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Role of Low-FODMAP diet in functional dyspepsia: "Why", "When", and "to Whom"

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ABSTRACT

Functional dyspepsia (FD) is a frequent disorder of gut-brain interaction, affecting 5–7% of people globally, with significant impairment in quality of life. The management of FD is challenging due to the lack of specific therapeutic approaches.

Although food seems to play a role in symptom production, its pathophysiologic role in patients with FD is not fully understood. Most FD patients report that their symptoms are triggered by food, especially in the post-prandial distress syndrome (PDS) group, although evidence to support the use of dietary interventions are limited.

FODMAPs can increase production of gas in the intestinal lumen, through fermentation by intestinal bacteria, can exert osmotic effects by increasing water volume and can cause an excessive production of short-chain fatty acids (propionate, butyrate, and acetate).

Emerging scientific evidence, confirmed by recent clinical trials, suggest that FODMAPs could be involved in the pathogenesis of FD. Given the consolidated approach of the Low-FODMAP Diet (LFD) in irritable bowel syndrome (IBS) management and emerging scientific evidence regarding the LFD in FD, a therapeutic role of this diet may be hypothesized also in FD, either alone or in combination with other therapies.

1. Introduction

Functional dyspepsia (FD) is a frequent disorder of gut-brain interaction (DGBI) affecting 5–7% of people globally [1], with significant impairment in quality of life [2].

The presence of one or more of the following symptoms, alone or in combination, is diagnostic for FD: bothersome epigastric pain; bothersome epigastric burning; bothersome postprandial fullness; bothersome early satiation [3]. Symptoms must have started at least six months before and must have been present at least three days per week in the previous three months [3,4]. The diagnosis is symptom-based and is made using the Rome IV criteria [3]. FD can be divided into two groups based on symptoms: post-prandial distress syndrome (PDS) and epigastric pain syndrome (EPS) [3].

The PDS subtype is characterized by post-prandial fullness or early satiation, whereas the EPS subtype symptoms lack a direct connection to meal consumption [5,6]. However, it is well known that EPS and PDS features might overlap in FD patients [7–9] (Table 1).

Belching, nausea, or abdominal bloating are taken into account as supportive symptoms. Heartburn alone is not a symptom of dyspepsia, even though it can coexist with it [3].

Currently, there is a significant clinical overlap between FD and other conditions, including irritable bowel syndrome (IBS) and gastro-esophageal reflux disease (GERD) [10–12].

Recent findings pointing out a possible role of food in the pathogenesis of FD have focused their attention on the role of fermentable oligo-, di-, and monosaccharide and polyols (FODMAPs) in symptom generation [13,14] and hypothesized the possible role of a Low FODMAP diet (LFD) in FD management.

Up to now a LFD has been proposed as second-line therapy for IBS by many international guidelines [15,16]. Recent studies suggest its possible application to FD, GERD-like symptoms, functional heartburning, fecal incontinence and to organic diseases [17].

The aim of this narrative review is to evaluate, on the basis of the

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Table 1
Diagnostic criteria for Functional Dyspepsia according to Rome IV criteria.

Diagnostic criteria for Functional Dyspepsia [3]	
1. *One or more* of the following[a]: 1. Bothersome postprandial fullness 2. Bothersome early satiation 3. Bothersome epigastric pain 4. Bothersome epigastric burning AND 2. No evidence of structural disease (including use of upper endoscopy) that is likely to explain the symptoms	
Diagnostic criteria for Postprandial Distress Syndrome (PDS)	Diagnostic criteria for Epigastric Pain Syndrome (EPS)
*Must include **one or both** of the following at least 3 days a week*[a]*:*	*Must include **one or both** of the following symptoms at least 1 day a week*[a]*:*
1. Bothersome postprandial fullness 2. Bothersome early satiation	1. Bothersome epigastric pain 2. Bothersome epigastric burning

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy).
Abbreviations: PDS=Postprandial Distress Syndrome; EPS = Epigastric Pain Syndrome.
[a] *Criteria fulfilled for the last* 3 months *with symptom onset at least* 6 months *prior to diagnosis*.

available scientific literature, the possible role of a LFD in the pathophysiology and management of FD.

2. Functional dyspepsia

The pathophysiological mechanisms of FD are complex and are not fully understood. These involve alterations in gastro-intestinal (GI) motility (delayed gastric emptying and impaired fundic accommodation), hypersensitivity to certain nutrients found in food, visceral hypersensitivity to both physical and chemical stimuli, central nervous system processing, psychopathological aspects, immunologic alterations and micro-inflammation, GI infections, changes in the gastric and small bowel microbiota, changes in epithelial permeability and genetic factors [4,18].

Although food seems to play a role in the production of symptoms, its pathophysiologic role in patients with FD is not entirely understood [19]. Food seems to be relevant especially in the PDS subgroup. Although a meta-analysis regarding the associations between food components and symptoms in people with FD found no clear links between symptoms and any particular food or drink [19]; however, several studies have reported that fats are an important factor associated with symptom production [20–25]. Symptoms brought on by meals are frequent and reproducible [26]. After meal ingestion, symptoms appear rapidly in FD patients, peaking within 15–30 min, and they frequently last for more than 4 h [5].

According to other studies, dairy products, alcohol, coffee, red meat, carbonated drinks, vegetables, spicy food, carbohydrates, wheat, and citrus fruits are the foods that are most frequently reported as food triggers for FD symptoms [27]. Soluble fibers, fats and carbohydrates are all shown to decrease gastric emptying and are associated with upper GI symptoms [28–31]. Meals high in fiber and fat, particularly long-chain triglycerides, trigger the release of cholecystokinin, which slows down gastric motility and makes the stomach more susceptible to distention. This mechanism may be accentuated in FD [25,32].

The management of FD includes lifestyle and dietary changes, and pharmacological therapies such as antiacids, prokinetics and neuromodulators [16,18].

Similarly to other DGBIs, the majority of available therapies have only modest success in treating FD symptoms [16].

Current guidelines recommend once-daily proton pump inhibitor (PPI) therapy for 4–8 weeks as a first line treatment for individuals who test negative for *H. pylori* (Hp). In Hp positive patients eradication therapy is recommended, but it did not alleviate their symptoms in most cases [18]. In some patients, especially in the PDS subgroup, the use of prokinetics as first-line therapy may be considered [16,18].

Lifestyle changes could improve FD symptoms: according to a recent small randomized controlled trial (RCT), adding aerobic exercise to first-line therapy (PPIs or prokinetics) significantly reduced the severity of dyspeptic symptoms when compared to conventional management alone [33]. Other possible therapies, considered to be second-line, are gut-brain neuromodulators [16,18], psychological approaches (cognitive behavioral therapy) [34], gut-directed hypnotherapy [35] or electrical stimulation [36].

Table 2
Low FODMAP diet.

	Cereals	Milk and Derivates	Vegetables and Legumens	Fruit
Allowed	Rice, quinoa, gluten free bread and cereals, buckwheat, amaranth, potato, polenta	Lactose free milk and yogurt, soy milk, rice milk, Greek yogurt, hard cheese, brie	Lettuce, spinach, carrot, potato, tomato, olive, zucchini, eggplant, red pepper, herbs, peas, soy products	Banana, strawberry, orange, mandarin, lemon, limes, kiwi, pineapple, melon, raspberry, blueberry
Forbidden	Bread, pasta, biscuits, couscous, kamut, rye, barley, croissant	Cow-goat-sheep milk, yogurt, butter, fresh cheese, custard, ice cream	Onion, pepper, mushroom, broccoli, chicory, radish, sprout, turnips, cauliflower, chickpeas, beans, lentils, soybeans	Pear, apple, watermelon, peach, apricot, prune, avocado, mango, blackberry

3. FODMAPs and Low-FODMAP diet

FODMAPs is an acronym which stands for Fermentable Oligo-, Di, Mono-saccharides And Polyols. They are a large class of short chain carbohydrates that are not readily absorbed in the gut. They can be found in a wide variety of foods: fruit, vegetables, cereals, milk and dairy products, legumes and sweeteners.

FODMAPs can increase the production of gas in the intestinal lumen, through fermentation by intestinal bacteria, and they can exert osmotic effects by increasing water volume [37] and can cause an excessive production of short-chain fatty acids (SCFAs) (propionate, butyrate, and acetate).

Gas generation and an increase in osmotic pressure, through the stimulation of mechano- and chemo-receptors, cause symptoms such as pain, changes of bowel habits, bloating and flatulence [38]. The overlap between FD and IBS suggests that these effects may also play a role in upper GI disorders.

If present in high concentrations, SCFAs an increase visceral sensitivity, can be toxic to the epithelium, and also, by stimulating the mucosa to release of 5-hydroxytryptamine (5HT), favor the onset of high-amplitude propagated colonic contractions, thus accelerating intestinal transit [39,40]. Acetate and other SCFAs can be absorbed and metabolized in the proximal small intestine, and emerging evidence suggests that fermentation of SCFAs may occur in the upper gastrointestinal tract. This supports the hypothesis of the role of FODMAPs in the pathogenesis of FD [41,42].

A low FODMAP Diet (LFD) (Table 2), consists in the reduction of FODMAPs during a period of 4–8 weeks. After the elimination phase, gradual reintegration of one category of these carbohydrates at a time is mandatory. This is to enable the patients, with the help of a skilled nutritionist, to identify the foods they are sensitive to, and to find alternatives, in order to design a less restrictive and more balanced LFD, an “adapted LFD” (AdLFD) tailored to the patient, which should be

Table 3
Studies on low FODMAP diet applied in patients with functional dyspepsia.

Diet	Comparison to	Duration (week)	N° of pts	Diagnosis	Evaluation criteria	Conclusion	Responders (%) – p value
LFD[56]	Abitual diet	6	25	FD	Symptoms	Significant improvement of symptoms	62 – NA
LFD/gluten free diet[58]	Abitual diet	4	11	FD	Symptoms (NDI)	Modest reduction in symptoms	NA – 0.087
LFD[13]	Standard dietary advice	NA	59	FD/IBS	Symptoms (SAGIS)	LFD more benefit	50–0.012
LFD[14]	Standard dietary advice	4	105	FD	Symptoms (SF-NDI)	No difference with both diets	67–0.32

Abbreviations: FODMAP = fermentable oligo-, di-, mono-saccharides and polyols; pts = patients; LFD = low FODMAP diet; IBS = irritable bowel syndrome; NA = not applicable; NDI=Nepean Dyspepsia Index; SAGIS=Structured Assessment of Gastrointestinal Symptom Scale; SF-NDI=Short-Form NDI.

recommended in the long term.

Before prescribing a restrictive diet such as the LFD, it is mandatory to consider the possible risks particularly if it is suggested for long periods, such constipation (limiting fiber intake), nutritionally deficiencies, changes of gut microbiota and eating behavior disorders [43].

A trained nutritionist should be involved in order to minimize the risks of nutritional deficiencies and to correctly identify the "trigger" FODMAPs able to provoke symptoms [37].

A nutritionist also ensures implementation of the diet in the long term, establishing an AdLFD, which is more sustainable in the long term.

The possible mechanisms underlying symptom reduction with dietary FODMAP restriction in patients with FD are still unclear. However, the role of FODMAPs in the pathogenesis of DGBI and the LFD therapeutic effect on IBS symptoms represent an interesting starting point to evaluate the applicability of the LFD also in patients with upper GI functional disorders such as FD.

4. FODMAPs, LFD and FD

FODMAPs may play a key role in the generation of FD's symptoms [19]. Some studies suggest an enhanced nutrient-induced gut-brain signaling underlying the perception of symptoms in FD [44]. As mentioned above FODMAPs lead to intestinal fermentation and increased osmotic pressure, in turn resulting in increased gas and water in the small intestine, with consensual stimulation of mechano-chemoreceptors, and this is likely to contribute to the development of symptoms [38,45,46]. In FD patients, this leads to increased discomfort, changes og gastro-intestinal motility, flatulence, and bloating [38].

It is reasonable to assume that FODMAPs are involved in FD, given that luminal distension is a key trigger for the development of gastrointestinal symptoms in patients with visceral hypersensitivity [47]. In this regard, pathophysiological studies on the upper gastrointestinal tract have demonstrated that acute infusion of fructans into the stomach lead to increased postprandial intragastric pressure at manometry and trigger bloating, cramping, and abdominal pain [48]. Furthermore, the rapid onset of symptoms starting 35 min after the beginning of FODMAP infusion rules out any colonic fermentation, since the mean gastric emptying half-time is around 80 min [48,49]. This suggests that the upper gastrointestinal tract may contribute to generation of FODMAP-induced symptoms, possibly through a gastroduodenal crosstalk [50]. Moreover, bloating and abdominal pain appear to be reduced by a LFD [51].

In vitro studies have demonstrated that FODMAPs may also be linked to mucosal inflammation or colonic barrier loss through microbiome-mediated mast cell activation [52,53], or directly through atypical food sensitivities [54]. These mechanisms, well established for the pathogenesis of FODMAP- induced symptoms in IBS, may also be relevant in FD. Additionally, a significant overlap between FD and IBS has been observed [55]. Interestingly, Van den Houte et al. showed in a preliminary report that FODMAPs can influence duodenal mucosal integrity; that is symptom improvement during a LFD correlated with an increase in transepithelial electrical resistance through the duodenal mucosa. In this study, 25 patients with FD underwent 6 weeks LFD, recording a 62% clinically significant improvement of symptoms. Subsequently, symptom recurrence occurred with a wide variety of FODMAPs during the blinded reintroduction phase of the study. The FODMAPs that most commonly triggered the recurrence of FD symptoms were mannitol and galacto-oligosaccharides (both 29%), followed by fructans (21%), sorbitol (14%), fructose (14%) and lactose (12%) [56].

However, only a few studies have examined the therapeutic efficacy of a LFD in FD [13,14,57,58] (Table 3).

A pilot randomized double-blind, placebo controlled, dietary crossover trial showed only a modest overall reduction in symptoms in a cohort of 11 patients with Rome III criteria FD following a gluten-free diet and a LFD (71.2% vs 47.1%, $p = 0.087$). Nine participants completed the four-week run-in phase with a gluten-free diet and a LFD; in turn, those with >30% response to Nepean Dyspepsia Index (NDI) ($n = 4$) were re-challenged with "muesli" bars containing gluten, fructans or placebo in randomized order. However, the re-challenge phase failed to identify a specific trigger between gluten and fructans [58].

Staudacher et al. compared in FD patients the effectiveness of a LFD with standard dietary advice. The study involved 59 patients with a diagnosis of FD, but a large number (81%) were also diagnosed with IBS. Forty patients followed a LFD, while the remaining 19 received standard dietary advice. Epigastric and overall gastrointestinal symptoms were assessed with the Structured Assessment of Gastrointestinal Symptom Scale. A higher rate of symptom relief occurred in subjects who received a LFD (50% vs. 16%, $p = 0.012$), with no different dietary adherence in the two groups [13].

Moreover, in a prospective, single-blind trial, 105 patients with Rome IV criteria positive for FD were randomized into a LFD or a traditional dietary advice group for four weeks; thereafter in a second eight-week phase, FODMAPs were reintroduced in the LFD group. Symptom severity and quality of life were assessed with Short-Form NDI (SF-NDI). At 4 weeks, both groups showed a significant improvement in SF-NDI symptom scores compared with the baseline, with no differences in response between groups (66.7% vs 56.9%; $p = 0.32$), although a higher response rate to LFD was recorded in patients with PDS or bloating ($p = 0.04$). On the other hand, with multivariate analysis, factors predicting response to the LFD were bloating and male gender [14].

5. Discussion

Even though most FD patients report that their symptoms are triggered by nutrient ingestion [19], evidence to support the use of dietary interventions in FD is limited, with data mainly derived from observational studies, not RCTs [16,59,60]. Clinical efficacy dietary trials regarding LFD are challenging owing to difficulty in implementing a sham diet and also by the co-presence in wheat of fructans and gluten,

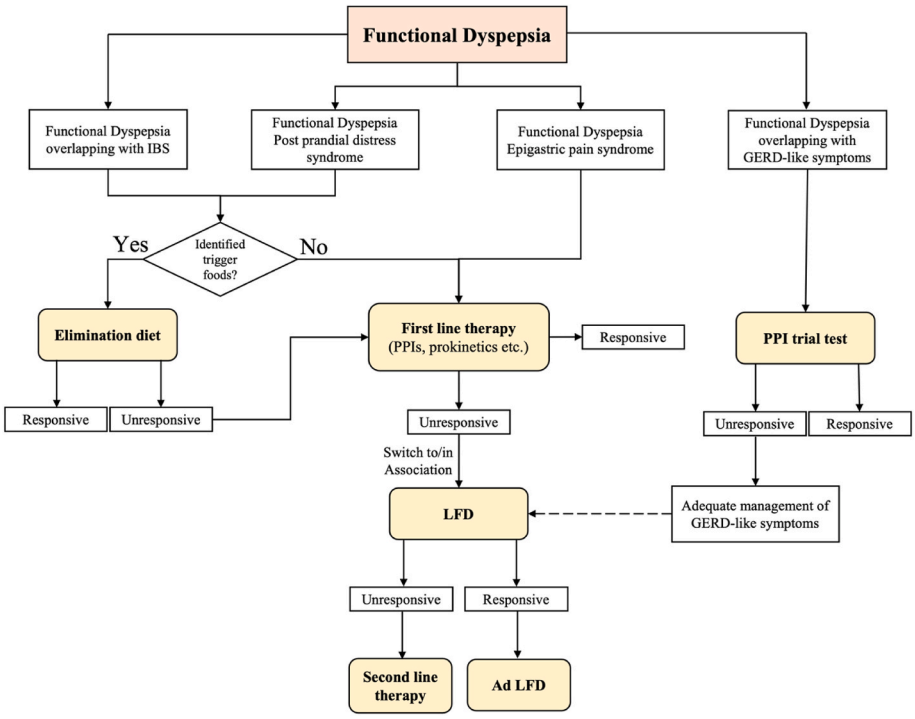

Fig. 1. Proposed algorithm for the Low-FODMAP diet in managing functional dyspepsia
Abbreviations: IBS = irritable bowel syndrome; GERD = Gastro-esophageal Reflux Disease; PPI=Proton Pump Inhibitor; LFD = low fermentable oligo-, di-, monosaccharides and polyols diet; AdLFD = Adapted LFD.

likely triggers of GI symptoms [61]. Moreover, an overlap of FD and IBS in clinical trials could interfere with clinical evaluation of LFD efficacy on FD symptoms [13]. Currently, dietary recommendations provided to patients are empirically derived and usually advise low-fat food and frequent small-size meals [26]. However, FODMAPs may contribute to the genesis of symptoms in FD due to their osmotic effect, gas production, and visceral hypersensitivity due to loss of the barrier effect and mucosal inflammation [38,46,54,56]. In a recent review on dietary approaches for DGBI, Tack et al. concluded that for FD only the LFD had sufficient emerging evidence to be considered in clinical practice [60]. The introduction of the LFD has represented an important turning point for IBS [37,62,63] This evidence leads us to suggest that a LFD could be indicated in FD patients with overlapping IBS. FD patients present a high rate of overlap not only with IBS, but also with typical GERD symptoms, and this may be explained by some common etiological risk factors and pathophysiological mechanisms [10,58,64–66]. The overlapping of FD with IBS or GERD is associated with more severe symptoms [55,67]. In addition, functional esophageal disorders, like reflux hypersensitivity and functional heartburn, frequently overlap with FD [10,64]. Food intake is well-known for having an impact on reflux mechanisms by inducing transient lower esophageal sphincter relaxations (TLESRs) through postprandial gastric distension, vago-vagal reflex and endocrine feedback [68]; moreover, patients frequently experience an increase in reflux symptoms following ingestion of particular foods [69]. Fructans have been shown to increase TLESRs also in healthy subjects and the number of gastroesophageal reflux events in GERD patients [70,71]. In the case of patients with FD overlap with typical GERD symptoms unresponsive to PPI therapy, an appropriate diagnostic work-up is required to establish the most suitable therapeutic intervention [72]. However, the feasibility of a LFD could also be considered in these patients also in association with PPI or with other therapeutic approaches. Hence, a LFD could improve dyspeptic symptoms, reducing both IBS and reflux-related symptoms.

Furthermore, a LFD may be indicated in patients with FD (both EPS and PDS) unresponsive to first-line therapy or to an elimination diet if trigger foods have been identified. If the LFD is clinically effective, it could be maintained and adapted to the patient's feedback, with the guidance of a specialist, in order to ensure adherence to the diet and avoiding any nutritional deficit. However, further RCT studies on a larger number of patients are mandatory to assess the real efficacy of a LFD in improving FD symptoms.

6. Conclusions

FD is a frequent DGBI with a heavy impact on the quality of life. The management of FD is challenging due to the lack of specific therapeutic approaches. Most FD patients report that their symptoms are triggered by food, especially in PDS, although evidence to support the use of dietary interventions is limited. Emerging scientific evidence, supported by some recent clinical trials, suggest that FODMAPs could play a role in FD physiopathology [13,14,56,58]. Consequentially, a LFD should be taken into account among the possible dietary options offered to FD patients (Fig. 1) in combination with specific therapeutic approaches, especially in FD patients with refractory symptoms and/or overlapping IBS.

Research agenda

- Understanding whether there are pathophysiological differences between patients with functional dyspepsia alone and overlapping with other gastrointestinal disorders.
- Confirming in clinical practice the efficacy of the Low-FODMAP Diet for the treatment of functional dyspepsia.

Practice points

- Functional dyspepsia management is challenging and available therapies have only modest success in treating symptoms.
- Emerging scientific evidence suggest that FODMAPs could be involved in the pathogenesis of functional dyspepsia.

- Understanding "why", "when", and "to whom" Low-FODMAP Diet should be used in the management of functional dyspepsia.

Specific author contributions

Conceptualization, F.R., C.L. and A.G.; Methodology, A.R. and L.C.; Writing-original draft preparation, F.R., C.L. and A.G.; Review and editing the final manuscript, R.T. and M.B.; Supervision, M.B.

Declaration of competing interest

All authors have no COI to be declared.

References

[1] Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of rome foundation global study. Gastroenterology 2021;160(1):99–114.e3. https://doi.org/10.1053/j.gastro.2020.04.014.

[2] Talley NJ, Locke 3rd GR, Lahr BD, et al. Functional dyspepsia, delayed gastric emptying, and impaired quality of life. Gut 2006;55(7):933–9. https://doi.org/10.1136/gut.2005.078634.

[3] Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. Gastroenterology 2016;150(6):1380–92. https://doi.org/10.1053/j.gastro.2016.02.011.

[4] Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. Lancet 2020;396(10263):1689–702. https://doi.org/10.1016/S0140-6736(20)30469-4.

[5] Bisschops R, Karamanolis G, Arts J, et al. Relationship between symptoms and ingestion of a meal in functional dyspepsia. Gut 2008;57(11):1495–503. https://doi.org/10.1136/gut.2007.137125.

[6] Vanheel H, Vanuytsel T, Van Oudenhove L, et al. Postprandial symptoms originating from the stomach in functional dyspepsia. Neuro Gastroenterol Motil 2013;25(11). https://doi.org/10.1111/nmo.12227. 911-e703.

[7] Ford AC, Bercik P, Morgan DG, et al. The Rome III criteria for the diagnosis of functional dyspepsia in secondary care are not superior to previous definitions. Gastroenterology 2014;146(4). https://doi.org/10.1053/j.gastro.2014.01.014. 932-e15.

[8] van Kerkhoven LA, Laheij RJ, Meineche-Schmidt V, et al. Functional dyspepsia: not all roads seem to lead to rome. J Clin Gastroenterol 2009;43(2):118–22. https://doi.org/10.1097/MCG.0b013e31815591f7.

[9] Fang YJ, Liou JM, Chen CC, et al. Distinct aetiopathogenesis in subgroups of functional dyspepsia according to the Rome III criteria. Gut 2015;64(10):1517–28. https://doi.org/10.1136/gutjnl-2014-308114.

[10] de Bortoli N, Tolone S, Frazzoni M, et al. Gastroesophageal reflux disease, functional dyspepsia and irritable bowel syndrome: common overlapping gastrointestinal disorders. Ann Gastroenterol 2018;31(6):639–48. https://doi.org/10.20524/aog.2018.0314.

[11] Ronkainen J, Aro P, Walker MM, et al. Duodenal eosinophilia is associated with functional dyspepsia and new onset gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2019;50(1):24–32. https://doi.org/10.1111/apt.15308.

[12] Garcia-Etxebarria K, Carbone F, Teder-Laving M, et al. A survey of functional dyspepsia in 361,360 individuals: phenotypic and genetic cross-disease analyses. Neuro Gastroenterol Motil 2022;34(6):e14236. https://doi.org/10.1111/nmo.14236.

[13] Staudacher HM, Nevin AN, Duff C, et al. Epigastric symptom response to low FODMAP dietary advice compared with standard dietetic advice in individuals with functional dyspepsia. Neuro Gastroenterol Motil 2021;33(11):e14148. https://doi.org/10.1111/nmo.14148.

[14] Goyal O, Nohria S, Batta S, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet versus traditional dietary advice for functional dyspepsia: a randomized controlled trial. J Gastroenterol Hepatol 2022;37(2):301–9. https://doi.org/10.1111/jgh.15694.

[15] Barbara G, Cremon C, Bellini M, et al. Italian guidelines for the management of irritable bowel syndrome: joint consensus from the Italian societies of: gastroenterology and endoscopy (SIGE), neurogastroenterology and motility (SINGEM), hospital gastroenterologists and endoscopists (AIGO), digestive endoscopy (SIED), general medicine (SIMG), gastroenterology, hepatology and pediatric nutrition (SIGENP) and pediatrics (SIP). Dig Liver Dis 2023;55(2):187–207. https://doi.org/10.1016/j.dld.2022.11.015.

[16] Black CJ, Paine PA, Agrawal A, et al. British Society of Gastroenterology guidelines on the management of functional dyspepsia. Gut 2022;71(9):1697–723. https://doi.org/10.1136/gutjnl-2022-327737.

[17] Biesiekierski JR, Tuck CJ. Low FODMAP diet beyond IBS: evidence for use in other conditions. Curr Opin Pharmacol 2022;64:102208. https://doi.org/10.1016/j.coph.2022.102208.

[18] Schol J, Wauters L, Dickman R, et al. United European gastroenterology (UEG) and European society for neurogastroenterology and motility (ESNM) consensus on gastroparesis [published correction appears in united European gastroenterol J. United European Gastroenterol J 2021 Sep;9(7):883–4. https://doi.org/10.1002/ueg2.12060. 2021;9(3):287-306.

[19] Duncanson KR, Talley NJ, Walker MM, et al. Food and functional dyspepsia: a systematic review. J Hum Nutr Diet 2018;31(3):390–407. https://doi.org/10.1111/jhn.12506.

[20] Carvalho RV, Lorena SL, Almeida JR, et al. Food intolerance, diet composition, and eating patterns in functional dyspepsia patients. Dig Dis Sci 2010;55(1):60–5. https://doi.org/10.1007/s10620-008-0698-8.

[21] Mullan A, Kavanagh P, O'Mahony P, et al. Food and nutrient intakes and eating patterns in functional and organic dyspepsia. Eur J Clin Nutr 1994;48(2):97–105.

[22] Akhondi-Meybodi M, Aghaei MA, Hashemian Z. The role of diet in the management of non-ulcer dyspepsia. Middle East J Dig Dis 2015;7(1):19–24.

[23] Göktaş Z, Köklü S, Dikmen D, et al. Nutritional habits in functional dyspepsia and its subgroups: a comparative study. Scand J Gastroenterol 2016;51(8):903–7. https://doi.org/10.3109/00365521.2016.1164238.

[24] Pilichiewicz AN, Feltrin KL, Horowitz M, et al. Functional dyspepsia is associated with a greater symptomatic response to fat but not carbohydrate, increased fasting and postprandial CCK, and diminished PYY. Am J Gastroenterol 2008;103(10):2613–23. https://doi.org/10.1111/j.1572-0241.2008.02041.

[25] Pilichiewicz AN, Horowitz M, Holtmann GJ, et al. Relationship between symptoms and dietary patterns in patients with functional dyspepsia. Clin Gastroenterol Hepatol 2009;7(3):317–22. https://doi.org/10.1016/j.cgh.2008.09.007.

[26] Duncanson K, Burns G, Pryor J, et al. Mechanisms of food-induced symptom induction and dietary management in functional dyspepsia. Nutrients 2021;13(4):1109. https://doi.org/10.3390/nu13041109. Published 2021 Mar 28.

[27] Enck P, Azpiroz F, Boeckxstaens G, et al. Functional dyspepsia. Nat Rev Dis Prim 2017;3:17081. https://doi.org/10.1038/nrdp.2017.81. Published 2017 Nov 3.

[28] Heddle R, Dent J, Read NW, et al. Antropyloroduodenal motor responses to intraduodenal lipid infusion in healthy volunteers. Am J Physiol 1988;254(5 Pt 1):G671–9. https://doi.org/10.1152/ajpgi.1988.254.5.G671.

[29] Barbera R, Feinle C, Read NW. Abnormal sensitivity to duodenal lipid infusion in patients with functional dyspepsia. Eur J Gastroenterol Hepatol 1995;7(11):1051–7. https://doi.org/10.1097/00042737-199511000-00007.

[30] Björnsson E, Sjöberg J, Ringström G, et al. Effects of duodenal lipids on gastric sensitivity and relaxation in patients with ulcer-like and dysmotility-like dyspepsia. Digestion 2003;67(4):209–17. https://doi.org/10.1159/000072059.

[31] Marciani L, Cox EF, Pritchard SE, et al. Additive effects of gastric volumes and macronutrient composition on the sensation of postprandial fullness in humans. Eur J Clin Nutr 2015;69(3):380–4. https://doi.org/10.1038/ejcn.2014.194.

[32] Barbera R, Peracchi M, Brighenti F, Cesana B, Bianchi PA, Basilisco G. Sensations induced by medium and long chain triglycerides: role of gastric tone and hormones. Gut 2000;46(1):32–6. https://doi.org/10.1136/gut.46.1.32.

[33] Rane SV, Asgaonkar B, Rathi P, et al. Effect of moderate aerobic exercises on symptoms of functional dyspepsia. Indian J Gastroenterol 2021;40(2):189–97. https://doi.org/10.1007/s12664-021-01174-8.

[34] Dehghanizade Z, Zargar Y, MehrabizadehHonarmand M, et al. The effectiveness of cognitive behavior stress management on functional dyspepsia symptoms. J Adv Med Educ Prof 2015;3(2):45–9.

[35] Popa SL, Chiarioni G, David L, et al. The efficacy of hypnotherapy in the treatment of functional dyspepsia. Am J Therapeut 2019;26(6):e704–13. https://doi.org/10.1097/MJT.0000000000001033.

[36] Chen JDZ, Ni M, Yin J. Electroacupuncture treatments for gut motility disorders. Neuro Gastroenterol Motil 2018;30(7):e13393. https://doi.org/10.1111/nmo.13393.

[37] Bellini M, Tonarelli S, Nagy AG, et al. Low FODMAP diet: evidence, doubts, and hopes. Nutrients 2020;12(1):148. Published 2020 Jan 4, 10.3390/.

[38] Tan VP. The low-FODMAP diet in the management of functional dyspepsia in East and Southeast Asia. J Gastroenterol Hepatol 2017;32(Suppl 1):46–52. https://doi.org/10.1111/jgh.13697.

[39] Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. Am J Gastroenterol 2013;108(5):707–17. https://doi.org/10.1038/ajg.2013.96.

[40] Iwasaki M, Akiba Y, Kaunitz JD. Duodenal chemosensing of short-chain fatty acids: implications for GI diseases. Curr Gastroenterol Rep 2019;21(8):35. https://doi.org/10.1007/s11894-019-0702-9. Published 2019 Jul 10.

[41] Vanhoutvin SA, Troost FJ, Kilkens TO, et al. The effects of butyrate enemas on visceral perception in healthy volunteers. Neuro Gastroenterol Motil 2009;21(9). https://doi.org/10.1111/j.1365-2982.2009.01324. 952-e76.

[42] Sivaprakasam S, Prasad PD, Singh N. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. Pharmacol Ther 2016;164:144–51. https://doi.org/10.1016/j.pharmthera.2016.04.007.

[43] Staudacher HM. Nutritional, microbiological and psychosocial implications of the low FODMAP diet. J Gastroenterol Hepatol 2017;32(Suppl 1):16–9. https://doi.org/10.1111/jgh.1368816–9.

[44] Farre R, Vanheel H, Vanuytsel T, et al. In functional dyspepsia, hypersensitivity to postprandial distention correlates with meal-related symptom severity. Gastroenterology 2013;145:566–73.

[45] Major G, Pritchard S, Murray K, et al. Colon hypersensitivity to distension, rather than excessive gas production, produces carbohydrate-related symptoms in individuals with irritable bowel syndrome. Gastroenterology 2017;152(1):124–33. https://doi.org/10.1053/j.gastro.2016.09.062. e2.

[46] Murray K, Wilkinson-Smith V, Hoad C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. Am J Gastroenterol 2014;109(1):110–9. https://doi.org/10.1038/ajg.2013.386.

[47] Gibson PR, Halmos EP, Muir JG. Review article: FODMAPS, prebiotics and gut health-the FODMAP hypothesis revisited. Aliment Pharmacol Ther 2020;52(2):233–46. https://doi.org/10.1111/apt.15818.

[48] Masuy I, Van Oudenhove L, Tack J, Biesiekierski JR. Effect of intragastric FODMAP infusion on upper gastrointestinal motility, gastrointestinal, and psychological symptoms in irritable bowel syndrome vs healthy controls. Neuro Gastroenterol Motil 2018;30(1). https://doi.org/10.1111/nmo.13167. 10.1111/nmo.13167.
[49] Hellmig S, Von Schöning F, Gadow C, et al. Gastric emptying time of fluids and solids in healthy subjects determined by 13C breath tests: influence of age, sex and body mass index. J Gastroenterol Hepatol 2006;21(12):1832–8. https://doi.org/10.1111/j.1440-1746.2006.04449.x.
[50] De Ponti F, Azpiroz F, Malagelada JR. Reflex gastric relaxation in response to distention of the duodenum. Am J Physiol 1987;252(5 Pt 1):G595–601. https://doi.org/10.1152/ajpgi.1987.252.5.G595.
[51] Black CJ, Staudacher HM, Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. Gut 2022;71(6):1117–26. https://doi.org/10.1136/gutjnl-2021-325214.
[52] Singh P, Grabauskas G, Zhou SY, Gao J, Zhang Y, Owyang C. High FODMAP diet causes barrier loss via lipopolysaccharide-mediated mast cell activation. JCI Insight 2021;6(22):e146529. https://doi.org/10.1172/jci.insight.146529. Published 2021 Nov 22.
[53] Ajamian M, Rosella G, Newnham ED, Biesiekierski JR, Muir JG, Gibson PR. Effect of gluten ingestion and FODMAP restriction on intestinal epithelial integrity in patients with irritable bowel syndrome and self-reported non-coeliac gluten sensitivity. Mol Nutr Food Res 2021;65(5):e1901275. https://doi.org/10.1002/mnfr.201901275.
[54] Pryor J, Burns GL, Duncanson K, et al. Functional dyspepsia and food: immune overlap with food sensitivity disorders. Curr Gastroenterol Rep 2020;22(10):51. https://doi.org/10.1007/s11894-020-00789-9. Published 2020 Aug 14.
[55] von Wulffen M, Talley NJ, Hammer J, et al. Overlap of irritable bowel syndrome and functional dyspepsia in the clinical setting: prevalence and risk factors. Dig Dis Sci 2019;64(2):480–6. https://doi.org/10.1007/s10620-018-5343-6.
[56] Van den Houte K, Carbone F. To the J, et al. Symptoms and duodenal mucosal integrity are improved by a dietary intervention in functional dyspepsia (abstract). UEG J 2021;9(S8):10.
[57] Adibi P, Esmaillzadeh A, Daghaghzadeh H, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet is associated with increased risk of uninvestigated chronic dyspepsia and its symptoms in adults. Minerva Gastroenterol 2021 May 10. https://doi.org/10.23736/S2724-5985.21.02852-7.
[58] Potter MDE, Duncanson K, Jones MP, et al. Wheat sensitivity and functional dyspepsia: a pilot, double-blind, randomized, placebo-controlled dietary crossover trial with novel challenge protocol. Nutrients 2020 Jun 30;12(7):1947. https://doi.org/10.3390/nu12071947.
[59] Popa SL, Dumitrascu DI, Pop C, et al. Exclusion diets in functional dyspepsia. Nutrients 2022 May 14;14(10):2057. https://doi.org/10.3390/nu14102057.
[60] Tack J, Tornblom H, Tan V, et al. Evidence-based and emerging dietary approaches to upper disorders of gut-brain interaction. Am J Gastroenterol 2022 Jun 1;117(6):965–72. https://doi.org/10.14309/ajg.0000000000001780.
[61] Mumolo MG, Rettura F, Melissari S, et al. Is gluten the only culprit for non-celiac gluten/wheat sensitivity? Nutrients 2020;12(12):3785. https://doi.org/10.3390/nu12123785. Published 2020 Dec 10.
[62] Bellini M, Tonarelli S, Mumolo MG, et al. Low fermentable oligo- di- and monosaccharides and polyols (FODMAPs) or gluten free diet: what is best for irritable bowel syndrome? Nutrients 2020;12(11):3368. https://doi.org/10.3390/nu12113368. Published 2020 Nov 1.
[63] Usai-Satta P, Bellini M, Lai M, Oppia F, Cabras F. Therapeutic approach for irritable bowel syndrome: old and new strategies. Curr Clin Pharmacol 2018;13(3):164–72. https://doi.org/10.2174/1574884713666180807143606.
[64] Geeraerts A, Van Houtte B, Clevers E, et al. Gastroesophageal reflux disease-functional dyspepsia overlap: do birds of a feather flock together? Am J Gastroenterol 2020;115(8). 1167-82.
[65] Quigley EM, Lacy BE. Overlap of functional dyspepsia and GERD−-diagnostic and treatment implications. Nat Rev Gastroenterol Hepatol 2013;10(3). 175-86.
[66] Ford AC, Marwaha A, Lim A, et al. Systematic review and metA−analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. Clin Gastroenterol Hepatol 2010;8(5). 401-9.
[67] Aziz I, Palsson OS, Törnblom H, et al. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. Lancet Gastroenterol Hepatol 2018;3(4). 252-62.
[68] Zerbib F, Bruley Des Varannes S, Scarpignato C, et al. Endogenous cholecystokinin in postprandial lower esophageal sphincter function and fundic tone in humans. Am J Physiol 1998;275. G1266–G1273.10.
[69] Tosetti C, Savarino E, Benedetto E, et al. Elimination of dietary triggers is successful in treating symptoms of gastroesophageal reflux disease. Dig Dis Sci 2021;66:1565–71.
[70] Geysen H, Gielis E, Deloose E, et al. Acute administration of fructans increases the number of transient lower esophageal sphincter relaxations in healthy volunteers. Neuro Gastroenterol Motil 2020;32. e13727.13.
[71] Piche T, des Varannes SB, Sacher-Huvelin S, et al. Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. Gastroenterology 2003;124:894–902.
[72] Rettura F, Bronzini F, Campigotto M, et al. Refractory gastroesophageal reflux disease: a management update. Front Med 2021 Nov 1;8:765061. https://doi.org/10.3389/fmed.2021.765061.