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STOMACH AND DUODENUM (J PISEGNA AND J BENHAMMOU, SECTION EDITORS)

Functional Dyspepsia and Food: Immune Overlap with Food Sensitivity Disorders

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Abstract

Purpose of Review Functional dyspepsia (FD) is a chronic functional gastrointestinal disorder characterised by upper gastrointestinal symptoms. Here, we aimed to examine the evidence for immune responses to food in FD and overlap with food hypersensitivity conditions.

Recent Findings A feature of FD in a subset of patients is an increase in mucosal eosinophils, mast cells, intraepithelial cytotoxic T cells and systemic gut-homing T cells in the duodenum, suggesting that immune dysfunction is characteristic of this disease. Rates of self-reported non-celiac wheat/gluten sensitivity (NCW/GS) are higher in FD patients. FD patients commonly report worsening symptoms following consumption of wheat, fermentable oligosaccharides, disaccharides, monosaccharides, or polyols (FODMAPs), high-fat foods and spicy foods containing capsaicin. Particularly, wheat proteins and fructan in wheat may drive symptoms.

Summary Immune mechanisms that drive responses to food in FD are still poorly characterised but share key effector cells to common food hypersensitivities including non-IgE–mediated food allergy and eosinophilic oesophagitis.

Keywords Functional dyspepsia · Food allergy · Diet · Non-celiac wheat sensitivity · Duodenum · FODMAPs

Introduction

Functional dyspepsia (FD) is a common functional gastrointestinal disorder (FGID) with a prevalence of approximately 10% in Western countries [1]. This condition is characterised by chronic upper gastrointestinal (GI) symptoms including epigastric pain, epigastric burning, early satiety, postprandial fullness (often referred to as bloating) and nausea. FD is diagnosed in patients with persistent symptoms, as defined by the Rome criteria, who have negative endoscopic findings and overt pathology upon examination [2]. Patients are generally assigned to one of two subtypes based on symptoms: postprandial distress syndrome (PDS) or epigastric pain syndrome (EPS) although pathophysiology of FD is poorly defined, and it is unclear if there is a biological basis for these subtypes [2]. Quality of life is poor in FD patients, with significant social and healthcare costs associated with the disorder [3]. This is partly due to the ineffectiveness of current FD therapeutics, which are largely based on symptom relief. A minority of patients report improved dyspeptic symptoms following *Helicobacter pylori* eradication [4]. Similarly, proton pump inhibitors (PPIs) show efficacy in a subset of FD patients and may suppress duodenal eosinophils, but there are questions of suitability for long-term use [5, 6]. Tricyclic antidepressants have been used but demonstrate modest benefit [7, 8]. Because patients often report symptoms following food consumption, there has been recent interest in dietary management as a therapeutic approach for FD, based on the hypothesis that sensitivity to dietary nutrients may drive symptoms in some FD patients (Table 1) [9]. This notion is supported by an

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Table 1 Foods associated with symptoms of functional dyspepsia and proposed mechanisms

Food component	Associated symptoms	Proposed immune mechanism	Proposed physiological mechanism
Gluten	Bloating Abdominal pain Epigastric pain	Toll-like receptor activation by gluten-derived peptides initiate inflammatory responses [61] Increased duodenal eosinophils promote inflammatory state and are associated with increased innervation, causing visceral hypersensitivity [36, 59••].	Gluten-derived peptides induce zonulin secretion causing a decrease in tight junction integrity [65].
FODMAPs	Bloating Gas production	Immunomodulation by some FODMAPs may contribute to inflammation [75].	FODMAPs are osmotically active and cause increased water volume in lumen of the GI tract, contributing to the sensation of feeling bloated [21•]. Fermentation by gastrointestinal microbiota into short-chain fatty acids produces excess gas [71].
Fats	Bloating Epigastric pain Nausea Postprandial fullness	Unknown	Overexpression of hormone cholecystokinin could cause overproduction of bile and digestive enzymes, affecting GI motor function resulting in symptoms [93–95].
Capsaicin	Epigastric pain Epigastric burning Nausea	Unknown	Capsaicin interaction with transient receptor potential vanilloid-1 receptor (TRPV1) may trigger visceral sensitivity and pain due to increased TRPV1-reactive nerves [99, 100].

Australian population-based study which identified a significant association between FD and food sensitivity, independent of psychological distress [10•].

The lumen of the GI tract is exposed to a vast range of microbial and dietary proteins. The interplay of the host immune system and the gut microbiota allows the gut to maintain homeostasis during encounters with foreign dietary antigens [11]. An active regulation of immune responses, known as oral tolerance, occurs when the small intestine is exposed to a food antigen and does not recognise it as a threat [12]. Following ingestion, dietary proteins undergo digestion by host-produced enzymes in the saliva and stomach and those produced by the microbiota in the intestines [13]. However, some dietary proteins (allergens) resist digestion and remain intact upon arrival to the duodenum, where they may be recognised by antigen-presenting cells (APCs) and activate immune responses, resulting in hypersensitivity reactions [14]. Some common allergens include proteins derived from wheat and peanut, and more recently, novel proteins derived from genetically modified foods have been identified as potential sources of allergens which could contribute to increased risk of hypersensitivity [15].

Food hypersensitivities are characterised as either immunoglobulin E (IgE)-mediated food allergy or non-IgE–mediated food sensitivity, and these conditions are distinct from food intolerances which do not have an immunological basis and occur, for example, due to enzymatic defects or reactions to natural or artificial chemicals in food [16].

Recent advances in our understanding of the role of dietary factors (e.g. gluten, fructans) that provoke symptoms in functional GI disorders, and the commonality of symptoms raised the question as to whether a proportion of FGID cases are driven by food sensitivity [17, 18]. For instance, a recent longitudinal cohort study identified overlap between self-reported wheat sensitivity and FGIDs [19••]. Other associations between food intake and FGID symptoms may be overlooked due to poor patient recall and common use of non-validated tools in assessing links between diet and symptoms [20]. Nevertheless, dietary interventions are often implemented to alleviate symptoms in FD patients to varying degrees of success and an increased understanding of immune responses to food in FD patients may improve the application of this approach for management of symptoms [21•, 22•].

FD Immunopathology

Specific mechanisms that drive loss of oral tolerance and promote hypersensitivity responses to food antigens are poorly characterised, and similarly, immune mechanisms in FD remain unclear. An increase of eosinophils in the duodenum is consistently reported in a subgroup of FD patients, as described in a recent systematic review (Fig. 1) [23••]. As eosinophils are involved in the pathology of not only IgE-mediated food allergy but also other food hypersensitivity conditions including food protein-induced enterocolitis syndrome (FPIES) and eosinophilic esophagitis (EoE), their increased presence in FD may be suggestive of a similar pathology to these conditions [24]. Eosinophilia in adult FD patients was first described in a Swedish cohort in 2007 and since then has

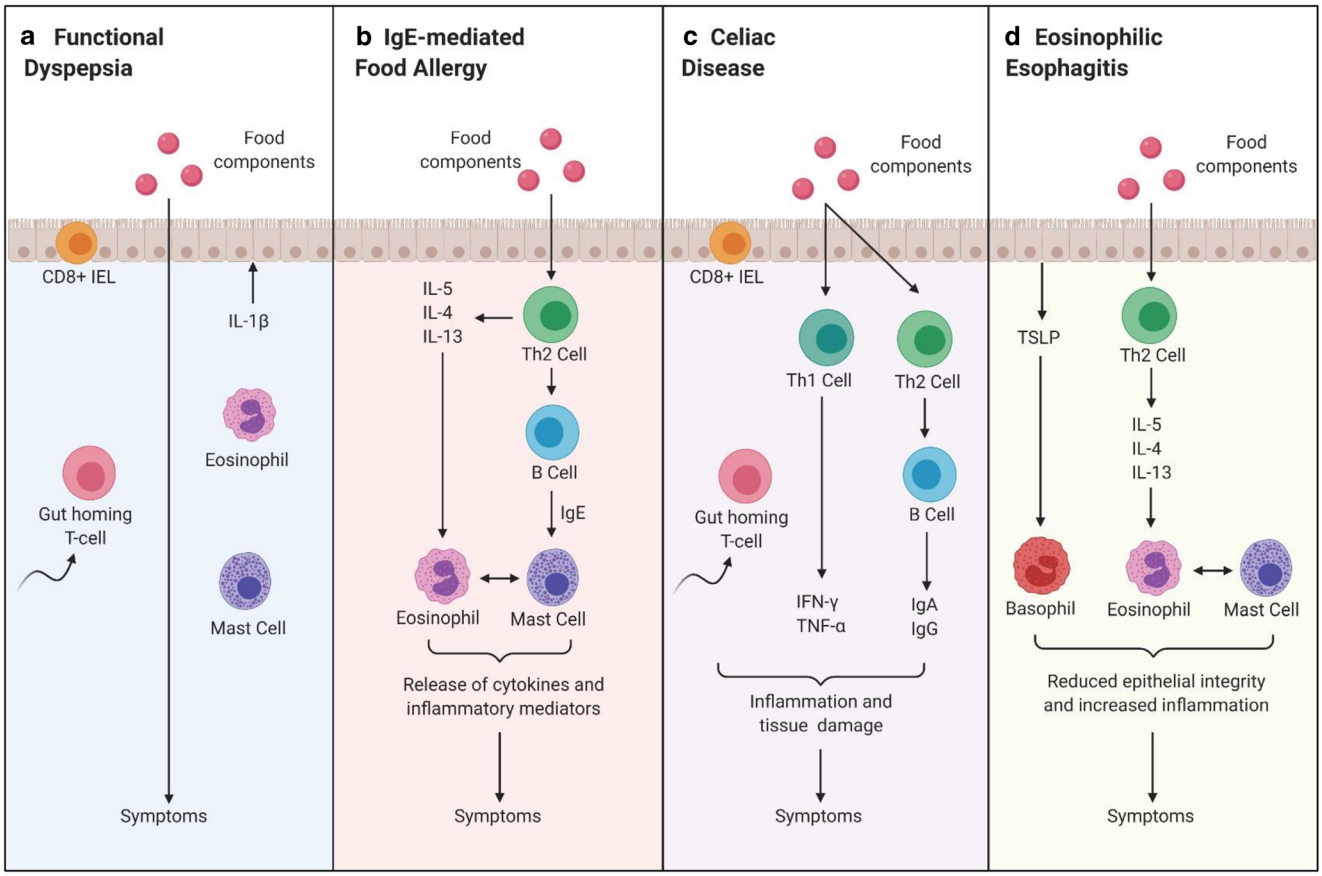

Fig. 1 Comparison of immune mechanisms driving pathology of food hypersensitivity conditions in the gastrointestinal tract. **a** Functional dyspepsia patients often report symptom onset following food ingestion; however, exact immune mechanism is not currently understood. An increased presence of eosinophils and mast cells in the duodenum and gut-homing lymphocytes in the circulation of patients is linked to disease [23••]. Increased IL-1β causes reduction in mucosal barrier function [66]. CD8+ Intra-epithelial lymphocytes (IEL) are more abundant in *H. pylori*–positive FD patients [62]. **b** IgE-mediated food allergy results from a T helper type (Th) 2 immune response which causes activation of B lymphocytes to release immunoglobulin (Ig) E. IgE activates mast cells for degranulation and release of inflammatory factors. Th2-associated cytokines, interleukin (IL)-5, IL-4, and IL-13 cause recruitment and activation of eosinophils, enhancing the inflammatory environment [41, 42]. **c** Celiac disease activates a Th1 response for the production of proinflammatory cytokines, interferon gamma (IFN-γ), and TNF alpha (TNF-α). A Th2 pathway is also activated resulting in the B cell production of IgA and IgG against gliadin and tissue transglutaminase. Increased CD8+ IELs are a common pathology identified in celiac disease. Gut-homing T cells are increased in circulation of celiac disease patients [52]. **d** In eosinophilic esophagitis a Th2-mediated pathway is activated where cytokine release causes recruitment of eosinophils which in turn can act on mast cells. Basophils are also recognised in eosinophilic oesophagitis, and are activated in a thymic stromal lymphopoietin (TSLP)-mediated manner [47]. Created with Biorender.com

been supported by studies globally [25–28]. Duodenal eosinophilia was specifically linked to FD patients with symptoms of early satiety and post-prandial fullness, and it was noted that these patients have a higher-than-normal incidence of atopic disease, including food allergy [10•, 29, 30]. The nature of FD-associated duodenal eosinophilia is not fully understood, particularly in the absence of strong evidence for a Th2 response in these patients; however, eosinophil degranulation has been observed through immunostaining and transmission electron microscopy (TEM) suggesting that in FD, eosinophils have an effector function [23, 28, 31]. Degranulation of eosinophils releases granular factors including major basic protein (MBP) and eosinophil peroxidase (EPO), which can be cytotoxic towards cells. The release of these proteins reduce epithelial barrier function in colonic cells and induce epithelial remodelling in airways, and thus have been linked to pathology of atopic conditions [32–34]. EPO and MBP can also cause dysfunction of vagal nerve muscarinic receptors, which induces smooth muscle hyperreactivity and could contribute to FD symptoms associated with visceral sensitivity [35]. A recent study has identified, through histological staining, that degranulation of eosinophils in FD patients was correlated with increased density of fine nerve fibres which may relate to symptoms of visceral hypersensitivity [36].

Alongside duodenal eosinophilia, increases in duodenal mast cell numbers have been frequently described in FD, which is of note as mast cells play a crucial role in driving symptoms in IgE-mediated food allergy [37]. Like eosinophils, duodenal mast cells demonstrate enhanced

degranulation in FD which may contribute to the heterogeneity of granular content observed in the histology of those patients [28, 31]. Altered granular contents may result from a distinct granular protease composition in FD patients, which could contribute to pathogenesis. Degranulation of mast cells releases a range of inflammatory mediators, including histamine and tryptase, which act on surrounding cells to increase tissue permeability and cause smooth muscle contraction, activating peristalsis [38]. This action may be linked to motility-related symptoms and abdominal discomfort in FD. Increases in duodenal mast cell numbers are not always observed in FD patients but have been associated with symptoms of nausea and psychological dysfunction in both FD and IBS patients which may point towards a subgroup of FGID patients with symptoms related to mast cell action [26, 39]. Further investigation is required to identify if these symptoms occur as a response to specific foods, but it is clear that there is an overlap between the subtle inflammation seen in FD and the pathology of common food hypersensitivities.

Immune Responses in Food Hypersensitivities Overlapping with FD

Aberrant immune responses to food occur in patients when a breakdown of immune tolerance to food antigens occurs. Under homeostatic conditions, T regulatory cells are produced in response to cellular recognition of specific food antigens [40]. These cells release interleukin (IL)-10 and transforming growth factor beta (TGF-β) for suppression of inflammatory T helper (Th) cell pathways and for activation of immunoglobulin A (IgA) production [40]. This anergic response is lost towards some food antigens in patients with food hypersensitivities and results in alternate immune pathways being activated.

Immune Responses in IgE-Mediated Food Hypersensitivities

In classical food allergy, the introduction of the offending food in the GI tract initiates class switching of naïve T cells to a Th2 phenotype for the production of IL-4, IL-5, and IL-13 (Fig.1) [41]. This cytokine profile promotes recruitment of mast cells and eosinophils and is also necessary for activation of B lymphocytes to produce IgE. IgE causes degranulation of mast cells, resulting in the release of inflammatory mediators including histamine, that produce allergy symptoms [42]. Interestingly, a study of FD patients has found that circulating levels of Th2-associated IL-4 and IL-5 are among cytokines which are significantly associated with dyspeptic symptoms, including epigastric pain and burning [43]. An earlier study described the expression of Th2-associated cytokines IL-5 and IL-13, by stimulated peripheral blood mononuclear cells (PBMCs), to be significantly increased in FD patients compared with controls [44]. Whilst these two studies are supportive of the presence of a Th2-associated cytokine environment in FD that is typical of allergic disease, there is overall a very limited consensus in the literature regarding the cytokine profile in FD, making it difficult to draw conclusions about the associated cytokine phenotype [23••].

Immune Responses in Non-IgE Mediated Food Sensitivities

Non-IgE–mediated food sensitivities trigger immune responses to food without the characteristic IgE production seen in food allergies. Symptoms of non-IgE conditions generally appear later following consumption of the offending food, compared with IgE-mediated food allergy [45]. Some associated conditions include celiac disease, EoE, and FPIES [46, 47]. The mechanisms driving many non-IgE–mediated food sensitivities are poorly established, and the late onset of symptoms and varied immune presentations make the conditions difficult to diagnose. However, despite heterogeneity among non-classical hypersensitivity reactions, cell-mediated immunity, potentially involving Th1 immune responses, is hypothesised to drive the immune response in these conditions [48–50]. This is the case in celiac disease, where activation of Th1 lymphocytes, in response to gluten antigens, results in the production of type 1 cytokines, including interferon gamma (IFN-γ) to drive an inflammatory response that results in tissue damage (Fig. 1) [51, 52]. Further, the increased intestinal permeability observed in FPIES is hypothesised to result from decreased TGF-β production in conjunction with increased production of TNF-α that promotes an inflammatory phenotype [50].

In FD patients, elevated levels of food antigen-specific IgG, but not IgE, have been reported, compared with a control population [53]. Elevated IgG has also been described in irritable bowel syndrome (IBS), another FGID with considerable symptom overlap with FD [54]. Use of confocal laser endomicroscopy in IBS patients demonstrated a cellular response to certain foods in more than 50% of patients [55••]. The observed response was not mediated by IgE production; however, increased activation of eosinophils was reported following challenge in these patients, suggesting the duodenal eosinophilia observed in FD may result from atypical food hypersensitivities [55••].

Specific Foods Trigger Symptoms in FD

Wheat

One of the most common food hypersensitivities reported by FD patients is in response to wheat or the group of proteins

present in wheat known as gluten. Non-celiac wheat/gluten sensitivity (NCW/GS) describes a condition where the consumption of wheat or gluten-containing foods results in GI and extra-intestinal symptoms [19••]. Many of these symptoms overlap with FD, leading to the hypothesis that NCW/GS may be a subtype of FD. An Italian survey of patients with suspected NCW/GS identified that greater than 80% of patients experienced bloating and abdominal pain, and 52% experienced epigastric pain, the defining symptoms of EPS, highlighting the overlap between these conditions [56]. NCW/GS is diagnosed in the absence of celiac disease and IgE-mediated wheat allergy and confirmed through a double-blind placebo-controlled wheat challenge. An Australian population-based study reported a significant association between self-reported NCW/GS and diagnosis with FD by a modified Rome criteria and reported that 29% of participants with FD avoided consuming gluten [19••, 57••]. The pathogenesis of NCW/GS is poorly characterised; however, there is some overlap with FD pathogenesis. Patients with a confirmed diagnosis of NCW/GS have increased mucosal eosinophil infiltration in the GI tract compared with IBS patients not reporting symptoms associated with gluten ingestion [58]. Similarly, a study by Carroccio et al. identified increased duodenal eosinophils in NCW/GS patients compared to controls [59••]. Moreover, this study found that within the NCW/GS cohort, there was a significantly greater number of eosinophils in NCW/GS patients experiencing upper GI symptoms, compared to the rest of the cohort, supporting the idea that NCW/GS exists in a subset of FD patients. Along with eosinophils, expression of toll-like receptors (TLRs) has also been implicated in the pathogenesis of NCW/GS. An increased expression of these receptors has been recognised in NCW/GS patients [60]. TLRs are innate antigen sensors, expressed on innate cells including eosinophils and macrophages, which can initiate inflammatory responses once activated [61, 62]. Gliadin, a gluten-derived immunogenic peptide has been suggested as a TLR ligand, and as in NCW/GS, TLR expression is increased in celiac patients [63, 64]. Gluten-derived peptides may disrupt epithelial tight junction integrity by promoting zonulin secretion, and impaired intestinal barrier function has previously been described in FD [65–67]. Adhering to a gluten-free diet has had some success in improving symptoms for FD patients. In an Italian study, 75% of FGID patients following a 3-week trial of a gluten-free diet experienced relief from symptoms [68]. Furthermore, a randomized double-blind placebo-controlled trial in FD patients alone found that 35% of patients had an improvement of symptoms, whilst on a gluten-free diet however, only 18% of those patients were confirmed to have NCW/GS with symptoms reoccurring following blind gluten challenge [69••]. As symptom reoccurrence only occurs in a relatively small percentage of gluten-challenged patients, it has been proposed that there is a different component of wheat-based foods triggering symptom onset. Such components may include amylase trypsin inhibitors, wheat germ agglutinins, or fructans [70].

FODMAPs

FODMAPs—fermentable oligosaccharides, disaccharides, monosaccharides, or polyols—are short-chain carbohydrates present in food considered to contribute to symptoms in FGIDs. FODMAPs are poorly absorbed in the GI tract and are readily fermented by the gastrointestinal microbiota into short-chain fatty acids (SCFAs), increasing gas production [71]. Whilst it has been found that high FODMAP ingestion prolongs hydrogen production from the intestines of both healthy and FGID patients, the effect is significantly greater in FGID patients compared with controls and is accompanied by an induction of gastrointestinal symptoms [71]. FODMAPs are also considered to be osmotically active, meaning they contribute to increased water volume in the lumen of the GI tract [21•]. It appears that in FGID patients, the effects of FODMAPs are heightened, contributing to symptoms. A systematic review of literature investigating the effects of food on FD presentation identified FODMAP-containing foods as some of the most commonly implicated foods to FD symptoms [72••]. FODMAPs are highly present in a range of fruits, vegetables, dairy products and importantly, wheat-based foods. Fructans are the main carbohydrate constituent of wheat and come under the classification of FODMAPs, and thus may contribute to the pathogenesis of NCW/GS. A double-blind crossover challenge of self-reported NCW/GS patients investigated the effect of fructans on symptoms and discovered that whilst gluten caused no significant change in these patients, fructan challenge resulted in significant worsening of symptoms, suggesting that the fructan component of wheat, as opposed to gluten, triggers symptoms in NCW/GS patients [22•].

A low FODMAP diet has consistently been shown to improve symptoms in IBS patients, for which there is significant clinical overlap with FD [54]. However, there is little literature describing the effect of low FODMAP diets in FD patients [21•]. In IBS patients, a long-term low FODMAP diet improved the presentation of symptoms and reduced levels of fatty acid-associated inflammatory markers, however there are concerns of long-term impact of low-FODMAP diet on the microbiota [73, 74]. The microbiota is responsible for the fermentation and digestion of FODMAPs and thus the low-FODMAP diet may negatively impact microbes that utilise these nutrients as a primary carbon source. Murine models have highlighted immunomodulatory capabilities of fructans which can occur in a microbiota-dependent manner [75].

Analysis of the GI microbiota of FD patients has identified a significant increase in the genus *Streptococcus* when compared with healthy controls, which positively correlated with increased upper GI symptoms [76•]. Increased severity of

symptoms also corresponded with increased bacterial load and reduced microbial diversity in the duodenal microbiota of FD patients, who also exhibited a significant reduction in the abundance of *Prevotella, Veillonella* and *Actinomyces* [77•]. With regard to diet and enterotypes, *Prevotella* is associated with high consumption of plant materials and fibre, and therefore carbohydrate metabolism via fermentation [78]. Interestingly, decreased abundance of *Prevotella* was associated with increased symptom severity in IBS patients, and probiotic supplementation results in restoration of *Prevotella* abundance and reduction in PDS symptoms in FD patients [79, 80]. As such, decreased *Prevotella* abundance in these patients may suggest altered carbohydrate metabolism is associated with symptoms in FD; however, this relationship requires further characterisation.

Alterations to the composition and bacterial load of the GI microbiota have also been regularly reported in patients with food hypersensitivities [81–83]. A reduction in *Prevotella* abundance has been described in the duodenum of celiac disease patients, which is consistent with the reported microbiota changes in FD [84]. Also in celiac disease, the abundance of the genus *Pseudomonas* is correlated with enhanced proteolytic activity in patients, and when patient microbiota is transferred into germ-free mice, it results in increased intraepithelial lymphocytes [85•]. In EoE, much like in FD, an increase in bacterial load is associated with disease state [83]. There is also an enrichment of the genus *Neisseria*, *Corynebacterium* and *Haemophilus* identified in EoE when compared to healthy controls [83, 86]. In IgE-mediated food allergy, a reduction in the diversity of microbial species is seen, with reduced abundance of Bacteroidetes, Proteobacteria and Actinobacteria and increased abundance of Firmicutes reported [81, 87]. The common presence of altered microbiota in food hypersensitivities may allow speculation that specific changes to the microbiota can predispose the immune system to susceptibility towards food antigens, resulting in food-triggered symptoms. However, it must also be considered that altered diets also drive changes in the microbiota, and this effect could account for some of the identified changes where diet has not been controlled for [88, 89•]. These pathways may be at play in FD; however, the exact driving mechanisms remain to be elucidated.

Fats

There is significant association between ingestion of high-fat foods and symptoms in FD patients, specifically postprandial fullness and bloating [90, 91]. These findings have been directly validated, and intraduodenal infusion of lipids, but not glucose, was found to cause nausea and provoke feelings of fullness in FD patients compared to controls [92]. A similarly enhanced symptom profile in FD patients was seen following consumption of a high-fat meal when compared with a high-carbohydrate or low-nutrient diet [93]. The same study recognised that concentrations of the hormone cholecystokinin were increased in FD patients after the high-fat meal. As this hormone plays a role in stimulating the release of bile and enzymes required for digestion, an overexpression may provoke symptoms in FD. Indeed, altered bile acid pools have recently been described in FD patients and may be a determinant of microbiota composition [94, 95]. However, a more recent study of FD patients found that symptoms of nausea and bloating were unchanged following the consumption of either low-fat or high-fat yoghurt [96•]. Moreover, these patients reported more rapid symptom relief towards yoghurt labelled as low-fat, and increased satiety after consuming yoghurt labelled as high-fat, irrespective of the actual fat content of the yoghurt. This emphasises the role for psychology in the pathogenesis of FD and indicates that psychological perceptions of high-fat food can influence symptom presentation.

Capsaicin

Capsaicin is the active compound in chilli peppers which causes the sensation of burning associated with spicy foods. Consumption of capsaicin containing foods causes an increase of symptoms in FD patients when compared to consumption of placebo and when compared with healthy controls [97, 98]. Capsaicin triggers sensations through interaction with the transient receptor potential vanilloid-1 receptor (TRPV1). Interestingly, the G315 polymorphism of the TRPV1 gene is significantly inversely associated with FD [99]. Visceral hypersensitivity associated with capsaicin has also been reported in IBS patients, where TRPV1-reactive nerve fibres and mast cells were significantly increased in colonic biopsies of patients compared with controls [100]. There is scant evidence of an immune mechanism driving symptoms in response to capsaicin in FD patients.

Conclusions

The pathogenesis of functional dyspepsia remains poorly characterised; however, there is emerging evidence for a link between the consumption of specific foods and the onset of symptoms in patients. There is subtle inflammation evident in the duodenum of FD patients, including increased eosinophils and mast cells, and these effector cells overlap with the pathology of food sensitivities, supporting the hypothesis that a subgroup of FD patients experience immune hypersensitivity to foods. Consumption of foods high in gluten, FODMAPs, fat, or capsaicin have all been linked to worse FD symptoms; however, the data is largely observational, and further research is warranted to investigate the mechanisms governing immune responses to these foods in FD patients.

Compliance with Ethical Standards

Conflict of Interest Grace Burns, Kerith Duncanson, Jennifer Pryor, Jay Horvat and Marjorie Walker declare that they have no conflicts of interest.

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