Chapter 2

Is Functional Dyspepsia Idiopathic?

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1. Introduction

Dyspepsia is currently defined by Rome III criteria for the diagnosis of functional gastrointestinal disorders (FGIDs), as the presence of one or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning [1] These are symptoms thought to originate from the gastroduodenal region. Bloating and nausea often coexist with dyspepsia but are considered nonspecific and are thus not included in the Rome III criteria. However, there have been attempts by some researchers to broaden this definition to include more symptoms. The Asian consensus guideline includes bloating, nausea, vomiting and belching in the definition of dyspepsia [2]

Dyspeptic patients who have not undergone any investigations are defined as having uninvestigated dyspepsia. An organic cause is found in only a minority who seek medical care [3, 4]. The remaining group is labeled as having functional dyspepsia (FD). Organic dyspepsia means there is a clear anatomic or pathophysiologic reason for the dyspeptic complaints, such as peptic ulcer or cancer. In contrast, when a diagnosis of functional dyspepsia has been made, it means that a number of investigations were performed including upper gastrointestinal endoscopy, and were found to be normal [5].

The need for more systematic description of FGIDs gave rise to the Rome process, which has evolved from Rome I in 1991 [6], Rome II in 1999 [7], to the most recent, which is Rome III [1]. According to Rome I and Rome II definitions, FD was defined as the presence of pain or discomfort centered in the upper abdomen, in the absence of organic disease that readily explained the symptoms [7]. While the meaning of pain is readily understood, the lack of an accurate definition for discomfort was a major limitation of Rome I. Rome I also included reflux symptoms in FD, and recognized a subgroup called "reflux-like dyspepsia". Rome II tried to correct this by excluding patients with predominant heartburn from the definition of FD. Rome

I and Rome II criteria did not account for meal-related symptoms and this was the fundamental change in Rome III criteria [8, 9].

Rome III criteria made a distinction between meal-induced symptoms and meal-unrelated symptoms, and this forms the basis of newly defined subcategories of FD:

1. Meal-induced dyspeptic symptoms (postprandial distress syndrome, which is characterized by postprandial fullness and early satiation)
2. Epigastric pain syndrome or EPS, characterized by epigastric pain and epigastric burning.

The traditional definition of FD portrays it as an idiopathic condition [10]. However, recent studies suggest that this condition have some pathophysiologic correlates. A diversity of changes in gastrointestinal structure and function has been described in this heterogeneous disorder. In this chapter, the author attempts to provide an overview of structural and physiological alterations in FD beyond those demonstrable by conventional tests used to separate organic dyspepsia from its functional counterpart.

2. Current definition of Functional Dyspepsia

According to Rome III criteria, FD must include one or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning; with no evidence of structural disease, including use of upper gastrointestinal 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 [1].

Older terms that represent FD are non-ulcer dyspepsia, idiopathic or essential dyspepsia. The term non ulcer dyspepsia is still popular but no longer recommended because it implies that the patient has symptoms similar to peptic ulcer disease without having an actual ulcer on endoscopic examination. The spectrum of symptoms in FD includes epigastric pain syndrome and postprandial distress syndrome

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
AND
No evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms.

Table 1. Rome III diagnostic criteria for functional dyspepsia [1]

3. Definitions of functional dyspepsia symptoms [1]

The Rome III committee proposed a distinction between meal-induced symptoms and meal-unrelated symptoms to be pathophysiologically, clinically and therapeutically relevant.

Epigastric pain syndrome:

1. Epigastric pain

Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring.

2. Epigastric burning

Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Burning refers to an unpleasant subjective sensation of heat.

Postprandial distress syndrome:

1. **Postprandial fullness:** An unpleasant sensation like the prolonged persistence of food in the stomach.
2. **Early satiation:** A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished. Previously, the term 'early satiety' was used, but satiation is the correct term for the disappearance of the sensation of appetite during food ingestion.

Recent research findings indicate that postprandial distress syndrome and epigastric pain syndrome overlap in majority of patients with FD [11]. The implication of this is that the value of dividing FD into the subgroups of postprandial distress syndrome and epigastric pain syndrome is thus questionable [11]

4. Evaluating a patient with dyspepsia

4.1. Symptom-based diagnosis

The introduction of Rome criteria and Rome process was a milestone in the management of FGIDs. However, the high turnover of Rome criteria is a testimony to the fact that symptom-based diagnosis has limitations. Symptoms may be perceived differently within different cultures and languages. It has been recommended that the current Rome III questionnaire be translated into local languages [12]. Symptoms are poor predictors of FD and significant overlaps are often seen with functional disorders including functional heartburn and irritable bowel syndrome. [13-22].

One of the difficulties encountered in evaluating a patient with dyspepsia is that symptoms are nonspecific and cannot accurately differentiate an organic process from a functional

disorder. Neither clinical impression, nor computer models incorporating patient demographics, risk factors, history items, and symptoms can distinguish between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia([23].

There is also a high degree of overlap between FD symptoms and those of gastroparesis [1, 24-29]. In FD, the predominant sensation of early satiety was found to be closely associated with impaired accommodation, although it was also present in more than 30% of patients with delayed gastric emptying [26]. Nausea and vomiting, thought to be cardinal symptoms of gastroparesis, are present in at least 20-50% of patients with FD [25, 30, 31]. Epigastric pain thought to be a cardinal symptom of FD is also present in up to 90% of patients with gastroparesis (GP) [32, 33]. Generally, common symptoms of gastric neuromuscular dysfunction are nonspecific and cannot reliably predict the underlying pathophysiology [24-26, 34]. Furthermore, recent research data indicate that rapid gastric emptying has been implicated in functional dyspepsia symptoms, especially in the postprandial distress syndrome [35, 36]. Enhanced antral contractility, decreased duodenal feedback inhibition and impaired accommodation represent the underlying mechanisms [37, 38].

The current approach is to view functional dyspepsia and idiopathic gastroparesis, not as completely distinct disorders, but as a broad, continuous spectrum, with significant overlap. It has been proposed that these 2 entities be reclassified under the umbrella term of functional dyspepsia with or without disordered gastric emptying [39], to enable clinicians and researchers to focus on predominant symptoms expressed by the majority of patients with this disorder.

4.2. Age

Older age is an important predictor for the presence of organic disease. The American Gastroenterological Association recommends proceeding directly to endoscopy in patients older than 55 years [40], however, there has been debate about a lower cut-off age of 35 to 45 years in men [41]. The optimal age threshold for endoscopy is unclear but 55 years seems a reasonable cut-off because cancer is rare in younger patients but no age threshold is absolute [42] Age specific thresholds to trigger endoscopic evaluation may differ by sex and locality [43, 44] Prompt endoscopy in patients over 50 years regardless of alarm status has been shown to increase the proportion of curable cases of upper gastrointestinal malignancies by as much as 30% [45-47], but the cost-effectiveness of initial endoscopy in this age group for improving survival of cancer patients is uncertain [47, 48]. Distinct upper gastrointestinal malignancy incidence rates and various distributions of its topographical types in different populations [49-52], as well as differences in Helicobacter pylori infection rates [53, 54] could partly explain the variable results.

4.3. Alarm features

Alarm features include unintended weight loss, family history of upper gastrointestinal cancer, gastrointestinal bleeding, progressive dysphagia, odynophagia, unexplained iron deficiency anemia, persistent vomiting, palpable mass, lymphadenopathy and jaundice. These features are useful in identifying high risk patients who need early endoscopy. The absence

of alarm features makes the likelihood of finding important structural causes for dyspepsia very low. However, a meta-analysis found that negative predictive value of alarm features was poor (6%) [55]. Worse still, subjects with organic pathologies may also have FD. [56]

4.4. Helicobacter pylori testing

Testing for Helicobacter pylori in dyspepsia may be used to select the subgroup of dyspeptic patients who have Helicobacter-related dyspepsia. The Asian consensus guideline posits that this is strictly not a form of FD. Proponents of this argue that gastritis can now be identified easily with advanced endoscopic techniques, and that Helicobacter pylori-dyspepsia is a form of post-infectious FD [2]. Exclusion of Helicobacter pylori infection should be an important part of diagnostic exercise in parts of the world where the burden of infection is high [2]. The effect of Helicobacter pylori eradication on the amelioration of symptoms in patients with FD has been evaluated in several large, well-designed, randomized controlled trials, but the results were conflicting [57-61]. Eradication of Helicobacter pylori in FD appears to improve dyspeptic symptoms more in the Chinese population than in Western populations [2]

4.5. Gastric accommodation and visceral hypersensitivity

The accommodation reflex is a vagally mediated volume response of the upper part of the stomach after a meal. After ingestion of food, the gastric fundus spontaneously dilates and begins to store food [62]. Impairment of this accommodation reflex is known to correlate well with dyspeptic symptoms especially early satiation [63, 64]. Enhanced perception of physiological signals arising from the stomach (visceral hypersensitivity) is considered a hallmark of functional gastrointestinal disorders including FD [65]. Such hypersensitivity can be reproduced acutely by different types of mechanical gastric distension [66, 67]. However, it has not been possible to conclusively identify the site and mechanisms underlying visceral hypersensitivity in FD.

Gastric barostat is gold standard for investigating gastric accommodation. It is however, invasive, time-consuming and uncomfortable to patients. Newer techniques include single photon emission computed tomography (SPECT) [64], 2- and 3- dimensional gastric ultrasound [68] and magnetic resonance imaging [69]. These are noninvasive but their high cost, sophistication and radiation exposure make them less attractive.

Drinking test is simpler [70]. It is based on the assumption that gastric volume is reduced with impaired accommodation and therefore limits the drinking volume. This test has been validated against the gastric barostat but the reproducibility is limited due to differences in types of drink and rates of drinking. In general these tests are poorly associated with dyspeptic symptoms and cannot predict a response to treatment in FD. Therefore they are not yet available for routine clinical use.

4.6. Gastric emptying

Gastroparesis is a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction. Its causes include diabetes mellitus, post-surgical and idiopathic [71].

Delayed gastric emptying occurs in 23-59% of patients with FD [72]. Research has shown that delayed gastric emptying may be related to postprandial fullness and vomiting with symptoms being more frequently found in female patients than in males [73-75]. Other studies have failed to confirm any difference in the occurrence of FD symptoms between patients with normal or delayed gastric emptying [76, 77]

Assessment of gastric emptying is commonly performed for such indications as nausea, vomiting and dyspepsia. However, there is a poor correlation of symptoms to observed abnormalities.

Techniques of gastric emptying include scintigraphy, which is the standard method in clinical practice, but is associated with radiation exposure. Newer non-invasive methods include wireless motility capsule and gastric emptying breath testing. Ultrasound, single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) are predominantly research tools.

4.7. Chemical hypersensitivity test

The duodenum is implicated in the pathophysiology of FD. Duodenal hypersensitivity and abnormal responses to various substances have been observed in FD.

Duodenal hypersensitivity to lipid: Duodenal infusion of lipid in subjects with FD increased gastric distension and symptoms in a dose-dependent fashion [78]. Symptom relief is achieved with administration of Loxiglumide, a cholecystokinin A receptor antagonist and this suggests that cholecystokinin release following a lipid stimulus is the mediator of gastric hypersensitivity in FD [79] Using cholecystokinin infusion as a challenge test is appealing [80] but is not yet available for clinical use.

Buspirone challenge test [81] is another chemical hypersensitivity test. This chemical is a serotonin 1A agonist that acts at the hypothalamic level to stimulate prolactin release. The extent of prolactin release following Buspirone challenge is a reliable measure of central 5HT sensitivity which can be impaired in patients with FD [82, 83].

Duodenal sensitivity to acid infusion: Studies on the presence of duodenal hypersensitivity to acid in FD patients and its role in the pathophysiology of FD remain controversial. Samson et al [84] reported that duodenal acid infusion induced nausea in a subset of FD patients, but not in healthy controls, suggesting the presence of duodenal hypersensitivity to acid in FD patients. However, other studies found that dyspeptic symptoms such as nausea could be induced by duodenal acidification in healthy volunteers [85].

5. Empirical treatment

Therapeutic trial may be employed as a means of diagnosis. This has proved successful in the management of GERD but the story in FD is entirely different because its pathogenesis is poorly understood and there is no effective treatment. Also, there is often a substantial placebo effect.

The new drug, Acotiamide, an acetylcholinesterase inhibitor is promising and has been shown to be efficacious and safe in the elimination of meal-related FD symptoms [86]. Though not yet approved for treatment of FD, it holds high promise as no adverse events were recorded.

5.1. Duodenal eosinophilia

Eosinophils and mast cells may be specifically recruited to the duodenum, altering sensation and motility [87]. The duodenum, which is often ignored in the search for pathophysiologic explanations for FD may be key to the symptom experience in FD. Mast cells induce eosinophil migration and eosinophils activate mast cells [88]. Degranulation from mast cells and eosinophils leads to neural stimulation and smooth muscle contraction, which in turn results in gastrointestinal symptoms, such as abdominal pain and bloating [89]. While a significant increase in mast cells has not been observed in the duodenum of patients with FD, duodenal eosinophilia in FD has been described [90, 91]. This finding is exciting, because, in patients undergoing endoscopy, duodenal biopsy is safe and easy to perform. This finding also has a potential therapeutic implication which further research would unravel.

Putative test/Abnormality	Comments/Pitfalls
Helicobacter pylori testing	Useful in identifying patients who have Helicobacter pylori – associated dyspepsia
Gastric accommodation test	Several tests have been developed. Invasiveness, high cost, patient discomfort and radiation exposure remain challenges
Gastric emptying test	Scintigraphy is currently available for clinical use.
Empirical treatment	Not a viable option because of poorly understood pathogenesis and lack of effective treatment
Duodenal eosinophilia	Initial studies promising. Larger studies needed.
Duodenal acid infusion	Results controversial
Duodenal lipid infusion	Duodenal hypersensitivity to lipids consistently obtained from most studies
Chemical hypersensitivity tests	Several candidate chemicals at various stages of development

Table 2. Summary of structural and functional abnormalities of the gastrointestinal tract in functional dyspepsia

In conclusion, dyspepsia is a very common clinical problem globally. Majority of patients with this problem have FD, defined traditionally as dyspepsia in which investigations, including upper gastrointestinal endoscopy fail to reveal a structural, biochemical or other pathophysiologic reason for the symptom. The pathophysiology of FD remains poorly understood.

Recent information from research shows that there are structural and physiological changes in FD that may hold the key to further understanding of the pathogenesis of this disease. These

include Helicobacter pylori infection, abnormalities of gastric accommodation, abnormalities of gastric emptying, duodenal eosinophilia duodenal hypersensitivity to acid and lipids. These changes have prospects of being deployed in future for the diagnostic evaluation of FD. The implication of this is that FD may not be idiopathic after all. Research is likely to shed more light on this in future.

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