



## Functional dyspepsia: Pathogenesis and management

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Dyspepsia is a common digestive complaint which is defined as persistent or recurrent abdominal pain or discomfort, localized in the epigastric region. In Western world, the problem is reported to occur in up to 20%-40% of the population in varying degrees of severity. One half to two thirds of investigated patients with dyspepsia have a normal upper gastrointestinal endoscopy and thus no obvious cause of their symptoms. Dyspepsia is not a narrowly defined entity caused by a single disease process, but a collection of symptoms due to multiple etiologies involving diverse mechanisms. The symptoms are assumed to arise from the upper gastrointestinal tract and may include heartburn and regurgitation, nausea and vomiting, early satiety or prolonged digestion, of anorexia and weight loss. In clinical practice, it is critical to differentiate organic causes of dyspepsia from those that are functional because the decision is important in determining the choice of diagnostic tests, a variety of therapeutic regimens, and the outcome of treatment<sup>[1,2]</sup>.

The organic disorders must be considered and appropriately evaluated by careful history, physical examination, and appropriate laboratory tests or in some cases, treated empirically. Heartburn and acid regurgitation are highly reliable symptoms of gastroesophageal reflux disease, and if these are the predominant symptoms, therapy may be initiated without testing. Certain historical features are highly predictive of organic disease and require further testing, including: (1) age over 45, (2) dysphagia, (3) recurrent vomiting, (4) evidence of gastrointestinal bleeding, and (5) jaundice or significant weight loss. Testing which may be considered to evaluate dyspepsia includes GI endoscopy or contrast radiography, abdominal ultrasound or computerized tomography, ambulatory pH monitoring, small bowel radiography or manometry, and ERCP with or without

manometry<sup>[3,4]</sup>.

Functional dyspepsia is the symptom complex described above in which no organic or structural reason can be found to explain the complaints. Some have employed the terms reflux-like, ulcer-like, motility-like, or non-specific to describe dyspepsia, but this classification has no scientific basis, it has not been established as defining the underlying pathogenic mechanisms, nor has it been helpful in predicting the response to specific therapies. The exception is reflux-like dyspepsia which accurately describes the underlying excessive esophageal acid exposure and the response to prokinetic or antisecretory drugs in up to 90% of cases<sup>[5]</sup>. Furthermore, if vomiting is the predominant complaint, it is essential to exclude outlet obstruction of the stomach or gastroparesis<sup>[6]</sup>.

The underlying mechanisms for functional dyspepsia are unlikely to be related to gastric hypersecretion, gastritis (although the issue with respect to *Helicobacter pylori* gastritis is still unresolved), prepyloric erosions, or alterations in the humoral milieu. Dietary and psychological factors play some modulatory role in some situations, but they are not likely to be primary factors in most. The two leading hypotheses to explain the underlying pathogenic mechanisms are upper gastrointestinal dysmotility and enhanced visceral sensation<sup>[4]</sup>.

A wide spectrum of myoelectrical and motor abnormalities have been described in patients with functional dyspepsia<sup>[7]</sup>: (1) delayed gastric emptying, (2) antral hypomotility<sup>[2]</sup>, (3) gastric dysrhythmias, (4) chemical gastritis (indirect histologic evidence of duodenogastric reflux or gastroduodenal incoordination), (5) abnormal small bowel transit, and (6) intestinal dysmotility. These abnormalities occur singly or in a variety of combinations in about 50% of cases.

Some patients with functional dyspepsia have a lowered pain threshold to gastric distension or various chemical stimuli including fat and acid. The reason for this finding is unknown, but it may explain the observation that these patients often experience pain or discomfort following a meal. Visceral hypersensitivity may be due to an altered threshold of enteric mechanoreceptors, altered afferent sensory signal processing, or a lowered pain threshold centrally<sup>[4]</sup>. These patients do not have lowered peripheral somatic pain thresholds, nor do they have altered gut compliance (pressure-volume relationships). Heightened visceral nociception or "visceral hyperalgesia" is a promising area of research, but more studies are required in order to apply sensory testing in routine clinical practice<sup>[1]</sup>. The ability to modify visceral sensation pharmacologically is also very limited and we are in great need of new therapeutic agents<sup>[4]</sup>.

The issue of *Helicobacter pylori*-induced gastritis and other types of gastritis continues to be controversial. The prevalence of *H. pylori* is not different than in the general population. Unfortunately the published trials show inadequacies in experimental design, but there is no convincing evidence that the treatment of *H. pylori* reliably relieves symptoms of dyspepsia better than placebo.

The therapy of functional dyspepsia remains difficult and somewhat empiric<sup>[7]</sup>. In the published literature, the definition of function-

al dyspepsia has been variable, different categories of patients have been included in the studies and the response to placebo has been high (30%-60%). However, an effective therapeutic program can frequently be designed. Dietary management plays a limited role, but patients may obtain some benefit if they avoid fatty foods and gastric irritants such as school, highly spiced foods, and aggravating drugs such as non-steroidal anti-inflammatory agents. Therapy of *H. pylori* is not reliable in relieving symptoms and is not recommended as a first step unless peptic ulcer is or has been demonstrated. Anti-secretory drugs, such as the H<sub>2</sub>-receptor antagonists or the proton pump inhibitors, are often tried first, but their utility is questionable. Overall, the therapeutic gain over placebo is about 20% and drugs which reduce gastric secretion should probably not be the first choice in functional dyspepsia.

In many series, the use of prokinetic drugs, especially cisapride has been effective in 60%-90% of patients<sup>[5]</sup>. Cisapride acts through the local release of acetylcholine through the action of 5HT<sub>4</sub> receptors<sup>[5]</sup>. The drug enhances lower esophageal sphincter pressure, accelerates gastric emptying, improves gastroduodenal coordination, and shortens small bowel transit. Fortunately, it has few side effects, but several drug interactions are worth noting. Drugs with anticholinergic effects such as atropine, antihistamines, and tricyclic antidepressants appear to block the action of the drug almost completely, and should be avoided. In addition, the concurrent use of azole antifungal drugs such as ketoconazole or itraconazole should be avoided because of prolongation of the Q-T interval and the induction of serious ventricular arrhythmias. Cisapride is preferred over metoclopramide because of the latter's problems with central

nervous system toxicity manifest by psychological and extra-pyramidal side effects.

Newer, but less well-established agents to treat functional dyspepsia have been explored including erythromycin for gastroparesis and 5HT<sub>3</sub>-receptor antagonists (ondansetron or granisetron), somatostatin analogs (octreotide), and a kappa-type opioid agonist (fedotozine) to modify sensory thresholds<sup>[6,7]</sup>. At this time, the only drugs which are accepted to modify visceral hypersensitivity are the tricyclic antidepressants (nortriptyline, amitriptyline, etc.). These are often quite effective, but new approaches are badly needed.

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