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Tangible pathologies in functional dyspepsia

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ABSTRACT

Functional dyspepsia (FD) is a common, costly and complex disease, currently defined by symptoms, directed by the Rome consensus on functional bowel disorders, which has evolved over the past two decades. Symptoms include abdominal pain, are often meal related and there are two major subtypes, postprandial distress syndrome and epigastric pain syndrome, not attributed to pathology.

Increasingly it is recognised that tangible pathologies occur in FD, for example *Helicobacter pylori* and other pathophysiological changes, most notably duodenal pathology, namely duodenal eosinophilia, permeability alterations, structural neuronal changes and microbial duodenal dysbiosis. This has led to the idea that FD is a true disease entity and triggers of this condition based on epidemiology studies point towards allergy, immune disorders and infection. Anxiety and depression may precede or follow FD, (brain-gut/gut–brain disorders).

Currently most therapies for FD are inadequate but underlying pathology may lead to targeted treatment success as an attainable goal.

Introduction

Whilst functional dyspepsia (FD) has been recognised for over 100 years, over the last two decades the definition of FD has been refined by the evolving Rome consensus (first proposed in 1990) to reflect a constellation of symptoms originating in the gastroduodenal region of the abdomen without an obvious structural cause, such as peptic ulcer, at endoscopy [1]. Rome II further defined dyspepsia as persistent or recurrent pain or discomfort centred in the upper abdomen; absent evidence of organic disease, including at upper endoscopy, with a division into ulcer-like dyspepsia (with predominant pain) and dysmotility – like dyspepsia (with predominant non-pain symptoms including upper abdominal fullness, early satiety, bloating, or nausea) [2]. With further studies it became apparent that FD could be categorised to two major subtypes as proposed by Rome III (2006) [3] and updated by Rome IV [4]. FD is currently subdivided into post-prandial distress syndrome (PDS), characterized by meal-induced dyspeptic symptoms and defined as bothersome postprandial fullness and/or early satiety occurring for at least three or more days per week [4]. Epigastric pain syndrome (EPS), with symptoms that may or may not be related to meals with bothersome epigastric pain and/or burning for one or more days per week - postprandial epigastric bloating, belching and nausea can also be present [4]. The two subgroups can and in clinical practice often do overlap, and symptoms of gastroesophageal reflux disease or the irritable bowel syndrome frequently coexist [4]. In terms of time scale, the symptom criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis. The Rome criteria specify there is no evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy) [4]. An often-overlooked associated but serious symptom is weight loss, linked to early satiety [5].

A major advance in Rome IV is the recognition of potential underlying pathologies in FD, including duodenal mucosal inflammatory and permeability changes [4]. In addition, a symptom response to successful *Helicobacter pylori* eradication now defines a syndrome distinct from FD referred to as *H. pylori* associated dyspepsia (HpD). HpD is distinguished from FD by sustained relief of dyspepsia (for at least 6 months) at 12 months following H. pylori

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eradication therapy [4,6]. In time, other subdivisions will likely ensue as our understanding of pathophysiology of FD emerges.

Together with the Rome consensuses, there are studies unravelling disordered pathophysiology in FD, drawing together observations from epidemiology and the complex interaction of genetics, the microbiome and the environment [7]. These include psychosocial events, the gut –brain/brain-gut pathway, environment (food and lifestyle), gut dysbiosis, post-infectious FD and gut dysmotility, leading to disordered neural and immune pathways - all have which been implicated to play a role in symptom generation in FD [8].

The lack of identification of a single unifying cause points to FD likely being a heterogeneous disease complex for which differing and subtle pathologies may lead to differing manifestations, and explains a rather poor track record in treatment as these are not tailored to pathology [9,10]. This review aims to illustrate progress in unravelling what is "real – i.e. tangible" pathology in "functional" dyspepsia. This lack of more tangible and measurable diagnostic parameters has hampered definition and treatments for FD in comparison to diseases conventionally defined by endoscopic and microscopic pathology, such as seen in gastro-oesophageal reflux disease, peptic ulcer, coeliac disease and inflammatory bowel disease.

Changing paradigms of functional dyspepsia

Epidemiology

Functional dyspepsia is common, as demonstrated by pooled studies revealing that one in five individuals in the community report symptoms of dyspepsia, and most have functional dyspepsia if investigated [11]. Worldwide, there is a variable prevalence, from 20 to 24% in Europe, the USA, South East Asia and Australasia, up to 35% in Africa and South America and 15% in the Middle East, but only 7% in Central America – of interest, the difference was not explained by differing criteria used to define dyspepsia [12]. Female gender, smoking, non-steroidal inflammatory drug use and *H. pylori* were only modestly associated with dyspepsia [12]. Dyspepsia, whilst not life threatening is a cause of significant morbidity - up to 40% of those with dyspepsia consult physicians [13] and experience a significant loss of productivity at work [14]. FD patients also incur very substantial direct and indirect costs, estimated at $18.4 billion per year [15].

Of the two major FD subtypes, the majority fall into PDS. In Italy of 115 with FD, 67.5% had PDS and 48% had EPS, with overlap in 16% [16]. In this study, smoking was associated with PDS, as was being unemployed or divorced, which are plausible stress factors [16]. Similarly, in a large community study in Sweden, EPS was reported by 5% and PDS in 12% individuals with overlap in 10% [17].

Genetics and epigenetics in FD

There are limited data on the influence of genetics on the pathogenesis of FD [18]. Recent studies implicate the inflammatory gene polymorphisms *CD14, GNB3, MIF*, and *TRPV1* associated with epigastric pain syndrome subtype FD in a Greek population [19]. Also inflammation is implicated by association of single nucleotide polymorphisms of *IL17F* (rs2397084) and *IL10* (rs1800871) with FD in an Indian population [20]. Previous evidence also links disturbed signal transduction in FD through the polymorphism *GNB3 C825T* in FD [21]. The TT genotype variants of *GNB3 C825T* has been associated with the epigastric pain syndrome FD subtype in Japanese populations [22], emphasising that FD is a heterogeneous condition with differing symptomatology likely attributable to this differing genetic susceptibility. Large-scale studies to align symptoms to gene expression should clarify these genetic differences [23].

Genetic susceptibility in FD may be influenced by epigenetics, which literally means "in addition to changes in genetic sequence" and is defined as any process that alters gene activity without changing DNA sequence that leads to alterations that can be transferred to daughter cells [24]. Epigenetic silencing of genes, when two people have the same gene copy, leads to differing disease risk, despite an identical genetic background [25]. Epigenetic alteration of gene activity is dependent on environmental change, and the gut is subject to constant external influence – digestion and absorption of nutrients from food, defence against allergens and pathogens and maintaining homeostasis through a vast and diverse microbiome, which also aids digestion and pathogen defence. These bacteria and other microorganisms interact with the adaptive and innate immune system in the gut that is kept in a fine balance [7].

Defining the pathophysiology of functional dyspepsia

Whilst we recognise the overt pathologies of inflammatory bowel disease (principally neutrophil driven and therefore clearly abnormal), the more subtle pathologies of innate immune activation are more difficult to recognise, as these cells are normally present in the gut and it is differences in quantity of these cells which herald pathology in FD [7,26].

There is emerging evidence that the diverse symptom presentation with two major subtypes - PDS and EPS in FD - may result from multifactorial environmental exposures in a genetically and perhaps microbiome primed host including psychosocial factors, diet, allergy and allergens, autoimmune disease and pathogen related factors.

Interactions between psychosocial and biological processes

It is recognized that complex interactions between psychosocial and biological processes are likely to result in FD [27]. As early as 1990, sexual and physical abuse in early life in women was described to be associated with functional gastrointestinal disorders (dyspepsia and irritable bowel syndrome) [28]. Since, several studies have confirmed this observation, including in a community setting [29] and it is concluded there is bidirectional comorbidity between mood and anxiety disorders and functional gastrointestinal disorders [30]. In FD, a direct effect of abuse history on somatic symptom reporting was found, but not mediated through psychological factors [31]. A very high prevalence (67%) of FD is seen in victims of domestic violence, considerably higher compared to the general female population of Spain (24%), and in 72% of this group, the start of abuse coincided with or was prior to symptom onset [32]. Abuse in early and adult life may also have a direct physiological effect as it is associated with alterations in gastric sensitivity and motor function [33]. Anxiety is a strong risk factor for FD; in a population-based endoscopically assessed cohort study, anxiety increased the risk for development of FD by 7.6-fold over the subsequent 10 years [17]. FD symptoms are also linked to disturbed sleep patterns and 70% of FD patients report problems both falling and staying asleep [34].

Brain-gut or gut-brain in functional dyspepsia?

A recent study has shown that in health care seekers, anxiety and/depression precedes the onset of functional gastrointestinal disorders in two thirds of patients, in comparison to community subjects whereby there is a more even split – only 47% of respondents report having anxiety and/depression before occurrence

of functional gastrointestinal disorders [35]. Conversely, FD also can drive anxiety and depression. In a prospective study at 12 years, depression was predictive of FD at follow-up [36]. Similarly, at one year, higher levels of anxiety and depression at baseline were significant predictors of developing FD [37]. The central nervous system (brain) communicates with the gut via the enteric nervous system (ENS) and there is bidirectional crosstalk from the gut to the brain and from the brain to the gut with reciprocal regulation [38]. Pathological gut–brain interaction is largely through the ENS and hypothalamic pituitary adrenal (HPA) axis [38,39]. The gut-brain pathway involves gut immune activation and disturbed microbial composition as potentially primary events, which can affect mood [38]. In contrast, brain-gut pathways resemble somatization disorders, with a primary mood disturbance and distorted pain perception expressed as disturbed gut function [38]. Both pathways appear capable of resulting in symptoms of FD.

Functional dyspepsia and the environment

Functional dyspepsia associated with atopy, autoimmune disease and intestinal eosinophilia

Recognised atopic diseases include asthma, rhinoconjunctivitis or eczema; those with atopy have a tendency to produce IgE antibodies responding to a regular exposure to allergens, usually proteins [40]. The prevalence of dyspepsia in asthmatic patients (21.1%) is significantly greater than in controls (11.3%) as is allergic rhinitis (15.4%) [41]. This also held true in a large general practice study of 23,471 patients in the UK [42]. In another large population study in Scotland, in those with asthma, the fourth most common comorbidity was dyspepsia, with a prevalence of 10.9% compared with 5.2% in normal controls [43]. There is also a significantly higher prevalence of autoimmune disorders among patients with FD [44]. In a large recent community study in Australia, self-reported atopic disease, asthma and food allergy were risk factors for FD, and not accounted for by psychological distress [45].

This association is in keeping with immune activation in the gut as a plausible mechanism for symptom generation.

Furthermore, duodenal eosinophilia (akin to eosinophilia in bronchial asthma) is seen in a subset of patients with FD and PDS. This observation of real pathology in FD, first observed by Talley et al. [46], and has been replicated globally [47–49]. Allergy has also been linked to PDS symptoms and duodenal eosinophilia [47] and mucosal inflammation leads to dysfunction of the intestinal epithelial barrier [48]. Also, eosinophils are implicated in activation of smooth muscle, as close proximity to enteric nerves is seen both in inflammatory bowel disease, in colon mucosa [50] and in FD in duodenal mucosa [38]. Early environmental risk factors i.e. contact with herbivore pets, including horses, is an increased risk for FD in later life, and proximity to these animals includes exposure to animal dander and pollens [51]. This may link to early observations showing that patients with atopy have increased numbers of activated eosinophils in the duodenum mimicking observations in the bronchial mucosa in asthma [52].

Diet, food allergy and food intolerance in functional dyspepsia

Whilst a large proportion of patients with FD report that their symptoms are triggered by meal ingestion, large scale studies are lacking [53]. Wheat and specifically gluten, and also fermentable carbohydrate (FODMAP) ingestion, high fat ingestion and naturally occurring food chemicals, may play key roles in the generation symptoms of FD [54]. Of interest is the obvious overlap of FD symptoms and those in patients with the recently described condition, non-coeliac gluten or wheat sensitivity (NCG/WS), a condition characterised by gastrointestinal and/or extra-intestinal symptoms associated with the ingestion of gluten- or wheat-containing foods, in the absence of celiac disease or wheat allergy [55]. Gastrointestinal symptoms that overlap FD and NCG/WS include abdominal pain, nausea and vomiting [56], as well as early satiety and postprandial fullness [57]. This condition is difficult to diagnose outside specialised practice [56], and it is important to be meticulous in excluding coeliac disease, as some patients purporting to have NCG/WS undoubtedly fall into the spectrum of potential coeliac disease [58], and the diagnosis is still often missed in practice [59].

Currently, general dietary measures in management of FD focus on eating low-fat, more frequent and smaller meals [53]. Of interest, at one year following eradication therapy for H. pylori in patients with peptic ulcer disease, or gastritis and duodenitis, the prevalence of food intolerance significantly decreased from 71% to 44% among patients with ulcers and from 76% to 63% among patients with gastroduodenal inflammation, and tolerance also improved for foods associated with dyspepsia - coffee, orange juice, fried foods, spicy foods and fruits [60].

Lifestyle factors in functional dyspepsia: alcohol, tobacco and exercise

A systematic review of the role of smoking and alcohol intake in functional gastrointestinal disorders (FGIDs) showed that whilst smoking seems to be associated with FD with a significant 50% increased risk of FD for current compared with never-smokers, this was not significant in irritable bowel syndrome (IBS) [61]. In a meta-analysis of nine studies, it was shown that there is a significantly higher prevalence of dyspepsia among smokers (OR = 1.35; 95% CI 1.17 to 1.56, $p < 0.001$) [12]. Of interest, smoking is associated with increased duodenal eosinophilia [49]. There are scant data on alcohol intake, but there was no association with any FGIDs and moderate alcohol intake [61] and specifically in FD a hospital based study found no association with alcohol intake [62]. The frequency of exercise reported by the FD/IBS subjects was significantly lower than that reported by the control subjects ($P < 0.01$) [63]. Following H. pylori eradication therapy, notably there was no significant change in smoking or alcohol consumption and no change in the time spent exercising in patients with peptic ulcer and gastroduodenal inflammation [60].

Pathogens and the microbiome - post-infectious functional dyspepsia and dysbiosis

Studies have concentrated on the role of H. pylori in FD, now designated as HpD and defined by sustained relief of dyspepsia (at least 6 months) at 12 months following eradication therapy for H. pylori [4,6]. However post infectious FD (PI-FD) is also recognised, and acute gastrointestinal infections can trigger FD in susceptible patients [4]. In a large Canadian study, it was shown that following the Walkerton outbreak of bacterial dysentery at 8 years, there was a greater than 2-fold increase in the prevalence of dyspepsia in subjects exposed to acute gastroenteritis compared with non-exposed individuals [64]. Predisposing factors to developing FD included abdominal cramps and duration of diarrhoea in the acute illness [64], also seen in a Spanish study of PI-FD when prolonged abdominal pain and vomiting during the acute phase of Salmonella gastroenteritis were positive predictors of new onset dyspepsia [65].

The pathogenesis of PI-FD is suggested to be residual disturbed immune activation [66] characterised by duodenal eosinophilia and macrophage infiltration in duodenal mucosa [67], or a transient inflammatory reaction that leads to permanent changes in both

structure and function of the gastrointestinal tract [68].

Another possibility in pathologenesis is post infectious change in the resident microbiome, either through displacement by pathogens or antibiotic use in acute infection rendering changes in barrier function. Tolerance to food allergens and also keeping the epithelial barrier intact are induced by the normal resident bacteria and this prevents sensitisation to food antigens [69]. Recent work on the mucosal associated microbiome in the duodenum in FD has shown that there is a positive correlation of increased mucosal bacterial load with more severe nutrient challenge related symptoms and, as total bacterial load increases, bacterial diversity decreases [70]. There is in parallel a significant correlation of increased duodenal mucosal bacterial load and poorer quality of life [70]. Thus the duodenal microbiome probably plays an important role in the generation of FD symptoms.

Whilst the upper gastrointestinal tract is traditionally been considered a hostile environment for bacteria due to rapid transit of food in the oesophagus, acid in the stomach and bile in the duodenum, disturbing this milieu has consequences that may result in FD. It is time to comprehensively study this microbiome and its role in functional gastrointestinal and other upper gut disease [71].

Gut dysmotility, disordered immune pathways

Endoscopy excludes overt pathology in FD that is, ulcers, carcinoma and oesophagitis, which can be a cause of dyspepsia-like symptoms (erosive oesophagitis in 6% and peptic ulcer in 11%), although the vast majority (82%) will have a normal endoscopy [11]. These conditions have underlying evident neutrophil-driven acute inflammation on histology. It has become apparent that in FD, whilst little is seen macroscopically, in depth microscopy and molecular pathways are now revealing innate immune mechanisms that may trigger symptoms through disordered physiology [8]. The symptoms of FD – recurrent pain, early satiety and a feeling of gastric fullness – suggest underlying gastroduodenal dysmotility and this is thus the plausible mechanism to link inflammation, neural pathology and physiological pathways.

Dysmotility, gastric emptying, dysaccommodation, and duodenal hypersensitivity

Orthodoxy has attributed FD to a disturbance of gastric physiology, slow gastric emptying, failure of the gastric fundus to relax after a meal (fundic dysaccommodation, a vagal reflex), or gastric hypersensitivity with distention of the stomach [68]. However, this is not a universal finding and the only reasonably consistent link to symptoms is early satiety and fundic dysaccommodation [72]. Gastric accommodation failure is also linked to transient relaxations of the lower oesophageal sphincter that occur in gastro-oesophageal reflux and may, in part, explain the overlap of GERD with functional dyspepsia [73]. Duodenal hypersensitivity to acid, lipids or distention has also been reproducibly identified [68].

Gastric and duodenal inflammation in functional dyspepsia

In immune function, the stomach is relatively inert, whilst mucosal acquired lymphoid tissue is most often seen in *H. pylori* infection and may persist following eradication, and HpD is now a separate entity to FD [4,6]. *H. pylori* infection manifests as acute and chronic gastritis, and following eradication therapy neutrophils are swiftly lost (and a good indicator of treatment success) although chronic gastric inflammation can persist in 51% at one year [74]. Eradication only resulted in normalization of gastric mucosa (no acute, chronic inflammation, intestinal metaplasia or atrophy) in 51% of patients at a mean follow up of 43 months [75]. This also provides evidence for using a separate definition of HpD, to be distinguished from FD by sustained relief of dyspepsia (at least 6 months) at 12 months following H. pylori eradication therapy [4,6].

In PDS, there is growing evidence that symptoms originate from duodenal pathology, specifically innate immune dysregulation with duodenal eosinophilia a key marker. This was first observed in 2007 in an adult community population in Sweden [46] and has since been confirmed in global studies in patients with PDS [8] (see Fig. 1). Other indicators of duodenal pathology are increased mast cells in a subset [76] and loss of epithelial integrity [48]. This subtle inflammation has been shown to be associated with neuronal function (decreased nerve calcium responses) and structural changes (gliosis, abnormal ganglion architecture) associated with increased eosinophils and mast cells in submucous ganglia in FD [77], which could explain dysmotility as a cause of symptoms and the duodenum as the key site for symptom generation. Alongside these observations, increased numbers of small-bowel homing T lymphocytes that are positive for both $\alpha 4\beta 7$ integrin and chemokine receptor 9 are seen in patients with functional dyspepsia, with cytokines (including tumour necrosis factor α), which have correlated to more severe symptoms and delayed gastric emptying [78].

A recent systematic review on immune activation in FD showed increases in circulating T helper cells expressing gut homing markers, which suggests FD is linked to loss of mucosal homeostasis [79]. The anti-inflammatory cytokine IL-10 can be also released by immune cells into the blood which may promote (in conjunction with small-intestinal-homing T cells) an anxiety or stress response, which in turn may lead to disordered motility and visceral hypersensitivity in the stomach and duodenum [8].

Tangible pathology in FD, a paradigm shift in rational diagnosis

These epidemiological, genetic, environmental and subtle histopathology observations thus may explain an underlying pathogenesis of FD, particularly PDS. The model presented by Talley [8] outlined below also explains the gastrointestinal and extra-intestinal manifestations of FD.

In a genetically predisposed individual with PDS, microbial disturbance/or a pathogen/or an allergen can induce subtle innate immune responses (eosinophils and mast cells in some cases) which when in excess actively degranulate disrupting duodenal epithelial permeability. This leads to perpetuation of antigen presentation to the mucosa and subsequent neural irritation, with feedback to the central nervous system which may be experienced as symptoms. Local feedback mechanisms impact on gastroduodenal function prompting early satiety. The release of cytokines and increase in homing small bowel T cells further alter gastroduodenal function and induce systemic symptoms. However, EPS likely has a different pathophysiological basis and may be induced by H. pylori infection, perhaps via antral predominant gastritis that increases gastric acid secretion, leading to excessive acid in the duodenum. Acid may activate duodenal sensory nerves and induce pain as seen in HpD.

Pathology of functional dyspepsia – tangible targets for treatment?

The therapeutic process begins with a secure diagnosis, explanation and reassurance that the condition is benign. Up to one third of patients may respond to this simple intervention alone, especially those with fluctuating symptoms [80]. Several treatment options exist, many with mechanisms that correspond with our increasing knowledge regarding the pathophysiology of the disease. Simple lifestyle measures of stopping smoking and securing sleep patterns are to be recommended, while the armamentarium for treatment includes eliminating dietary triggers, acid

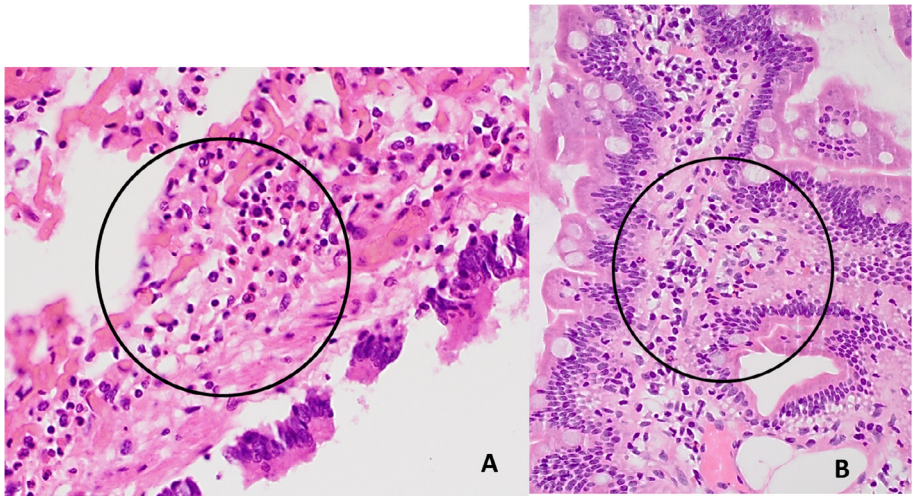

Fig. 1. A: Bronchial mucosa with eosinophilia in the lamina propria (circled) in an asthma patient. B: Duodenal mucosa with eosinophilia in the lamina propria (circled) in an FD patient with early satiety.

suppression, microbiome rescue, motility agents and gut-brain targets.

Dietary triggers

Traditionally, dietary advice has focused on small regular low-fat meals [8]. Although a variety of different foods are linked with functional dyspepsia, dietary trials are lacking [54]. One study has explicitly investigated the overlap between functional dyspepsia and gluten sensitivity [81]. In a double blind, randomized, placebo controlled study, 82% of dyspeptic patients reported symptomatic improvement with a run-in non-blinded gluten free diet, but only 24% of these responders had reproducible symptoms when challenged with gluten in a double blind randomized placebo controlled dietary trial, suggesting nonetheless that a small subset may benefit from an exclusionary diet [81]. Further studies are required.

Dysbiosis

Helicobacter pylori eradication therapy is recommended as first line therapy in infected individuals [82]. A recent meta-analysis of 22 RCTs that evaluated 4, 896 H. pylori positive FD patients who were treated with either eradication or placebo antibiotics, observed a presence of continued dyspeptic symptoms in 67.9% of the eradication group compared with 76.4% of the placebo group (RR for dyspepsia remaining = 0.91, 95% CI 0.88–0.94) [82]. Whilst reviews have shown the number needed to treat to gain relief is 14, a large scale recent study puts this number at 8 and there are no predictive criteria for instituting treatment [6] although EPS rather than PDS may respond [83].

Other treatments may also influence the microbiome. In a RCT of 86 subjects with FD in Hong Kong, treatment with the non-absorbable antibiotic rifaximin for 2 weeks was superior to placebo, leading to adequate relief in 78% of subjects, compared with 52% in the placebo group ($p = 0.02$) [84]. The mechanism of action is believed to be secondary to its antibiotic properties, affecting the altered duodenal microbiome, but may also be secondary to anti-inflammatory properties [84].

Acid suppression and low grade inflammation

Acid suppression is recommended first line therapy in those not infected with H. pylori [82]. In a meta-analysis of 25 RCTs examining the role of acid suppression therapy in FD, proton pump inhibitors were superior to placebo in relief of global symptoms of dyspepsia (RR 0.88, 95% CI 0.82–0.94) [82]. This effect was independent of dose, duration, or FD subtype [82]. There was no significant difference in PPI therapy when compared with H2 receptor antagonist treatment (RR 0.88, 95% CI 0.74–1.04). This response rate to PPI therapy (31% reporting minimal or no symptoms) is lower than that seen in erosive [85], and non-erosive gastro-oesophageal reflux disease [86], suggesting the mechanism by which acid suppression reduces symptoms may be independent of its effect on gastric pH. One possible mechanism is through an anti-inflammatory effect. PPIs are known to inhibit eotaxin [87], offering a potential mechanism through which PPIs may suppress duodenal eosinophilia. A case control study suggests that PPIs may suppress duodenal eosinophilia but requires confirmation [88].

Histamine-2 receptor antagonists have similar efficacy to PPIs, based on a meta-analysis of 7 RCTs including 2456 dyspeptic patients, with a non-significant difference when compared with PPI therapy (RR for remaining dyspepsia 0.93, 95% CI 0.76–1.16) [82].

Supporting the anti-inflammatory hypothesis is a small cohort study in which 42 pediatric patients with duodenal eosinophilia (>10 eosinophils per HPF) were treated with a combination of combination of H2-receptor antagonist (ranitidine) and H1-receptor antagonist (loratidine) leading to improvement of symptoms in 70% of patients [89]. Montelukast, an eosinophil stabilizing agent, has been used with some success in FD with duodenal eosinophilia. In a crossover RCT of 40 children and adolescents, montelukast was associated with symptom improvement 62% of patients, compared with only 32% in the control group ($p < 0.02$) [90]. No adult data are available.

Dysmotility

Agents affecting gastric motility have been extensively evaluated, given the observations regarding dysaccommodation and

delayed gastric emptying seen in FD. Prokinetics have been evaluated in several studies. In a meta-analysis of 26 RCTs, prokinetic therapy was superior to placebo (RR of remaining symptomatic in the dyspeptic group = 0.92, 95% CI 0.88–0.97) [82]. This effect was largely driven by cisapride, a 5HT-4 agonist (and 5HT3 antagonist) which has been removed in many countries due to the risk of death secondary to cardiac arrhythmias [91]. Domperidone, a peripherally acting dopamine-2 receptor agonist, has also been evaluated, although studies largely employed non-standard definitions of dyspepsia or did not perform endoscopy to establish the diagnosis [82]. A meta-analysis of these studies demonstrated a significant benefit over placebo (RR remaining symptomatic with domperidone 0.71, 95% CI 0.53–0.97). Again, safety concerns exist regarding prolongation of the QT interval with this medication [91]. There are no RCTs evaluating the use of metoclopramide in FD, and side effects including tardive dyskinesia limit its usefulness [91]. Tardive dyskinesia is a feared complication as it is often irreversible despite stopping metoclopramide therapy but recent reviews suggest the risk is less than 1% with chronic use even in the elderly [92,93]. Alternatives shown to have significant evidence of benefit in a meta-analysis include acotiamide, tegaserod, alosetron and tandospirone [79]. Acotiamide has been approved in Japan and India for FD with ongoing phase 3 trials in Europe; this drug relaxes the gastric fundus and improves PDS versus placebo [9,94].

Gut-brain/brain -gut interactions

A number of agents targeting the gut-brain/brain -gut pathway have been evaluated. Tricyclic antidepressants have modest efficacy in functional dyspepsia [95,96]. The largest trial to date (n = 292) compared amitriptyline and escitalopram with placebo in FD patients [97]. Amitriptyline (50 mg per day) demonstrated modest benefit over both escitalopram and placebo; 53% reported adequate relief with amitriptyline vs. 38% with escitalopram and 40% with placebo (p = 0.05) [97]. A meta-analysis of RCTs evaluating tricyclic antidepressants in FD (3 studies) gave a pooled relative risk of 0.74 (95% CI 0.61–0.91) for remaining dyspepsia after treatment [95]. Mirtazapine, a tetracyclic antidepressant with anti-histamine properties has also demonstrated encouraging results in a small RCT of 34 patients, in which symptom scores at weeks 4 and 8 significantly improved in the treatment group but not the controls [98]. Other antidepressant classes, including selective serotonin reuptake inhibitors and serotonin-noradrenalin uptake inhibitors have been ineffective in trials to date [95,96].

Behavioural therapy is another approach targeting gut-brain interactions. A number of studies, employing a range of behavioural interventions including cognitive behavioural therapy and psychotherapy, have shown benefit over usual care, although this was a conditional recommendation, with very low quality evidence [82]. A meta-analysis of 4 RCTs in 789 patients evaluating the role of psychological intervention on dichotomous outcomes in FD reported a significant benefit (RR 0.53, 95% CI 0.44–0.65) with a NNT of 3 [82].

Summary

Functional dyspepsia is a common, costly and complex disease, which has been defined by symptoms alone with guidance from the Rome consensus on functional bowel disorders. The symptoms may include but are not limited to abdominal pain and are often meal related. Rome definitions of FD have evolved over the past two decades. It is recognised that in patients with FD, two major subtypes emerge, post prandial distress syndrome (a majority) characterised by early satiety or feeling of fullness and also epigastric pain syndrome with bothersome epigastric pain/or burning that may or may not be related to meals. Symptoms must be present within certain time scales and for a specified period. Rome IV is the latest iteration, and whilst FD previously has been defined as being without attributable macroscopic or microscopic pathology, there is now the recognition that in some cases H. pylori may play a role and other pathogens (pathogenic E. coli for example) can cause post infectious FD. Recent work has identified pathophysiological changes in FD, most notably duodenal pathology, namely duodenal eosinophilia, permeability alterations, structural neuronal changes and microbial duodenal dysbiosis, which can be related to symptoms. This has led to the idea that FD is a tangible disease entity and triggers of this condition based on epidemiological studies point towards allergy, immune disorders and infections. Anxiety and depression may precede or follow FD, termed brain-gut or gut–brain disorders and the progression to one another may be linked through active immune pathways, driven by gut or brain pathologies. Currently most therapies for FD are inadequate but knowing and defining underlying pathology may lead to targeted treatment success, which is becoming an attainable goal.

Practice points

Functional dyspepsia is a common, costly and complex heterogeneous disease, which affects one in five individuals in the community.

It is important to make a secure diagnosis and exclude other disease as a cause of functional dyspepsia by endoscopy (gastro-oesophageal reflux disease, peptic ulcers and cancer) and other testing as clinically indicated. *H. pylori* infection should be diagnosed and treated appropriately.

Using the Rome IV classification symptoms can be grouped to those which are predominately meal related (postprandial distress syndrome) and epigastric pain symptoms (epigastric pain syndrome). Dyspepsia associated with *H. pylori* (HpD) is now a separate entity.

Up to one third of patients may respond to reassurance alone that the problem is not life threatening.

Treatment should be targeted at triggers of symptoms if possible. Treat *H. pylori* if present. A trial of acid suppression is standard of care. Low dose tricyclic antidepressant therapy may provide a benefit in those failing first line therapies.

Research agenda

- Causality is multifactorial and is likely a combination of lifestyle, genetic, early life events, environment, diet and microbiome disturbance, and although this work is ongoing and speculative, there is major progress in this area.
- Recent studies show tangible pathology, principally in the duodenum, with duodenal eosinophilia, increased mast cells, neuronal structural alterations, and altered cytokine circulation linked to disturbed gastroduodenal pathophysiology, with local and central generation of symptoms of FD.
- Future success may reside in targeted anti-inflammatory agents, manipulation of the microbiome and altered diet.

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None.

Conflict of Interest

None.

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