Functional Dyspepsia: Mechanisms of Symptom Generation and Appropriate Management of Patients

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With the exception of predominant heartburn, which can be easily distinguished from dyspepsia using simple questionnaires [1], the management of upper abdominal symptoms not caused by an organic disorder remains a challenge. Systematic reviews of large trials show that suppressing acid secretion and eradicating Helicobacter pylori, prokinetics, and antidepressants have inconsistent effects on the treatment of functional dyspepsia [2,3]. This inconsistent therapeutic efficacy has been attributed to the heterogeneity of patients, and the contribution of multiple mechanisms to development of symptoms. To achieve greater therapeutic efficacy, it may be necessary to target the therapeutic approach to a specific pathophysiology (e.g., impaired gastric emptying).

To provide more homogeneous patients for inclusion in clinical trials, the Rome II consensus criteria recommended distinguishing between patients with epigastric pain and those with discomfort as a means of identifying pathophysiologically distinct subgroups [4]. This recommendation was partly evidence based, if one accepted the notion that the term “discomfort” was a catch-all for a variety of symptoms other than pain. Those “discomfort” symptoms included nausea, early satiety, and postprandial fullness.

The Rome III consensus criteria [5] proposed differentiating two subcategories of functional dyspepsia: postprandial distress syndrome (early satiation or postprandial fullness) and epigastric pain syndrome (pain or burning in the epigastrium). Moreover, these disorders were distinguished from:

- Belching disorders, comprising aerophagia (troublesome repetitive belching with observed excessive air swallowing) and unspecified belching (no evidence of excessive air swallowing)
- Nausea and vomiting disorders, comprising chronic idiopathic nausea (frequent bothersome nausea without vomiting); functional vomiting (recurrent

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vomiting in the absence of self-induced vomiting, or underlying eating disorders, metabolic disorders, drug intake, or psychiatric or central nervous system disorders); and cyclic vomiting syndrome (stereotypical episodes of vomiting with vomiting-free intervals)

- Rumination syndrome, characterized by effortless regurgitation of recently ingested food into the mouth followed by rechewing and reswallowing, or expulsion of food

The new classification of functional dyspepsia requires further validation with physiologic measurements. Symptom or symptom combinations, however, have already been shown to be significantly associated with specific disturbances of gastric function in relatively large studies in the literature.

Almost 80% of patients with dyspepsia have two or more gastrointestinal symptoms [6]. Clinicians should comprehensively characterize dyspeptic symptoms rather than focusing on the predominant symptom. The term “dyspepsia” is derived from the term for “bad digestion” in Greek. The relationship between meals and dyspeptic symptoms is also critical, as evidenced by a large epidemiologic study in the United States [7] and a population-based study in Olmsted County, Minnesota [8]. The latter identified that meals evoked symptoms in 60% of those with dyspepsia. The timing of symptoms in relation to meals may also be useful: symptoms occurring relatively promptly (eg, during or within 30 minutes after food ingestion) are less likely to be caused by delayed gastric emptying, but they may result from rapid initial gastric emptying that delivers a high osmotic load to the small intestine. As discussed later, the small intestine may be the source of dyspeptic symptoms (eg, because of mechanical distention).

**MECHANISMS IN FUNCTIONAL DYSPEPSIA**

Fig. 1 summarizes the mechanisms considered to be important in the etiology of functional dyspepsia [6]. Although some studies suggest association of *H pylori* infection with epigastric pain in dyspeptics [9,10], systematic review of the epidemiologic studies of *H pylori* infection and functional dyspepsia found no evidence for a significant association [11]. Moreover, there are no consistent differences in the prevalence and severity of individual dyspeptic symptoms, gastric emptying rate, gastric relaxation after a meal, and sensitivity to gastric distention based on *H pylori* positive or negative status [12–14].

Delayed gastric emptying in functional dyspepsia reflects the overlap between the functional syndrome and idiopathic gastroparesis. Delayed gastric emptying may result from antral hypomotility and, possibly, duodenjejunal dysmotility, which have been documented in functional dyspepsia [15]. In the largest of the studies reported in the literature, gastric emptying of solids was delayed in about 30% of the patients with functional dyspepsia [16–18]. Patients with delayed gastric emptying of solids are more likely to report postprandial fullness, nausea, and vomiting [16,19], although a large multicenter study using a stable isotope breath test to measure gastric emptying failed to find any association between symptoms and gastric emptying status [20]. Delayed gastric emptying for liquids has been reported to be associated with postprandial fullness [16]. In a study from France,
only 5% of 190 patients with nonulcer dyspepsia had delayed gastric emptying of liquids measured by scintigraphy [21], and delayed gastric emptying of solids is more frequently encountered.

Efferent vagal dysfunction has been observed in several studies [22,23] and has been proposed to be a possible mechanism underlying both impaired accommodation to a meal [24] and antral hypomotility [22].

Accommodation of the stomach provides a reservoir for the meal, enabling an increase in gastric volume without an increase in pressure, and facilitating intragastric digestion. Preferential accumulation of food in the distal stomach was interpreted as indicative of reduced accommodation of the proximal stomach [25–28], and subsequent studies have shown reduced proximal gastric relaxation in response to a meal in patients with functional dyspepsia [29,30]. Impaired gastric accommodation (tone measured by barostat or volume measured by $^{99m}$Tc single-photon emission CT [SPECT]) was present in about 40% of the patients with functional dyspepsia [29,31–34]. Together, impaired gastric emptying and reduced gastric volume response to feeding were observed in 60% of a tertiary care group of patients with functional dyspepsia (Fig. 2) [34].

Excessive proximal gastric contraction in the postprandial period is also evident by phasic contractility. The latter is usually suppressed with the receptive relaxation and accommodation response to feeding. A Mayo Clinic study first documented increased phasic volume events in the postprandial period in
patients with functional dyspepsia [12]. In a study from Leuven, a small subset (15%) of dyspeptic patients displayed this unsuppressed phasic contractility of the proximal stomach [35] and was associated with bloating and, paradoxically, with absence of nausea. Phasic fundic contractions induce transient increases in gastric wall tension, and careful and detailed observations suggest that such contractions can be perceived and cause postprandial symptoms in functional dyspepsia [36].

Patients with functional dyspepsia have enhanced sensitivity to gastric distention [32,37–41]. The distal stomach is less compliant than the proximal stomach and may be the site of origin of symptoms caused by distension [42]. In general, gastric hypersensitivity was associated with symptoms of postprandial pain, belching, and weight loss [37], although other studies have failed to confirm association between hypersensitivity and symptom pattern [32,43]. Whereas dyspeptic symptoms are triggered or aggravated by meal ingestion in approximately 60% of patients [8], it is relevant to note that postprandial (rather than fasting) sensitivity to gastric distention was significantly associated with the severity of meal-related symptoms in functional dyspepsia [44].

In functional dyspepsia, symptoms (eg, nausea) may be induced by meals rich in fat [45]. Increased sensitivity to lipid emulsion or hydrochloric acid infusion into the duodenum was documented in functional dyspepsia [46,47], but
it is unclear whether either of these studies apply to the delivery of fat in meals or of acidic content to the duodenum [48–50]. Spontaneous duodenal exposure to endogenous acid was increased in patients with functional dyspepsia who displayed delayed clearance of exogenous duodenal acid [51]. Such patients had higher severity scores of several dyspeptic symptoms.

There is evidence of an association between psychopathology and functional dyspepsia [52] and between psychologic factors, gastric function, and symptoms in functional dyspepsia [53,54]. A community-based study demonstrated high somatic symptom scores were the most closely related disturbance in patients with functional dyspepsia. In contrast, gastric motor physiology and satiation testing were not abnormal in patients recruited from the community [8].

**THE ASSOCIATION BETWEEN SYMPTOMS AND PATHOPHYSIOLOGY IN DYSPEPSIA**

Previous studies have typically appraised the association between severity of individual symptoms and pathophysiology (Table 1). A review of these studies summarized that 40% to 50% of patients with dyspepsia have impaired gastric accommodation after meal ingestion, 34% to 66% have gastric hypersensitivity, and 23% to 59% have delayed gastric emptying [6]. Moreover, delayed gastric emptying was associated with early satiety; nausea; vomiting and fullness; impaired gastric accommodation with early satiety and fullness and weight loss in two of four studies; and visceral hypersensitivity with pain, belching, and weight loss in one of four studies [6].

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Associated symptoms</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Unsuppressed phasic contractility</td>
<td>Bloating, absence of nausea</td>
<td>Simren, et al [35]</td>
</tr>
<tr>
<td>Duodenal lipid hypersensitivity</td>
<td>Nausea</td>
<td>Barbera, et al [46,47]</td>
</tr>
<tr>
<td>Duodenal acid hypersensitivity</td>
<td>Nausea</td>
<td>Samsom, et al [50]</td>
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</table>

The ability to address the mechanisms causing symptoms is hindered by the limited repertoire of symptoms and by the relatively large number and spectrum of underlying physiologic disturbances in dyspepsia. The available evidence suggests that the symptom profile is not specific for a particular physiologic disturbance. For example, early fullness, nausea, bloating, and upper abdominal discomfort may be associated with delayed gastric emptying [16,18,55], accelerated gastric emptying [55], or gastric dysaccommodation [29]. The latter may be associated with accelerated emptying of liquids or delayed emptying of solids and may reflect impaired vagal function in dyspepsia [15,22,23].

To assess further the relationship between dyspepsia symptoms and potential risk factors, the Leuven group undertook a factor analysis of their rich clinical experience [56]. This analysis revealed four main factors in patients with dyspepsia:

- **Factor 1**: nausea, vomiting, early satiety, and weight loss; and associated with younger age, female gender, and sickness behavior
- **Factor 2**: postprandial fullness and bloating
- **Factor 3**: pain symptoms and several psychosocial dimensions
- **Factor 4**: belching unrelated to psychosocial dimensions

Factors 1 and 2 were associated with delayed gastric emptying, and factors 3 and 4 were associated with gastric hypersensitivity to mechanical distention of the stomach.

Karamanolis and colleagues [57] mined the same large database: 720 patients were screened for *H pylori* infection; 592 prospectively underwent noninvasive gastric emptying test for solids and liquids, and 332 had gastric accommodation and sensation test with an invasive barostat method. They assessed whether the predominant upper gastrointestinal symptom was a good predictor of pathophysiology in dyspepsia. Although the association of early satiety after meals and impaired gastric accommodation is impressive and confirms prior studies [29], the “predominant” symptom does not allow greater prediction of the pathophysiology demonstrable in functional dyspepsia.

The barostat-based method used in the study to assess gastric accommodation and sensitivity does not reliably assess gastric physiology during fasting, however, because of the perturbation associated with the intrabag pressure necessary to maintain the bag in apposition with the gastric wall to measure tone. Moreover, it measures proximal but not distal gastric function, and the intragastric bag displaces the meal to the antrum, causing antral distention [58] and, potentially, increased reflex fundic relaxation.

Recent studies suggest that both fasting gastric volume and antral function may be important determinants of symptoms in dyspepsia. Fasting gastric volume (measured noninvasively by SPECT) is a significant contributor to development of symptoms following a challenge meal in dyspepsia [55]. Antrofundic reflexes are impaired in dyspepsia [59], and the sensation of fullness has been associated with antral rather than fundic dimensions in other studies in health or dyspepsia [32,60].
Using noninvasive, validated techniques, the author showed that 72% of patients with functional dyspepsia had increased postprandial upper gastrointestinal sensitivity to a challenge liquid nutrient meal and 52% had reduced postmeal gastric volume [55]. Gastric emptying of solids measured by scintigraphy was accelerated in 41% of patients at 1 hour, whereas 41% had delayed emptying at 4 hours [55]. Half of the variability in dyspepsia symptom scores (Fig. 3) was attributable to the combination of rapid gastric emptying (at 1 hour); delayed gastric emptying at 4 hours and gastric volumes (particularly fasting gastric volume); in addition to the demographic factors, age, and body weight [55].

TREATMENT OF FUNCTIONAL DYSPEPSIA

Given the new insights [5] on the classification of functional upper gastrointestinal syndromes, it is relevant carefully to evaluate the patient’s symptoms before applying an empirical approach to treatment. There is ample evidence from meta-analyses that eradication of *H pylori* and anti–acid secretory therapy (Fig. 4) are ineffective in functional dyspepsia that is not dominated by heartburn. Fig. 5 provides a proposed algorithm for management of patients with dyspepsia that reflects the recent classification of upper functional upper gastrointestinal syndromes [5], data from the literature, and clinical experience.

General Measures

By definition, most patients presenting with functional dyspepsia have undergone upper gastrointestinal endoscopy, and biopsies and these are normal or unremarkable. Reassurance and education are the first steps in management. Dietary recommendations have not been systematically studied. Eating more frequent, smaller meals and avoiding food that aggravates symptoms are logical. Eradication of *H pylori* infection has no place in the treatment of functional dyspepsia.
Acid-Suppressive Drugs
In patients with concomitant or dominant symptoms of gastroesophageal reflux, specifically heartburn and regurgitation, a trial of antisecretory therapy is indicated. Large studies in functional dyspepsia have shown that treatment with proton pump inhibitors was approximately 10% to 15% better than placebo in patients with functional dyspepsia \[61\]; this positive effect seems to be related to relief of reflux-like symptoms.

Prokinetic Agents
Metoclopramide, domperidone, cisapride, and tegaserod are widely used in functional dyspepsia, but evidence of efficacy is most convincing for those with delayed gastric emptying. Because some patients with dyspepsia have accelerated gastric emptying, a gastric emptying test should be performed to select patients for prokinetic therapy.

Metoclopramide and domperidone are dopamine receptor agonists (that confers some of their antinausea properties) with a stimulatory effect on upper gastrointestinal motility. Unlike metoclopramide, domperidone does not cross the blood-brain barrier. Cisapride facilitates the release of acetylcholine in the myenteric plexus by stimulation of 5-HT\(_4\) receptors and accelerates gastric emptying. Cisapride availability is restricted because of cardiac safety issues, and coadministration with drugs that inhibit cytochrome P-450 3A4 should be avoided or cautiously monitored. Tegaserod, a 5-HT\(_4\) agonist,
also accelerates gastric emptying [62], but its efficacy in dyspepsia remains unclear.

Prokinetics are the only pharmacotherapies with any substantive evidence to support use to correct gastric emptying and relieve symptoms in patients with dyspeptic symptoms and delayed gastric emptying (Table 2) [63–79]. Even the most robust papers in the literature, however, used trial methods that are suboptimal by current standards. Itopride is an anticholinesterase that showed significant promise in a phase IIB trial [80]; however, subsequent studies (as yet unreported) have not confirmed the initial promise.

Antidepressants and Behavioral Approaches
There is some evidence that tricyclic antidepressants affect gastric sensitivity [81], but large controlled trials have not been conducted. Pharmacodynamic studies [82] do not suggest that antidepressants alter the maximum tolerated volume of a nutrient meal. Controlled trials of antidepressants and behavioral therapy have shown benefit in dyspepsia but the generalizability of the data, the specific subgroup that benefits, and the cost-effectiveness require further study [83,84]. Hypnotherapy is effective in specialized centers [85], and this may be achieved in part by acceleration of gastric emptying [86]. This author restricts the use of antidepressants to patients with functional abdominal pain syndromes, including epigastric pain syndrome.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Medication and study design</th>
<th>No.</th>
<th>Cause</th>
<th>Dose</th>
<th>Study length</th>
<th>Outcome results</th>
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</thead>
<tbody>
<tr>
<td>Perkel, et al [63]</td>
<td>Metoclopramide DB, PC, PG, RCT</td>
<td>28</td>
<td>Diabetic (5), postsurgical (4), idiopathic (19)</td>
<td>10 mg QID</td>
<td>3 wk</td>
<td>Improved symptoms by 29%</td>
</tr>
<tr>
<td>McCallum, et al [64]</td>
<td>Metoclopramide, PC, RCT</td>
<td>18</td>
<td>Diabetic</td>
<td>10 mg QID</td>
<td>3 wk</td>
<td>Improved symptom score by 25%; improved GE by 25%</td>
</tr>
<tr>
<td>Patterson, et al [65]</td>
<td>Metoclopramide RCT, DB, multicenter</td>
<td>45</td>
<td>Diabetic</td>
<td>10 mg QID</td>
<td>4 wk</td>
<td>Symptoms improved by 39%</td>
</tr>
<tr>
<td>Abell, et al [66]</td>
<td>Cisapride, open label</td>
<td>21</td>
<td>Diabetic (9) Idiopathic (12)</td>
<td>10 mg TID</td>
<td>1 y</td>
<td>Reduction on symptoms score by 25%; increased weight</td>
</tr>
<tr>
<td>Richards, et al [67]</td>
<td>Cisapride, DB, PC, RCT</td>
<td>38</td>
<td>Diabetic (7); scleroderma (2); idiopathic (29)</td>
<td>20 mg TID</td>
<td>6 wk</td>
<td>Improved GE solid without significantly reducing symptoms</td>
</tr>
<tr>
<td>Kendall, et al [68]</td>
<td>Cisapride, open label</td>
<td>30</td>
<td>Diabetic (6); idiopathic (24)</td>
<td>20 mg TID</td>
<td>2 y</td>
<td>10 patients improved GE; 7 patients &gt;20% improved overall symptom score</td>
</tr>
<tr>
<td>Dutta, et al [69]</td>
<td>Cisapride, RCT, DB, PC</td>
<td>51</td>
<td>Diabetic</td>
<td>10 mg TID</td>
<td>2 wk</td>
<td>Symptoms improved; GE decreased by 72%</td>
</tr>
<tr>
<td>Braden, et al [70]</td>
<td>Cisapride, RCT, DB, PC</td>
<td>19</td>
<td>Diabetic</td>
<td>10 mg QID</td>
<td>1 y</td>
<td>Symptoms improved by 55%; GE improved by 24%</td>
</tr>
<tr>
<td>Authors</td>
<td>Treatment</td>
<td>N</td>
<td>Condition</td>
<td>Dose</td>
<td>Duration</td>
<td>Outcome</td>
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<tr>
<td>Champion, et al</td>
<td>Domperidone DB, PC, PG RCT</td>
<td>19</td>
<td>Diabetic</td>
<td>20 mg QID</td>
<td>4 wk</td>
<td>Improved symptoms; improved GE by 37%</td>
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<tr>
<td>Soykan, et al</td>
<td>Domperidone open label</td>
<td>17</td>
<td>Diabetic (3), postsurgical (2), idiopathic (12)</td>
<td>20 mg QID</td>
<td>2 y</td>
<td>Symptom score improved by 68%</td>
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<td>Silvers, et al</td>
<td>Domperidone single-blind</td>
<td>287</td>
<td>Diabetic</td>
<td>20 mg QID</td>
<td>4 wk</td>
<td>Symptoms improved in 208 of 269 patients by 63%</td>
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<tr>
<td>Patterson, et al</td>
<td>Domperidone DB, RCT</td>
<td>48</td>
<td>Diabetic</td>
<td>20 mg QID</td>
<td>4 wk</td>
<td>Symptom score improved by 41%</td>
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<tr>
<td>Franzese, et al</td>
<td>Domperidone versus cisapride RCT</td>
<td>28</td>
<td>Diabetic children</td>
<td>D: 0.9 mg/kg, C: 0.8 mg/kg</td>
<td>8 wk</td>
<td>Domperidone superior for symptom relief and improved GE</td>
</tr>
</tbody>
</table>

This provides an appraisal of the outcomes that might be expected in functional dyspepsia with delayed gastric emptying.

Abbreviations: CT, randomized controlled trial; DB, double blind; GE, gastric emptying; PC, placebo controlled; PG, parallel group; XO, crossover.
Experimental approaches using medications that relax the gastric fundus include sildenafil (phosphodiesterase-5 inhibitor), clonidine (α2-adrenergic receptor agonist), sumatriptan (5-HT1 receptor agonist), buspirone (nonselective 5-HT1 receptor agonist) may have promise in functional dyspepsia based on pharmacodynamic studies. However, formal trials are awaited. The 5-HT3 receptor antagonist, alosetron, showed benefit in a phase IIIB study in functional dyspepsia [87], but the mechanism of the efficacy is unclear and it has not been pursued. Although dysaccommodation and gastric hypersensitivity are relevant mechanisms for dyspepsia, there is as yet no treatment proved to benefit patients’ symptoms.

A LOOK TO THE FUTURE
The availability of valid, noninvasive point-of-service methods (eg, stable isotope gastric emptying tests) to determine whether gastric emptying is rapid or delayed, and of imaging methods, such as MRI, SPECT or three-dimensional ultrasound, to measure fasting and postprandial gastric volumes may help triage patients to receive therapy that is more likely to be effective than the current empirical approaches with acid suppressants, prokinetics, or antidepressants, which are based on individual physician preference. Functional dyspepsia remains a challenge and presents unmet clinical need.

References


