Causes and Treatment of Functional Dyspepsia

Jan Tack, MD, PhD, Raf Bisschops, MD, and Brunello DeMarchi, MD

Address
Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Herestraat 49, B-3000 Leuven, Belgium.
E-mail: Jan.Tack@med.kuleuven.ac.be

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Introduction
Functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms whose cause cannot be identified 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.

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...
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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 nitricergic 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