	>20 ppm over baseline twice in succession	Every 15 min for 2 h
Wilder-Smith 2013[54]	50 g	35 g	>20 ppm over baseline twice in succession	>10 ppm over baseline twice in succession	Hourly for 5 h
Melchior 2014[52]		25 g	>20 ppm over baseline twice in succession	>20 ppm over baseline twice in succession	Every 30 min for 5 h

N/A measurement not carried out.

gastrointestinal disorders respectively.[54] For patients who malabsorb fructose, only 40% showed symptoms of intolerance and for those who malabsorb lactose, intolerance was identified in 28%. Melchior *et al.* report fructose malabsorption in 22% and intolerance in 25% of IBS patients.[52] For patients who malabsorbed fructose only 35% showed symptoms of intolerance during the test. Breath testing for sorbitol and mannitol has not been shown to be useful and there is little correlation between malabsorption and intolerance of these carbohydrates.[33] Breath testing for fructan or galacto-oligosaccharide malabsorption would not be useful as almost all fructans and galacto-oligosaccharides will be available for fermentation.

Hydrogen and methane breath testing can be useful in the diagnosis of lactose and fructose malabsorption. However, the results must not be over-interpreted particularly as these carbohydrates have osmotic effects in the gastrointestinal tract as outlined below (see Mechanisms of action). Furthermore, carbohydrate breath tests only measure the amount of the microbial fermentation products hydrogen and/or methane which exceeds uptake by the gastrointestinal mucosa. There appears to be huge individual inter- and intra-variability in the amount and duration of gas production, however, this does not correlate to symptom profile or severity. Methane producers tend to have up to 75% less volume of gas production but how this relates to symptom profile is not clearly understood and it has been proposed that methane producers are associated with constipation,[55, 56] however, this has not been confirmed in more recent studies.[54]

Confocal laser endomicroscopy (CLE)

Confocal laser endomicroscopy (CLE) is a novel endoscopic imaging technique that facilitates visualisation of changes in the gastrointestinal mucosa. A recent study in 36 patents with IBS and suspected food intolerance has demonstrated that CLE revealed a real-time response to food antigens in 61% of patients.[57] Diluted food antigens were directly administered to the duodenal mucosa via the endoscope and within 5 min of exposure, there were significant increases in intraepithelial lymphocytes (IEL), epithelial leaks formed and intervillous spaces widened compared to baseline. Baseline IEL were higher in patients who had a positive response to food antigens when compared to patients with a negative response. This is potentially an exciting advancement into not only developing a useful diagnostic test for food intolerance but also for understanding the mechanisms underlying gastrointestinal symptom development. Further studies are warranted to validate the methodology and determine whether it may have a role in clinical practice.

Unvalidated tests

There are a number of commercially available unvalidated tests that patients often undertake due to their degree of desperation to find out what foods might be responsible for their symptoms (see Table 4). These patients are a particularly vulnerable group and such investigations should not be encouraged as there is a lack of evidence to support their use, they can be extremely costly and most importantly often lead patients to inappropriately over-restrict their diet which can limit nutritional adequacy and lead to undernutrition, and detrimentally affect the social aspects of their quality of life.

In addition to the unvalidated tests mentioned in Table 4, there are a growing number of other commercially available tests to patients from alternative practitioners and often via the internet. They may be undertaken by patients who are keen to explore the cause of their gastrointestinal symptoms. These unvalidated tests include faecal microbial analysis, faecal short-chain fatty acids, intestinal permeability and salivary IgA and although they are not directly aimed to identify food intolerance specifically, clinicians should be aware of their existence. The results of such tests may be inconsistent and not provide any interpretable data for use in clinical practice. They require further research to determine their validity in clinical practice and have been reviewed elsewhere.[58]

MECHANISMS

Historically, there has been little mechanistic evidence to support the role of food or food components in the generation of gastrointestinal symptoms. However, more recently, mechanistic studies have demonstrated how FODMAPs contribute to gastrointestinal symptom

Table 4 | Unvalidated tests with no scientific evidence to support their use in the diagnosis of food intolerance

Test	Description
Allergen-specific IgG or IgG4	Serological testing for IgG or IgG4 against several foods can be performed by enzyme-linked immunosorbent assays and radioallergosorbent assays. The presence of IgG or IgG4 against foods represents exposure to that particular food and indicates immunological tolerance.[92] Therefore, increases in IgG or IgG4 concentration against food or food components are common and clinically irrelevant. However, these commercially available tests are widely available and may lead to inappropriate dietary over-restriction.
Cytotoxic assays	Cytotoxic food testing involves the addition of whole blood to a food extract and is based on the assumption that leucocytes reacting to food antigen exposure can predict intolerance to food. However, the test is not reproducible and positive cytotoxic effects are frequently obtained with foods that produce no clinical symptoms while negative results are obtained with foods that do produce clinical symptoms.[93, 94]
Electrodermal test	A galvanometer is used to measure skin conductivity. The patient holds a negative electrode in one hand and a positive electrode is placed on specific acupressure points. Food extracts in sealed glass vials are put in contact with an aluminium plate within the circuit. Food intolerance is diagnosed when there is a drop in electrical conductivity of the skin. No studies have demonstrated its usefulness to detect food intolerance.[94]
Hair analysis	Bio-resonance analysis of hair based on the belief that anything living emits electromagnetic waves that can be measured as good or bad. However, there is no explanation of how hair analysis might detect food intolerance.[95]
Iridology	Iridology involves the analysis of the iris assuming that all organs are represented in the iris and any irregularities in pigmentation represent dysfunction. There is no scientific evidence to support the use of iridology in the diagnosis of food intolerance.[96]
Kinesiology	The patient holds a sealed glass bottle that contains a test food or food extract while an investigator estimates muscle strength in the other arm. A decrease in muscle power while the food is held is considered to indicate food intolerance. Another method of kinesiology called DRIA measures a change in muscle strength in response to a food extract being placed under the tongue.[93] These tests have no scientific support and have not been validated.
Pulse test	This may be used in combination with provocation-neutralisation or independently. A 16 beats per min change in the pulse rate from baseline indicates food intolerance following sublingual or intradermal exposure to the specific food extract. There is no clinical evidence to support the use of this test.[94]
Sublingual or intradermal provocation-neutralisation	Aqueous food extract is placed under the tongue or intradermally and observed for symptoms to occur (usually 10 min). If symptoms occur, a neutralising dose (diluted dose of the same food extract) is given in the same way. Symptoms are expected to disappear in about the same time period. Adverse outcomes are rare but these tests have failed to show any usefulness in food intolerance.[94]

generation in susceptible individuals. They can increase small intestinal water content due to being osmotically active in the gastrointestinal lumen and their presence in the colon can increase gas production due to fermentation by the gastrointestinal microbiota.

In a single-blind cross-over study of twelve patients with an ileostomy, either a high FODMAP diet or a low FODMAP diet was provided for 4 days with a washout period of at least 10 days in between.[59] A high FODMAP diet significantly increased the ileal effluent water content by 20%, dry weight by 24% and total output by 22% when compared to a low FODMAP diet and patients perceived the ileostomy output consistency as thicker when on a low FODMAP diet. An ileostomy model is well established for studying the absorption of dietary components.[60, 61] However, it can be argued that an ileostomy is not ideal to measure how FODMAPs may affect an intact gastrointestinal tract due to adaptation of the remaining ileum to prevent chronic dehydration.

Magnetic resonance imaging (MRI) has been used in healthy volunteers to measure small intestinal water content and small intestinal and colonic gaseous distension. One study involved 11 subjects ingesting a solution containing 17.5 g mannitol or an equal amount of glucose. The mannitol rapidly increased small intestinal water content by up to 10 fold in comparison to the glucose which resulted in net absorption.[62] A second study in 16 subjects, which also measured breath hydrogen production, used a four arm single-blind cross-over design. The four test solutions were 40 g fructose, 40 g glucose, a mixture of 40 g glucose and 40 g fructose, 40 g fructans (inulin). The study showed that fructose increased small intestinal water content whereas glucose or fructans did not.[63] The addition of glucose to fructose resulted in less small intestinal water than fructose alone but not to the level of glucose confirming that there is threshold to how much glucose can improve fructose absorption. Fructose and fructans distended the colon with gas and increased hydrogen production. This was more pronounced with fructans rather than fructose and along with the earlier study[62] supports the differing effects of fructose, mannitol and fructans related to DP and molecular structure.[64] The healthy volunteers in these studies did not develop gastrointestinal symptoms despite the differing effects of the different carbohydrates. A separate single-blind cross-over study comparing 2 days of a high FODMAP diet (50 g/day) with 2 days of a low FODMAP diet (9 g/day) in 15 healthy volunteers and 15 patients with IBS reported patients with IBS, but not healthy volunteers, had increased gastrointestinal symptoms while on the high FODMAP diet.[65] This study also demonstrated that there is a higher production of breath hydrogen following a high FODMAP diet versus a low FODMAP diet.

Visceral hypersensitivity and rectal sensitivity have been directly associated with increased gas production following 20 g lactose ingestion in patients with IBS and lactase-nonpersistence ($n = 277$).[66] Significantly less healthy volunteers with lactose-nonpersistence ($n = 64$) developed gastrointestinal symptoms following 20 g lactose and had significantly higher thresholds for visceral hypersensitivity and rectal sensitivity.

Gastrointestinal motility is also affected by FODMAPs. A double-blind cross-over study of 11 healthy volunteers used scintigraphy to measure orocaecal transit time and has shown that a mixture of 25 g fructose and 5 g sorbitol increased gastrointestinal motility whereas 30 g glucose had no effect. ^{99m}Tc confirmed that this difference was due to reduced small intestinal transit time.[38] Whether this finding explains another role for FODMAPs in susceptible individuals remains to be confirmed. Future studies in patients with functional gastrointestinal disorders are warranted to better understand how symptoms may be generated in response to individual FODMAPs.

CLINICAL EVIDENCE

There has been much interest over the years regarding food intolerance and what dietary triggers are responsible. Several studies have reported a range of foods and food components as being perceived to induce gastrointestinal symptoms in patients with IBS.[4–6, 67, 68] However, there is little evidence to support individual food exclusion with substantial improvement in symptoms. Individual and mixtures of two FODMAPs have been reported to provoke gastrointestinal symptoms,[34–41, 69–71] however, excluding these individually does not consistently lead to substantial symptom improvement. More recently, understanding some of the mechanisms by which FODMAPs exert their effects in the gastrointestinal tract have led to much interest in whether collectively (i) they are the dietary triggers responsible for so many patients with gastrointestinal symptoms and (ii) their exclusion leads to gastrointestinal symptom improvement. Certainly, the evidence base for uncontrolled and more recently controlled studies on the efficacy of a low FODMAP diet is increasing (Table 5).[37, 54, 59, 65, 72–76, 78, 80, 81]

Table 5 | Clinical studies assessing alterations in the dietary intake of FODMAPs

Reference	Design	Subjects	Intervention	Scoring system	Findings
Shepherd 2006[72]	Retrospective, uncontrolled	IBS and fructose malabsorption (n = 62)	Previously educated (median 14 months ago) on restriction of fructose and fructans	Telephone questionnaire using unvalidated symptom score (−10 to +10)	74% of all patients responded positively to all symptoms
Shepherd 2008[37]	Randomised placebo controlled re-challenge	IBS and fructose malabsorption who had responded to a low FODMAP diet (n = 25)	Low FODMAP diet and washout ≥10 days. Doses for 3 days of fructose: 14 g, 28 g or 50 g, fructans 7 g, 14 g, 19 g or mixture fructose-fructans or glucose 7 g, 14 g, 20 g	Adequate relief question	For fructose 70%, for fructans 77%, for fructose-fructan mix 79% and glucose 14% of patients reported symptoms were not adequately controlled
Gearry 2009[74]	Retrospective uncontrolled	Inactive Crohn's disease (n = 52) and ulcerative colitis (n = 20) and functional gastrointestinal symptoms	Previously educated (median 17 months ago) on low FODAMP diet	Telephone questionnaire using unvalidated symptom score (−10 to +10)	56% of all patients responded positively to overall symptoms
Ong 2010[65]	Randomised, cross-over, single-blinded	Patients with IBS (n = 15) and healthy subjects (n = 15)	Feeding study of 4 days of low or high FODMAP diet	Unvalidated scoring system (0 [no symptom] to 3 [severe])	High FODMAP diet significantly induced gastrointestinal symptoms in patients with IBS but only flatulence in healthy volunteers
Staudacher 2011[78]	Nonrandomised	Patients with IBS (n = 82)	Low FODMAP (n = 43) or standard diet (n = 39) for 2–6 months	Unvalidated scoring system (7 point scale from substantially worse to substantially improved)	76% reporting satisfaction with symptom response with low FODMAP diet versus 54% with standard advice
Staudacher 2012[81]	Randomised controlled trial	Patients with IBS (n = 41)	Low FODMAP (n = 22) or habitual diet (n = 19) for 4 weeks	Adequate relief question	68% reported adequate symptom relief with low FODMAP diet vs. 23% on habitual diet.
Ostgaard 2012[73]	Retrospective case-control	Patients with IBS (n = 79) and healthy subjects (n = 35)	IBS split into guided dietary advice including low FODMAP diet (n = 43) and unguided (n = 36)	Birmingham IBS symptom score	65% completed. The guided group reported significant improvement in pain versus unguided group, but not total symptoms, diarrhoea or constipation

Table 5 | (Continued)

Reference	Design	Subjects	Intervention	Scoring system	Findings
De Roest 2013[75]	Prospective uncontrolled	Patients with IBS (n = 90)	Low FODMAP diet for mean 16 months	GI symptom rating scale	72% were satisfied with their symptom improvement
Mazzawi 2013[76]	Prospective uncontrolled	Patients with IBS (n = 46)	Low FODMAP (n = 17)	Birmingham IBS symptom score	Improvement in total symptoms, pain and diarrhoea
Wilder-Smith 2013[54]	Prospective uncontrolled	Patients with a functional gastrointestinal disorder (n = 312)	Low FODMAP diet for 6–8 weeks	Unvalidated symptom score (1–10)	76% completed. Adequate symptom relief in 93% and 96% of patients with fructose or lactose malabsorption and concurrent intolerance respectively
Halmos 2014[80]	Randomised controlled, single-blinded cross-over	Patients with IBS (n = 30) and healthy subjects (n = 8)	Feeding study of low FODMAP diet versus typical Australian diet	Unvalidated symptom score (100 mm VAS)	83% completed. Patients with IBS had significantly lower overall symptoms on a low FODMAP diet versus typical Australian diet

A double-blind quadruple challenge cross-over feeding study was carried out to confirm that FODMAPs are responsible for symptom generation. Patients who had previously had symptom improvement following low FODMAP dietary advice were provided with a low FODMAP diet for the duration of the study. Symptoms were assessed and patients were challenged with increasing doses of fructose and/or fructans and glucose as a control. The challenges showed that fructose and/or fructans significantly induced overall and individual symptoms (i.e. bloating, abdominal pain and flatulence) whereas glucose alone did not. Furthermore, a dose response to fructose or fructans and an additive effect of fructose with fructans was demonstrated with increasing symptoms at higher doses.[37]

As FODMAPs may be responsible for symptom generation, there has been increasing interest in whether their exclusion can lead to symptom improvement. Three retrospective studies have assessed the clinical effectiveness of a low FODMAP diet. The first was in patients with fructose malabsorption who had adhered to a low FODMAP diet and showed that 85% had improvement in all IBS symptoms.[72] In another study, patients with IBS who had previously been advised on a low FODMAP diet reported significant improvement in abdominal pain but not other symptoms when compared to patients who had received no dietary advice.[73] A third study, in patients with inactive inflammatory bowel disease and functional gastrointestinal symptoms, showed that 56% of patients reported overall symptom improvement after having followed a low FODMAP diet.[74] Retrospective studies are open to bias and do not provide sufficient strength to change clinical practice. Despite this, curiosity was growing and three prospective studies assessed a low FODMAP diet in patients with IBS and showed satisfaction with overall symptoms, pain, bloating and quality of life,[54, 75, 76] however, without a control group it is difficult to apply these to clinical practice. A nonrandomised trial compared symptoms at follow-up in patients with IBS who had been treated with a low FODMAP diet or as the control, standard dietary advice based on national UK guidelines.[77] Seventy-six per cent of patients who had been given low FODMAP advice had an improvement in overall symptoms compared to 54% in the standard dietary advice group.[78] Limitations of this study were that it was not randomised and only recorded symptoms at follow-up.

Three randomised controlled trials (RCTs) have assessed a low FODMAP diet in patients with IBS. The first was a cross-over feeding study and showed that

symptoms were much lower on a low FODMAP diet compared to a high FODMAP diet but the diets were only for 4 days each.[65]Another feeding study with a cross-over design compared a low FODMAP diet with a typical Australian diet for 21 days. It showed that overall symptoms, abdominal pain, bloating and flatulence were all significantly lower following a low FODMAP diet when compared to a typical Australian diet.[80] Although feeding studies enable better control of dietary intake, they do not reflect normal every day challenges faced when choosing food on a restrictive diet. The final RCT to date compared 4 weeks of a low FODMAP diet with a habitual diet and showed that symptoms were adequately controlled in 68% of patients following a low FODMAP diet compared to only 23% in the control group.[81] However, one criticism of this study design was that the low FODMAP group were not blinded to the treatment. Control diets in RCTs are extremely difficult to design due to other dietary components being potential confounding factors. The ideal control would be a sham diet that is similar to the treatment diet from a nutritional perspective and in the number of food changes without restricting the dietary components of interest in the active treatment arm. In addition, reporting on the success of blinding to treatment options should be provided and, if positive, it will add strength to the study.

Overall, the low FODMAP diet provides symptom improvement in approximately 70% of patients with IBS and the number needed to treat is four[97] although further evidence is required to confirm this due to different outcome measures being used in so many differing study designs. However, some studies reported here have used a binary outcome measure or the IBS symptom severity scale that are recommended for use as outcome measures in studies of IBS treatments.[98]

Safety

The evidence for using a low FODMAP diet to alleviate gastrointestinal symptoms is stacking up, however, currently there is no long term safety data. Altering the dietary intake of FODMAPs does alter the gastrointestinal microbiota in the short term[82] and a significant decrease in the concentration of luminal bifidobacteria after 4 weeks of a low FODMAP diet has been reported.[81] However, whether this change has any long term implications is unknown.

A low FODMAP diet restricts a wide variety of foods from different food groups (cereals, fruit and vegetables, milk and milk products). Alternative suitable foods are a key component of patient education and even with dietetic advice, nutrient intakes, calcium in particular, can be compromised on a low FODMAP diet.[81]

Practical application

In clinical practice, patients with food intolerance should be advised to avoid dietary triggers for as short a time as possible to induce symptom improvement, usually 3–4 weeks. At the same time, patients should be given information on suitable alternative foods with a similar nutritional profile to maintain nutritional adequacy during dietary exclusion. This period should be followed by gradual food reintroduction to individual tolerance to increase dietary variety, ensure nutritional adequacy and have minimal impact on the gastrointestinal microbiota.[44]

CONCLUSION

For many years, food intolerance has been associated with gastrointestinal symptoms. It is only in recent years that there have been sufficient advances in understanding the scientific basis of why certain foods or food components are implicated. Food exclusion to achieve symptom improvement followed by gradual food reintroduction is still the best diagnostic test. There are other tests available, some potentially useful (e.g. breath tests), but many are unvalidated and costly.

Recent mechanistic and effectiveness evidence clearly supports using a low FODMAP diet in clinical practice. However, changes to diet clearly have a dramatic effect on the gastrointestinal ecosystem and it is unknown what the long term removal of specific foods or food components may have. Furthermore, nutritional adequacy may be reduced. Thus, exclusion of potential dietary triggers should be for as short a period as necessary to achieve symptom improvement, followed by gradual food reintroduction to individual tolerance.

AUTHORSHIP

Guarantor of the article: MCE Lomer.
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