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MINIREVIEWS

Diet and functional dyspepsia: Clinical correlates and therapeutic perspectives

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Abstract

Hypervigilance and symptoms anticipation, visceral hypersensitivity and gastroduodenal sensorimotor abnormalities account for the varied clinical presentation of functional dyspepsia (FD) patients. Many patients recognize meals as the main triggering factor; thus, dietary manipulations often represent the first-line management strategy in this cohort of patients. Nonetheless, scarce quality evidence has been produced regarding the relationship between specific foods and/or macronutrients and the onset of FD symptoms, resulting in non-standardized nutritional approaches. Most dietary advises are indeed empirical and often lead to exclusion diets, reinforcing in patients the perception of "being intolerant" to food and self-perpetuating some of the very mechanisms underlying dyspepsia physiopathology (*i.e.*, hypervigilance and symptom anticipation). Clinicians are often uncertain regarding the contribution of specific foods to dyspepsia physiopathology and dedicated professionals (*i.e.*, dietitians) are only available in tertiary referral settings. This in turn, can result in nutritionally unbalanced diets and could even encourage restrictive eating behaviors in severe dyspepsia. In this review, we aim at evaluating the relationship between dietary habits, macronutrients and specific foods in determining FD symptoms. We will provide an overview of the evidence-based nutritional approach that should be pursued in these patients, providing clinicians with a valuable tool in standardizing nutritional advises and discouraging patients from engaging into indiscriminate food exclusions.

Key words: Functional dyspepsia; Dietary habits; Food intolerances; Fermentable oligosaccharides, disaccharides, monosaccharides and polyols; Gluten-sensitivity; Diet

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Core tip: The spread on the internet of indiscriminate exclusion diets and food intolerance tests often reinforces in patients with functional dyspepsia (FD) the idea of being allergic or intolerant to foods. Physicians are often uncertain regarding the contribution of specific foods in FD and the lack of guidelines and dedicated dietitians, ultimately, leads to conflicting and uneven dietary advises. Here, we provide a pathophysiological-based review of the putative causal relationship between specific foods and symptoms generation in FD and then provide an evidence-based standardized dietary approach, applicable in clinical practice. Moving forward, international guidelines are eagerly awaited to standardize FD dietary management.

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INTRODUCTION

Current guidelines[1] define functional dyspepsia (FD) as a complex and multifactorial condition characterized by a broad spectrum of symptoms centered in the gastroduodenal region. It is a highly prevalent disorder, reaching prevalence as high as 40% of the general population in western countries[2] and it is characterized by a highly varied clinical presentation, ranging from upper abdominal bloating to nausea and vomiting. The high degree of overlap with gastro-esophageal reflux[3] and other functional gastrointestinal disorders (FGDIs) accounts for the complexity in categorizing dyspeptic patients into clinically and pathophysiological meaningful subgroups.

Though, Rome criteria[4,5] have identified two main subgroups based on the principal clinical pattern: Epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS).

EPS is characterized by the recurrence of epigastric pain or burning, independently from meal. On the contrary, PDS is unequivocally related to early post-prandial onset of fullness or early satiation. However, food ingestion seems to elicit also meal-unrelated symptoms such as pain or burning in over 75% of patients with PDS; hence, a clear-cut distinction between these two symptomatic presentations is challenging in real-world clinical practice[6]. Dyspepsia pathophysiology is heterogeneous and complex and both cognitive and behavioral factors, such as anticipation and arousal, and/or gastric sensorimotor dysfunction are well-established factors at play in FD symptoms induction and perception[6,7]. Aside from the role of central nervous system and gastric dysfunction, increasing evidences also demonstrated that duodenal abnormalities (duodenal hypersensitivity and small intestinal dysmotility) and subtle mucosal inflammation (duodenal eosinophilia and mast cell infiltration) could also play a role in generating FD symptoms[8-11].

Since the meals are recognized as triggers for at least a subset of symptoms, dietary and lifestyle modifications often represent the first line management in FD patients[12], despite the scanty quality evidence produced so far.

In this review, we summarize the current evidences regarding the role of diet in FD, focusing on the proposed underlying pathophysiological mechanisms. We will then explore the current treatment strategies in FD and the possible future targeted dietary treatments.

CALORIC INTAKE AND FD SYMPTOMS

Defective accommodation of the proximal stomach and delayed gastric emptying are recognized as two of the main mechanisms implicated in FD pathogenesis; hence, several studies investigated the potential role of caloric intake and food intake on symptoms development[13,14].

Tack *et al*[15] confirmed a possible correlation between caloric intake and gastric accommodation demonstrating that FD patients exhibited significantly higher satiety scores compared to controls, with maximum satiety reached at significantly lower

caloric amount in patients. However, this eating behavior does not necessarily correlate with a consistent weight loss, as one would expect[16-18].

Furthermore, Boeckxstaens *et al*[19] also described an impaired drinking capacity for both water and nutrient liquid meal in FD patients compared to healthy volunteers, even though no association with specific symptoms pattern had emerged.

This evidence suggests that probably meal volume and gastric distension could be implicated in triggering symptoms, rather than caloric intake *per se*[19]. Therefore, the consumption of small and frequent meals may be a reasonable advice in order to reduce FD symptoms. Beyond the effect of caloric intake and food amount itself, nutrient composition should not be underestimated.

NUTRIENT COMPOSITION AND FD SYMPTOMS

In the last decade, the interest on the correlation between physicochemical properties of macronutrients and dyspeptic symptoms is growing. Indeed, food consumption can influence gastrointestinal functions by means of either mechanical or chemical stimulation. A recent review, systematically analyzing over 6400 studies, concluded that wheat and high fat foods are two of the major players in FD[20].

Proteins, carbohydrates and lipids could all be implicated in symptoms onset, but the latter seems to be the most effective in eliciting the symptoms. Although a high protein intake may induce an increase of satiety in healthy subjects, little is known about the impact of high-protein meals on dyspeptic symptoms[21].

The role of carbohydrates on FD symptoms is still unclear, too. In the cross-sectional study "Study on the Epidemiology of Psychological, Alimentary Health and Nutrition", a large cohort of subjects has been evaluated to assess the potential effects of carbohydrates, in terms of glycemic index and load. The high glycemic load seemed to be associated with an increased risk of uninvestigated chronic dyspepsia and heartburn, in male subjects with normal body weight[22].

It is plausible that a high intake of carbohydrates could induce PDS-like symptoms due to its possible effect on gastric fundus accommodation. Furthermore, a high glycemic index meal physiologically determines an increase of glucagon- like peptide 1 and cholecystokinin (CCK) release, which can, in turn, delay gastric emptying and induce prolonged satiety.

An analysis of recent literature showed that the most common culprit foods, recognized by FD patients, appeared to be high in concentration of either gluten (grain/wheat products, takeout foods, processed foods) or fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) (fruit, wheat and grain products, soft drinks, processed foods)[16,20].

FODMAPs are a group of poorly absorbed and osmotically active carbohydrates, naturally contained in a wide array of common foods. Due to their physiological effects, FODMAPs are widely accepted as potential triggers for gastrointestinal symptoms in functional gastrointestinal disorders, particularly in irritable bowel syndrome (IBS) and residual functional bowel symptoms in inflammatory bowel diseases[23-25]. The combination of abnormal gas production, caused by an increased intestinal fermentation, and the luminal water retention secondary to their osmotic activity, seems to enhance abdominal distension and to induce abdominal pain and bloating in patients with altered visceral sensitivity[24]. Besides these well-known effects, their impact on FD physiopathology could be linked to qualitative changes in microbiome composition and/or on duodenal homeostasis secondary to an enhanced duodenal inflammation[24].

On the contrary, the role of lipids in FD has been better characterized. It has been demonstrated that a high fat-meal can induce greater nausea, pain and fullness both respect to a low-calorie meal and an equicaloric meal, high in carbohydrates for the same volume. The main mechanisms by which fatty foods could exacerbate FD symptoms are related to delayed gastric emptying and hypersensitivity to gastrointestinal hormones[26].

It is known that an intraduodenal lipid infusion can increase the sensitivity of the proximal stomach to distention, probably due to a fat specific effect on CCK release[26]. Indeed, the administration of a CCK-A receptor antagonist seems to overturn the inhibition of gastric motility and emptying caused by the ingestion of a high-fat meal[26-28].

SPECIFIC FOODS

Although the contribution of specific foods identified as triggers from FD patients is

empirical and diversified, some causal relationships between specific culprit foods and symptoms have been demonstrated. The retrospective nature of most studies and the lack of a standardized method to verify the food-symptom association accounts for the difficulty in drawing up an ultimate list of culprit or beneficial foods. Some of the most frequently reported triggering foods are fatty and acidic foods, wheat products and several types of fruit such as watermelon and fruit juices[16,24,29-31]. Despite the known evidences about fatty foods, almonds seem not to aggravate FD symptoms as expected[29]. This effect might be related to the high content of tryptophan, a serotonin precursor. Serotonin (5-hydroxytryptamine) is a key neurotransmitter involved in the regulation of gastrointestinal motility and sensory function. Indeed, the stimulation of serotoninergic 5-HT1 and 5-HT4 receptors induce gastric smooth muscle contractions, enhancing gastric emptying and seem to improve abdominal symptom in FD patients[32,33]. The culprit effect of pepper and chili may be mediated by its main active ingredient, capsaicin. Indeed, this alkaloid can exacerbate FD symptoms inducing hyperalgesia, through the activation of the transient receptor potential vanilloid subtype 1 (TRPV1) receptors, expressed on sensory afferent neurons[34-36]. Nonetheless, chronic capsaicin administration could lead to TRPV1 downregulation and reduce visceral hypersensitivity. Effectively, in a small-sized (30 FD subjects) randomized control trial over placebo, red pepper powder (Capsicum annuum) significantly improved overall symptom scores, including epigastric pain, fullness, and nausea[37]. Capsaicin is the paradigmatic example of how complex is the interplay between food ingestion and FD symptoms, with nutrients that can be at both beneficial or culprit foods, depending on the compensatory downregulation of visceral nociceptors.

The prevalent dyspepsia subtype also seems to play a role in predicting the response to dietary interventions. Being prevalently meal-related, PDS subtype has been the most studied pattern for nutritional intervention in FD. In a recent survey on 1304 Chinese FD patients, the authors found that unhealthier dietary habits, such as dining irregularly, having night snacks, skipping breakfast, and dining out, were more frequently associated with FD. The authors also evaluated the impact of specific dietary habits and dyspepsia subtypes, concluding that, although there was a large degree of overlap; certain foods, such as alcohol and coffee, were associated with EPS-FD[38]. Only few other studies have analyzed the impact of diet on the prevalent symptom pattern, revealing possible links between the consumption of specific foods and epigastric burning (coffee, pepper, chocolate and onions), fullness (red meat, wheat products, beans, fried foods, sweets, chocolate) and bloating (carbonated drinks, onions, bananas, milk)[16,20].

A factor that has to be taken into account is the lack of effective methods to assess potential food intolerances and allergies in most studies. The effect on FD symptoms could actually be influenced by the presence of gluten or lactose intolerance[31]. Further studies are needed to deepen this aspect.

Analogously to the culprit foods, very few data is available about putative "beneficial" foods and most of these studies have investigated herbal supplements, often used as complementary and alternative treatments[39,40]. In particular, caraway seeds, apple, quince and rock candy seem to have beneficial effects on FD symptoms[15,20,29]. Oil extracts of both peppermint (Mentha piperita) and caraway seeds (Carum carvi), as single supplements or in combination[41] have been proven beneficial in treating FD symptoms, but little is known about their physiological activity. The antiemetic action of menthol and peppermint oil seems to be related to an allosteric effect on 5-HT 3 receptors; however, this may be clinically irrelevant [42]. Peppermint oil has been traditionally used in FD and IBS due to its choleretic action and spasmolytic effects in the esophagus, lower stomach and duodenal bulb and colonic spasm during barium enema[43]. In several trials, peppermint and caraway oil were found to be more effective than placebo in improving dyspeptic symptoms, with an average decreased intensity of epigastric pain compared to placebo[44].

Furthermore, the consumption of rice seems to be safe and well tolerated by FD patients[45,46]. One could speculate that the lower content of gluten and FODMAPs compared to wheat and grain products could be involved in this favorable effect, but there are no evidences demonstrating this association to date.

Another emerging beneficial actor is ginger, thanks to its anti-inflammatory and antiemetic properties and its action on gastrointestinal motility[46]. The main polyphenolic components of ginger, gingerols and shogaols, have an inhibitory effect on cholinergic M3 and serotonergic 5-HT3 receptors improving gastric motility, reducing nausea and vomiting and inducing an acceleration of gastric emptying[47-51]. Despite the increasing knowledge of its physiological effects, in a small-sized open study, involving 11 FD patients, Ginger had no impact on gastric sensation, dyspeptic symptoms or gut peptides/hormones, while it displayed prokinetic effects[50]. Table 1 provides an overview of the role of specific foods and their contribution to FD

symptoms.

NUTRITIONAL APPROACH

In current clinical practice, dietary measures are often provided by physicians rather than nutritionists or dieticians and are frequently not supported by strong scientific evidences or are not systematically studied[52].

No standardized nutritional guidelines for FD are available, to date.

This reflects the poor methodology and quality evidence and the considerable heterogeneity in dietary assessment methodology (food frequency questionnaires, 24-h recall methods) and outcomes measures (gastrointestinal symptoms scores, gastroduodenal motility, gastric emptying rates *etc*.), observed in published food-based trials[20]. Most studies also fail to exclude the most common food intolerances (*i.e*. lactose intolerance) and/or are country or region-specific, exposing to an interpretation bias of published results.

A recent survey from China found a positive association between dyspepsia and irregular eating habits (skipping meals, dining out *etc*.), regardless of FD phenotype[38]. According to the above, it is reasonable to advice the consumption of smaller and more frequent meals during the day. Moreover, a reduction of spicy, hot, acid-stimulating and high-fat foods seems to be effective in a subgroup of patients.

Due to its efficacy in reducing abdominal symptoms as pain, flatulence and bloating a dietician-led low-FODMAP diet can be now considered as a viable first-line therapy in IBS[53]. Despite the known pathogenic and clinical overlap with IBS currently, there is lack of evidence demonstrating the effect of a FODMAPs reduction in FD[54,55]. Only one recent Asiatic review examined the feasible role of low-FODMAPs diet in the management of FD[56]. In 2017, Tan[56] speculates on several expected mechanism of action by which a reduction of these carbohydrates could improve dyspeptic symptoms. Specifically, the reduction of both intestinal fermentation and osmotic load could correlate with a decreased stimulation of mechanoreceptors. On the other hand, a decreased production of short chain fatty acids could either reduce chemoreceptors stimulation or modulate immune response.

To date, the increasing evidences showing an implication of wheat-containing foods in inducing FD symptom, led several authors to investigate the effects of gluten-free regimens in FD patients[30,31,57,58]. However, the gluten-free diet results in a marked reduction of dietary FODMAPs as well, offering potential interpretation biases[59]. A specific investigation on the differential impact of gluten and FODMAPs restrictions on FD symptoms is necessary to clarify the mechanisms by which these nutrients could act on FD pathogenesis.

Taking to account the beneficial effect of ginger mentioned above, it could be reasonable to encourage its addition to diet. However, the effectiveness of ginger action seems to be dose-related and influenced by the instability and the ease of oxidation typical of polyphenolic compounds and their different bioavailability. Indeed, gingerols and shogaols concentrations strongly differ based on product type (fresh, dry, ground, crystallized…)[60]. The role of dietary manipulations and specific foods in FD pathophysiology is summarized in Figure 1.

CONCLUSION

At present, googling the entries "dyspepsia AND diet" leads to over 2570000 hits, witnessing the public interest on this topic. This combined with the lack of standardized dietary guidelines for FD, the uneven information provided by specialists and the vast diffusion of not validated nutritional advices results in an increasingly frequent tendency of patients to self-manage their symptoms. FD patients often tend to self-diagnose with "food intolerances" and arbitrarily restrict their diet, solely on the basis of their personal experience or anecdotal information from questionable sources. These improvised elimination diets are often nutritionally unbalanced and, if prolonged, could therefore cause nutritional deficiencies. Furthermore, long-term exclusion diets could enhance anxiety toward that food, increasing visceral hyperalgesia and contributing to symptoms anticipation.

This improper loop leads functional patients to perpetuate these eating-avoidant behaviors and to erroneously convince themselves of being "intolerant" to specific trigger foods[61-63].

In spite of the growing public interest and pressing requests for standardized dietary advises from patients, very few randomized controlled trials were included in the present review and most available evidences represent extrapolations from

Table 1 Role of specific foods and their contribution to functional dyspepsia symptoms

Food	Active molecules	Study characteristics	Outcomes measurement	Proposed mechanisms of action	Effects	Ref.
Fatty foods	Lipids	Cross-sectional study (4 health subjects); Loxiglumide *vs* Loxiglumide plus fat	Gastrointestinal contractile activity (manometry)	Increased CCK release	(1) Hypersensitivity to gastrointestinal hormones; (2) Delayed gastric emptying; and (3) Symptoms exacerbation	[27]
		Randomized crossover study (20 FD patients); Duodenal infusion of saline *vs* lipid solutions	Gastric volume measurement (gastric barostat)			[28]
Almond	Tryptophan	Cross-sectional study (384 FD patients); Symptoms correlation with the intake of 114 different foods	Gastrointestinal symptoms measurement (VAS)	Indirect stimulation of serotoninergic 5-HT1 and 5-HT4 receptors	(1) Improved gastric emptying; and (2) Symptoms improvement	[29]
		Double-blind RCT over placebo; Tandospirone *vs* placebo				[33]
Pepper and Chili	Capsaicin	Cross-sectional study (121 FD patients); Symptom generation according to TRPV1 genotypes and the intake of spicy food	TRPV1 polymorphisms (on blood samples)	Regulation of TRPV1 receptors	(1) Hyperalgesia (acute administration); and (2) Reduced visceral hypersensitivity (chronic administration)	[35]
		Randomized crossover study (20 IBS-D patients); Standard meal *vs* spicy meal *vs* chili	Gastrointestinal symptoms measurement (VAS)			[36]
		Double-blind trial over placebo (30 FD patients); Pepper *vs* placebo	Gastrointestinal symptoms measurement (VAS)			[37]
Peppermint and Caraway oil		Cross-over study (6 health subjects); Peppermint caraway oil combination (enteric *vs* non enteric coated capsules)	Gastroduodenal motility (manometric study)	Allosteric effect on 5-HT3 receptors	(1) Antiemetic, Choleretic and spasmolytic action; and (2) Symptoms improvement	[41]
		Randomized, double-blind trial over placebo (96 FD patients); Peppermints caraway oil *vs* placebo	Gastrointestinal symptoms measurement (VAS)			[44]
Ginger	Gingerols and Shogaols	Double-blind trial over placebo (24 health subjects); Ginger *vs* placebo	Gastric emptying (US)	Inhibition of cholinergic M3 and serotoninergic 5-HT3 receptors	(1) Enhanced gastric emptying; (2) Improved gastric motility; (3) Reduced nausea and vomiting; and (4) educed inflammation	[47]
		Randomized, double-blind trial over placebo 126 FD patients); inger *vs* placebo	Gastrointestinal symptoms score (VAS)			[48]
		RCT over placebo (11 FD patients); inger *vs* placebo	Gastrointestinal symptoms (VAS) Gastric emptying (US), circulating hormones (GLP-1, motilin and ghrelin)			[50]

FODMAPs	FOS, GOS, Lactose, Fructose (excess), Polyols	Randomized crossover study (30 IBS patients and 8 health subjects); LFD *vs* Australian diet	Gastrointestinal symptoms score (VAS)	Increased intestinal fermentation Increased osmotic load	(1) Abnormal gas production; (2) Luminal water retention and abdominal distension; (3) Symptoms exacerbation; and (4) Enhanced duodenal inflammation	[25]

5-HT1: 5-hydroxytryptamine subtype 1; 5-HT4: 5-hydroxytryptamine subtype 4; CCK: Cholecystokinin; FD: Functional dyspepsia; FODMAPs: Fermentable oligosaccharides, disaccharides, monosaccharides and polyols; FOS: Fructo-oligosaccharides; GOS: Galacto-oligosaccharides; LFD: Low fodmaps diet; M3: Muscarinic receptor subtype 3; TRPV1: Transient receptor potential vanilloid subtype 1; GLP1: Glucagon-like peptide 1, US: Ultrasound, GI: Gastrointestinal; VAS: Visual analogue scale.

observational studies. Complicating the matter further stands the high degree of overlap between FD, gastro-esophageal reflux disease and IBS. For instance, the effects of a low-FODMAPs diet in FD could be overshadowed by the overlap with IBS symptoms, under- or over-estimating the effects of this dietary approach in FD patients[56].

Taking into account the above considerations, it is vital to pursue a uniform and evidence-based nutritional approach in the management of FD patients and to design high-quality studies evaluating the impact of nutritional intervention. The growing number of mobile and smartphone-based apps, designed to collect dietary data and to objectively record nutritional interventions, offers the possibility to overcome the current limitations.

Therefore, well-structured and standardized guidelines are eagerly awaited in order to standardize the nutritional approach and satisfy FD patients unmet clinical needs.

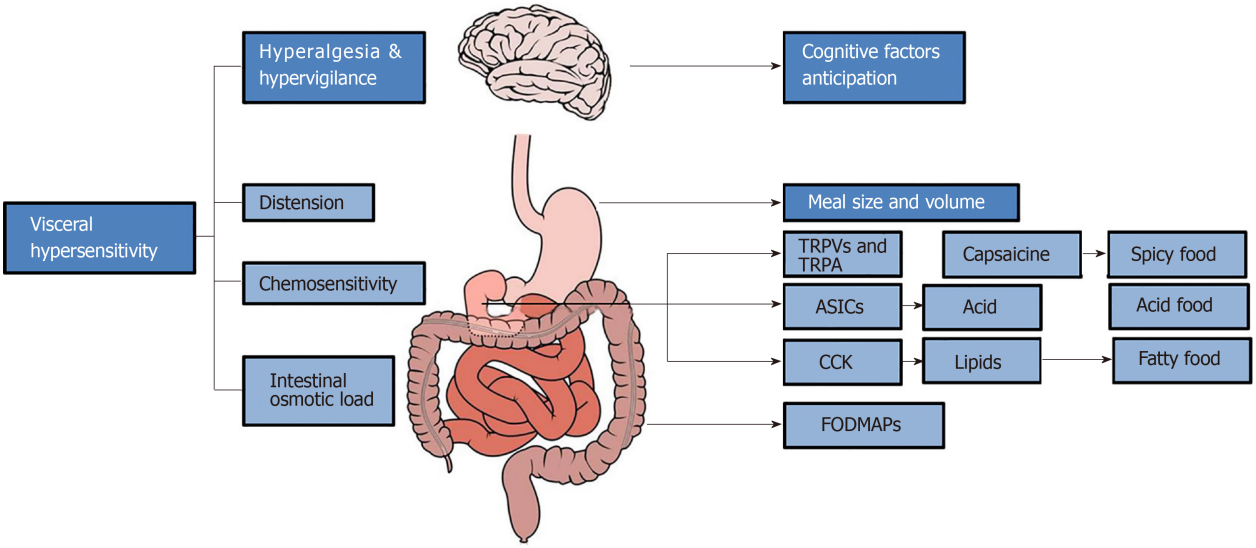

Figure 1 Role of dietary manipulations and specific foods in functional dyspepsia pathophysiology. ASICs: Acid-sensing ion channels; CCK: Cholecystokinin; FD: Functional dyspepsia; FODMAPs: Fermentable oligosaccharides, disaccharides, monosaccharides and polyols; TRPA: Transient receptor potential ankyrin; TRPV: Transient receptor potential vanilloid.

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