Etiopathogenesis of Functional Dyspepsia

Rakesh K Tandon

Dyspepsia is a term used to characterise a heterogenous group of upper abdominal symptoms, mainly pain and abdominal distension central to the epigastrum. Diseases that may cause such symptoms include peptic ulcer disease, gastro-oesophageal reflux disease, giardiasis, and pancreatic and biliary diseases. If none of them is found after conventional investigations like ultrasound examination of the upper abdomen and upper gastrointestinal (GI) endoscopy, the dyspepsia is labelled as Functional Dyspepsia (FD).

To give objectivity to this concept, Rome criteria were developed in 1994 and subsequently refined in 2002 and 2006. The final product i.e. Rome III criteria must include one or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning with no evidence of structural disease, including the use of upper GI endoscopy, which is likely to explain the symptoms. Criteria should be fulfilled for at least 3 months with symptom onset at least 6 months previously (Table 1). Furthermore, FD is divided into two groups – one with predominantly having epigastric pain or burning (the epigastric pain syndrome) and the other, meal-related early satiety or postprandial fullness (the postprandial distress syndrome) (Table 2).

Etiopathogenesis

Increased gastric acid secretion, H pylori infection, alterations in fundal or antral accommodation of food, antro-duodenal motility and gastric emptying; gastric hypersensitivity triggered by chemo- or mechanoreceptors; and hormonal disturbances have all been suspected as possible underlying causes of functional dyspepsia, but none is proven. Genetic abnormalities have also been suspected recently. Perhaps a combination of these is operative in reality; specific combinations of physiologic, genetic, environmental, and psychological factors in an individual patient lead to a variety of symptoms grouped as dyspepsia. There is growing evidence that brain-gut interactions at different levels are also involved. A short discussion of some of these factors is given below.

Gastric Hyperacidity

The rationale for the wide use of acid suppression medications in functional dyspepsia is that acid could be involved in pain producing mechanisms such as occurs in peptic ulcer disease and many patients get relief from acid suppression. Ironically however, normal gastric acid secretion has been documented in individuals with FD. A possible mechanism of pain in such a situation is hypersensitivity to normal acid secretion (vide infra).

Visceral Hypersensitivity

Visceral hypersensitivity plays an important role in FD. Fundic barostat studies have been used to detect gastric hypersensitivity. Recently, Kindt et al demonstrated the existence of a relationship between symptoms, gastric emptying measured by scintigraphy, and gastric sensitivity measured by barostat inflation. Patients with hypersensitivity to distension had significantly higher scores for fullness/satiety. Patients with delayed emptying had significantly higher scores for heartburn/regurgitation, nausea/vomiting, fullness/satiety, bloating, and lower abdominal pain. As a result, many of these patients are misinterpreted as having gastroesophageal reflux disease (GERD); in about 33.8% of patients they may however, coexist (an overlap syndrome). In fact, the overlap of FD is much more often with nonerosive reflux disease (NERD) – a condition well described, in which GI reflux is present but no mucosal erosions or inflammation in the esophagus. The people who have both FD and GERD or NERD are more likely to benefit from treatment with proton pump inhibitors.

Helicobacter Pylori

The role of Helicobacter pylori in the pathogenesis of FD has been extensively explored. H pylori may cause inflammation and dysmotility, initiate visceral hypersensitivity, and alter acid secretion. Large population studies have shown that H pylori is more frequently detected in dyspeptic patients than in controls. Other studies have however, failed to show such an association. In fact, the bulk of evidence suggests that H pylori

Table 2: Criteria for differentiating Postprandial Syndrome and Epigastric Pain Syndrome

<table>
<thead>
<tr>
<th>Postprandial Distress Syndrome</th>
<th>Epigastric Pain Syndrome</th>
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<tbody>
<tr>
<td>1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week AND/OR</td>
<td>1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week AND</td>
</tr>
<tr>
<td>2. Early satiation that prevents finishing a regular meal, at least several times per week</td>
<td>2. The pain is intermittent AND</td>
</tr>
<tr>
<td>Supportive criteria</td>
<td>3. Not generalized or localized to other abdominal or chest regions AND</td>
</tr>
<tr>
<td>1. Upper abdominal bloating, postprandial nausea or excessive belching can be present</td>
<td>4. Not relieved by defecation or passage of flatus AND</td>
</tr>
<tr>
<td>2. Epigastric Pain Syndrome may coexist</td>
<td>5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders</td>
</tr>
<tr>
<td>Epigastric Pain Syndrome</td>
<td>Supportive criteria</td>
</tr>
<tr>
<td>1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week AND</td>
<td>1. The pain may be of a burning quality but without a retrosternal component</td>
</tr>
<tr>
<td>2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting</td>
<td>2. Postprandial distress syndrome may coexist</td>
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Table 1: Rome III diagnostic criteria for functional dyspepsia

At least 3 months, with onset at least 6 months previously, of one or more of the following:
- bothersome postprandial fullness
- early satiation
- epigastric pain
- epigastric burning
- no evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms

*Taken from ref. 5

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Ex-Head, Dept of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029
is not a major pathogenetic factor in patients with functional dyspepsia. A recent meta-analysis, however, did show a small but consistent benefit from H pylori eradication with 8% pooled risk reduction compared with placebo at 12 months of follow up. Thus, H pylori possibly plays a significant role only in small proportion of patients with FD.

**Gastrointestinal Motility**

Gastric dysmotility has traditionally been considered a major pathophysiological mechanism underlying symptoms in functional dyspepsia. The abnormalities range from delayed to accelerated gastric emptying, abnormal antral and fundic contractions, and accommodation issues in the fundus and antrum. A large-scale study suggested an association between delayed emptying for liquids and symptoms of postprandial fullness. Conversely, Delgado-Aros and associates found that low fasting gastric volumes and faster gastric emptying were associated with functional dyspepsia. Thus, a liquid gastric emptying study may result in identification of subgroups of dysmotility induced functional dyspepsia; however, this has not been validated. Recently, two subgroups of PDS-related dyspepsia were identified as having either accelerated gastric emptying in the early postprandial period or impaired inhibitory gastric emptying in the mid postprandial period supporting the observation that functional dyspepsia is a heterogeneous disorder.

Accommodation is the ability of the stomach to distend appropriately to the size and timing of a meal, allowing an increase in gastric volume without an increase in pressure. Accommodation problems may be expressed as pain during meal ingestion or early satiation. Impaired accommodation has been demonstrated in 40% - 47% of patients with FD, using single photon emission computed tomography (SPECT) or fundic barostat and the impaired accommodation is associated with early satiety. Decreased meal size and postmeal symptoms in FD patients have been shown to be associated with low fasting gastric volumes and faster gastric emptying. Accelerated gastric emptying in the early postprandial period is associated with postprandial distress syndrome (PDS) type of dyspepsia (about 27% patients).

More than two-thirds of patients with FD show abnormalities with electrogastrography (EGG) and antral/duodenal manometry. A subgroup of FD patients with postprandial symptoms show abnormal intragastric distribution of food, independent of the gastric emptying rate. Whether or not such subgroups benefit from different pharmacological approaches is not known.

**Postinfections**

Postinfectious irritable bowel syndrome is well described. A similar phenomenon is seen in some patients with FD. Compared with patients who had functional dyspepsia of unspecified onset, patients with a history suggestive of postinfection functional dyspepsia were more likely to report symptoms of early satiation, weight loss, nausea, and vomiting and had a significantly higher frequency of impaired accommodation of the proximal stomach, which was attributed to dysfunction at the level of gastric nitrergic (nitroxidergic) neurons. Salmonella gastroenteritis in particular has been found to be a significant risk factor not only for IBS but also for dyspepsia; at 1 year of follow up after acute S. gastroenteritis, one in seven subjects developed dyspepsia. Another study found increased prevalence of FD after Giardia lamblia infection.

**Food Intolerance**

Patients with FD often report their symptoms in relation to certain foods, but objective data implicating specific food items have been lacking. The suspected 'culprit' food items have been lactose containing foods, wheat containing foods, fructose containing beverages, caffeinated drinks, green salad and vegetables like beans, radish etc and alcoholic beverages. However, the couple of systematic studies done to see if omitting them benefitted these patients did not bring out a positive result. Hence, their relationship with symptoms remains controversial. Most probably the intolerance for foods suggests a hypersensitivity issue such as with sea food, and not a uniform effect of certain dietary components on FD symptoms.

**Brain Gut Axis / Interaction**

A higher than normal prevalence of psychiatric comorbidity among patients with FD is well known. Investigation of psychological factors characterizing the FD personality identifies some traits such as association with familial aggregation, sleep dysfunction, somatisation, and anxiety, and anxiety disorders being the commonest. Of many they give a recent or past history of physical or sexual abuse.

In the DIGEST study, which investigated the prevalence of upper GI symptoms over 3 months among 5581 healthy subjects from the general population, the major risk factors were psychological stressors, particularly recent life events. Hui et al found that the number of positive and negative life events were similar in both subjects with dyspepsia and control subjects, but the former had a higher negative perception of major life events and daily stresses.

FD patients have a lower vagal tone and a higher sympathetic tone than healthy control subjects. Impaired proximal gastric accommodation response to meals, causing postprandial distress, has been described in these patients, possibly related to stress-induced chronic vagal suppression. The latter effect is likely mediated through stress induced release of corticotrophin-releasing factor acting on specific type-2 receptors in the paraventricular nucleus and dorsal vagal nucleus.

Other investigators have found evidence of altered gastric perception in subjects with dyspepsia, leading to upper abdominal discomfort on isobaric gastric distension compared with control subjects.

Brain imaging studies have shed some light into the processing and perception of different stimuli from the gastrointestinal tract. Vandenbergh and colleagues conducted a study in FD patients with symptoms of hypersensitivity; positron emission tomography (PET) imaging was performed during proximal gastric distension. In patients with hypersensitivity, activation of components of the lateral pain system and bilateral frontal inferior gyri, putatively involved in the regulation of hunger and satiety, occurred at significantly lower distension pressures than in healthy volunteers. These findings suggest common triggers which may initiate pathologic processes involving central nervous and gastrointestinal systems.

**Immune System Involvement**

There is increased recognition of the involvement of the immune system in functional gastrointestinal diseases, based on the observation of common onset timing after acute gastrointestinal infections. Some observations may indicate impaired ability of the immune system to terminate the inflammatory response after acute insult as seen in patients after Salmonella or Giardia infections.
Genetic Factors

There may be a genetic basis for certain individuals to react excessively to normal psychological or physical stresses. The single-nucleotide polymorphism in the 825T allele of the secondary messenger GNB3 gene,\textsuperscript{20} has been reported, perhaps promoting an abnormal perception of visceral pain in FD.\textsuperscript{26}

Conclusion

Functional dyspepsia is an identifiable syndrome and the diagnosis should be based on universally agreed Rome III criteria. Its etiology is multifactorial, but perhaps all different causes act through neurohormonal mechanisms to alter the gastrointestinal motility. Altered gastric motility best explains the clinical manifestations of FD.

References