Visceral sensitivity and functional dyspepsia: Or much more than this?

Jaime Alvarado Bestene, MD.[1]

Abstract

Visceral sensitivity is a normal physiological response of digestive tract hollow structures. Hypersensitivity and hypo sensitivity have been involved in the genesis of most functional disorders. Currently correction or modulation is usually based on pharmacological efforts which seek to eliminate or alleviate symptoms associated with these disorders. Functional dyspepsia is a poorly understood physiopathological disorder still associated with diagnostic misunderstandings and permanently changing definition, classification and therapeutic approaches. Given the prevalence of this entity it seems useful to review the current conceptualization of dyspepsia and the role of visceral sensitivity as the physiological timer of motility in its physiopathology.

Keywords

Visceral sensitivity, functional dyspepsia, motility, functional disorders, Rome III.

INTRODUCTION

Visceral sensitivity, including hyper-or hypo-sensitivity, is a normal physiological response of the hollow structures of the alimentary tract. Visceral sensitivity is involved in the genesis of most functional disorders. Correcting or modulating this response underlies most current pharmacological efforts seeking to suppress or alleviate symptoms associated with these disorders (1, 2).

The pathophysiology of functional dyspepsia is poorly understood. Diagnoses are still often misleading while its definition and classification and the therapeutic approach are all permanent subjects of change. This is combined with an absence of rigor in the use of the term by physicians and patients alike, who frequently use the term to designate any upper abdominal discomfort (3).

A clear example of the difficulty of diagnosis can be seen by checking the successive diagnostic criteria employed in Rome I, II and III. They show a radical change of criteria from one to the other, since none has proven to be fully useful clinically or for research.

Given the prevalence of this entity, it seems that a review of the current conceptualization of dyspepsia and the role of visceral sensitivity as the physiological trigger element of motility in its pathophysiology might be useful.

DEFINITIONS

Dyspepsia is derived from the Greek *dis* meaning difficulty, and *peptein* meaning cooking (δυσπεψία). The word dyspepsia was borrowed by Latin. It literally means difficulty with cooking or, as defined in the *Diccionario de la Real Academia,* Med. chronic disease characterized by laborious and imperfect digestion.

In gastroenterology the word *dyspepsia* is now used clinically to describe an episodic or persistent upper gastrointestinal abdominal pain or discomfort. Several subgroups, more or less accepted by all clinicians, can be observed in

patients under study with nonspecific symptoms: reflux type dyspepsia, ulcer type dyspepsia, dysmotility type dyspepsia and nonspecific dyspepsia. The absence of structural lesions in these subgroups of patients make possible to group them together as functional dyspepsia.

The Rome III committee of experts' criteria recommended calling functional dyspepsia a "dyspepsia symptom complex" (Table 1), and classified it into postprandial distress syndrome and epigastric pain syndrome (Tables 2 and 3) (4-6).

Table 1. Rome III diagnostic criteria for functional dyspepsia.

Functional Dyspepsia
Symptoms of at least 3 months duration, with onset at least 6 months before one or more of the following criteria
- Postprandial fullness
- Early Satiety
- Epigastric pain
- Epigastric Burning
and
- No evidence of structural disease (including upper endoscopy) that can explain symptoms

Table 2. Rome III: diagnostic criteria for epigastric pain syndrome.

Epigastric pain syndrome
Symptoms of at least three months' duration, with onset at least six months before, ALL of the following criteria
Pain and/or burning that is
1. Intermittent
2. Located in the epigastrium
3. Of at least moderate to severe intensity
4. At least once a week
and:
1. Is not generalized to, or located in, other abdominal or thoracic regions
2. Is not associated with defecation or flatulence
3. Does not fulfill criteria for disorders of the gallbladder or sphincter of Oddi

Table 3. Rome III diagnostic criteria for postprandial distress syndrome.

Postprandial distress syndrome
Symptoms of at least three months' duration, with onset at least 6 months before one or more of the following criteria:
- Postprandial fullness.
  1. Appearance following a conventional meal
  2. Occurs at least several times a week
Or:
- Early Satiety
  1. Prevents completion of a regular meal
  2. Occurs at least several times a week

PROPOSED PATHOPHYSIOLOGICAL MECHANISMS FOR UPPER DIGESTIVE TRACT MOTILITY

The stomach is basically a muscular organ that serves as a reservoir of ingested food. There are two mechanisms: gastric receptive relaxation and accommodation, especially in the proximal stomach. These two mechanisms are mediated by the vagus nerve. They allow the proximal contents to accumulate and the distal contents to macerate and mix.

Specialized and ordered muscular activity occurs in response to a biological electrical system with rhythmic action similar to a pacemaker. It generates pulses of depolarization three times per minute. Slow waves are released and propagated in the transverse and longitudinal directions, causing a high pressure area with tonic properties extending to the pylorus.

Gastric accommodation is influenced by the reduction of tone in the fundus (adaptive relaxation). This increases the ability to relax and hold food that arrives without any serious increase of cavity pressure. This is known as adaptability or "compliance" (receptive relaxation).

Motor, sensory and secretory activity of the entire digestive tract is the result of a bidirectional interaction among the central nervous system (CNS), autonomic nervous system (ANS) and the enteric nervous system (ENS) (the so-called brain gut axis). Symptoms of functional dyspepsia can be caused by poor regulation of this axis. The most recent studies focus on the apparent alteration of the CNS in processing visceral signals that are accompanied by emotional changes and anxiety and which are very often associated with dyspepsia.

Alterations in gastric accommodation have been reported in post vagotomy patients as well as in many upper gastrointestinal disorders including functional dyspepsia, rumination syndrome, achalasia, gastroesophageal reflux disease syndrome and vagal neuropathy.

There are also phasic contractions of the gastric fundus which cause transient increases in gastric wall tension. This is usually imperceptible, but its accentuation may be associated with functional symptoms of dyspepsia. This occurs as a result of the absence of contractions of migratory motor activity in the presence of waves of permanent contraction or tone in the gastric fundus.

Alterations of antral hypo-motility and gastric emptying are conditioned by impaired antral, pyloric and duodenal coordination of gastric emptying through the pylorus. After the solid components of food have remained in the proximal stomach, they pass through the antrum for grinding by powerful phasic contractions of the antral muscle. These contractions reduce the solids

to particles which are smaller than 1mm. Disruption of coordination of emptying is related to the postprandial fullness present in the postprandial distress syndrome. It has been demonstrated that up to 78% of all patients with dyspepsia have delays in gastric emptying. Gastric manometry and transmural stimulation provide evidence that in cases of dyspepsia with normal antral motility, the electrical stress suppresses the normal work of emptying. This is not achieved in dyspepsia with basic hypomotility (6, 7).

Disorders of stomach rhythm and myoelectric activity have also been implicated. Some studies found that up to 60% of the patients with functional dyspepsia may have abnormally slow gastric emptying concomitant with abnormalities in gastric electrical activity as shown by the differences between the gammagraphic curves of dyspeptic patients and those of asymptomatic controls.

Among the disorders or alterations of sensory perception, hypersensitivity to visceral distension is most closely linked to epigastric pain, belching and weight loss than to other symptoms of dyspepsia. However, its features and significance remain uncertain despite the fact that there is plenty of evidence that patients with functional dyspepsia have a lower hypersensitivity threshold than do patients with organic causes of dyspepsia. Hypersensitivity is clearly related to motor and sensory disturbances, particularly abdominal pain.

Neuroendocrine cells play an important role in the appearance of abdominal pain. They act as chemical and mechanical transducers that facilitate the emergence of local reflexes and signals to the CNS that ascend in three neural stages to the cortex. These neuron bonds are noradrenergic and serotonergic. The presence of these mediators explains the appearance of cardiovascular and vagal symptoms associated with pain in patients with functional dyspepsia.

The study of patients with visceral hypersensitivity associated with stimuli other than distention has led to the discovery that duodenal infusion of acid in dyspeptic patients is associated with greater sensitivity of the stomach to balloon distention (barostat) in patients with functional dyspepsia. It is accompanied by impaired gastric accommodation.

Evidence exists that stress and anxiety modify sensory perception among patients with dyspepsia and irritable bowel syndrome through the abnormal processing of nociceptive stimuli that reach the gastrointestinal tract from the brain and the ANS. It has also been established that dyspeptic symptoms are more common among patients with functional dyspepsia than among patients with organic dyspepsia. It has been postulated that central nervous system mechanisms underlie this process, possibly originating in the so-called "stress release center" which is located deep in the cerebral cortex.

Inflammatory disorders have also been included among pathogenic factors related to dyspepsia. These of course include course the H pylori infection, the eradication of which is recommended despite the weakness of scientific evidence for a causal role for H. pylori (8-14).

Functional dyspepsia´s complex etiology is located in the gastroduodenal region and is related to pathophysiological disorders that include disorders of gastrointestinal motility and disturbances of sensory perception (2). In the absence of organic, systemic or metabolic disease that could explain dyspepsia, functional dyspepsia is indicated.

Documented alterations related to disorders of gastrointestinal motility occur in gastric accommodation to diet, phasic contractions of the proximal stomach, antral hypomotility, gastric emptying, rhythm disturbances and myoelectric activity of the stomach.

Documented types of sensory perception disturbances involved in functional dyspepsia include visceral hypersensitivity to distension, visceral hypersensitivity to stimuli other than distention, abnormal processing of nociceptive stimuli that reach the gastrointestinal tract from the brain and ANS, inflammatory disorders and genetic disorders.

There are numerous potential elements involved in the pathophysiology of dyspepsia, but the two with strongest evidence are alterations in the motor complex and visceral sensory dysfunction. Some of the changes involved are shown in the figure 1.

This syndrome is much more than an isolated disturbance of gastric physiology. Ignorance of its complex pathophysiology makes its pharmacological management extremely difficult, while at the same time that very complexity makes the continuation of research so very necessary. Based upon clinical trials, and depending upon the predominant pathophysiology, therapeutic approaches are possible could be done. Nevertheless, it should be noted that there is no solid evidence to suggest that there is any particular drug that might be useful to any particular patient with dyspepsia. Consequently, we continue to rely on the trial and error method to manage these patients (15-19).

Table 4 shows the type of agent, the proposed mechanism and the physiological response expected for so-called prokinetic medications commonly used to treat functional dyspepsia (20).
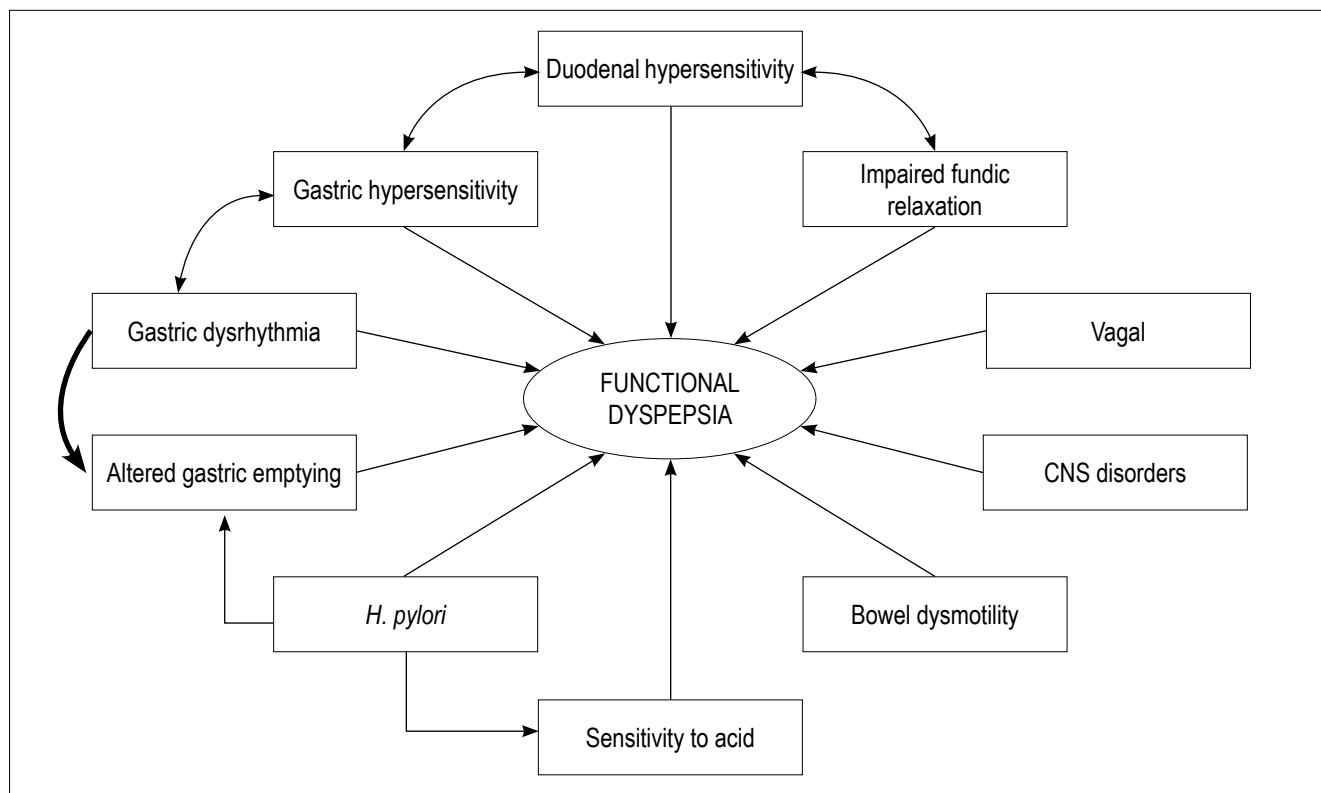
Figura 1. Mecanismos implicados en la dispepsia funcional.

Table 4. Prokinetic medications used to treat functional dyspepsia.

Agent	Mechanism	Physiological effects
Metoclopramide	Dopamine receptor 2 antagonist 5-HT4 agonist	Dopaminergic Antiemetic Accelerates gastric emptying Decreases visceral sensitivity Increases antral motility
Domperidone	Dopamine receptor 2 antagonist	Antiemetic Accelerates gastric emptying Decreases visceral sensitivity
Itopride	Dopamine receptor 2 antagonist Cholinesterase Inhibitor	Antiemetic Accelerates gastric emptying Decreases visceral sensitivity
Levosulpiride	Dopamine receptor 2 antagonist 5-HT4 agonist	Dopaminergic Antiemetic Accelerates gastric emptying Increases antral motility
Erythromycin (Motilin)	5-HT4 agonist 5-HT4 agonist 5 HT3 antagonist	Accelerates gastric emptying Antiemetic Accelerates gastric emptying Increases antral motility

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