Novel insights in the pathophysiology and management of functional dyspepsia

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Abstract

Functional dyspepsia is a common functional gastrointestinal disorder with bothersome symptoms in the upper abdomen without an organic lesion that is likely to explain the complaints. Traditionally, changes in gastric physiology were held responsible for the symptoms, including delayed gastric emptying, impaired gastric accommodation and hypersensitivity to distension. However, gastric sensorimotor disturbances correlated only poorly to symptom severity and treatments targeting these abnormalities are not very effective. In the last decade, the duodenum has been identified as a key integrator in the pathophysiology of functional dyspepsia with an impaired barrier function and immune activation with a particular role for eosinophils and mast cells. Moreover, changes in the duodenal microbiota were associated to dyspeptic symptoms and eosinophil counts. PPIs – still the first line treatment for functional dyspepsia – have been shown to reduce symptoms through anti-inflammatory effects in the duodenum, similar to their effect in eosinophilic esophagitis. Finally, specific probiotic strains were effective in improvement of postprandial symptoms, most likely through an anti-inflammatory effect as demonstrated by reduced Th17 signaling. These novel insights in pathophysiology and treatment provide novel hope for patients with this challenging condition. (Acta gastroenterol. belg., 2023, 86, 68-73).

Keywords: functional dyspepsia, intestinal permeability, duodenum, eosinophil, mast cell, probiotic.

Functional gastrointestinal disorders are defined by abdominal symptoms in the absence of structural or metabolic abnormalities which are likely to explain the complaints (1). Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the two most common functional gastrointestinal disorders and are characterized by lower abdominal symptoms, with an altered stool pattern, and upper abdominal symptoms, which can be related to meal intake, respectively (2). Even if pathophysiology is still incompletely elucidated, it is well established that alterations can be found both in the gastrointestinal tract (e.g. dysmotility, increased permeability, immune activation, etc.) but also in the central nervous system with a higher than expected incidence of psychological comorbidity (e.g. anxiety disorders, stress, …) (3). Therefore, terminology is shifting from 'functional gastrointestinal disorders' to 'disorders of gut-brain interaction' (1).

A biomarker is still lacking for these conditions and therefore diagnosis is based on symptom criteria of which the Rome IV consensus criteria are the most frequently used and best validated (4). The Rome IV criteria distinguish between two subgroups within the functional dyspepsia spectrum: the postprandial distress syndrome (PDS) with postprandial fullness or pain and early satiety and the epigastric pain syndrome (EPS) with meal-unrelated pain or epigastric burning as the predominant symptoms (4). In about 75% of patients presenting with the above symptoms, further investigation, including gastroduodenoscopy, will fail to reveal an underlying abnormality and therefore they are diagnosed with functional dyspepsia (5).

Traditional Gastric pathophysiology

Based on the location of the symptoms and their relationship to the meal, perturbations in gastric pathophysiology have traditionally been hypothesized to explain the symptoms in functional dyspepsia. Gastric hypersensitivity to distention (6), impaired accommodation (7) and delayed gastric emptying (8) were identified as the most common gastric sensorimotor alterations, each present in 30-40% of patients. However, the prevalence of these gastric abnormalities was shown to be similar in FD patients with PDS, EPS and a PDS-EPS overlap group in a large series from our center and therefore the correlation of gastric abnormalities to symptoms seems poor (9). Of the gastric mechanisms, delayed gastric emptying as an explanation for functional dyspepsia is most controversial, especially since a recent large US study demonstrated that around 40% of patients switched from normal to delayed gastric emptying and vice versa after 1 year even if the symptoms remained stable (10). Nevertheless, recent evidence from our group did identify a subgroup of patients with a higher prevalence of delayed gastric emptying which was characterized by a symptom cluster of at least moderate nausea combined with PDS-like symptoms (11). A recent European guideline also supported nausea and vomiting combined with PDS symptoms as the most relevant symptom pattern in gastroparesis (12). Nevertheless, therapies focusing on ameliorating gastric emptying are poorly efficacious in functional dyspepsia and the correlation between improvement of symptoms and emptying is absent or poor at best (13).

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Submission date: 12/02/2023
Acceptance date: 12/02/2023

Paradigm switch: time to focus on the duodenum

Barrier function and immune activation

In the last two decades the attention of the research in functional dyspepsia has shifted to the duodenum since the first report of duodenal eosinophil infiltration in a small American pediatric cohort (14) and since then also reported by several other groups (reviewed in (15)). In a first study from our group we evaluated the duodenal pathophysiology in 15 Rome III defined functional dyspepsia patients vs. 15 age- and sex-matched healthy controls (16). We confirmed an increased number of eosinophils and mast cells in the duodenal lamina propria in this cohort which also showed signs of activation and degranulation in a follow-up electron microscopy study (17). The cause of this duodenal immune activation is still unclear but a commonly cited hypothesis is that luminal antigens can penetrate the epithelium through a leaky barrier, triggering a local immune response (Figure 1). To investigate this claim, biopsies of FD patients and healthy controls were mounted in modified Ussing Chambers to investigate the permeability. The transepithelial electrical resistance (TEER), which measures the permeability to ions through claudin-formed pores, was decreased and paracellular permeability for larger, fluorescein-labeled molecules (4kDa in this case) was higher, both supporting the concept of an impaired barrier function in this condition (16,18). At the molecular level, this was associated with altered expression of tight-junction associated proteins, including occludin. Moreover, the protein expression of phosphorylated occludin correlated to eosinophil and mast cell numbers and also to epithelial barrier function. Since then several groups have confirmed increased duodenal permeability in functional dyspepsia with variable – and poorly reproducible – alterations in expression of intercellular junction proteins, but the question remains whether this is of relevance for symptom generation or rather a consequence of the low-grade inflammatory response (19). Solving this question in the absence of treatments which can restore permeability has been proven challenging. The underlying cause of the barrier defect is unknown, but suitable candidates are psychological stress, (bile) acid, microbiota and food components (Figure 1). Indeed, in 2014 we showed that psychological stress in the form of an oral defense in front of a jury increased intestinal permeability in healthy students (20). Moreover, we were able to block this response when the volunteers were pretreated with disodium cromoglycate, a mast cell stabilizer.

In a larger, more recent study we confirmed a correlation between dyspeptic symptoms and duodenal eosinophil counts, but also between duodenal permeability and gastric emptying rates, suggesting that the previously discussed gastric pathophysiology may be secondary to a disturbed duodenal physiology (21,22). However, a word of caution is needed, since all of these studies are still only based on statistical correlations and mechanistic

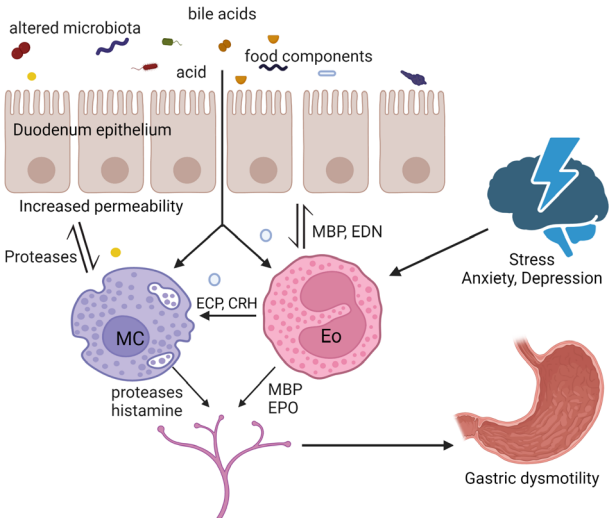

Figure 1. — Duodenal pathophysiology of functional dyspepsia.
Alterations in the duodenal micriobiota, (bile)acid, food components and psychological stress can contribute to an impaired barrier function of the duodenum and activation of eosinophils and mast cells. These immune cells can further perpetuate the barrier defect through release of soluble mediators, including proteases, major basic protein (MBP) and eosinophil-derived neurotoxin (EDN). Furthermore, both eosinophils and mast cells can activate neurons of the enteric nervous system which is hypothesized to trigger symptoms and changes in gastric physiology. CRH : corticotropin-releasing hormone ; EDN : eosinophil-derived neurotoxin, EPO : eosinophil peroxidaseEo : eosinophil ; MBP : major basic protein ; MC : mast cell.

evidence is largely lacking (23,24). Moreover, the results of duodenal eosinophil counts are highly variable across studies and the largest study to date in 178 patients failed to confirm increased duodenal eosinophil counts even if this study could be criticized for selecting mainly older, male patients based on the outdated Rome II criteria (25). One of the additional explanations besides patient selection and geographical difference is definitely also the variability in quantification and poor reproducibility of eosinophil counts in the duodenum. We have recently presented an optimized and more reproducible protocol incorporating larger countable areas and correcting for the regions on the slide where no eosinophils can reside (e.g. lumen, gland regions) (26). Secondly, advanced assessment of immune activation beyond cell counts will be more relevant than cell counts in the future to better characterize duodenal pathophysiology in FD. These studies are currently ongoing in our group. Thirdly, most of the data in the literature are biased because of the confounding effect of medication, most notably proton pump inhibitors (PPI) which affect immune activation as discussed below.

Duodenal microbiota

The gut microbiota have an essential function in assimilation of nutrients, colonization resistance mucosal barrier function and development of the immune system (27). Changes in the microbiome have been implemented in pathophysiology for a variety of gastrointestinal

diseases, ranging from inflammatory bowel disease to celiac disease and cirrhosis, but also in disorders of gut-brain interaction (28). However, most studies investigated the fecal microbiota, which do not accurately reflect the mucosa-associated microbiota. Although a previous pilot study showed changes in the duodenal microbiota of FD patients, sample size was small and concomitant therapy including PPI may again have confounded the results (29-31). In an attempt to further clarify the composition of the duodenal microbiota in functional dyspepsia and its contribution to symptom generation, we sampled the duodenal microflora with two different methodologies: 1/ using an aseptic biopsy device (32) to study the mucosa-associated microorganisms and 2/ with a brushing of the mucosa, likely also sampling the more luminal flora (33). Contrary to our hypothesis, the sterile biopsies did not reveal any relevant effect of PPI or the presence of functional dyspepsia on the mucosa-associated microbiome. However, in the luminal samples a lower richness was found in functional dyspepsia and a decrease in Shannon and Simpon's index as markers for α-diversity. Moreover, changes in particular genera were identified in functional dyspepsia with a lower abundance of luminal *Porphyromonas* and *Neisseria*, which inversely correlated to the symptom severity and duodenal eosinophil counts (*Porphyromonas* only). After PPI treatment a higher abundance of oral flora (mainly *Streptococci*) was detected which correlated to increased eosinophil counts in healthy individuals during PPI intake, suggesting PPI-induced duodenal dysbiosis leading to immune activation (33). More recently, investigators from Australia also reported changes in the duodenal microbiome of FD patients with an inverse correlation between the abundance of Veillonella and gastric emptying (34).

Novel treatment options targeting the duodenal pathophysiology

The novel insights discussed above suggest that addressing the activation of eosinophils and mast cells could alleviate symptoms resulting from inflammation-induced intestinal hypersensitivity. Furthermore, with the recognition of dysbiosis in a subset of FD patients, both pro- and antibiotic therapies have been investigated in FD.

Treatments targeting immune activation

PPIs are still recommended as first line therapy in functional dyspepsia by the European and American/Canadian guidelines (35,36). A Cochrane meta-analysis confirmed efficacy of PPI in FD over placebo with a number needed to treat of 11 (37). While previously only recommended for the EPS subgroup based on older studies (4), efficacy in PDS tended to be higher compared to EPS (37). Intriguingly, the mechanism through which PPIs improve dyspeptic symptoms remained nebulous. Overlap between gastro-esophageal reflux disease (GERD) and FD is common with 41% of FD patients also having reflux symptoms and, vice versa, 31% of GERD patients complaining of dyspeptic symptoms (38). However, reducing reflux in dyspepsia patients seems insufficient to explain the symptom response in functional dyspepsia. To further elucidate the effect of PPI in FD patients, we performed a prospective interventional study in which we treated 27 FD patients (Rome IV; 54% PDS; 11% EPS and 35% overlap) and 30 healthy volunteers with 40mg of Pantoprazole during 4 weeks (21). At the end of treatment a significant improvement of symptoms (evaluated through the PAGI-SYM questionnaire), duodenal permeability (Ussing Chambers) and eosinophil counts was demonstrated. Moreover, an association was present between the level of symptom improvement and the reduction in eosinophils, suggesting that PPIs reduced symptoms through an anti-inflammatory effect. This finding is not without precedence as PPIs also exhibit anti-inflammatory properties in the esophagus of patients with eosinophilic esophagitis through suppression of eotaxin-3 expression (39). Studies investigating whether a similar mechanism is at play in the duodenum of FD patients are currently ongoing. Interestingly, in healthy individuals an inverse effect, i.e. a decrease in eosinophils and barrier function was found during PPI treatment, which may be related to duodenal dysbiosis (cf. supra).

Besides the negative effects on the microbiota and other long-term adverse effects, it is clear that PPIs are not a powerful anti-inflammatory treatment and is not providing sufficient symptom relief in all patients. Also in eosinophilic esophagitis, PPI suppress esophageal inflammation in only about 50% of patients (40). Therefore – in analogy to eosinophilic esophagitis – more powerful anti-inflammatory drugs are being explored in FD. A small-scale study involving 11 patients with FD failed to demonstrate an effect of the locally-acting corticosteroid budesonide in reducing symptoms and eosinophil counts (41). Evidently, this study was not sufficiently powered, and it is unclear whether the delivery form used was effective in targeting the duodenum. A larger-scale study with an adapted delivery form of budesonide is currently being conducted in our group as a proof of concept that immune activation con-tributes to symptoms or not. Nevertheless, it is important to keep in mind that similar attempts using corticosteroids (42) and mesalamine (which has mast cell stabilizing properties) were not successful in IBS (43,44). More targeted immunomodulators, specifically addressing eosinophil and/or mast cell activation or their mediators may be more promising for a long-term treatment in FD. Indeed, the histamine 1 receptor blocker ebastine reduced abdominal pain in a pilot study in IBS (45). Protease inhibitors have proven efficacy in animal models of functional gastrointestinal disorders, but clinical studies are still missing (46).

Anti-inflammatory therapies studied in other eosinophil-mediated diseases may be promising in FD as well.

For example, Lirentelimab – an anti Siglec-8 monoclonal antibody which depletes eosinophils and inhibits mast cell activation, significantly reduced symptoms and eosinophil counts in patients with eosinophilic gastritis and/or duodenitis (47). The distinction between eosinophilic gastroduodenitis and functional dyspepsia is still a matter of an ongoing debate and it is not unlikely that these conditions are on a spectrum of conditions with duodenal eosinophilia (48).

Treatments targeting the microbiota

Eradication of *H. pylori* remains a (cost)-effective treatment in FD and is recommended in the guidelines (35,36). However, uncertainty remains on whether the effect of the antibiotic treatment is limited to eradication of *H. pylori* or whether other, non-specific effects on the microbiome can play a role as well. Indeed, a study from Hong Kong evaluated the effect of the non-absorbable antibiotic rifaximin in 95 FD patients and found higher rates of adequate relief compared to placebo, demonstrating that antibiotics can be effective outside the context of *H. pylori* (49).

Probiotics – specific micro-organisms which confer a health-benefit to the patient – are an alternative strategy to modulate the microbiome. The consumption of yoghurt containing the *Lactobacillus gasseri LG21* strain had no impact on *H.pylori* colonization but it did result in a reduction of postprandial complaints compared to the placebo group (50). Furthermore, the supplementation of *LG21* also improved symptoms in *H. pylori* negative FD patients and changed the gastric microbiota towards a healthy phenotype (51,52). Unfortunately, most studies on efficacy of probiotics do not provide a mechanistic insight and therefore these treatments have not found their way into the guidelines.

We recently evaluated the effectiveness of a combination of two spore-forming probiotic strains in 68 patients FD: *Bacillus coagulans* MY01 and *Bacillus subtilis* MY02 2.5 * 10^9 colony-forming units per capsule, twice daily (53). The primary endpoint was a decrease in the Leuven postprandial distress scale (LPDS) of at least 0.7 points and was achieved in 48% of the patients treated with probiotics vs. 20% with placebo after 8 weeks ($p<0.05$). We also observed a progressive decrease in circulating Th17 cells and a drop in serum interleukin 17A concentrations, which were associated to the improvement of symptoms, suggesting an immunomodulatory effect of the probiotic strains. A higher abundance of the butyrate-producing *Faecalibacterium* was found with probiotic treatment which was also statistically linked to reduction of symptoms. Finally, a reduction in abnormal bile acid breath testing was observed among PPI users treated with the probiotic strains, suggesting a reduction of small intestinal bacterial overgrowth (53). Larger, multi-centric studies are needed to confirm efficacy of these spore-forming probiotics.

Conclusion

The traditional view on the pathophysiology of functional dyspepsia with an emphasis on gastric sensorimotor dysfunction, including delayed gastric emptying, impaired accommodation and hypersensitivity, has not translated into effective treatment options. Moreover, the correlation between gastric disturbances and symptom severity is poor at best. A shift of the research field to the duodenum as a core integrator in the pathophysiology of functional dyspepsia has resulted in the identification of several factors which likely contribute to symptom generation: impaired duodenal permeability, changes in acid and bile acid exposure, altered duodenal microbiota, infiltration and activation of eosinophils and mast cells and changes in activity of neurons of the enteric nervous system. We are only beginning to understand the mechanism of action of old treatments such as duodenal anti-inflammatory effects of PPI. Novel treatments which target the duodenum and beyond, including probiotics and immunomodulatory drugs, are currently being explored in functional dyspepsia, offering new hope for patients with this challenging condition.

Acknowledgments

TV is supported by a senior clinical research fellowship of the Flanders Research Foundation (FWO Vlaanderen; 1830517N). The figure was created with BioRender.com.

I want to express my sincere gratitude to the members of the Georges Brohée Prize for granting me this award for my scientific work.

Conflicts of interest

TV has received research grants from Danone and MyHealth; has served on the speaker bureau of Abbott, Biocodex, Dr. Falk Pharma, Menarini, MyHealth, Schwabe and Truvion, has provided scientific advice to Biocodex, BMS and Dr. Falk Pharma.

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