Dyspeptic symptoms, defined as discomfort or pain in the upper part of the abdomen, occur very commonly in the general population. Epidemiologic surveys suggest that 15%–20% of the general population in Western countries experience dyspepsia over the course of 1 year.\(^1,2\) Despite the fact that only about 1 in 4 people with dyspeptic symptoms choose to consult a physician,\(^1\) dyspepsia is a clinical problem of considerable magnitude for the health care system due to the high prevalence and the chronic or recurrent nature of symptoms.\(^3\)

Most of these patients have no identifiable cause of dyspepsia by standard diagnostic tests,\(^4\) which is referred to as functional dyspepsia. According to international consensus, the definition of functional dyspepsia is persistent or recurrent pain or discomfort centered in the upper abdomen without evidence of organic disease likely to explain the symptoms (Table 1).\(^5\) Discomfort refers to unpleasant sensations that the subject does not interpret as pain and may be characterized by upper abdominal fullness, early satiety, bloating, belching, or nausea. Furthermore, there is no relation between dyspeptic symptoms and bowel movements (i.e., irritable bowel syndrome does not explain the symptoms), and patients with predominant heartburn should be excluded.\(^3\)

**The Dyspepsia Symptom Complex**

The symptom complex includes epigastric pain, bloating, early satiety, fullness, epigastric burning, belching, nausea, and vomiting. Although often chronic, the symptoms in functional dyspepsia are frequently intermittent, even during a period with marked symptoms.\(^6\) In patients with functional dyspepsia seen at a tertiary referral center, the most prevalent symptoms were postprandial fullness and bloating, followed by epigastric pain, early satiety, nausea, and belching.\(^7-11\) However, there is considerable heterogeneity as shown, for instance, in the number of symptoms that patients are reporting (Figure 1). In the general population, the most prevalent dyspeptic symptoms are postprandial fullness, early satiety, upper abdominal pain, and nausea.\(^12,13\)

Attempts have been made to simplify the intricate heterogeneity of the dyspepsia symptom complex. The Rome II committee proposed a subdivision according to the predominant symptom of either pain or discomfort (Table 1). Studies have shown correlations between this subdivision and the presence of *Helicobacter pylori* infection or delayed gastric emptying\(^14\) and between this subdivision and response to acid-suppressive therapy.\(^15\) However, the subdivision has also been criticized because of the significant overlap between the symptom subgroupings, the considerable number of patients who do not fit into one of the subgroups, and, above all, the lack of adequate value in predicting underlying organic disease.\(^2,16\)

A factor analysis of dyspeptic symptoms in tertiary care patients did not support the existence of functional dyspepsia as a homogeneous (unidimensional) condition. A 4-factor model (nausea/vomiting/satiety/weight loss, bloating/fullness, pain/burning, and belching) was found to be valid, with differential distribution within the patient population according to cluster analysis.\(^17\) In the general population, factor analysis identified 2 factors (early satiety/fullness/pain and nausea/vomiting), with differential distribution within the population according to cluster analysis.\(^13\) These studies confirm the heterogeneity of the dyspepsia symptom complex, but there is no proof that these provide a clinically meaningful subdivision of the syndrome.

Dyspeptic symptoms are often aggravated by food ingestion. Studies using questionnaires showed that \(>75\%\) of dyspeptic patients report a relationship between aggravation of symptoms and ingestion of a meal.\(^18,19\) Registration of symptoms before and after ingestion of a standardized meal showed that dyspeptic symptoms increase with meal ingestion in \(>90\%\) of dyspeptic patients and that maximum symptom severity

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**Abbreviations used in this paper:** 5-HT, 5-hydroxytryptamine; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

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occurs between 45 and 90 minutes after ingestion of a standardized 250-kcal meal.18,19

Weight loss is traditionally considered an alarm symptom, pointing toward diagnoses other than functional dyspepsia. Recent studies in tertiary care patients reported the presence of weight loss as a symptom associated with functional dyspepsia,8–11 but this was considered to reflect the situation in tertiary care only. However, more recent, preliminary observations in the general population also report an association between dyspeptic symptoms and weight loss.13

Pathophysiologic Mechanisms and Their Relation to Symptom Pattern

Several pathophysiologic mechanisms have been suggested to underlie dyspeptic symptoms. These include delayed gastric emptying, impaired gastric accommodation to a meal, hypersensitivity to gastric distention, H. pylori infection, altered response to duodenal lipids or acid, abnormal duodenojejunal motility, or central nervous system dysfunction (Figure 2). At present, the pathophysiology of functional dyspepsia is only partially elucidated. However, there is growing evidence that functional dyspepsia is in fact a very heterogeneous disorder and different subgroups can be identified based on different demographic, clinical, and pathophysiologic features.7–11

Table 1. Definition of Functional Dyspepsia and Subgroups According to the Rome II Working Committee5

<table>
<thead>
<tr>
<th>Definition of functional dyspepsia, according to the Rome II working team:</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 12 weeks (which need not be consecutive), within the preceding 12 months, of the following:</td>
</tr>
<tr>
<td>Persistent or recurrent pain or discomfort centered in the upper abdomen;</td>
</tr>
<tr>
<td>No evidence of organic disease (including upper endoscopy) that is likely to explain the symptoms; and</td>
</tr>
<tr>
<td>No evidence that the dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome)</td>
</tr>
</tbody>
</table>

Dyspepsia subgroups based on the predominant or most bothersome symptoms, according to the Rome II working team:

- Ulcer-like dyspepsia
  - Pain centered in the upper abdomen is the predominant (most bothersome) symptom

- Dysmotility-like dyspepsia
  - An unpleasant or troublesome nonpainful sensation (discomfort) centered in the upper abdomen is the predominant symptom; this sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating, belching, or nausea

- Unspecified dyspepsia
  - Cannot be classified as above

Delayed Gastric Emptying

Delayed gastric emptying is traditionally considered a major pathophysiological mechanism underlying symptoms in functional dyspepsia and idiopathic gastroparesis.7,11,20–29 Several studies have investigated the relationship between delayed gastric emptying and symptom pattern and severity. Depending on the study, the percentage of dyspeptic patients with delayed gastric emptying ranges from 20% to 50%.7,11,20–29 In a meta-analysis of 17 studies involving 868 dyspeptic patients and 397 controls, significant delay of solid gastric emptying was present in almost 40% of patients with functional dyspepsia.23 However, most of the studies were performed in small groups of patients and small control groups. In the largest studies, gastric emptying of solids was delayed in about 30% of the patients with functional dyspepsia.27

Most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern.20–22 More recently, 3 large-scale single-center studies showed that patients with delayed gastric emptying for
Solids are more likely to report postprandial fullness, nausea, and vomiting, although a large multicenter study failed to find any association (Table 2). Almost all studies focused on solid emptying rate only. A recent large-scale study suggested an association between delayed emptying for liquids and symptoms of postprandial fullness.

**Impaired Gastric Accommodation to a Meal**

The motor functions of the proximal and distal stomach differ remarkably. Whereas the distal stomach regulates gastric emptying of solids by grinding and sieving the content until the particles are small enough to pass the pylorus, the proximal stomach serves mainly as a reservoir. Accommodation of the stomach to a meal consists of a relaxation of the proximal stomach, providing the meal with a reservoir and enabling an increase in volume without an increase in pressure.

Scintigraphic and ultrasonographic studies have shown an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach. These findings suggest defective postprandial accommodation of the proximal stomach. Consistently, studies using a gastric barostat have shown reduced proximal gastric relaxation in response to a meal in patients with functional dyspepsia. Insufficient accommodation of the proximal stomach during and after the ingestion of a meal may be accompanied by increased intragastric pressure and activation of mechanoreceptors in the gastric wall, thus inducing symptoms.

Using a gastric barostat in 40 consecutive dyspeptic patients, we showed that impaired gastric accommodation was present in 40% of the patients and that this impairment was associated with symptoms of early satiety and weight loss. The relation between impaired gastric accommodation and early satiety was also apparent from the correlation between the amplitude of the meal-induced relaxation and the amount of calories ingested at maximum satiety in patients with early satiety. Others, using single-photon emission computed tomography, scintigraphy, or barostat studies of the proximal stomach, have confirmed the prevalence of impaired accommodation in approximately 40% of dyspeptic patients, but the relationship with symptom pattern has been found to be less consistent (Table 3).

An unsolved issue is the site of symptom generation in patients with impaired accommodation. When the proximal stomach is not relaxing properly, ingestion of a meal may be accompanied by activation of tension mechanoreceptors in the proximal stomach wall and generation of symptoms. On the other hand, insufficient accommodation of the proximal stomach may force the meal into the distal stomach, thereby creating a distended antrum. Studies on the induction of symptoms during proximal and distal gastric distention in humans have shown conflicting results that are at least partly attributable to technical and methodological differences. The gold standard for assessment of gastric sensitivity to distentions is currently the gastric barostat; however, instead of dual barostat distentions, these studies used ultrasound measurements or single water-filled or barostat balloons. In a recent study using a double gastric barostat assembly, we showed that symptom profiles induced by gastric distention did not differ between

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**Table 2. Prevalence of Delayed Emptying and Relationship With Symptoms in Functional Dyspepsia in Literature Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Prevalence of delayed emptying (%)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener et al., 1989</td>
<td>43</td>
<td>30</td>
<td>No correlation</td>
</tr>
<tr>
<td>Jian et al., 1989</td>
<td>28</td>
<td>59</td>
<td>No correlation</td>
</tr>
<tr>
<td>Talley et al., 1989</td>
<td>32</td>
<td>30</td>
<td>No correlation</td>
</tr>
<tr>
<td>Waldron et al., 1991</td>
<td>50</td>
<td>42</td>
<td>No correlation</td>
</tr>
<tr>
<td>Klausner et al., 1993</td>
<td>69</td>
<td>35</td>
<td>No correlation</td>
</tr>
<tr>
<td>Scott et al., 1993</td>
<td>75</td>
<td>28</td>
<td>No correlation</td>
</tr>
<tr>
<td>Stanghellini et al.,</td>
<td>343</td>
<td>34</td>
<td>Associated with female sex, postprandial fullness, vomiting</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maes et al., 1997</td>
<td>344</td>
<td>30</td>
<td>Not studied</td>
</tr>
<tr>
<td>Perri et al., 1998</td>
<td>304</td>
<td>33</td>
<td>Associated with postprandial fullness, nausea, and vomiting</td>
</tr>
<tr>
<td>Sarnelli et al., 2003</td>
<td>392</td>
<td>23</td>
<td>Associated with postprandial fullness, nausea, and vomiting</td>
</tr>
<tr>
<td>Talley et al., 2001</td>
<td>551</td>
<td>24</td>
<td>No correlation</td>
</tr>
</tbody>
</table>
proximal and distal gastric distention and that mechanoreceptors from both sites may contribute to symptoms. However, because the distal gastric wall is less compliant than the proximal gastric wall, the distal stomach may produce greater symptoms in response to the same volume of distention.

**Hypersensitivity to Gastric Distention**

Physiologic stimuli during the digestive process are not normally perceived but in some circumstances may induce conscious sensations. During the past decade, it has been suggested that patients with functional gastrointestinal diseases may have a sensory dysfunction of the gut, so that physiologic stimuli would induce symptoms. Several studies have clearly established that, as a group, patients with functional dyspepsia have enhanced sensitivity to gastric distention. However, in these studies, different approaches to calculate sensitivity to gastric distention and to determine the range of normality have been used.

A systematic analysis in a large group of controls and patients indicated that the increase in the intra-balloon pressure over intra-abdominal pressure needed to induce discomfort or pain is the most appropriate expression of sensitivity to gastric distention. However, in these studies, different approaches to calculate sensitivity to gastric distention and to determine the range of normality have been used.

Perception of gastric distention requires the activation of mechanoreceptors, and studies in healthy volunteers have suggested involvement of “in series” mechanoreceptors that respond to increases in tension within the stomach wall. By analyzing the relationship between changes in perception and increases in pressure in an isovolumetric balloon in the proximal stomach, we were able to show that dyspeptic patients with hypersensitivity to gastric distention perceive isovolumetric phasic contractions of the proximal stomach. Fundus-relaxing drugs decrease sensitivity to gastric distention and decrease meal-induced symptoms in these patients. These findings are compatible with involvement of tension mechanoreceptors in the symptom generation in dyspeptic patients with visceral hypersensitivity.

Because patients with hypersensitivity to gastric distention have more prevalent symptoms of epigastric pain and because they experience pain during gastric balloon distention at levels of distention that are normally not painful, these patients have visceral hyperalgesia. According to the neurophysiologic theory of pain, pain can be encoded by activation of high-threshold nociceptive pathways or by intense stimulation of low-threshold multimodal pathways. To determine whether gastric hypersensitivity in functional dyspepsia reflects a selective sensitization for painful sensations or whether the sensitivity for nonpainful stimuli is also enhanced in patients with visceral hypersensitivity, we analyzed the relationship between intensity scores for pain and nonpainful sensations during gastric balloon distention in dyspepsia. In both normosensitive and hypersensitive dyspeptic patients, the elevation of intensity scores for pain paralleled the elevation of intensity scores for the nonpainful sensations of nausea, satiety, and fullness. These findings are compatible with up-regulation of multimodal afferent pathways and argue against isolated up-regulation of pain-specific afferent pathways in functional dyspepsia with visceral hyperalgesia.

**Table 3. Prevalence of Impaired Accommodation and Relationship With Symptoms in Functional Dyspepsia in Literature Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Technique</th>
<th>Prevalence of impaired accommodation (%)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tack et al., 1998&quot;</td>
<td>40</td>
<td>Barostat</td>
<td>40</td>
<td>Early satiety, weight loss</td>
</tr>
<tr>
<td>Kim et al., 2001&quot;</td>
<td>32</td>
<td>Single-photon emission computed tomography</td>
<td>40</td>
<td>Weight loss&quot;</td>
</tr>
<tr>
<td>Boeckxstaens et al., 2002&quot;</td>
<td>44</td>
<td>Barostat</td>
<td>40</td>
<td>No correlation</td>
</tr>
<tr>
<td>Piessevaux et al., 2003&quot;</td>
<td>40</td>
<td>Scintigraphy</td>
<td>50</td>
<td>Early satiety</td>
</tr>
</tbody>
</table>

"The symptom of early satiety was not assessed in this study.

**Table 4. Prevalence of Hypersensitivity to Gastric Distention and Relationship With Symptoms in Functional Dyspepsia in Literature Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Prevalence of hypersensitivity (%)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertz et al., 1998&quot;</td>
<td>24</td>
<td>66</td>
<td>No correlation</td>
</tr>
<tr>
<td>Rhee et al., 2000&quot;</td>
<td>64</td>
<td>50</td>
<td>No correlation</td>
</tr>
<tr>
<td>Tack et al., 2001&quot;</td>
<td>160</td>
<td>34</td>
<td>Pain, belching, weight loss</td>
</tr>
<tr>
<td>Boeckxstaens et al., 2002&quot;</td>
<td>44</td>
<td>48</td>
<td>No correlation</td>
</tr>
</tbody>
</table>
Dyspeptic symptoms are usually triggered or aggravated by meal ingestion, suggesting that sensitivity to gastric distention in the postprandial period might be involved in symptom generation. In a preliminary study, we showed that postprandial sensitivity to gastric distention, but not fasting sensitivity, was indeed related to the severity of meal-related symptoms in functional dyspepsia.53

**H. pylori Infection**

Soon after the discovery of *H. pylori*, a causal relationship between *H. pylori* infection and the occurrence of duodenal and gastric ulcers was established.51 In functional dyspepsia, the role of *H. pylori* is less clear. A recent systematic review of the epidemiologic evidence on a relationship between *H. pylori* infection and functional dyspepsia found no evidence for a strong association. However, according to the investigators, many of the studies had important weaknesses in design and execution and there was not enough evidence to rule out a modest association.55

Several studies have investigated the association between *H. pylori* infection and dyspeptic symptoms or pathophysiologic mechanisms.56–61 However, 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 were found between *H. pylori*-positive and *H. pylori*-negative subjects. Initial studies reported associations between *H. pylori* infection and epigastric pain or burning,56 delayed gastric emptying,57 or impaired accommodation.58 However, more recent and larger-scale studies failed to find any of these correlations.59–61

**Altered Duodenal Sensitivity to Lipids or Acid**

Dyspeptic symptoms in functional dyspepsia are commonly exacerbated by meals rich in fat.62 Studies in health have shown that duodenal infusion of lipids, but not glucose, induces a relaxation of the proximal stomach and enhances the sensitivity to proximal stomach distention.63,64 These influences of duodenal lipid infusion require lipid digestion and subsequent release of cholecystokinin,64,65 and they can be blocked by administration of a lipase inhibitor or a cholecystokinin-A receptor antagonist.64–66 It was reported that increased sensitivity to duodenal lipid infusion may be a relevant pathophysiologic mechanism in functional dyspepsia.67,68 However, the numbers of patients studied in this manner remained small, and it is unclear whether this affects a subgroup of dyspeptic patients or all dyspeptic patients (Table 5). Furthermore, all of these studies used intraduodenal mode administration, and recent data have shown that observations derived from intraduodenally administered lipids do not necessarily apply to orally ingested lipid-containing meals.69,70

Duodenal infusion of hydrochloric acid was found to induce nausea in a small group of patients with functional dyspepsia but not in healthy controls, suggesting duodenal hypersensitivity to acid. Furthermore, previous studies have shown that the duodenal motor response to acid was decreased in patients with functional dyspepsia, resulting in reduced clearance of exogenous duodenal acid.71 We confirmed that spontaneous duodenal acid exposure to endogenous acid was increased in patients with functional dyspepsia who displayed delayed clearance of exogenous duodenal acid.72 Patients with functional dyspepsia with duodenal acid exposure above the normal range had higher severity scores of several dyspeptic symptoms. However, the severity of individual symptoms was weakly correlated to duodenal pH and brief duodenal acid infusion did not affect any symptoms, suggesting that duodenal acid exposure is poorly related to symptom severity.72

**Altered Antroduodenojejunal Motility**

Manometry studies in functional dyspepsia have shown antral hypomotility to be a common feature.73 It is presently unclear whether this reflects true hypomotility or a poor registration of contractions in a dilated antrum in patients with impaired accommodation, be-

<table>
<thead>
<tr>
<th>Study</th>
<th>n Technique</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbera et al., 1995</td>
<td>10 patients Duodenal lipid infusion, duodenal saline infusion, gastric balloon distention</td>
<td>Duodenal lipids sensitize the stomach to distention in patients with dyspepsia but not in controls</td>
</tr>
<tr>
<td>Barbera et al., 1995</td>
<td>9 patients Duodenal lipid infusion, duodenal glucose infusion, gastric balloon distention</td>
<td>Duodenal lipids but not glucose sensitize the stomach to distention in dyspepsia</td>
</tr>
<tr>
<td>Samsom et al., 1999</td>
<td>12 patients Duodenal acid infusion, duodenal manometry and pH monitoring</td>
<td>Acid clearance is decreased in dyspepsia; hypersensitivity to duodenal acid induces nausea</td>
</tr>
<tr>
<td>Feinle et al., 2003</td>
<td>12 patients Duodenal lipid infusion, gastric balloon distention, CCK-A antagonist</td>
<td>CCK-A receptors are involved in sensitization by duodenal lipids</td>
</tr>
</tbody>
</table>

CCK, cholecystokinin.
cause manometry only registers lumen-obliterating contractions. Small bowel motor alterations, usually hypermotility with burst activity or clusters, and an increased proportion of duodenal retrograde contractions have been reported. No clear correlation with symptoms has been found.

Abnormalities of Gastric Electrical Rhythm

There is also evidence that abnormalities in the underlying gastric myoelectrical activity, as measured by cutaneous electrogastrography, are found in up to two thirds of patients with functional dyspepsia. The relevance of this finding for gastric emptying and symptom patterns remains to be established. No correlation was found between dyspeptic symptom pattern and the presence of findings on electrogastrography. A good correlation between the presence of delayed gastric emptying and abnormalities of gastric electrical rhythm has been reported.

Unsuppressed Postprandial Phasic Contractility in the Proximal Stomach

Besides the relaxatory response of the proximal stomach after a meal, other motor aspects of the proximal stomach have not been particularly frequently addressed in the literature. With the barostat technique, it is also possible to detect phasic volume fluctuations from the baseline volumes (“volume waves”), reflecting contractions superimposed on the background state of contractility or tone. These contractions occur at a frequency that differs from antral contraction waves. One study suggested the occurrence of increased phasic volume events in the postprandial period in patients with functional dyspepsia. In a recent study, we observed that, compared with healthy controls, a small subset (15%) of dyspeptic patients displayed unsuppressed postprandial phasic contractility of the proximal stomach. Persistence of postprandial phasic contractions of the proximal stomach was associated with H. pylori infection and relevant or severe bloating, but also with the absence of nausea. The abnormality is of potential relevance because phasic fundic contractions induce transient increases in gastric wall tension, which can be perceived in functional dyspepsia.

Autonomic Nervous System/Central Nervous System Dysregulation

Abnormalities within the autonomic nervous system have been suggested to be of importance in some patients with functional dyspepsia. More specifically, an efferent vagal dysfunction has been observed in several studies and has been proposed to be a possible mechanism underlying impaired accommodation to a meal and antral hypomotility. Furthermore, there is evidence of an association between psychopathology and functional dyspepsia and between psychological factors and gastric functioning and symptoms in functional dyspepsia, for which low vagal activity was proposed to be the mediating mechanism.

In a recent factor analysis of dyspeptic symptoms and their relationship with physiopathology and psychopathology, the heterogeneity and complexity of these interactions was clearly shown. Factor analysis identified 4 separate symptom factors within functional dyspepsia, each of which was associated with a measurable abnormality of gastric function, and of which 2 were associated with specific psychosocial characteristics. The factor that consists of nausea, vomiting, early satiety, and weight loss was associated with female sex and physician visits and sickness leave, and the factor that consists of epigastric pain was associated with several psychosocial dimensions, including medically unexplained symptoms and conditions, and with low health-related quality of life.

Relevance of Putative Pathophysiologic Mechanisms to Symptom Generation

Although several pathophysiologic abnormalities are related to the dyspepsia symptom pattern and severity, as summarized in the previous section, this does not establish causality. It is conceivable that both simply coexist or that both depend on a presently unspecified causal mechanism. A close correlation between presence and severity of a certain pathophysiologic abnormality and presence and severity of certain symptoms adds strength to the association between both. A very strong case is made when induction of a pathophysiologic abnormality in healthy subjects also induces dyspeptic symptoms.

Delayed Gastric Emptying

The studies investigating the relationship between delayed emptying and symptom pattern generally used questionnaires that assessed symptom severity over a time frame of weeks to months, whereas the emptying test reflects the situation at a single point in time. Several studies have shown that gastric emptying in functional dyspepsia has large intraindividual variability. Attempts have been made to find a better correlation between symptoms and emptying rate by assessing symptom severity during the measurement of the emptying rate of a standardized meal. However, this did not result in a better correlation between symptoms and emptying rate.
Furthermore, induction of delayed gastric emptying in healthy subjects by pharmacologic or dietary interventions is not associated with the occurrence of dyspeptic symptoms. These observations question the relevance of delayed emptying as a mechanism underlying dyspeptic symptoms.

**Impaired Accommodation**

A close correlation exists between impairment of gastric accommodation, severity of early satiety, and the amount of liquid meal ingested at maximum satiety during a slow satiety drinking test. Erythromycin and motilin induce a contraction of the proximal stomach. When these agonists are administered at the time of meal ingestion, this results in impaired accommodation and is associated with early satiety. Relaxation of the proximal stomach can be activated by duodenal distention or nutrient infusion via a vagovagal reflex pathway, and it requires activation of intrinsic nitrergic neurons in the stomach. Administration of a nitric oxide synthase inhibitor induces impaired accommodation in humans, and this is associated with early satiety. These observations add further support to the hypothesis that impaired accommodation is the mechanism underlying the symptom of early satiety.

**Hypersensitivity to Gastric Distention**

One study found an association between hypersensitivity to gastric distention, as determined by a gastric barostat study, and symptoms of pain and belching. However, this apparent association could be influenced by a bias to report pain. In keeping with this possibility, a significant association was found between symptoms of pain, hypersensitivity to gastric distention, and several psychopathologic mechanisms, including neuroticism, somatization, a history of abuse, and health-related quality of life dimensions. Attempts to induce hypersensitivity in healthy subjects using a nitric oxide synthase inhibitor were not successful. Recent data showed that the N-methyl-D-aspartate receptor antagonist dextrimethorphan sensitized the stomach to distention in the absence of an effect on gastric compliance. However, this drug is not very selective, and it is unclear whether this constitutes a valid model of visceral hypersensitivity and whether pretreatment with an N-methyl-D-aspartate antagonist induces dyspepsia-like symptoms after ingestion of a meal.

**Other Mechanisms**

Acute *H. pylori* infection induces dyspepsia-like symptoms, but these are transient. Nausea induced by vestibular stimulation is also associated with abnormalities of gastric electrical rhythm, suggesting that this may be a secondary phenomenon accompanying nausea rather than a primary mechanism. These observations question the direct pathophysiologic relevance of *H. pylori* and gastric electrical dysrhythmias.

In healthy subjects, duodenal acid infusion sensitizes the proximal stomach and the duodenum to distention and is able to induce dyspepsia-like symptoms. Administration of the cholinesterase inhibitor neostigmine before a meal induces unsuppressed postprandial phasic contractions in healthy subjects, and this is associated with increased scores for several dyspeptic symptoms. These observations suggest that increased duodenal acid exposure and unsuppressed postprandial phasic contractility of the proximal stomach are mechanisms potentially involved in the pathogenesis of dyspeptic symptoms. Table 6 summarizes the reported associations between symptom patterns and pathophysiologic mechanisms in functional dyspepsia.

**Pathogenesis**

The pathogenesis of functional dyspepsia is obscure, but a postinfectious or inflammatory origin has been suggested for irritable bowel syndrome. Moreover, gastroparesis has been reported after a viral infection. Using a questionnaire in 400 consecutive patients with functional dyspepsia, we found that 17% had a history with acute onset, suggestive of a postinfectious origin. These patients had a particularly high preva-
lence of impaired accommodation. Because the proximal stomach in these patients relaxed to administration of a nitric oxide donor but did not respond to sumatriptan, which releases nitric oxide through activation of 5-hydroxytryptamine (5-HT)1 receptors on nitrigic neurons, the abnormality is attributable to a dysfunction at the level of gastric nitrigic neurons.10

As previously mentioned, whether psychological factors have a pathogenetic role in functional dyspepsia, especially in patients with hypersensitivity to gastric distention, or whether they are disease modulators determining health care seeking, perception of symptoms, and the outcome of the disorder is not known. There are several sources of evidence for a role of the central nervous system in visceral hypersensitivity. Studies in experimental animals indicate that acute psychological stress facilitates increased sensitivity to visceral stimuli.105 In line with such a finding, rats genetically predisposed to anxiety have been shown to display an increased visceral sensitivity.106 Similarly, in humans, the perception of gut distention has been found to be reduced during periods of distraction and increased during periods of attentiveness or during mental stress associated with anxiety.107 However, the role of central factors and stress in visceral hypersensitivity and symptom generation in functional dyspepsia remains to be established.

Finally, an association between dyspeptic symptoms and a functional polymorphism in a G-protein subunit was reported.108 It remains to be established whether this genotype is associated with any specific pathophysiologic mechanism, the likelihood of postinfectious functional disorders, or altered psychosocial features.

**Clinical Presentation and Diagnosis**

Patients with predominant heartburn or acid regurgitation should, according to the Rome II criteria, not be included in the dyspeptic spectrum but should be referred to as having gastroesophageal reflux disease because the management differs substantially.5 It has been proposed that a substantial number of patients with predominant discomfort or pain centered in the upper abdomen actually have atypical reflux disease.109 However, by using a simple questionnaire to screen for reflux symptoms,110 only a minority of patients with predominant dyspeptic symptoms have pathologic reflux as shown by 24-hour pH measurement.111 The use of these questionnaires in clinical practice may prove useful to detect patients who actually have reflux disease, with a higher likelihood of being responders to treatment with proton pump inhibitors (PPIs).

There is also a huge overlap between functional dyspepsia and irritable bowel syndrome.2 For instance, in a referral center, 46% of patients with functional dyspepsia proved to have concomitant irritable bowel syndrome, and these patients were more likely to be female, have gastric hypersensitivity, and have more severe symptoms in general.112 Furthermore, many subjects change from predominant dyspeptic symptoms to bowel-related symptoms, indicating irritable bowel syndrome, or the opposite during a 1-year follow-up period.2

When a patient presents with dyspeptic symptoms, careful clinical evaluation and history taking are essential features to make a correct diagnosis of dyspepsia and to distinguish it from gastroesophageal reflux disease and irritable bowel syndrome. Routine biochemistry is usually included in the diagnostic workup, but the clinical value of this has not been formally validated. So-called alarm symptoms (prominent weight loss, recurrent vomiting, bleeding, anemia, dysphagia, jaundice, palpable mass) should be looked for with great care and, if present, require additional diagnostic investigation. If there are no sinister symptoms and the patient is young (younger than 45–50 years) and does not take nonsteroidal anti-inflammatory drugs, upper endoscopy is rarely needed in the first line. However, early endoscopy is of course the gold standard in the diagnostic workup of dyspeptic patients with more severe symptoms and may be associated with greater patient satisfaction,113 but it is not possible to perform this procedure in all patients because of financial, practical, and patient-related factors and other factors such as availability. Instead, other strategies can be considered, namely initial empirical therapy114–116 or a “test and treat” approach.14

The American Gastroenterological Association presented a medical position statement regarding the evaluation of dyspepsia in 1998 and recommended the “test and treat” strategy,117 meaning initial testing for the presence of *H. pylori* infection and, if present, eradication therapy. *H. pylori*–negative patients should be offered empirical antisecretory or prokinetic therapy. Based on the existing studies on the effect of *H. pylori* eradication on functional dyspepsia,13 it can be assumed that most patients will still be symptomatic after treatment of *H. pylori* and should in that case be offered endoscopy. These guidelines were recently questioned by Spiegel et al., who by using a so-called decision analysis found empirical PPI therapy to be more cost effective, either as a first step or following a “test and treat” approach, when the patient has not responded favorably to eradication therapy.118 Moreover, these decision analyses cannot be extrapolated to every country because of major differences in the prevalence of *H. pylori* infection, prevalence of ulcers, accessibility of endoscopy, and cost of endoscopy.
A head-to-head comparison of these strategies is needed, but in the meantime both strategies may be used and have support in the literature. Although often used in clinical practice, the empirical prokinetic therapy has been less well studied. An in-depth analysis of clinical management steps in dyspepsia was recently published in GASTROENTEROLOGY.119 In general practice, the initial empirical therapy is probably still the most widely used approach. A clinical management algorithm based on currently available management guidelines and clinical experience is summarized in Figure 3.

Other investigations that might be considered in the workup are, for instance, upper abdominal ultrasonography or computed tomography, small bowel radiography, duodenal biopsy to exclude celiac disease, 24-hour esophageal pH monitoring, and manometric studies of the upper gastrointestinal tract. These investigations should not be performed in all patients but instead should be based on the clinical picture, severity of symptoms, and refractoriness of the patient.

Psychological symptoms are also common in patients with functional dyspepsia as compared with patients with organic causes of dyspepsia, such as duodenal ulcer.85 This may be more related to being a patient seeking health care for dyspepsia than related to dyspepsia per se. A review found several psychosocial factors such as life event stress, psychological morbidity, personality, abuse history, and abnormal illness behavior and beliefs to be important factors in the process that determines who will seek medical attention.120 The presence of psychosocial factors in these patients should be addressed carefully but should not be overemphasized because a causal role has not been established so far.

**Treatment**

**General Measures**

Reassurance and education is of primary importance in patients with functional dyspepsia. It has been shown in irritable bowel syndrome that a positive physician-patient interaction can reduce health care seeking, and these findings are probably also valid for functional dyspepsia.121 Lifestyle and dietary measures are usually prescribed, although they have not been systematically studied. It seems logical to have patients eat more frequent, smaller meals and desirable to avoid food that aggravates symptoms. Because the presence of lipids in the duodenum enhances the mechanosensitivity of the stomach, avoiding meals with a high fat content might be advisable.57,68 Coffee and spicy foods containing capsaicin are usually discouraged, although there is no evidence to link these food components to symptoms.122,123

In some patients, pharmacologic therapy will be considered. The pharmacologic treatments available to date for the management of functional dyspepsia have only been shown to be of limited efficacy. It seems logical that directing therapeutic approaches toward the underlying pathophysiologic disturbances should increase the efficacy,124 but this has not been proven.

**Acid-Suppressive Drugs**

In patients with gastroesophageal reflux, a trial of antisecretory therapy has both therapeutic and diagnostic value. Several studies have evaluated the use of H2-receptor antagonists in functional dyspepsia, and a recent meta-analysis showed superiority over placebo in improvement of pain but not for overall symptom improvement.125 PPIs have proven to be more effective than H2-receptor antagonists and antacid-alginate in relieving symptoms of uninvestigated dyspepsia (comparable to the initial empirical PPI treatment previously mentioned).114–116 Of course, these studies not only included
patients with functional dyspepsia but also patients with peptic ulcer disease and with gastroesophageal reflux disease. Large and well-controlled studies in functional dyspepsia have shown that treatment with omeprazole was approximately 10%–15% better than placebo in patients with functional dyspepsia. However, this positive effect was restricted to patients with reflux-like dyspepsia, a subgroup that actually is no longer considered to belong to functional dyspepsia, and to a lesser degree in patients with ulcer-like dyspepsia. In patients with dysmotility-like dyspepsia, no effect could be observed.

In a recent study in consecutive patients with functional dyspepsia without dominant symptoms of heartburn, pathologic esophageal acid exposure was present in a subset of patients who were characterized by a higher prevalence of epigastric pain. This finding suggests that patients with ulcer-like dyspepsia who respond to acid-suppressive therapy may actually have gastroesophageal reflux disease. On the other hand, recent studies have suggested a role for increased duodenal acid exposure and duodenal acid hypersensitivity in the pathogenesis of functional dyspepsia. Treatment with PPIs tended to decrease duodenal acid hypersensitivity, but so far no symptomatic benefit in this group of patients has been shown.

Prokinetic Agents

Prokinetic agents, including metoclopramide, domperidone, and cisapride, are widely used in functional dyspepsia. The rationale is to use prokinetic drugs in patients with delayed gastric emptying, in which they should improve symptoms of postprandial fullness, nausea, and vomiting. However, studies available so far fail to prove this hypothesis, and evidence that the symptomatic improvement is related to enhancement of gastric emptying is lacking.

Metoclopramide and domperidone are dopamine receptor agonists 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 via 5-HT₄ receptor agonism and accelerates gastric emptying. The availability of cisapride is restricted due to cardiac safety issues. Recently, tegaserod, a partial 5-HT₄ agonist, was found to accelerate gastric emptying, indicating its possibility as a prokinetic agent.

Recent reviews suggest that prokinetics, especially domperidone and cisapride, are more effective than placebo, but the trials were often of poor quality with significant heterogeneity between studies. However, the gastroprotective effects of these drugs are limited, and the finding of the strong gastrokinetic actions of erythromycin, a macrolide antibiotic that acts as a motilin receptor agonist, was met with great enthusiasm. Several short-term studies reported beneficial effects of treatment with erythromycin in gastroparesis. Different macrolide prokinetics, devoid of antibiotic properties, were developed and one of these, ABT-229, was studied in large clinical trials. However, the outcomes of clinical trials with ABT-229 were unequivocally disappointing with regard to symptom improvement, both in dyspeptic patients with and without delayed emptying. It has been argued that the negative outcomes of the studies with ABT-229 show that acceleration of gastric emptying is not the correct therapeutic target in functional dyspepsia, but there are also strong indications of tachyphylaxis with macrolide prokinetics. Furthermore, it is well established that erythromycin and related compounds impair gastric accommodation to a meal, thereby enhancing sensitivity to gastric distention, which may have contributed to the overall poor symptomatic effect. Cisapride and tegaserod were shown to enhance gastric accommodation to a meal and are therefore less likely to worsen or induce symptoms related to impaired accommodation. In addition, in preliminary studies, we showed a tendency for tegaserod to improve upper gastrointestinal symptoms in female patients with functional dyspepsia with normal gastric emptying, suggesting that it may affect pathophysiologic mechanisms other than delayed gastric emptying.

Eradication of H. pylori

The 4 largest published randomized trials on the effect of H. pylori eradication on symptoms in functional dyspepsia show somewhat conflicting results. A single-center trial suggested a small superiority of eradication treatment versus PPI treatment alone, but 3 multicenter trials had negative findings. Taken together, these 4 large studies suggest that the potential symptomatic benefit of H. pylori treatment in functional dyspepsia is probably of limited importance. Other arguments in favor of the use of eradication therapy are protection against peptic ulcer, putative protection against gastric cancer, and the short-term nature of the treatment.

Antidepressants

There is some evidence that tricyclic antidepressants are effective in treating patients with functional gastrointestinal disorders, including functional dyspepsia. Generally, lower doses are used than for treatment of depression. Mianserin, at a high dose, was also shown to be superior to placebo in patients with functional gastrointestinal disorders, including dyspepsia. The mechanism behind the positive effect has been proposed to be due to an effect on gastric sensitivity, but
this could not be confirmed in the study by Mertz et al. In clinical practice, it seems that the positive effect is not clearly related to the presence or absence of depression. It is unclear whether selective serotonin reuptake inhibitors (SSRIs) are also effective treatment alternatives for functional gastrointestinal disorders. These drugs increase the availability of synaptically released 5-HT not only in the central nervous system but also at the level of the enteric nervous system. Pretreatment with the SSRI paroxetine strongly enhanced the meal-induced relaxation of the proximal stomach in healthy subjects. This observation suggests involvement of 5-HT in the gastric accommodation reflex in humans as well as a potential beneficial effect of SSRIs in dyspeptic patients with impaired accommodation. In an open-label study in dyspeptic patients with abnormalities on electrogastrography, only patients with coexisting depression improved and gastric myoelectrical activity did not improve.

**Fundus-Relaxing Drugs**

It seems logical that restoring gastric accommodation in patients with impaired accommodation is likely to improve symptoms of early satiety. Short-term studies have shown some benefit of nitrates, but prolonged use is generally associated with undesirable vascular side effects due to the lack of specificity. Sildenafil blocks phosphodiesterase type 5, which degrades nitric oxide–stimulated guanosine 3′,5′-cyclic monophosphate, thereby relaxing smooth muscle in various organs. Pretreatment with sildenafil also relaxes the proximal stomach, and trials evaluating phosphodiesterase inhibitors in functional dyspepsia seem warranted. Similar to the central nervous system, serotonin reuptake in the enteric nervous system is also inhibited by SSRIs. The enhancement of gastric accommodation by pretreatment with the SSRI paroxetine suggests involvement of 5-HT in the control of the accommodation reflex in humans. The 5-HT receptor involved has not been identified, but both 5-HT1 and 5-HT4 receptors can mediate enhanced postprandial gastric relaxation. Pretreatment with the 5-HT4 receptor agonists cisapride and tegaserod enhances gastric accommodation in healthy subjects. Administration of sumatriptan, a 5-HT1 receptor agonist used in the treatment of migraine, relaxes the proximal stomach in healthy subjects. In short-term studies, subcutaneous administration of sumatriptan was shown to restore meal-induced relaxation in patients with impaired gastric accommodation and to increase the amount of calories ingested at maximum satiety in patients with early satiety. Due to its pharmacologic properties, cost, and mode of administration, subcutaneous sumatriptan is not suitable for long-term treatment of functional dyspepsia. A nasal-spray formulation of sumatriptan had no significant effect on proximal stomach function. Buspirone is a nonselective 5-HT1 receptor agonist used in the treatment of panic attacks. In a placebo-controlled study in patients with functional dyspepsia, we confirmed that buspirone was superior to placebo in alleviating dyspeptic symptoms and that this was associated with an enhancement of the accommodation to a meal. Clonidine, an α2 receptor agonist, also relaxes the stomach and reduces gastric sensation. Short-term administration of clonidine was found to decrease meal-induced symptoms in functional dyspepsia.

**Other Drugs**

Dose-finding studies with the 5-HT3 receptor antagonist alosetron showed potential benefit in functional dyspepsia. The mechanisms behind its effect are at present unclear. No effect on gastric sensitivity in healthy volunteers has been shown, but 5-HT3 receptor antagonism reduces duodenal lipid sensitivity. Alosetron was on the U.S. market for approximately 6 months for diarrhea-predominant irritable bowel syndrome, but its use is now restricted due to safety issues. Cholecystokinin receptor antagonists also reduce duodenal lipid sensitivity and are currently under evaluation. The κ opioid agonist fedotozine decreases gastric sensitivity to distentions, and it showed superiority over placebo in a placebo-controlled study in patients with functional dyspepsia. However, development of this drug has not continued. Asimadoline, another κ opioid agonist that was shown to decrease satiation and meal-induced fullness, is currently still under evaluation.

A recent study showed that long-term administration of red pepper was more effective than placebo in decreasing the intensity of dyspeptic symptoms in patients with functional dyspepsia. Such a contradictory result might be explained by the finding that capsaicin initially produces sensitization but repeated stimulation of the capsaicin receptor on capsaicin-sensitive primary afferents leads to desensitization. Studies of the effect of capsaicin on gastric sensitivity in humans, which showed acute sensitization followed by decreased perception of epigastric symptoms, are in keeping with this mechanism of action. In a controlled trial in patients with functional dyspepsia, artichoke leaf extract was significantly better than placebo in alleviating symptoms and in improving quality of life. The basis for this improvement remains to be identified.
Psychological Interventions

Psychological factors are considered important contributors to symptom severity in patients with functional gastrointestinal disorders, including functional dyspepsia. This suggests that psychological treatment alternatives might be useful in these patients.

A review of clinical trials of psychological interventions for functional dyspepsia showed potential benefits in the treatment of functional dyspepsia. However, several studies did not control for additional time and attention the patients received in the psychological intervention arms, making it difficult to exclude a contribution of nonspecific factors. Another study controlled for this factor compared psychodynamic-interpersonal psychotherapy with supportive therapy in 95 consecutive patients with functional dyspepsia who had failed to respond to conventional pharmacologic treatments. At the end of treatment, patients receiving psychotherapy had a significantly better outcome than those receiving supportive therapy. One year after treatment, the symptom scores were similar in both groups, but a post hoc analysis excluding patients with severe heartburn also showed a positive effect of psychotherapy at 1 year. Hypnotherapy was also shown to be useful in functional dyspepsia in a randomized study compared with supportive or medical therapy. In a follow-up of 1 year, the effect was maintained. Hence, assessing psychosocial issues and intervening at this level in patients with functional dyspepsia seems to be a reasonable approach. However, in clinical practice, this approach is usually reserved for those with severe and extensive symptomatology or refractory disease.

Conclusions

Functional dyspepsia is one of the most common disorders seen in general practice and by gastroenterologists. Functional dyspepsia seems to be a heterogenous disorder in which different pathophysiological disturbances are associated with different symptom profiles. The available options for the treatment of functional dyspepsia are of limited efficacy, which probably reflects the incomplete understanding of the nature of this disorder. Current knowledge is in support of empirical treatment with acid-suppressive agents and prokinetics as well as identification and treatment of H. pylori infection. Refractory patients may benefit from treatment with antidepressants or psychological interventions. More effective approaches are badly needed, and this will probably require ongoing efforts to elucidate underlying pathophysiology.

References


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Address requests for reprints to: Jan Tack, M.D., Ph.D., Division of Gastroenterology, Department of Internal Medicine, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. e-mail: jan.tack@med.kuleuven.ac.be; fax: (32) 16-34-44-19.