Functional Dyspepsia: a Pragmatic Approach

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Functional dyspepsia includes one or more of four cardinal symptoms: postprandial fullness, early satiety, pain or burning in the epigastrium. According to the Rome III diagnostic criteria for functional dyspepsia, these symptoms must be present for the last 3 months with symptom onset at least 6 months prior to diagnosis. Functional dyspepsia is not the result of an underlying structural abnormality, but rather the consequence of multiple pathophysiological mechanisms such as abnormal gastric motility, gastric and duodenal hypersensitivity to acid, Helicobacter pylori infection. Dyspeptic patients over 50 or those with alarm symptoms should be investigated to detect any structural abnormality such as cancer, peptic ulcer or esophagitis. After structural abnormalities and gastroesophageal reflux disease are excluded the management of functional dyspepsia consists of either a test and treat approach (non invasive detection of Helicobacter pylori infection followed by eradication therapy) or empirical therapy. Although endoscopy was traditionally reserved for those patients without symptom relief after 6–8 weeks of therapy, the significant percentage of patients with functional dyspepsia with symptom breakthrough or relapse after antisecretory or prokinetic therapy discontinuation makes an initial endoscopic study a logical choice. Therapy with proton pump inhibitors yields results especially in those patients with regurgitation and epigastric burning sensation, while prokinetic agents with no extrapyramidal side effects (such as Domperidone and Itopride) alleviate satiation, bloating and nausea by accelerating gastric emptying. Second-line drugs with encouraging results in clinical trials which can be used in functional dyspepsia are low-dose tricyclic antidepressants as well as selective serotonine reuptake inhibitors.

Key words: Functional dyspepsia, Rome III Criteria, proton pump inhibitors, prokinetics, endoscopy, antidepressants.

Dyspepsia is a nonspecific term used to describe upper abdominal discomfort caused by disorders of the upper digestive tract.

An important distinction has to be made between dyspepsia caused by a structural abnormality (peptic ulcer, reflux esophagitis, gastric cancer or biliary and pancreatic disorders) and functional dyspepsia presenting with no underlying structural abnormality. The latter accounts for approximately 60% of all dyspeptic syndromes. The remaining 40% are divided up among various disorders of the digestive tract, with peptic ulcer accounting for 25% and gastric and esophagean cancer for 2% of all dyspeptic syndromes [1].

DIAGNOSTIC CRITERIA

Dyspepsia is a protean concept which can accommodate a variety of symptoms such as epigastric discomfort, bloating, anorexia, early satiation, belching, regurgitation, nausea and heartburn. The very meaning of the word dyspepsia – bad digestion – underlies the imprecision of this particular notion. The wide variety of symptoms related to dyspepsia reflect the high prevalence of functional disorders as well as an insufficient understanding of this phenomenon. In order to facilitate the management of functional dyspepsia, the Rome II diagnostic criteria were revised and the Rome III criteria were defined. They consist of one or more of the following symptoms [2]:

a. Bothersome postprandial fullness
b. Early satiation
c. Epigastric pain
d. Epigastric burning

AND

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

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

Patients in whom heartburn is the main symptom are not considered to have functional dyspepsia since in all likelihood their diagnosis is gastroesophageal reflux disease. Patients receiving
nonsteroidal antiinflammatory drugs and patients with irritable bowel syndrome will not be diagnosed with functional dyspepsia either [3].

The Rome II diagnostic criteria which defined functional dyspepsia as ulcer-like, dysmotility-like and nonspecific were abandoned in favour of the more precise Rome III [4] criteria based on the four cardinal symptoms already presented. Two types of functional dyspepsia are as follows:

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 satiation that prevents finishing a regular meal, at least several times per week

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

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 epigastrum 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 [4] disorders

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

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

The Rome criteria ought to be applied by all physicians when confronted with a patient without a clear diagnosis, in whom a structural abnormality (peptic ulcer, cancer, esophagitis) is unlikely. A superficial approach to such patients will result in an imprecise diagnosis such as dyspeptic syndrome and referrals for further invasive and costly studies, such as upper digestive endoscopy, in order to exclude the aforementioned disorders. Upper digestive endoscopy has no diagnostic or therapeutic role in the management of functional disorders and it should be recommended with the sole purpose of excluding structural abnormalities of the digestive tract.

MECHANISMS OF DISEASE

Several pathophysiological mechanisms have been proposed to explain functional dyspepsia: delayed gastric emptying, impaired accommodation, unsuppressed phasic contractility, duodenal lipid hypersensitivity, duodenal acid hypersensitivity, *Helicobacter pylori* infection as well as a dysfunction of the central or autonomous nervous system. According to several studies [5], delayed gastric emptying was present in 25–40% of patients with functional dyspepsia and it was associated with postprandial satiation, nausea and vomiting.

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 vaso-vagal reflex which requires nonadrenergic and noncholinergic pathways [6].

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 a pain threshold 2 standard deviations below that of normal voluntaries, is associated with postprandial epigastric pain and weight loss. The role of *Helicobacter pylori* infection in gastric hypersensitivity is still open to debate [7].

5HT3 receptors might be involved in the abnormal distension of the stomach in response to the perfusion of a fatty solution in the duodenum in patients with functional dyspepsia [8].

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 [9].

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 [10].

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 psychologic factors and dyspeptic symptoms, *via* diminished vagal activity [11].

Manometric studies have also shown antral hypomotility as well as numerous retrograde contractions from the duodenum towards the stomach. Unsuppressed phasic contractility increases 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 [12].

Symptoms described by patients with functional dyspepsia have been linked by researchers with the following possible mechanisms [12]: (data from Tack J., Bisschops R., Sarnelli G., Gastroenterology 2004)

- Helicobacter pylori – epigastric pain
- Postprandial fullness, nausea, vomiting – delayed gastric emptying
- Early satiety, weight loss – impaired accommodation
- Bloating, absence of nausea – unsuppressed phasic contractility
- Nausea – duodenal acid and lipid hypersensitivity [13].

This pairing of symptoms and pathophysiological mechanisms is limited by the numerous physiological disorders overlapping in functional dyspepsia which in turn account for the lack of specificity of any such pairing.

**MANAGEMENT OF FUNCTIONAL DYSPEPSIA**

From the insufficient understanding of the pathogenic mechanisms of functional disorders stems the difficulty of setting up diagnostic and therapeutic guidelines.

Confronted with a patient with dyspepsia the practicing physician is required to avoid two equally unproductive approaches – under or over-estimating the symptoms. The lack of any structural abnormality does not solve the patient’s troubles, improved quality of life being an important criterion for validating any medical act. Unfortunately, many patients risk not getting the attention they deserve because functional disorders are frequently regarded as a false problem.

The first step in diagnosing functional dyspepsia has to be the exclusion of any structural abnormality. Since endoscopy is now more readily available, it is the preferred method of excluding peptic ulcers, gastric and esophageal cancers. However, endoscopic studies are limited by their diagnostic possibilities (since they cannot diagnose gastroesophageal reflux disease) and their fairly high costs. This is why attention must be payed to the so-called alarm symptoms (Table I). Any of these signs and symptoms requires an endoscopic study to assess a possible malignancy. The American Society of Gastroenterology (ASGE) guidelines emphasise 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% [1][2]. 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 [3].

**Table I**

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<th>Alarm symptoms</th>
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<td>Age &gt; 50 yrs</td>
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<td>Family history of digestive malignancy</td>
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<td>Involuntary weight loss</td>
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<td>Progressive dysphagia</td>
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<td>Odinophagia</td>
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<td>Palpable tumor or adenopathy</td>
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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 [14].

Among the noninvasive studies the most widely used in managing functional dyspepsia are the urea breath test and the stool antigen test for Helicobacter pylori(HP). Some countries, including Romania, do not utilise the first test while the latter is not widely accessible. As such, HP infection is diagnosed either serologically or endoscopically, using the rapid urease test.

Tertiary centres can also study gastric motility (through scintigraphic studies of gastric emptying) [15] and gastric accommodation, using a barostat. These studies are not performed in current medical practice, being used for research purposes. If the correlation between altered gastric motility and dyspeptic symptoms is confirmed, these refined studies might become the basis for a pathogenic approach to functional dyspepsia management.

The most debated problem in the management of dyspepsia is the role of an initial upper digestive endoscopy. Endoscopy [16–18] has the advantage of excluding peptic ulcer, esophagitis and cancer as causes of dyspepsia. Also, clinical trials show that simply being subjected to an endoscopic study increases the patient’s level of satisfaction and confidence [19]. Supporters of empiric therapy argue that a low incidence of cancer (under 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 [20], 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 [17].

Empiric treatment for HP in countries where HP infection has a prevalence greater than 10–20% or the test-and-treat approach (after breath test or stool antigen confirmation of HP infection) is no longer the main therapeutic mainstay because only 1 out of 15 patients treated for HP will be symptom free at 1 year post-therapy [21][22]. Furthermore, this modest benefit must be weighed against the adverse effects of the triple therapy employed in eradicating HP infection.

General measures such as smaller, more frequent meals, seem in order, although there is little evidence supporting their use [23].

IPP treatment is successful especially in patients who associate regurgitation and heartburn, but the results are far from satisfactory [24].

The most diverse and promising class of drugs available are the prokinetics, among which the newer drugs such as domperidone and itopride, lacking the extrapyramidal adverse effects of metoclopramide, are most prominent. Prokinetic therapy has the advantage of addressing one of the suspected pathogenic mechanisms in functional dyspepsia, abnormal gastric motility. These drugs might help alleviate satiation, abdominal distension and nausea, but the link between symptom relief and increased gastric motility is not yet proven [21][23].

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 serotonin reuptake inhibitors (SSRI) such as paroxentine have shown promising results in clinical trials [23].

CONCLUSIONS

As long as we cannot fully explain the mechanisms of disease involved in functional dyspepsia we cannot hope for an adequate therapy. As such we 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, associating an IPP and a prokinetic for 4–8 weeks seems the best option available. In case of recurrent or persistent symptoms, the patient will be reevaluated by a specialist (Fig. 1). New drugs such as antidepressants might be employed or the initial regimen can be continued, with or without an increase in dosage. A successful treatment with prokinetics and IPPs does not mean that the patient will be treated indefinitely; the best option would be for the patient to have on demand drugs available in case of recurrent symptoms.
In conclusion we must once again underline the fact that the diagnostic and therapeutic options available for managing functional dyspepsia are still limited, but this must not deter the physician from seeking an increased quality of life for his patient.

endoscopic pentru depistarea unor boli organice ca esofagita, cancerul eso-gastric sau ulcerul peptic. După excluderea unei leziuni structurale și a bolii de reflux gastroesofagian, următoarele opțiuni în abordarea sindromului dispeptic sunt: depistarea infecției cu Helicobacter pilori prin teste noninvazive (test respirator sau antigen fecal) sau terapia empirică. Deși clasic endoscopia era rezervată acelor pacienți care nu răspundea la tratament în 6–8 săptămâni, dat fiind procentul important de pacienți a căror simptomatologie nu poate fi controlată medicamentos sau revine după o perioadă variabilă de la sistarea terapiei, pare mai prudent ca prima evaluare să cuprindă și un examen endoscopic. Terapia cu inhibitori ai pompei de protoni dă rezultate mai ales la acei pacienți care asociază în simptomatologia lor regurgitația și senzația de arsură epigastrică, pe când agenții prokinetici (cei mai noi și fără efecte adverse extrapiramidale – Domperidona și Itoprida) ar combate sațietatea, senzația de balonare și greața, prin accelerarea golirii gastrice. Ca medicamente de a doua linie rămân dozele mici de antidepresive triciclice sau inhibitori selectivi ai recaptării serotoninii, cu rezultate încurajatoare în studiile clinice.

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