Causes and Treatment of Functional Dyspepsia

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Functional dyspepsia is a clinical syndrome defined by upper abdominal symptoms without identifiable cause by conventional diagnostic means. Recent studies have established that functional dyspepsia is a heterogeneous disorder in which different pathophysiologic disturbances underlie different symptom profiles. Delayed gastric emptying is associated with postprandial fullness, nausea, and vomiting; impaired accommodation is associated with early satiety and weight loss; and hypersensitivity to gastric distention is associated with epigastric pain, belching, and weight loss. The pathogenesis of functional dyspepsia is unknown but may be postinfectious in a subgroup of patients. The role of psychological disturbances and of duodenal hypersensitivity requires further study. Treatment of the underlying pathophysiologic abnormality seems logical, but options for pharmacotherapy are limited to acid suppression, prokinetic drugs, and antidepressants. Psychotherapy can be considered for refractory patients. Several novel drug therapies are under evaluation.

Introduction

Functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms whose cause cannot be identified by conventional diagnostic means [1•]. The symptom complex is often related to feeding and includes epigastric pain, fullness, bloating, early satiety, belching, nausea, and vomiting. Dyspepsia accounts for 10% to 20% of general practitioners' consultations, and functional dyspepsia accounts for about 20% to 30% of gastroenterology consultations. These data indicate that functional dyspepsia is a clinical problem of considerable magnitude with obvious implications for the consumption of medical care.

Pathophysiology

The pathophysiology of functional dyspepsia is unknown, but many mechanisms have been suggested. These include delayed gastric emptying, hypersensitivity to gastric distention, impaired accommodation to meal, *Helicobacter pylori* infection, abnormal duodenojejunal motility, hypersensitivity to lipids or acid in the duodenum, or central nervous system dysfunction (Sarnelli *et al.*, Submitted for publication) [3–6,7•,8–16]. Recent studies suggest that functional dyspepsia is in fact a heterogeneous disorder, with different pathophysiologic disturbances underlying different symptom profiles (Fig. 1).

Several studies have investigated the relationship between delayed gastric emptying of solids and dyspeptic symptom pattern and severity. In the largest studies, around 30% of dyspeptic patients had delayed gastric emptying of solids (Sarnelli *et al.*, Submitted for publication) [2,3]. Most small studies failed to find a convincing relationship between dyspeptic symptoms and delayed solid gastric emptying. In a large study, Stanghellini *et al.* [2] reported that dyspeptic patients with delayed gastric emptying were more likely to have postprandial fullness and vomiting. We recently confirmed that delayed emptying in functional dyspepsia is associated with postprandial fullness, nausea, and vomiting (Sarnelli *et al.*, Submitted for publication).

Accommodation of the stomach to a meal consists of relaxation of the proximal stomach, providing the meal with a reservoir and enabling a volume increase without a rise in pressure (Fig. 2). Scintigraphic and ultrasonographic studies have demonstrated an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach. This finding suggests defective postprandial accommodation of the proximal stomach [4–6]. Using a gastric barostat, we showed that 40% of dyspeptic patients have impaired gastric accommodation and that this impairment is associated with symptoms of early satiety and weight loss [7•].

During the past decade, it has been suggested that visceral hypersensitivity might be a major pathophysiologic mechanism in functional gastrointestinal diseases [8,9,10•]. Gastric barostat studies have confirmed that, as a group, patients with functional dyspepsia have lower thresholds

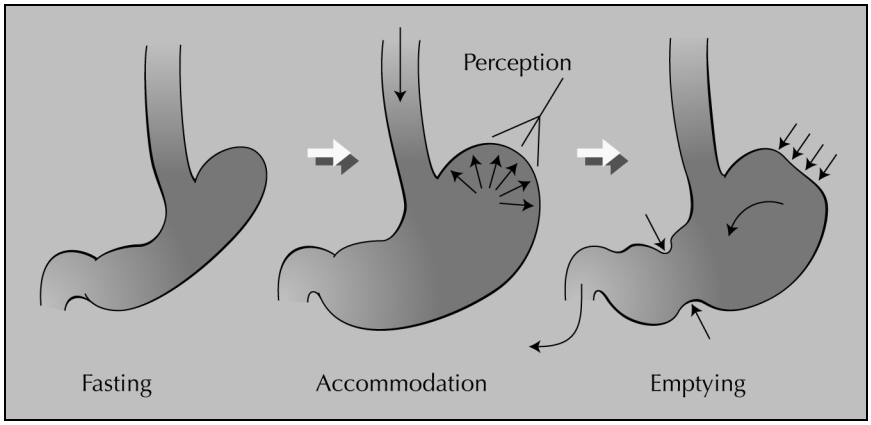

Figure 1. Pathophysiologic concepts and relation to symptom profile in functional dyspepsia.

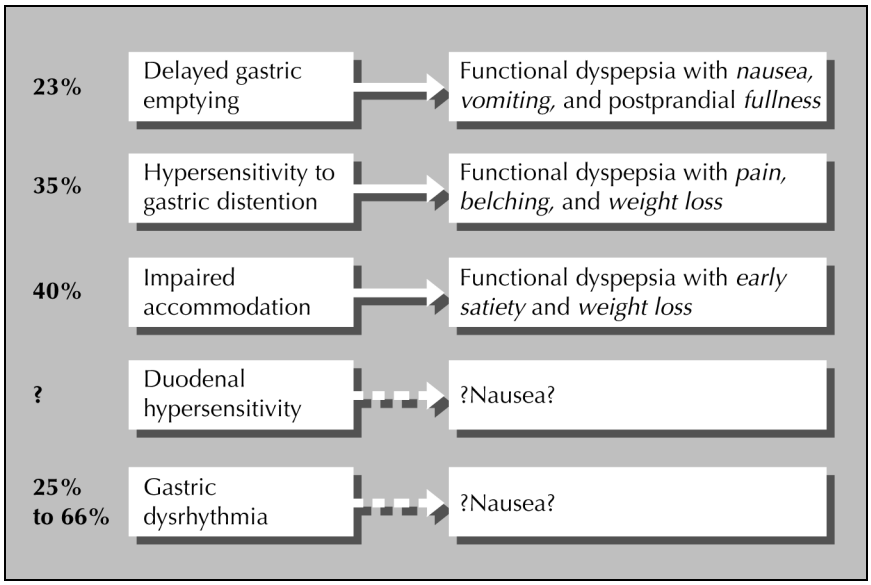

Figure 2. Gastric sensorimotor function in relation to meal intake.

for discomfort or pain during balloon distention of the proximal stomach [9]. Hypersensitivity to gastric distention, defined as perception or discomfort thresholds outside the normal range, is found in a subset of patients with functional dyspepsia but not in patients with organic causes of dyspepsia [10•]. We reported that 35% of dyspeptic patients had hypersensitivity to gastric distention and that these patients are more likely to have postprandial pain, belching, and weight loss [11•].

The presence of *H. pylori* infection or the presence of abnormal small-intestinal motility in dyspeptic patients is not associated with a specific symptom profile [12,13]. Balloon distention primarily assesses mechanosensitivity of the proximal gastrointestinal tract, but chemosensitivity may also play a role in the pathophysiology of functional dyspepsia. Recent studies reported that, as a group, patients with functional dyspepsia have increased sensitivity to duodenal perfusion with acid [14•] or with lipids [15•]. The prevalence of these abnormalities and their association with the symptom pattern must be determined in large groups of patients.

Cutaneous electrogastrography can demonstrate abnormalities of gastric myoelectrical activity in up to two thirds of patients with functional dyspepsia [16]. However, it is unclear whether these patients are primarily those that have delayed gastric emptying or whether this is associated with a specific symptom pattern.

Pathogenesis

The pathogenesis of functional dyspepsia has remained obscure, but a postinfectious origin has been suggested for some other functional bowel disorders. Both retrospective and prospective studies have shown that irritable bowel syndrome may follow an acute intestinal infection [17,18]; another study reported the occurrence of the gastroparesis syndrome after viral infection [19]. Using a questionnaire in 400 consecutive patients with functional dyspepsia, we found that 17% had a history suggestive of postinfectious dyspepsia [20]. These patients had a particularly high prevalence of impaired accommodation, which is attributable to a dysfunction at the level of gastric nitrergic neurons [20].

Several studies have reported an association between dyspepsia and psychopathology [21–23], but again the relevance to symptom pattern is unknown. In a recent factor analysis of dyspepsia symptoms, we demonstrated that

nausea, vomiting, early satiety, and weight loss were associated with female sex and with sickness behavior and that epigastric pain was associated with several psychosocial dimensions, including medically unexplained symptoms and conditions, as well as with health-related quality of life dimensions (Fischler *et al*., Submitted for publication).

It is unclear whether the associated psychopathologic abnormalities have a pathogenetic role or whether they are influencing symptom perception or health care–seeking behavior in dyspeptic patients.

Diagnosis

In patients with dyspeptic symptoms, organic disease is usually excluded by careful history taking and clinical examination, upper gastrointestinal endoscopy, routine biochemistry, and upper abdominal ultrasonography. *Giardia* infection or celiac disease should be considered in the differential diagnosis, and in selected patients, more extensive investigations, such as small-bowel radiography or computed tomography of the pancreas may be required.

It is well known that dyspeptic symptoms may be the manifestation of gastroesophageal reflux disease. Erosive esophagitis is readily recognized during endoscopy. In patients with nonerosive reflux disease, 24-hour pH monitoring may help to rule out reflux disease, but a course of empiric proton-pump inhibitor therapy is often more practical.

Determining Underlying Pathophysiology

Because of the relationship with symptom pattern, it seems logical to target potential therapeutic approaches toward the underlying pathophysiologic abnormality. This would require an easy, noninvasive method to determine underlying pathophysiology.

The Rome II committee proposed to subdivide functional dyspepsia into ulcer-like dyspepsia (pain is the dominant symptom), motility-like dyspepsia (discomfort-type symptoms are the dominant symptom), and unspecified dyspepsia (none of the previous) [1•]. However, when applying the Rome II subdivision to 105 consecutive functional dyspepsia patients, we could not show a correlation between the Rome II subdivision and pathophysiologic mechanism or symptom pattern [24].

In 167 patients with functional dyspepsia, we confirmed that the symptom pattern was related to the underlying pathophysiology but found that analysis of the symptom pattern lacked the specificity and sensitivity to adequately predict underlying pathophysiologic mechanisms [25].

It seems, therefore, that targeting therapy at the underlying disorder in functional dyspepsia will require some type of pathophysiologic testing to identify the appropriate patient population. We studied the use of a slow caloric drinking test to estimate gastric accommodation. Participants were studied in the morning after an overnight fast. A peristaltic pump filled one of two beakers with a liquid meal at a fixed rate. The participants were requested to maintain intake at the filling rate, thereby alternating the beakers as they were filled and emptied. At 5-minute intervals, they were asked to score their satiety and were instructed to cease the meal intake when maximum satiety was reached. In patients with functional dyspepsia, satiety scores were higher, and maximum satiety occurred at lower calories compared with control subjects. The maximum ingested calories decreased with increasing early satiety. The endpoint of the test (amount of ingested calories at maximum satiety) was significantly correlated to accommodation but not to gastric emptying or sensitivity. The satiety test had good sensitivity and specificity to predict impaired accommodation in patients (Tack *et al*., Submitted for publication). In healthy participants, pharmacologic agents affected the result of the satiety test according to their effect on gastric accommodation, suggesting that the satiety test provides an attractive noninvasive method for predicting impaired accommodation and for quantifying pharmacologic influences on gastric accommodation (Tack *et al*., Submitted for publication).

Treatment

Lifestyle and dietary measures are usually prescribed for functional dyspepsia. Thus far, dietary therapy has not been systematically studied. It seems logical to have patients eat more frequent, smaller meals. Because the presence of lipids in the duodenum enhances mechanosensitivity of the stomach, avoiding meals with a high fat content may be advisable [26].

For many patients, pharmacotherapy will be considered. Acid-suppressive drugs have been reported to relieve symptoms in some patients [27]. This seems to occur primarily in patients who also have some reflux symptoms, suggesting that the effect of acid suppression is really limited to patients with gastroesophageal reflux disease that has a dyspepsia-like symptom pattern [28].

Targeting potential therapeutic approaches toward the relevant, specific underlying pathophysiologic disturbance seems logical (Fig. 3). In patients with delayed emptying, gastroprokinetic drugs should improve symptoms of postprandial fullness, nausea, and vomiting. Studies available so far fail to prove this hypothesis convincingly. Prokinetic agents, including metoclopramide, domperidone, and cisapride, have traditionally been used to enhance gastric emptying rate and to improve symptoms in these patients. However, their prokinetic effect was moderate and the symptomatic response was often poor [27]. In view of the limited options for treating these patients, the report of the strong gastrokinetic effect of erythromycin [29•], related to its ability to act as a motilin receptor agonist, was met with great enthusiasm. As a result, several motilin agonists lacking antibiotic activity were developed.

In a large double-blind, placebo-controlled study, the motilin agonist ABT-229 did not improve symptoms. Even when only the subgroup of patients with delayed gastric

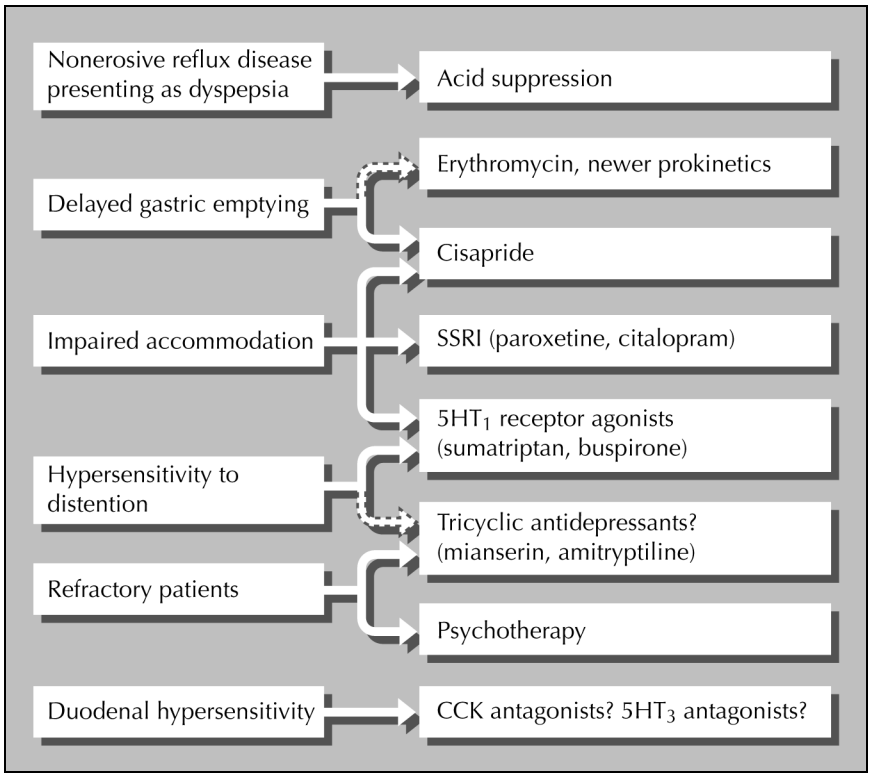

Figure 3. Pathophysiology-based treatment approach in functional dyspepsia. CCK—cholecystokinin; $5HT_3$—serotonin.

emptying was analyzed, no symptomatic benefit was obtained and, on the contrary, higher doses of the drug apparently prevented the beneficial placebo effect [30]. Several factors connected with the drug and with the study design may have contributed to the negative outcome [31]. The extent to which tachyphylaxis played a role in the therapeutic failure in patients with delayed gastric emptying is unclear. Moreover, erythromycin and related compounds reduce the meal-induced relaxation of the proximal stomach [32], thereby mimicking impaired accommodation to a meal and enhancing sensitivity to gastric distention [33], which may worsen dyspeptic symptoms.

In patients with impaired accommodation during and after the ingestion of a meal, restoring gastric accommodation is likely to improve symptoms of early satiety. Unfortunately, little is known about the control of the gastric accommodation reflex in humans. Studies in animals have shown that the gastric accommodation reflex is mediated via a vagovagal reflex pathway that activates nitrergic neurones in the gastric wall [34]. In animals, 5-hydroxytryptamine ($5HT_1$)-like receptors on intrinsic nitrergic neurons are involved in the vagally mediated gastric relaxation [35].

Short-term studies have shown that administration of nitric oxide donors relaxes the proximal stomach [36], but prolonged use of these drugs is usually associated with undesirable vascular side effects. Selective serotonin reuptake inhibitors (SSRIs) increase the availability of synaptically released 5HT, not only in the central nervous system but also at the level of the enteric nervous system. We observed that pretreatment with the SSRI paroxetine strongly enhanced the meal-induced relaxation of the proximal stomach (Tack *et al.*, Submitted for publication). This observation suggests involvement of 5HT in the gastric accommodation reflex in humans, as well as a potential beneficial effect of SSRIs in dyspeptic patients with impaired accommodation. Clinical studies addressing this question seem warranted.

The $5HT_4$ receptor agonist cisapride is often used to treat functional dyspepsia. In healthy persons, we observed that pretreatment with cisapride significantly enhanced accommodation to a meal [37]. Clinical studies assessing the effect of cisapride in dyspeptic patients with impaired accommodation are lacking and are unlikely to be performed because the drug was withdrawn from the US market due to cardiac safety issues. Subcutaneous administration of sumatriptan, a $5HT_1$ agonist used to treat migraine, relaxes the proximal stomach in humans [38] and, in short-term studies, restored meal-induced relaxation and decreased meal-induced satiety in patients with impaired gastric accommodation [7•]. However, the drug is not suitable for long-term studies.

Buspirone is a nonselective $5HT_1$ receptor agonist used in the treatment of panic attacks. In a placebo-controlled study in patients with functional dyspepsia, we confirmed that buspirone, 10 mg three times daily, was superior to placebo in alleviating dyspeptic symptoms and that this effect was associated with an enhancement of the accommodation to a meal (Tack *et al.*, Submitted for publication).

The treatment approach to patients with hypersensitivity to gastric distention has not been established. Earlier studies suggested a beneficial effect of the peripheral opioid agonist fedotozine [39], but development of this drug has not

been continued. Antidepressants were reported to improve symptoms of functional dyspepsia [40,41]. A recent study showed that symptomatic benefit occurred in the absence of an effect on gastric sensitivity to distention [41].

Studies evaluating *H. pylori* eradication in functional dyspepsia yielded conflicting results. Meta-analyses show no or limited benefit from eradication. It is unclear whether eradication might be cost-effective or the marginal benefit truly represents an effect on functional dyspepsia, or if this is more related to prevention of peptic ulcer disease [42–44].

A recent study demonstrated reduction in dyspepsia symptoms in patients treated with the $5HT_3$ receptor antagonist alosetron [45•]. The mechanism underlying this effect remains to be elucidated, but $5HT_3$ antagonists seem to have no effect on the gastric emptying rate or on sensitivity to gastric distention [46]. Alosetron has been withdrawn because of side effects; thus, additional studies with this drug are unlikely. It is unclear whether $5HT_3$ antagonists can improve impaired accommodation, but they were reported to decrease duodenal lipid sensitivity [44]. Similarly, cholecystokinin receptor antagonists also decrease duodenal lipid sensitivity [15•].

In view of the association of functional bowel disorders with psychological factors and with psychopathology, psychotherapy has been used to treat these patients. In a randomized, controlled trial of psychotherapy versus supportive therapy in functional dyspepsia, no difference in symptoms after 1 year was recorded [48]. However, in a *post hoc* analysis that eliminated dyspeptic patients with severe heartburn, a significant difference in favor of psychotherapy was found. It is unclear whether patients with more severe symptoms responded less favorably or if patients with true reflux disease responded less favorably. Hence, it has not been established which patients are most likely to benefit from psychotherapy.

Conclusions

Functional dyspepsia is a highly prevalent disorder. It is now clear that the pathophysiology of functional dyspepsia is heterogeneous. The pathogenesis is unclear but may be postinfectious in a subgroup of patients. Therapeutic approaches are limited, but they seem best directed at the underlying pathophysiology.

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- •• Of major importance

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