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**TITLE PAGE**

**Title:** Postprandial symptoms in disorders of gut-brain interaction and their potential as a treatment target.

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**Abbreviations:** CLE confocal laser endomicroscopy

CRH corticotrophin-releasing hormone

DGBI disorder of gut-brain interaction

EoE eosinophilic oesophagitis

EPS epigastric pain syndrome

FD functional dyspepsia

FBD functional bowel disorder

FODMAP fermentable oligo-, di-, and monosaccharides, and polyols

H1RA histamine-1-receptor antagonist

H2RA histamine-2-receptor antagonist

HPA hypothalamic-pituitary-adrenal

IBS irritable bowel syndrome

IBS-D irritable bowel syndrome with diarrhoea

IL interleukin

PDS postprandial distress syndrome

PPI proton pump inhibitor

RCT randomised controlled trial

TNF-α tumour necrosis factor-α

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**ABSTRACT**

Postprandial, or meal-related symptoms, such as abdominal pain, early satiation, fullness, or bloating, are often reported by patients with disorders of gut-brain interaction, including functional dyspepsia (FD) or irritable bowel syndrome (IBS). We propose that postprandial symptoms arise via a distinct pathophysiological process. A physiological or psychological insult, for example acute enteric infection, leads to loss of tolerance to a previously tolerated oral food antigen. This enables interaction of both the microbiota and the food antigen itself with the immune system, causing a localised immunological response, with activation of eosinophils and mast cells, and release of inflammatory mediators, including histamine and cytokines. These have more widespread systemic effects, including triggering nociceptive nerves and altering mood. Dietary interventions, including a diet low in fermentable oligo-, di-, monosaccharides, and polyols, elimination of potential food antigens or gluten, IgG food sensitivity diets, or salicylate restriction may benefit some patients with IBS or FD. This could be because restriction of these foods or dietary components modulates this pathophysiological process. Similarly, drugs including proton pump inhibitors, histamine-receptor antagonists, mast cell stabilisers, or even tricyclic or tetracyclic antidepressants, which have anti-histaminergic actions, all of which are potential treatments for FD and IBS, act on one or more of these mechanisms. It seems unlikely that food antigens driving intestinal immune activation is the entire explanation for postprandial symptoms in FD and IBS. In others, fermentation of intestinal carbohydrates, with gas release altering reflex responses, adverse reactions to food chemicals, central mechanisms, or nocebo effects may dominate. However, if the concept that postprandial symptoms arise from food antigens driving an immune response in the gastrointestinal tract in a subset of patients is correct, it is paradigm-shifting, because if choice of treatment were based on one of more of these therapeutic targets, patient outcomes may be improved.

**INTRODUCTION**

There are 33 adult disorders of gut-brain interaction (DGBI), affecting up to 40% of people worldwide.[1] Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are two of the most prevalent, affecting between 5% and 10% of the population,[1] depending on criteria used to define their presence.[2, 3] DGBI are chronic, with a relapsing and remitting natural history.[4, 5] They incur a burden on patients, healthcare systems, and society. Symptoms in DGBI impact on quality of life to the same degree as other chronic diseases, including inflammatory bowel disease, diabetes mellitus, or chronic obstructive pulmonary disease.[6-8] DGBI represent a substantial cost to health services due to investigations performed to reach a diagnosis, consultations, and prescribed drugs.[9, 10] They also impact on activities of daily living, with high rates of absenteeism, presenteeism, and impairment in social and leisure activities.[11, 12]

The cause of DGBI is incompletely understood.[13, 14] Although once considered to be functional gastrointestinal disorders, these were reframed as DGBI in 2016.[15] This is not only because the term “functional” is viewed as non-specific and questioning the legitimacy of such conditions,[16] leading to stigmatisation,[17, 18] but also because there is increased understanding DGBI arise, in part, due to gut-brain axis dysregulation. In fact, there is emerging evidence that the pathophysiology of DGBI has an organic basis in some individuals. In this review, we consider the role of postprandial, or meal-related, symptoms in DGBI as being both generated by a distinct pathophysiological process, and hence indicative of an underlying organic cause, and a potential treatment target in a subset of patients. Although perhaps controversial, this fits within the concept of a dysregulated brain-gut axis, proposed to be involved in DGBI.[19]

**EPIDEMIOLOGY OF POSTPRANDIAL SYMPTOMS IN DGBI**

In the Rome Foundation Global Epidemiology Study, among 54,127 participants, 11% reported abdominal pain frequently associated with ingestion of a meal in the prior 3 months.[20] A diagnosis of any DGBI was more common in these individuals, and presence of meal-related abdominal pain was associated with higher rates of psychological symptoms and reduced quality of life. Likelihood of consultation with a doctor increased with higher frequency of meal-related abdominal pain.

Postprandial symptoms are, therefore, common in DGBI, often peaking within 1 hour of meal ingestion (Figures 1a and 1b). In FD, meal-related symptoms are incorporated into the Rome diagnostic criteria for postprandial distress syndrome (PDS).[21] First described as part of the Rome III process,[22] PDS requires presence of either early satiation during a meal or bothersome postprandial fullness following a normal-sized meal, with the other subtype, epigastric pain syndrome (EPS), consisting of epigastric pain or burning. However, using the Rome III criteria for FD, there is considerable overlap between the two, particularly in referral populations.[23] The recognition that epigastric pain or burning are also often meal-related in Rome IV FD (Figure 1a),[24, 25] and incorporating their presence into the definition of PDS,[26] has led to a substantially higher proportion of people with FD meeting criteria for PDS, rather than EPS,[1, 3] and less overlap.[27] Therefore, according to Rome IV criteria, more than 60% of individuals with FD report postprandial or meal-related symptoms,[3] which are associated with higher rates of depression and reduced quality of life.[28, 29] Despite the high prevalence of meal-related symptoms in FD, any association with physiological parameters is modest. Gastric emptying is delayed in up to one-third of patients,[30] but symptoms do not correlate with this.[31] Impaired gastric accommodation may also be associated with postprandial symptoms, but only in a subset of patients.[32]

Meal-related symptoms are also common in patients with functional bowel disorders (FBD),[33] although more often in IBS than functional diarrhoea or functional constipation.[34] In one study, the need to defaecate after a meal was reported by one-in-five patients with a FBD.[35] Postprandial symptoms occurred in up to 25% of patients with IBS, irrespective of subtype.[34] Symptoms included abdominal pain or discomfort, fullness, gas, and bloating (Figure 1b),[36] with abdominal pain present in 45% of patients with IBS in another study.[37] These postprandial symptoms are associated with depression, somatoform symptom-reporting, and reduced quality of life.[38, 39] However, similar to FD, correlation between these symptoms and physiological measures, such as gastrointestinal transit or visceral hypersensitivity, is inconsistent.[40, 41] Unlike FD, meal-related symptoms are not part of current diagnostic criteria for any FBD.[42]

**PATHOPHYSIOLOGY OF POSTPRANDIAL SYMPTOMS IN DGBI**

The epidemiological and clinical evidence above implicates perturbations of the small intestine, and not the colon, in the pathogenesis of FD and IBS in some individuals, as symptoms often occur shortly after eating in a major subgroup and, arguably, in most of these cases there is insufficient time for food contents to reach the colon to explain symptom induction.[25, 36] Further, there is emerging evidence specific foods play a direct role in symptom induction through short-lived immune activation. Other evidence suggests pain-related regions of the brain are activated differentially in IBS in response to certain food components (e.g., fructan) supporting gut-brain interactions in the pathogenesis.[43]

**Small Intestinal Immune Activation and Inflammation**

Multiple studies have identified intestinal immune activation in FD and IBS.[44] Several cytokines were elevated in blood supernatants from patients with IBS, for example, compared with controls, including interleukin (IL)-1β, IL-6, IL-10 and tumour necrosis factor-α (TNF-α), and induced mechanical hypersensitivity in colonic afferents.[45] Immune activation is also increased in the small intestine in FD and IBS, with a significant increase in small intestinal gut homing CD4+α4+ β7+CCR9+ T- cells compared with healthy controls.[46, 47] These homing T-cells develop in response to specific small intestinal luminal antigens and are also found in Crohn’s disease, further implicating underlying low-grade small intestinal inflammation in FD and IBS.[48] One of the mysteries surrounding DGBI is the prominence of extra-intestinal symptoms including fatigue, generalised pain (e.g., headache, backache, or myalgia), and anxiety. Although these have often been attributed to central mechanisms, intestinal immune activation from low-grade inflammation with a cytokine response (e.g., via increased TNF-α) is a plausible alternative explanation.[46, 49, 50]

In FD, duodenal eosinophilia has been observed. The first case-control study to document this evaluated a randomly selected community sample, among whom 16% had FD, as confirmed by a structurally normal upper endoscopy. Individuals with FD were compared with healthy controls from the same population who also had a structurally normal endoscopy.[51] The study identified eosinophil activation in FD, as shown by increased eosinophil degranulation. Subsequent studies have confirmed these observations, including a meta-analysis of 22 case-control studies.[52, 53] Symptom severity is associated with increased duodenal eosinophil counts in FD and, when eosinophil counts are reduced by proton pump inhibitor (PPI) treatment, this correlates with symptom improvement.[53] In IBS, in the fasting state, eosinophil counts are only variably elevated and this may be more likely in IBS and FD overlap.[54, 55] In IBS and FD, mast cells are also variably increased in the duodenum.[52, 54, 55] Although increased duodenal permeability has been observed in IBS and FD, it is unclear if this is a primary mechanism of disease or secondary to intestinal inflammation.[53, 56]

However, endoscopy is undertaken while the patient is fasting yet, by definition, postprandial symptoms occur after meals and, therefore, these studies may underestimate the prevalence of pathologic findings. In addition, duodenal biopsies are not routinely taken in FD or IBS and eosinophils are not counted in a standardised way; hence, acute inflammation may be underdiagnosed.

**Atopy and Food Allergy**

Indirect evidence also supports immune activation occurring in DGBI. The prevalence of asthma, allergic rhinitis, and other atopic conditions is higher in adults with DGBI compared with individuals without DGBI.[57] Moreover, atopic disease is associated with an increased risk of food allergy in childhood; atopic dermatitis often presents with, and can be the first manifestation of, non-IgE-mediated food allergy.[58] There is an established link between food allergy and future gastrointestinal dysfunction. Cow’s milk protein allergy in early life is associated with higher likelihood of recurrent abdominal pain or constipation in later childhood.[59] The risk of abdominal pain or IBS in childhood increases with increasing numbers of allergy-related diseases.[60, 61] The 97% recovery rate from childhood cow’s milk allergy suggests some adults have underlying IgE-mediated or non-IgE-mediated allergy predisposing to an atopic gastrointestinal immune response to one or more food antigens,[62] continuing into adulthood and misdiagnosed as IBS.

**Classical IgE-mediated Food Allergy**

Classical IgE-mediated food allergy in DGBI (e.g., to peanut) is considered uncommon and routine testing is not recommended. However, food allergy may be more important in the pathogenesis of DGBI than recognised previously. The alpha-gal syndrome is an example of a food allergy syndrome inducing typical IBS-like symptoms,[63] although the exact prevalence in patients fulfilling criteria for IBS remains to be determined. In alpha-gal syndrome, a tick bite exposes the host to a foreign carbohydrate antigen, galactose-alpha-1,3 galactose, inducing an IgE-mediated immune response. Later, consuming mammalian meat or mammalian products, such as milk or butter, induces an allergic reaction within hours resulting in abdominal pain and diarrhoea, often without other allergic manifestations. This occurs because galactose-alpha-1,3 galactose is not normally present in humans but is found in other mammals and, therefore, our food sources.[63]

**Atypical (Non-IgE-mediated) Food Allergy**

Direct evidence for an atypical, non-IgE-mediated, food allergy in people with IBS comes from confocal laser endomicroscopy (CLE) studies after direct instillation of food challenges onto the duodenal mucosa.[64, 65] After four duodenal challenges to five common food antigens (wheat, soy, egg, milk, and yeast), over 50% of patients with IBS exhibited almost immediate disruption of the intestinal barrier with low-grade inflammation, including eosinophil degranulation as confirmed by increased eosinophil cationic protein in duodenal fluid.[64] Similar preliminary results have been observed in FD.[66]

Wheat remains the most common food component implicated in CLE studies,[64, 65] and in lamina propria mononuclear cells from patients with FD, gliadin, but not gluten, provoked a duodenal effector T-helper 2-like response, suggesting digested wheat protein may result in immune activation.[67] Animal and human studies support the food antigen hypothesis in IBS.[68] Injection of food antigens, including wheat, gluten, soy, and milk, into the rectosigmoid mucosa of patients induced a local reaction with mast cell degranulation in 100% of patients with IBS but only 25% of controls. However, mimicking colonic exposure to partially digested foods is extremely challenging, and whether food antigens penetrate the colonic mucosa in IBS is unclear.

**Interactions Between Food and Bacteria**

Duodenal dysbiosis has been observed in both FD and IBS.[69, 70] In one study, aseptic duodenal biopsies were obtained from patients with FD and controls.[71] Using 16S rRNA sequencing, the dominant duodenal mucosal bacterial genus identified was Streptococci, and the higher the bacterial load the greater the symptom burden and impairment in quality of life.[72] Subsequent studies have confirmed a higher Streptococci load in the duodenum in FD.[73, 74] A novel *Streptococcus salivarius*, which appears to be a pathobiont, has been isolated from the duodenal mucosa of patients with FD.[75]

In another study, those with FD and/or IBS who self-reported wheat-induced symptoms had higher abundance of Streptococci, in contrast to those without wheat sensitivity, and gut homing CD4+α4+ β7+CCR9+ T-cells were increased in those with self-reported wheat sensitivity.[76] There is evidence Streptococci can digest wheat proteins, promoting presentation of antigens to the small intestinal mucosa.[77, 78] Therefore, the interaction between dietary components and bacteria may contribute to induction of atypical non-IgE-mediated food reactions in FD and IBS, although these findings need replication.

**Role of Stress or Infection**

Stress or acute infection may break oral tolerance, leading to food antigen-driven diseases we categorise as FD or IBS. Locally acting hypothalamic-pituitary-adrenal (HPA) axis hormones have been implicated in barrier disruption. It has been observed that patients with FD have reduced duodenal corticotrophin-releasing hormone (CRH)-receptor 2, indicating a dysregulation of duodenal HPA signalling.[79] Loss of CRH-receptor 2 correlated with goblet cell dysfunction, including reduced NOD-like receptor family pyrin domain-containing 6 inflammasome expression and autophagy, and duodenal goblet cell numbers and mucin were reduced, implicating stress-induced barrier disruption in the pathogenesis, a brain-gut process.

FD or IBS, or both together, arise after infectious gastroenteritis in at least 10% of cases,[80, 81] although this could be an underestimate as patients may fail to recall the link. In a mouse model of IBS, acute infection with *C. rodentium* broke oral tolerance in the colon due to increasing intestinal permeability and an adaptive immune response to food antigens, via activated mast cells primed with allergen-specific IgE that degranulated.[68] The outcome was pain with abnormal pain signalling and diarrhoea. A similar mechanism of infection-induced breaks in oral tolerance, resulting in new food allergen exposure, may result in immune activation and loss of homeostasis in DGBI.

**Role of Histamine in Food Reactions**

Adverse reactions to histamine occur in at least 1% of the population but may be under-recognised.[82] Histamine is routinely released from food when it interacts with intestinal bacteria that breakdown dietary histidine, and histamine can then be absorbed, activating histamine receptors on mucosal cells. Although *Klebsiella aerogenes*, present in the microbiota of up to 25% of patients with IBS, is an important bacterial producer of histamine,[83] many other intestinal bacteria are potential histamine producers, via histidine decarboxylase.[84] Dietary histamines, and other biogenic amines (e.g., tyramine or cadaverine), can also be released as a result of bacterial fermentation of food during processing and storage; concentrations increase with food maturation.[82] Histamine is also released from activated mast cells in the mucosa that are increased in DGBI. Impaired diamine oxidase activity, the primary human enzyme responsible for histamine degradation, is proposed as one cause of excess serum histamine, but this is controversial and testing probably has little value.[85]

Histamine induces abdominal pain in mice.[83] Ingestion of high histamine-containing foods has been reported to induce IBS symptoms,[86] and urinary histamine is reduced on a diet low in fermentable oligo-, di-, and monosaccharides, and polyols (FODMAPs).[87] Further evidence implicating histamine comes from observations in IBS that neuronal excitability may be reduced by histamine-1-receptor antagonists (H1RAs) or commencing a low FODMAP diet.[88]

**Role of Nocebo**

Nocebo effects, or the effects of patients’ negative expectations on their state of health,[89] may play a role in inducing postprandial symptoms in some patients with DGBI. The nocebo effect includes all negative expectations, as well as the consequences of past negative experiences with treatment, and is highly relevant in DGBI, where symptoms fluctuate and patients are often offered multiple treatments.[90] Although the nocebo phenomenon can be protective, allowing the detection of possible physical harm when encountering new substances, in clinical practice nocebo may be problematic, clouding judgement of the effect of a treatment or, in this case, a food. Nocebo effects have been demonstrated in individuals with non-coeliac gluten sensitivity, where expectation of gluten, but not actual gluten intake, worsens gastrointestinal symptoms.[91] In another study, almost 50% of individuals referred for lactose breath testing who were symptomatic during the test reported symptoms during a subsequent ‘sham’ breath test, in which they were given an insignificant dose of glucose.[92] Broadly speaking, nocebo effects are more likely in individuals with psychological distress or medically unexplained symptoms,[89] which are both common in DGBI.

**Summary**

There is emerging evidence to suggest that in a subset of patients with DGBI, symptoms relate to a physiological or psychological insult (Figure 2), for example an acute enteric infection, leading to loss of tolerance to a previously tolerated oral food antigen.[68] This enables interaction of both the microbiota and the food antigen itself with the human immune system, causing a localised immunological response, with activation of eosinophils and mast cells, and the release of inflammatory mediators.[51, 65, 93, 94] The latter can then have more widespread systemic effects, including triggering nociceptive nerve fibres and even altering mood.[47] A new disease model that takes this into account could, potentially, be used to direct both dietary and drug therapies.

**WHY SOME DIETARY THERAPIES MAY IMPROVE POSTPRANDIAL SYMPTOMS IN DGBI**

**Low FODMAP Diet**

The predominant focus of dietary research in DGBI over the last two decades has been the low FODMAP diet. Multiple randomised controlled trials (RCTs) have been conducted and a network meta-analysis confirmed its superiority over other diets for IBS.[95] Limited evidence in FD suggests it has similar efficacy to traditional dietary advice.[96] There have been considerable efforts to identify mechanisms of effect. Magnetic resonance studies demonstrate profound increases in colonic volume in response to oral inulin in IBS, with a delayed peak symptom intensity at 4 hours.[97] However, this delay between intake and symptom exacerbation is at odds with the time frame of postprandial symptoms in many patients. In FD, FODMAPs may elicit symptoms more rapidly than would be expected if driven by colonic distension. In a retrospective study in FD, 50% of patients reported symptomatic response with a low FODMAP diet, and postprandial epigastric pain improved compared with controls,[98] suggesting strongly that FODMAPs drive postprandial symptoms in at least some patients.

Several overlapping mechanisms could be responsible. Compared with a low FODMAP diet, a high FODMAP diet induces mucosal inflammation.[99] Although not a consistent finding,[100] this may be mediated by increased colonic short-chain fatty acid concentrations and low luminal pH due to FODMAP fermentation.[101] A low FODMAP diet also reduces intake of food antigens implicated in some patients with IBS (Table 1); therefore, reducing colonic fermentation may not fully explain the benefits reported. Other studies suggest FODMAP restriction improves markers of epithelial injury and small intestinal permeability in humans.[102, 103]

Rapid onset of FODMAP-induced symptoms may also occur due to luminal distension by small intestinal water accumulation.[97] This could amplify mechanical forces locally, with mast cell degranulation, histamine release, and resultant visceral hypersensitivity. FODMAPs may also drive postprandial symptoms through crosstalk with the distal gut. Intragastric infusion of fructan in people with IBS led to more abdominal cramping, bloating, and flatulence compared with healthy individuals, with some symptoms occurring 30 minutes post-infusion.[104] There was a greater intragastric pressure over the entire 180-minute study period with fructan, compared with glucose infusion, which may have been responsible. It was postulated the effect was mediated by gastroduodenal and/or gastrocolonic crosstalk, but it is also possible fructan reached the duodenum driving an immune response.

Finally, central mechanisms may explain rapid symptom onset. In IBS, differential activation of pain-related regions of the brain occurred within 50 minutes of intragastric fructans.[43] Potential mediating psychological factors were not explored, but expectation or fear of imminent symptoms may be important.

**Table 1. Commonly Reported Foods Implicated in IBS and FD Symptoms, and the FODMAP and Food Antigens in These Foods.**

|  |  |  |
| --- | --- | --- |
| **Food item** | **FODMAP** | **Food antigen** |
| Wheat or rye-containing products | Fructan | Gluten or ATI |
| Dairy foods | Lactose | Cow’s milk protein |
| Soybeans | Fructan | Soy protein |
| Cashew or pistachio nuts | GOS or fructan | Tree nut protein |
| Egg | N/A | Egg protein |
| Seafood | N/A | Shellfish or fish protein |

ATI; amylase trypsin inhibitors, GOS; galacto-oligosaccharide, N/A; not applicable.

**Food Antigen Elimination**

CLE studies in the duodenum and studies applying food antigens to the rectosigmoid mucosa support a potential role of non-IgE-mediated allergic responses as triggers for postprandial symptoms.[64, 65, 68] A limitation remains that the benefit of individualised elimination diets for patients with positive CLE examinations has only been examined in one uncontrolled and one sham-controlled study,[64, 65] in which composition of participants diets was not reported. There are no RCTs of wheat-free or milk-free diets in IBS or FD.

Gluten elimination has been studied in DGBI, with the hypothesis that gluten induces immune reactivity to proteins of wheat and other gluten-containing cereals, leading to symptoms. Although some RCTs show a benefit of a gluten-free diet in IBS,[105] this is either associated with reduced FODMAP intake or dietary composition is not reported. Therefore, confirming whether it is exclusion of gluten or, again, other wheat proteins responsible for symptom improvement needs further work and the findings may only apply in a subgroup of patients. Gluten-challenge studies do not support a role for gluten exclusion in either IBS or FD.[106-108] The nocebo effect may also be an important factor in generating postprandial symptoms after gluten-challenge, as demonstrated in individuals with non-coeliac gluten sensitivity.[91]

**IgG Food Sensitivity Diets**

Postprandial symptoms in DGBI have also been proposed to be mediated through IgG4 antibody-induced inflammation. One quasi-randomised trial reported reduced symptom frequency in patients with IBS following an elimination diet based on reactivity to a panel of 39 food antigens,[109] but between-group analyses were not performed, meaning placebo effects cannot be ruled out. In a 12-week sham diet-controlled study in IBS, symptom reduction was superior in the intervention group, but only based on per protocol analysis, and diet composition was not reported.[110] Therefore, allergy societies and clinical guidelines for IBS recommend against diets based on IgG4 testing currently, due to both a lack of high quality evidence to support their use and their restrictive nature.[111-113]

**Salicylates and Biogenic Amines**

Other dietary constituents that may induce postprandial symptoms are bioactive food chemicals, including salicylates, and biogenic amines, such as histamine. It is hypothesised that cumulative intake of food chemicals over time leads to patients exceeding their individual threshold for symptoms.[114] A food chemical-sensitive individual may, therefore, present with acute symptoms in response to intake of a high chemical food(s). Salicylate-induced symptoms are postulated to occur as a result of a pseudo-allergic hypersensitivity reaction to salicylic acid, or its derivatives, via cyclo-oxygenase-1.[115, 116] Reactions occur from within 1 hour to several days later, affecting the gut, skin, respiratory tract, or central nervous system.[117] Dietary salicylates occur naturally in plant foods, including certain fruits (e.g., berries, cherries, or dried fruit), vegetables (e.g., avocado, spinach, or tomato), herbs and spices (e.g., ginger, pepper, or cumin), fruit juices, and wines. Gastrointestinal symptoms in response to salicylate-challenge were reported in a case series,[118] but in one trial of a low salicylate diet in IBS, there was no improvement in symptoms compared with a FODMAP and fibre-equivalent diet that was four-fold higher in salicylates.[119] Sources of amines include fish (e.g., canned tuna or prawn), cheese, meat (e.g., salami or sausages), and other products (e.g., condiments or wine). There are no RCTs of a low histamine diet in DGBI.

**Clinical Application**

Evidence for each of these dietary interventions is provided in Table 2. Dietetic clinical guidelines for IBS recommend standard dietary advice first-line, focusing on healthy eating principles, regular meals, and restriction of common dietary triggers, such as caffeine.[120] If ineffective, this can be followed by a low FODMAP diet. Broadly speaking, in the absence of formal dietary guidelines, the same clinical algorithm is applied for FD. Although some IBS guidelines recommend against a gluten-free diet, this could be considered, if fructan sensitivity has been excluded. Although evidence from clinical trials is insufficient to support integration of food antigen elimination, elimination diets based on IgG4 antibody testing, or salicylate- or biogenic amine-restriction into DGBI management guidelines, there may be specific patients who benefit from careful restriction. The potential benefit of dietary restriction or an elimination diet must, however, be balanced against risks. They should only be considered in patients having attempted standard first- and second-line dietary approaches unsuccessfully. Salicylate or biogenic amine restriction should generally be considered only in patients also reporting food-related non-gastrointestinal symptoms (e.g., skin symptoms or headache).

Specialist dietetic support should be enlisted, with a careful assessment of medical, clinical, and dietary history. Identifying dietary triggers is challenging due to the complexity of diet. Many foods contain multiple disparate dietary triggers (Figure 3). Therefore, one dietary approach may lead to partial improvement in symptoms but not address the primary trigger(s) for symptoms. Thorough assessment of previous dietary restrictions enables triage of patients to the most appropriate approach. For example, individuals with a history of atopy who report milk product-related symptoms, with no response to lactose restriction, could have underlying IgE-mediated or non-IgE-mediated milk allergy, and may benefit from a trial of milk exclusion.[121]

**Table 2. Summary of Evidence for Efficacy of Diets That May Improve Postprandial Symptoms in Disorders of Gut-brain Interaction.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Diet studied** | **Population** | **No. of studies** | **No. of patients** | **Comparator** | **Reported effect** |
| **Low FODMAP diet** | Mainly unselected patients with IBS (some trials only IBS-D)  Patients with FD | 13 RCTs summarised in a network meta-analysis[95]  1 RCT[96]  1 case series[98] | 944  105  59 | British Dietetic Association first-line dietary advice for IBS  Habitual diet  Sham diet  Standard dietary advice  Standard dietary advice | RR of persistence of global IBS symptoms = 0.81; 95% CI 0.67-0.97  RR of persistence of global IBS symptoms = 0.67; 95% CI 0.48-0.91  RR of persistence of global IBS symptoms = 0.70; 95% CI 0.52-0.95  ≥50% decrease in FD symptoms in 67% vs. 57% at 4 weeks, *p*=0.32  Mean decrease [95% CI] in epigastric symptoms  −3.6 [−4.9, −2.2] vs. −0.9 [−2.9, 1.1], *p*=0.032  ≥30% decrease in epigastric symptoms in 50% vs. 16%, *p*=0.012 |
| **Food antigen elimination** | Patients with IBS with CLE response to food antigens | 1 crossover RCT[64]  1 case series[65] | 76  22 | Sham diet  N/A | 68% of CLE response group had a >80% improvement in overall IBS symptoms at 6 months, between group differences not reported  >50% decrease in IBS symptoms in 86% at 4 weeks, reduction in overall IBS symptom score by 74% at 6 months |
| **Gluten elimination** | Patients with IBS | 9 RCTs summarised in a meta-analysis[105] | 620 | FODMAP diet, Mediterranean diet, traditional diet, or placebo (in double-blind placebo-challenge trials) | Standardised mean difference [95% CI] in overall symptoms − 0.31 [95% CI −0.92, 0.31], bloating −0.37 [95% CI −1.03, 0.30], and abdominal pain –0.68 [95% CI −1.36, −0.00] |
| **IgG food sensitivity diets** | Patients with IBS  Female patients with IBS-M | 1 RCT[110]  1 quasi- RCT[109] | 131  73 | Sham diet  FODMAP diet or dietary advice from a gastroenterologist | Mean change in IBS symptom score -100 vs. -61.5 at 12 weeks, p = 0.024  Improvement in abdominal pain (*p<*0.001), abdominal pain after a meal (*p<*0.001), and abdominal pain after defaecation (*p*=0.008) in IgG food sensitivity diet group at 8 weeks, between group differences not reported |
| **Salicylate restriction** | Patients with IBS | 1 crossover RCT[119] | 10 | High-salicylate diet | No differences in overall symptom scores between groups across baseline, high-salicylate diet, low-salicylate diet, or washout periods (*p*=0.625). |

FD; functional dyspepsia, FODMAP; fermentable oligo, di, or monosaccharides, and polyols, IBS; irritable bowel syndrome, N/A; not applicable, RCT; randomised controlled trial.

Patients with suspected food allergy should be referred to a dietitian with allergy expertise. In all other cases, an elimination diet of 2 to 6 weeks is recommended to confirm whether suspected foods, or dietary constituents, are responsible for symptoms. The duration should be minimised in patients with red flags, such as risk of nutritional deficiency or psychological harm.[122] Importantly, when undertaking any elimination or restrictive diet, patients need support from an experienced dietitian to enhance success of the intervention, whilst accounting for variation in individual tolerance to foods or food components,[116] to minimise nutritional risks, enhance confidence when outside the home, guide reintroduction, and initiate referral for psychological support, if required.[123]

Finally, education about nocebo effects,[124] emphasising positive outcomes, such as that a liberal diet better enables eating outside the home, and minimising negative outcomes may mitigate nocebo potency in clinical practice.[89] Exposure-based cognitive behavioural therapy,[125] in which exposure to dietary stimuli is promoted, may also help to improve gastrointestinal symptoms in DGBI. Calls have been made for improved clinician awareness of how to minimise nocebo effects, strategies for optimal verbal and non-verbal communication, and future research into education and training of health professionals in relation to nocebo effects.[126]

**WHY SOME DRUGS MAY IMPROVE POSTPRANDIAL SYMPTOMS IN DGBI**

A variety of drugs act on one or more of the pathophysiological mechanisms discussed earlier. This may explain why only some patients respond to drugs used to treat FD and IBS, but also suggests that, if drug selection were based on one of more of these therapeutic targets in those with postprandial symptoms, patient outcomes may be improved. Evidence for candidate drugs is summarised in Table 3.

**Table 3. Summary of Evidence for Efficacy of Available Drugs That May Improve Postprandial Symptoms in Disorders of Gut-brain Interaction.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug studied** | **Population** | **No. of studies** | **No. of patients** | **Comparator** | **Reported effect** |
| **Proton pump inhibitors (e.g., lansoprazole 30mg o.d. for 4 weeks)** | Mainly unselected patients with FD | 18 RCTs summarised in a meta-analysis[127] | 6172 | Placebo | RR of FD symptoms persisting = 0.88; 95% CI 0.82-0.94 |
| **Liquid budesonide (e.g., 9mg per day for 8 weeks)** | Patients with FD with duodenal eosinophilia | 1 RCT[128] | 13 | Placebo | Mean change [SD] in eosinophil counts −9.4 [11.2] vs. −17.4 [10.5], *p*= 0.168  *Effect on FD symptoms not reported* |
| **Lirentelimab (e.g., 0.3mg/kg, 1mg/kg, 1mg/kg, and 1mg/kg infusions each month for 4 months)** | Patients with eosinophilic gastritis or duodenitis | 1 RCT[129] | 65 | Placebo | 63% met criteria for treatment response (a >75% reduction in eosinophil counts and a >30% improvement in symptom scores) vs. 5%, *p*<0.001 |
| **Histamine-2-receptor antagonists (e.g., nizatidine 300mg o.d. for 4 weeks)** | Unselected patients with FD | 12 RCTs summarised in a meta-analysis[130] | 2268 | Placebo | RR of FD symptoms persisting = 0.79; 95% CI 0.68-0.92 |
| **Dual histamine blockade (e.g., ranitidine 150-300mg daily and loratadine 10-20mg daily for 4 months)** | Patients with PPI-refractory FD | 1 case series[131] | 14 | N/A | Symptom improvement in 71% of patients |
| **Histamine-1-receptor antagonists (e.g., ebastine 20mg o.d. for 12 weeks)** | Unselected patients with IBS  Patients with non-constipated IBS | 1 RCT[132]  1 RCT[133] | 55  202 | Placebo  Placebo | Considerable relief of IBS symptoms for ≥6 of 12 weeks in 25% vs. 4%, *p*=0.097  Relief of abdominal pain for ≥6 of 12 weeks in 41% vs. 20%, *p*=0.19  Clinical response (composite of global relief of IBS symptoms and a ≥30% reduction in average abdominal pain score for ≥6 of 12 weeks) in 12% vs. 4%, *p*=0.047  Global relief of IBS symptoms for ≥6 of 12 weeks in 15% vs. 7%, *p*=0.072  ≥30% reduction in average abdominal pain score for ≥6 of 12 weeks in 37% vs. 25%, *p*=0.081 |
| **Ketotifen (e.g., titrated from 2mg b.i.d. to 3mg b.i.d. or 1mg b.i.d.)** | Unselected patients with IBS  Patients with IBS-D | 1 RCT[134]  1 RCT[135] | 60  116 | Placebo  Placebo | Considerable relief of IBS symptoms in 20% vs. 10%, *p*=N/S  Proportion of patients with abdominal pain (*p*=0.02), bloating (*p*=0.02), flatulence (*p*=0.04), diarrhoea (*p*=0.05), and incomplete evacuation (*p*=0.04) lower with ketotifen  Improvement in symptoms in 76% vs. 38%, *p*<0.001 |
| **Disodium cromoglycate (e.g., 600mg/day)** | Patients with IBS-D | 1 RCT[136] | 43 | No treatment | ≥50% improvement in abdominal pain in 77% vs. 28%, *p*=0.002 |
| **Tricyclic antidepressants (e.g., amitriptyline 10-30mg o.d. or imipramine 50mg o.d.)** | Unselected patients with IBS  Unselected patients with FD | 12 RCTs summarized in a meta-analysis[137]  1 subsequent RCT[138]  3 RCTs summarised in a meta-analysis[139] | 787  463  339 | Placebo  Placebo  Placebo | RR of IBS symptoms persisting in 787 patients in 12 RCTs = 0.65; 95% CI 0.55-0.77  RR of abdominal pain persisting in 184 patients in 4 RCTs = 0.59; 95% CI 0.42-0.83  OR for relief of IBS symptoms = 1.78; 95% CI 1.19-2.66  OR for ≥30% improvement in abdominal pain = 1.66; 95% CI 1.12-2.46  RR of FD symptoms persisting = 0.74; 95% CI 0.61-0.91 |
| **Mirtazapine (e.g., 15mg or 30mg o.d.)** | Patients with FD and weight loss  Patients with IBS-D | 1 RCT[140]  1 RCT[141] | 34  67 | Placebo  Placebo | Dyspepsia severity score 10.9 at week 0 and 8.6 at week 8, *p*=0.017, vs. 11.4 and 10.4, *p*=0.72  Early satiation score 1.88 at week 0 and 1.11 at week 8, *p*=0.0003, vs. 1,53 and 1.77, *p*=0.56  ≥50-point decrease in IBS symptom scores in 62% vs. 30%, *p*=0.01  Median change in stool consistency score –1.25 vs. -0.30, *p*<0.001 |

FD; functional dyspepsia, IBS; irritable bowel syndrome, IBS-D; IBS with diarrhoea, N/A; not applicable, N/S; not significant, OR; odds ratio, RCT; randomised controlled trial, RR; relative risk.

**Drugs Acting on Eosinophils**

PPIs reduce gastric acid production and are a well-established treatment for FD.[142] However, excess acid production is not implicated in its pathophysiology,[143] and although PPIs were superior to placebo for FD in a meta-analysis of 16 RCTs, efficacy was modest and there was no dose-response effect.[127, 130] Only two RCTs have examined efficacy according to FD subtype, meaning that in a prior meta-analysis it was difficult to draw meaningful conclusions from subgroup analysis.[127] PPIs were no more efficacious than placebo for EPS, but for PDS there was a trend towards a benefit. Importantly, no trials have examined impact of PPIs on postprandial epigastric pain or burning specifically. Importantly, PPIs have anti-inflammatory effects independent of acid suppression. In eosinophilic oesophagitis (EoE), T-helper 2 cytokines recruit eosinophils, via the chemoattractant eotaxin-3, which PPIs block.[144] This, presumably, explains why a subset of patients with EoE respond to PPIs.[145] One study demonstrated that among patients with unexplained gastrointestinal symptoms, over 40% had evidence of gastric or duodenal eosinophilia, of whom 55% had a pre-existing diagnosis of IBS and 17% FD.[146] In FD, PPIs reduce duodenal eosinophil counts, an effect not observed in healthy controls, and this reduction correlates with symptom improvement.[53, 147] These studies give insights into why PPIs may be beneficial in some patients.

Other drugs for EoE may be efficacious in DGBI. There has been one RCT of liquid budesonide in FD with duodenal eosinophilia, but there was no effect of budesonide over placebo in terms of reduction in eosinophil counts,[128] although reduction in counts among all patients, irrespective of assigned treatment, correlated with symptom improvement. Biologics, such as dupilumab, benralizumab, or lirentelimab, induce histological remission in EoE,[148] but there is no direct evidence for a benefit in patients with DGBI. In a RCT of lirentelimab, an anti-siglec-8 antibody, in patients with eosinophilic gastritis or duodenitis, eosinophil counts were reduced significantly compared with placebo,[129] but further development of the drug has ceased.

**Drugs Acting on Histamine or Mast Cells**

Although superseded by PPIs, histamine-2-receptor antagonists (H2RAs) were an established treatment for acid-related disorders for many years. Their efficacy in FD has been the subject of numerous RCTs. Most trials used historical criteria to define FD and, hence, trial populations probably included patients with gastro-oesophageal reflux. In addition, endpoints used to define treatment success were less stringent than those used currently. Nevertheless, H2RAs were more efficacious than placebo for FD in a meta-analysis of 12 RCTs.[130] More recently, efficacy of dual histamine blockade, using both an H2RA and loratadine, a non-sedating H1RA, was reported in a retrospective case series in PPI-refractory FD.[131] Overall, more than 70% of patients had symptomatic improvement. Responders had higher eosinophil counts at baseline than non-responders.

The efficacy of H1RAs has been assessed in IBS. Ebastine, a non-sedating H1RA licensed for urticaria and allergic rhinitis, was studied in a pilot RCT in IBS.[132] The drug led to significant reductions in visceral hypersensitivity and abdominal pain, and higher rates of relief of global IBS symptoms for 50% of weeks compared with placebo. A subsequent phase II RCT demonstrated ebastine was superior to placebo in non-constipated IBS.[133] Rates for the primary endpoint, a composite of global relief of IBS symptoms and improvement in abdominal pain, were significantly higher with ebastine, although response rates for either global relief or abdominal pain improvement alone were not significantly different.

In a RCT of ketotifen, an H1RA and mast cell stabiliser, in Rome II-defined IBS, considerable relief of symptoms was reported by more patients receiving ketotifen than placebo,[134] although this was not statistically significant. Ketotifen decreased abdominal pain significantly, and thresholds for rectal sensitivity to discomfort on barostat testing were increased in patients with visceral hypersensitivity, but not in normosensitive patients. However, ketotifen had no effect on mast cell counts or histamine or tryptase release. In another trial, in IBS-D, there was a significant benefit of ketotifen over placebo.[135] In this RCT, there was also a significant reduction in mucosal mast cell counts and the proportion of degranulated mast cells with ketotifen. The effect of disodium cromoglycate, another mast cell stabiliser, has been studied in one RCT in IBS-D;[136] significantly more patients randomised to cromoglycate experienced improvement in abdominal pain, compared with no treatment. There were also significant improvements in stool frequency and consistency with cromoglycate. Luminal tryptase levels were significantly lower with cromoglycate, and there was a significant reduction in levels of tryptase gene expression.

**Other Drugs**

Tricyclic and tetracyclic antidepressants, which are used as gut-brain neuromodulators in DGBI, have anti-histaminergic effects among their many actions and act as H1RAs. Tricyclic antidepressants are efficacious for IBS; a meta-analysis of 12 trials demonstrated a significant benefit over placebo.[137] However, many of these trials were small, underpowered, and used less stringent endpoints than those recommended currently. In a subsequent UK phase III trial in IBS of all subtypes who had not responded to first-line therapies, low-dose amitriptyline demonstrated a significant benefit over placebo in terms of both global symptom relief and improvement in abdominal pain.[138] The benefit was apparent across all IBS subtypes. In a meta-analysis of three RCTs, TCAs were efficacious for FD symptoms.[139] In the largest trial in FD to date, using low-dose amitriptyline, adequate relief of symptoms was reported by significantly more patients receiving active drug, compared with placebo.[149] The effect was strongest in those with EPS. Mirtazapine, a tetracyclic antidepressant, has also been studied in both IBS and FD. In a RCT in FD,[140] mirtazapine led to a significant decrease in dyspepsia severity scores, an effect not seen with placebo, and seemed particularly efficacious for early satiation. In a trial in IBS-D, mirtazapine was superior to placebo.[141] However, there remains uncertainty as to whether the beneficial effects of tricyclic and tetracyclic antidepressants arise from their anti-histaminergic effects, in the absence of mechanistic data in these RCTs , and also which patients are likely to respond to these drugs.

**CONCLUSIONS**

DGBI impact almost one-in-two people worldwide but the underlying aetiology has been elusive, and the intestinal and extra-intestinal symptoms continue to impact quality of life despite current therapies. If the concept that postprandial symptoms identify a subset of patients with DGBI, including some with IBS and many with FD, that arise from food antigens driving an immune response in the gastrointestinal tract is correct it is paradigm-shifting, offering new and more effective treatment possibilities. Given the temporal relationship between onset of symptoms and food ingestion in many patients with DGBI, this suggests the small intestine is the anatomical site of symptom generation. However, the underlying mechanisms underlying this may differ between IBS and FD.

Several converging lines of evidence support the concept that food often drives symptoms through the intestinal immune system in both FD and IBS, including the early response to meal ingestion in a major subgroup, evidence of low-grade intestinal inflammation with circulating homing small intestinal T-cells and a cytokine response, and direct evidence from injecting or placing food antigens in or on the human intestine *in vivo*. It is established that a low FODMAP diet is efficacious in both IBS and, albeit with weaker evidence, FD. However, a low FODMAP diet also reduces intake of common food antigens implicated in other food allergic disorders, such as eosinophilic oesophagitis. Emerging and established drugs for IBS and FD, including gut-brain neuromodulators, may work, in part, through blocking the involved pathways, such as histamine release from mast cells, activated via food-induced allergic mechanisms.

It seems unlikely that food antigens driving intestinal immune activation is the entire explanation for postprandial symptoms in FD and IBS. In others, fermentation of intestinal carbohydrates, with gas release altering reflex responses, adverse reactions to food chemicals, such as salicylates, central mechanisms, or nocebo effects may dominate. However, even if food-induced immune activation accounts for symptoms in only a subgroup of patients with DGBI, the implications are major because removing or blocking the antigenic stimulus, thereby attenuating immune activation, might provide not just symptom improvement, but disease remission, or even cure.

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**Guarantor:** ACF is guarantor. He accepts full responsibility for the work and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**FIGURES**

**Figure 1a. Relationship Between Symptoms and Time from Ingestion of a Meal in 110 Patients with FD.**

Adapted from Carbone F, Vanuytsel T, Tack J. Analysis of postprandial symptom patterns in subgroups of patients with Rome III or Rome IV functional dyspepsia. Clin Gastroenterol Hepatol 2020;18:838-46.[25]

**Figure 1b. Relationship Between Symptoms and Time from Ingestion of a Meal in 67 Patients with IBS.**

Adapted from Posserud I, Strid H, Störsrud S, Törnblom H, Svensson U, Tack J*, et al.* Symptom pattern following a meal challenge test in patients with irritable bowel syndrome and healthy controls. United European Gastroenterol J 2013;1:358-67.[36]

**Figure 2. Hypothetical Mechanisms of Postprandial Symptoms in IBS and FD: Role of Dietary Antigens and Histamine from Mast Cells, Dietary Intake (Including FODMAPs and Salicylates), and Bacteria.**

APC; antigen-presenting cell, EBP; enhancer-binding protein, Eos; eosinophil, IL; interleukin, MC; mast cell, NGF; nerve growth factor, SCF; stem cell factor, SCFA; short-chain fatty acids, Th2; T-helper 2. Created with BioRender.

**Figure 3. Overlap of Dietary Components as Potential Gastrointestinal Symptom Triggers in Patients with DGBI.**

There are several groups of dietary components that may be triggers, with varying levels of evidence for their restriction in DGBI. The Venn diagram illustrates the substantial overlap between these. The food supply here is presented simplistically and reflects a minimally processed food supply. For example, many high FODMAP foods are also high in salicylates (e.g., apple) or gluten (e.g., rye bread), and most wheat-containing foods also contain gluten (e.g., wheat cereal). For foods with higher degrees of processing, there will be even greater overlap. For example, a ready-made tomato-based pasta meal may contain all the dietary components presented.