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Functional Dyspepsia Today

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ABSTRACT

Functional dyspepsia (FD) is a disorder presenting with symptoms such as postprandial fullness, early satiety or epigastric pain. Although there is a 10 to 30% reported prevalence worldwide, there is currently no clear explanation of the pathophysiology behind this condition. Motility disorders, visceral hypersensitivity, acid disorders, Helicobacter pylori *infection or psychosocial factors have all been reported to play a part in the pathophysiology of FD. The diagnosis of FD is one of exclusion, based on the Rome III criteria. The main therapeutic modalities include lifestyle changes, eradicating* Helicobacter pylori *infection and treatment with either proton pump inhibitors, prokinetics or antidepressants.*

INTRODUCTION

Dyspepsia is a clinical syndrome which comprises a series of symptoms such as postprandial fullness, early satiety, or epigastric pain, symptoms which can accompany a number of gastrointestinal disorders. Although functional dyspepsia (FD) is diagnosed in more than 60% of patients complaining of these symptoms, the diagnosis remains one of exclusion (1) after structural disease (such as peptic ulcer, esophagitis or digestive malignancy) has been ruled out.

Large studies have shown a 10-30% prevalence of FD worldwide, highlighting the importance of FD as a healthcare issue (2).

Pathophysiology

The cause of functional dyspepsia remains unknown despite a great body of work in this field in the last decades. A variety of theories have been proposed in the attempt to better understand the pathopysiological mechanisms behind FD, but none have been conclusively proven.

There are currently five main theories regarded as possible explanations for FD symptoms and, while it now seems unlikely that any one of them can account for the entire disease burden on its own, they each merit an individual discussion of pathophysiological mechanism and its implications in FD treatment.

1. Motility disorders

Altered motility of the GI tract is an apparently simple and elegant explanation for the whole spectrum of FD symptoms, from epigastric pain to early satiety, nausea and belching.

According to some researchers, delayed gastric emptying was present in 25-40% of patients with functional dyspepsia and it was as-

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sociated with postprandial satiation, nausea and vomiting (3).

Ultrasound, barostat and single photon emission tomography studies demonstrated impaired accommodation, an abnormal distribution of ingested food in the stomach, with an increased proportion of the food being distributed in the antrum compared to the proximal portion of the stomach. The impaired accommodation of the stomach is caused by a vasovagal reflex which requires nonadrenergic and noncolinergic pathways (4).

Recent studies suggest that delayed gastric emptying leading to FD symptoms may be the result of an altered migrating motor complex (MMC) (5). There is also evidence linking the presence of HP infection to altered phase III gastric MMC (6), thus suggesting an interrelation between these two pathogenic mechanisms of FD.

Another theory which is interesting also from a therapeutic viewpoint is the possibility that 5HT 3 receptors might be involved in the abnormal distension of the stomach in response to the perfusion of a fatty solution in the duodenum (7).

A disorder of the central or autonomous nervous systems has been studied as a possible mechanism for the impaired gastric accommodation and the antral hypomotility. There is some indirect evidence of a correlation between emotional and psychological factors and dyspeptic symptoms, via diminished vagal activity (8).

Manometric studies have also shown antral hypomotility as well as numerous retrograde contractions from the duodenum towards the stomach. Unsuppressed phased contractility increase parietal tension in the stomach which is, in turn, perceived as postprandial discomfort. This abnormality has been linked by some researchers with Helicobacter pylori infection (9).

Despite the continued development of sophisticated methods allowing the minute exploration of GI tract physiology, correctly quantifying the motility patterns of normal and FD patients is still proving a major obstacle in providing adequate support for this theory.

2. Visceral hypersensitivity

Some of the earliest studies in FD suggested a role for altered visceral sensitivity as an important mechanism for dyspeptic symptoms. Increased sensitivity to lipids in the duodenum was one of the first investigated pathways in FD (10).

Other studies focused on the role of mechanic stimulation of gastric and duodenal receptors. Results of gastric barostat studies have shown that patients with functional dyspepsia have a lower sensitive threshold to the distension of the barostat inside the proximal regions of the stomach and the duodenum. This gastric hypersensitivity, defined as pain threshold 2 standard deviations below that of normal voluntaries, is associated with postprandial epigastric pain and weight loss. Whether concomitant Helicobacter pylori infection contributes to gastric hypersensitivity is a matter still open to debate (11).

3. Acid disorders

Because FD symptoms are virtually indistinguishable from those of peptic ulcer disease (PUD) and because PPI treatment is a mainstay of FD treatment, many research groups have long advocated the role of abnormal gastric and duodenal acid levels in FD. Studies have shown that acid secretion is normal in a majority of dyspeptic patients but recent evidence suggests an abnormal acid clearance from the duodenum as well as a decreased motor response of the duodenum when acid is present. pHmetry studies lasting 24 hours have shown an increased exposure to acid after a meal, but no direct link between this exposure and dyspeptic symptoms has been proven (12). These observations have been recently confirmed by radiotelemetry pH monitoring over 48 hour periods (13).

4. Helicobacter pylori infection

One of the main arguments behind the possible role of Helicobacter pylori (HP) infection in FD is derived from clinical experience, with a systematic review showing the positive impact of HP eradication on FD symptoms (14) with a NNT of 15 (15). However, there is conflicting data on this matter, with a systematic review of studies striving to prove a causal relation between Helicobacter pylori infection and functional dyspepsia were inconclusive; a modest relationship seems to exist but evidence is lacking to support an important role of HP infection in patients with functional dyspepsia (16).

5. Psychosocial factors

There has been a longstanding interest in the role of psychological factors in the onset and symptom severity in FD. Studies have established that psychosocial stressors influence FD symptoms (17) and that depressive mood and altered quality of life were more frequent among FD and FD and IBS overlap patients (18). However, antidepressant treatment in FD, the next logical step in this pathophysiological chain, has been disappointing so far, raising questions over the validity of this particular approach to FD (19).

6. Allergic disorders

Recently, the role of various allergens has been studied in both FD and IBS, with studies showing an increase in the prevalence of food allergies (e.g.: eggs, soybeans) in FD and IBS patients (20). Furthermore, pathological studies have shown eosinophilia in the mucosa of FD patients, but its relationship to food allergens still needs further evaluation (21).

Symptoms and diagnosis

The cardinal symptoms of FD are epigastric pain, postprandial discomfort often described as postprandial fullness and early satiety. Additional symptoms such as nausea and belching may be present. Patients complaining of heartburn as a main symptom will usually receive a GERD diagnosis, although there is probably an important overlap between GERD and FD (22). The lack of sensitivity and specificity of the clinical diagnosis of FD has been highlighted by a clinical trial, which showed that only endoscopy was capable of correctly differentiating between peptic ulcer disease, esophagitis and FD (23).

While the continued development of functional explorations tests has allowed for a more refined exploration of the physiology of the GI tract, no correlation has been found between impaired mechanisms and FD symptoms as had been previously suggested (24). Due to the imprecise nature of its symptoms, functional dyspepsia has been defined using a set of periodically revised diagnostic criteria. The Rome III criteria, published in 2006, are the most commonly employed. They consist of one or more of the following symptoms (25): bothersome postprandial fullness, early satiety, epigastric pain, epigastric burning and no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms. The criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

The older Rome II criteria which classified functional dyspepsia as ulcer-like, dysmotility-like and nonspecific were abandoned in favor of the more precise Rome III (22) criteria based on the four cardinal symptoms already presented. According to the dominant presenting symptom, two subtypes of FD were defined as follows (Table 1):

A. Postprandial Distress Syndrome
Diagnostic criteria must include one or both of the following:*
Bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week
Early satiety that prevents finishing a regular meal, at least several times per week
Supportive criteria
Upper abdominal bloating or postprandial nausea or excessive belching can be present
Epigastric pain syndrome may coexist
B. Epigastric Pain Syndrome
Diagnostic criteria must include all of the following:*
Pain or burning localized to the epigastrium of at least moderate severity, at least once per week
The pain is intermittent
Not generalized or localized to other abdominal or chest regions
Not relieved by defecation or passage of flatus
Not fulfilling criteria for gallbladder and sphincter of Oddi (26) disorders
Supportive criteria
The pain may be of a burning quality, but without a retrosternal component
The pain is commonly induced or relieved by ingestion of a meal, but may occur while fasting
Postprandial distress syndrome may coexist

TABLE 1. Functional dyspepsia subtypes

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Therapy of functional dyspepsia

The heterogeneous nature of the functional dyspepsia patient population makes it difficult to have a representative study group, which is one of the reasons that the results of drug trials tend to be discordant. During the past decades, many trials have addressed the problem of FD therapy, with unsatisfying and sometimes contradictory results.

Lifestyle alteration

General measures such as smaller, more frequent meals, avoiding caffeine, alcohol, NSAIDs, fatty or spicy meals, seem in order, al-

though there is little evidence supporting their use (27).

Pump proton inhibitor

Two regimens of antisecretory therapy were proposed: „step-up" (e.g., start with antacids, then H2-blockers and then proton pump inhibitors) or „step-down". A metanalysis comparing these two strategies has showed similar success rate, but with higher costs for step-down approach at six-months (28).

Several placebo-controlled trials had the same results regarding the efficacy of PPI, a meta-analysis finding an NNT of 10 and a relative risk reduction of 13%, without difference between doses of PPIs (29). However, the relief of symptoms was greatest in patients with ulcer-like and reflux-like symptoms, but not in those with dysmotility-like symptoms or unspecified dyspepsia.

H2-receptor antagonists (H2RA)

Many trials, which probably included GERD patients, found a significant benefit and a relative risk reduction of 23% with a number to treat of 7, but better quality trials showed a low efficacy for H2RA therapy (30).

Prokinetics

Prokinetics act on three different types of receptors in order to enhance gastric motility. These drugs might help alleviate satiation, abdominal distention and nausea, but the link between symptom relief and improved gastric emptying is not yet proven (31).

Several studies have symptom relief for cisapride and domperidone, with a reduction in relative risk of 50% (32). Cisapride, however, has been withdrawn because of safety concerns and domperidone is not widely available.

Metoclopramide may also be effective, but is associated with several potential side effects, particularly with long-term use. Itopride, a dopamine D2 antagonist, was effective in a phase III multicenter trial; the suggested mechanism of action being its effect on gastric accommodation and hypersensitivity (33).

Antidepressants

If initial treatment with IPPs or prokinetics fails, antidepressants can be employed, in lower doses than required in the treatment of depression. Tricyclic antidepressants as well as selective serotonine reuptake inhibitors (SSRI) such as paroxentine, valexetine, were no more effective than placebo on improving symptoms, according to results of a randomized placebo-controlled trial (34).

The role and the mechanism of antidepressants in functional dyspepsia remain unsettled.

Management of functional dyspepsia

From the insufficient understanding of the pathogenic mechanisms of functional disorders stems, to the difficulty of setting up diagnostic and therapeutic guidelines. Furthermore, there is a logical incongruity between the diagnostic criteria for FD and its management. Although a diagnosis of FD requires the absence of any structural disease, including at endoscopy, management guidelines support empiric antisecretory or prokinetic therapy in patients with suspected FD who show no alarm symptoms (35). Endoscopy is recommended only in those cases where alarm symptoms are present or patients are non-responders to at least 4 weeks of empiric therapy. As such, a vast majority of FD patients will most likely receive treatment without undergoing endoscopy for diagnosis confirmation.

The first step in evaluating any patient is history taking and physical examination, which can help suggest either a structural or a functional disorder. Routine lab tests (e.g.: blood count) can also be helpful in an initial workup of the patient.

In addition, the physician needs to pay attention to the so-called „alarm symptoms", which increase the likelihood of a structural disease (Table 2). Any of these signs and symptoms requires an endoscopic study to assess a possible malignancy. The American Society of Gastroenterology (ASGE) guidelines emphasize

Alarm symptoms
Age > 50 yrs
Family history of digestive malignancy
Involuntary weight loss
Unexplained anemia or iron deficiency
Progressive dysphagia
Hematemesis
Odinophagia
Recurrent vomiting
Palpable tumor or lymphadenopathy
Jaundice
Previous gastric surgery

TABLE 1. Alarm symptoms

the fact that the positive predictive value of these symptoms is low (11%). However, their negative predictive value in excluding gastrointestinal malignancy is very high, approximately 97% (36). This is the logical consequence of the fact that only 2% of dyspeptic syndromes are caused by esophageal or gastric cancer, 30 times fewer than functional dyspepsia (37). Conversely, the presence of alarm symptoms provides reasonable guidance, and has been included in consensus recommendations on functional dyspepsia management.

Excluding gastroesophageal reflux disease (GERD) as the cause of dyspeptic symptoms is also of paramount importance because GERD has a different treatment and prognosis and requires a particular management strategy involving long-term proton pump inhibitor therapy (IPP) and active surveillance for reflux esophagitis, Barrett's esophagus as well as esophageal cancer. Many GERD patients are diagnosed with functional dyspepsia because of the lack of structural abnormalities in endoscopic studies and the great variety of symptoms of functional dyspepsia (including heartburn) which in turn has lead to confusing results in many clinical trials (38).

A drug-induced dyspepsia must be also taken into account, especially nonsteroidal anti-inflammatory drugs (NSAIDs) commonly associated with dyspepsia. In this case, the offending agent should be discontinued, if possible, or a proton pump inhibitor can be added (PPI) (39). Patients on long term NSAID treatment can be considered at risk for peptic ulcer disease and the physician should decide whether endoscopy is warranted from the first visit.

The optimal approach for a patient with uninvestigated dyspeptic symptoms is far from being decided. Several strategies for the management of these patients have been proposed, but several systematic reviews have failed to settle the dispute.

The options taken into discussion were:

1. Prompt endoscopy
2. Empiric antisecretory therapy
3. Noninvasive testing for Helicobacter pylori, followed by treatment or endoscopy if positive (test-and-treat strategy)

1. The role of endoscopy in FD

The most debated problem in the management of FD, as already shown above, is the role of an initial upper digestive endoscopy. Endoscopy (40-42) has the advantage of excluding peptic ulcer, esophagitis and cancer as causes of dyspepsia. A meta-analysis of nine studies with 5389 patients showed that the most common finding in patients with dyspeptic symptoms was erosive esophagitis (pooled prevalence 13%), though the prevalence was much lower when dyspepsia was defined using the Rome criteria (6 %) (43).

In addition, clinical trials show that simply being subjected to an endoscopic study increases the patient's level of satisfaction and confidence (44). Supporters of empiric therapy argue that a low incidence of cancer (less than 2% of dyspeptic patients) and the high costs incurred by endoscopy should preclude upper digestive endoscopy as a first step in investigating these patients. Accordingly, patients under 45-50 years of age without any alarm symptoms could be treated empirically with minimal risks (45), endoscopic studies being reserved for those patients who are nonresponsive to 6-8 weeks of therapy. However, given that many patients do not achieve full symptomatic relief with medical therapy, requiring further investigations, it seems more prudent to perform endoscopy in the initial workup. If this initial endoscopic study is normal, endoscopy will not be repeated unless alarm symptoms develop.

The American Gastroenterology Association's guidelines from 2005 also suggest that endoscopy should be performed in patients with dyspepsia who have alarm symptoms or those without alarm symptoms who are ≥55 years of age (46). The authors point out that in some regions where cancer incidence is higher (such as Alaska), lower age thresholds are appropriate, for example 45 years rather than 55 years of age. Patients who receive medication should be evaluated for symptomatic improvement at approximately eight weeks.

2. Empiric antisecretory therapy

The empiric antisecretory therapy has advantages and disadvantages, according to conflicting results of studies. Many patients can have a favorable symptomatic response, but this does not exclude a malignant gastric ulcer and it can delay the diagnosis. Also, the recurrence of the symptoms is common after one year (47) and the lack of H. pylori eradication increases the risk of ulcer recurrence.

3. Test and treat strategy

The relationship between Helicobacter pylori infection and peptic ulcer disease is well known but H. Pylori infection alone can account for a minority of cases of chronic dyspepsia. For this reason, the consensus of European H. Pylori Study Group (March 2005) suggested a „test-and-treat" approach for patients less than 45 years old with persistent dyspepsia (a remark is made for the age cutoff, which may vary with the prevalence of gastric cancer in different countries). Another conclusion was that, in countries with low prevalence of H. pylori infection (<20%), the empirical therapy with PPI is preferred to the test and treat strategy (48).

Among the noninvasive studies the most widely used in managing functional dyspepsia are the 13C-urea breath test and the stool antigen test for Helicobacter pylori (HP), the IgG serology being reserved for the cases where pretest probability is high, followed by a confirmation by one of the methods mentioned above. ❑

CONCLUSIONS

As long as the mechanisms of disease involved in functional dyspepsia are not fully understood we cannot hope for an adequate treatment for FD. Consequently, physicians must rely on empiric therapies, choosing those drugs that have a good safety profile and whose effectiveness has been validated by clinical trials. For the time being, use of a PPI or/and a prokinetic for a minimum of 4 to 8 weeks seems the best option available (Figure 1). New drugs such as antidepressants might be of use in treatment failures but further research is needed in order to provide better care for FD patients.

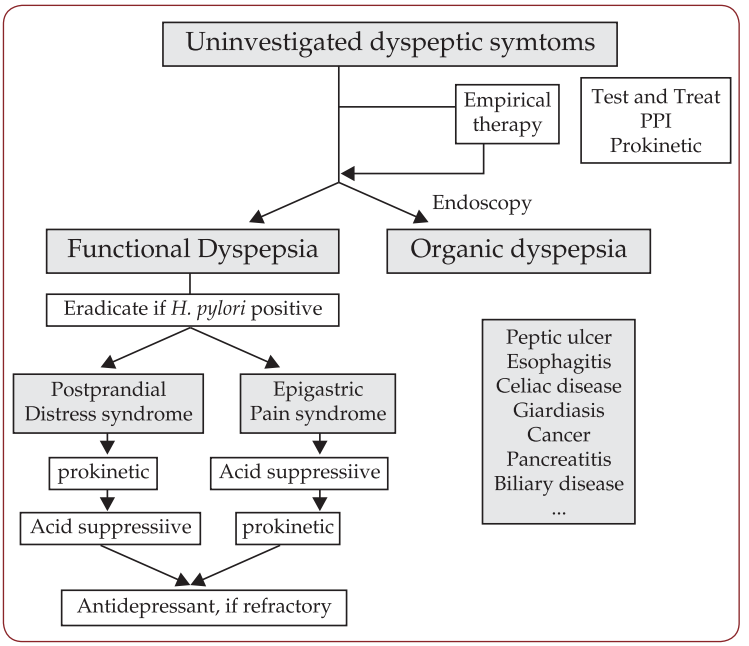

FIGURE 1. Treatment algorithm for FD.

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