MÆDICA - a Journal of Clinical Medicine

STATE-OF-THE-ART

Functional dyspepsia: recent advances (progresses) in pathophysiology and treatment

Vasile DRUG, MD, PhD; Carol STANCIU, MD, PhD

Institute of Gastroenterology and Hepatology, Iasi, Romania

ABSTRACT

The new developed Rome III criteria are believed to better characterize functional dyspepsia. Several possible explanations for the occurring of functional dyspepsia have developed during recent years. These are: H. pylori *infection, delayed gastric emptying, altered gastric electrical activity and antral hypomotility, impaired gastric accommodation and unsuppressed phasic fundic contractility, disturbed brain-gut interactions, altered bacterial flora, alteration of gastrointestinal hormones and psychosocial factors. The therapy implies* H. pylori *infection eradication, the use of proton pomp inhibitors and prokinetic drugs associated with psychological therapy in severe cases.*

Keywords: functional dyspepsia, H. pylori, gastrointestinal motility

Functional dyspepsia is a part of functional gastrointestinal disorder (FGID) and has common features characterized by the presence of gastrointestinal symptoms and the absence of structural abnormalities. FGID is a common condition in the daily clinical practice representing half of the referrals for gastroenterological consultation (1). Recently, updated Rome III criteria for functional digestive disorders have been published (2).

The diagnostic criteria for Functional Dyspepsia must include:

1. One or more of: a) bothersome postprandial fullness; b) early satiation; c) epigastric pain; d) epigastric burning; and
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

These criteria must be fulfilled for the last 3 months with symptoms onset at least 6 months before diagnosis.

Two forms of functional dyspepsia have been defined: a) postprandial distress syndrome, and b) epigastric pain syndrome.

The diagnostic criteria for postprandial distress syndrome must include one or both of the following: 1) bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week, and 2) early satiation that prevents finishing a regular meal, at least several times per week. Supportive

Address for correspondence:
Vasile Drug, MD, PhD, Institute of Gastroenterology and Hepatology, 1 Independentei Blvd., Iasi, Zip Code 6600, Romania
email address: vasidrug@email.com

criteria for postprandial distress syndrome are the following:

a) upper abdominal bloating or postprandial nausea or excessive belching can be present, and

b) epigastric pain syndrome may coexist.

The diagnostic criteria for epigastric pain syndrome must include all of the following:

1. pain or burning localized to the epigastrium of at least moderate severity at least once per week;
2. the pain is intermittent;
3. not generalized or localized to other abdominal or chest regions;
4. not relieved by defecation or passage of flatus;
5. not fulfilling criteria for gallbladder and sphincter of Oddi disorders.

Supportive criteria for epigastric pain syndrome are the following:

1. the pain may be of a burning quality but without a retrosternal component;
2. the pain is commonly induced or relieved by ingestion of a meal but may occur while fasting;
3. postprandial distress syndrome may coexist. ❑

RECENT ADVANCES IN PATHOPHYSIOLOGY

Pathophysiology of FGID includes several possible mechanisms: *Helicobacter pylori (H. pylori)* infection, delayed gastric emptying, altered gastric electrical activity and antral hypomotility, impaired gastric accommodation, and unsuppressed phasic fundic contractillity, disturbed brain-gut interactions, altered bacterial flora, alteration of gastrointestinal hormones, psychosocial factors (3). In this paper we shall review the recent advances in pathophysiology of functional dyspepsia and we shall present its implications for the therapy. However, all available studies have not used for the setup the updated Rome III criteria which were just recently launched (4).

H. pylori infection

Several studies attempted to answer the question if there is a relation between *H. pylori* infection and functional dyspepsia. Different approaches have been used such as epidemiological, therapeutical, and experimental studies. Basal gastric acid secretion is normal in functional dyspepsia (5). A meta-analysis showed that the prevalence of *H. pylori* infection is more common in patients with functional dyspepsia than in control (6), but other study demonstrated that this statement is valid more for ulcer-like dyspepsia than for the dismotility type (7). Different meta-analyses showed a trend or a small benefit in terms of symptoms elevation after eradication of *H. pylori* infection (8). According to the 2006 Maastricht III European Consensus eradication of *H. pylori* infection is recommended in patients with investigated functional dyspepsia (2).

However, a relation between *H. pylori* infection and gastrointestinal dysmotility has never been definitely proven. Even if the reduction of gastric corpus inflammatory activity after *H. pylori* eradication infection is associated with changes in gastric hysteresis, several other studies have shown that the presence of *H. pylori* infection did not affect the gastric emptying rate, gastric accommodation and sensitivity (3,8).

Delayed gastric emptying

Several methods such as scintigraphy, ultrasonography, and ^{13}C-octanoic acid breath test have shown a delayed gastric emptying in 20-60% of patients (9,10). A recent meta-analysis of 17 studies revealed a significant delay in gastric emptying in about 40% of patients (3). The majority of studies demonstrated, however a poor correlation between symptoms and gastric emptying rate (9, 10).

Altered gastric electrical activity and antral hypomotility

Electro-gastrography (EGG) studies showed both tachigastria and bradigastria (alteration of electric gastric activity) (11). This abnormal electrical activity is correlated with delayed gastric emptying and may be associated with functional dyspepsia. Abnormal duodenal exposure to acid, even in the presence of normal gastric acid secretion may induce abnormal gastric motor responses, with generation of nausea and vomiting. This may represent the pathophysiological fundamentum for anti-acid positive response in some patients with functional

dyspepsia. Other disturbances of upper gut motility are reduced frequency of migrating motor complexes, impaired duodenal motor responses to acid and nutrient infusion and excess phasic contraction of fundus after meal (8,11).

Impaired gastric accommodation and unsuppressed phasic gastric accommodation

Different methods such as: barostat balloon study, trans-abdominal ultrasound, magnetic resonance imaging, three-dimensional computer tomography used in patients with functional dyspepsia suggests a proximal stomach defective relaxation. As consequence, an altered intragastric distribution of the food with preferential accumulation in the distal stomach may occur (3,12-14).

Disturbed brain-gut interactions

Impaired efferent vagal function was suggested to be present in patients with functional dyspepsia by several authors, in a similar manner like in the post-vagotomy patients (10). This vagal abnormality may lead to antral hypomotility and impaired gastric accommodation. Gastric hypersensitivity is another possible link to the gastrointestinal symptoms in which central serotoninergic and noradrenergic processing or altered neural conduction may be involved (3,8,9).

Altered bacterial flora

It is now well recognized that irritable bowel syndrome may occur in patients after an episode of gastroenteritis. Mearin et al showed that functional dyspepsia may also follow after gastroenteritis with Salmonella (15). Other authors also confirmed a relation between bacterial gastroenteritis and functional dyspepsia (3,8,9).

Alteration of gastrointestinal hormones

Several hormonal factors such as gastrin, neurotensin, CCK, motilin, ghrelin, progesteron, estradiol and prolactin have been studied in patients with functional dyspepsia. Plasma gastrin, neurotensin and ghrelin abnormalities have also been shown in a patient subgroup. However, there is no clear conclusion for the involvement of gastrointestinal hormones in genesis of symptoms in functional dyspepsia patients (3, 8, 9, 16).

Psychological factors

Similar with other functional gastrointestinal disorders, psychological problems such as anxiety, depression, learning disease behavior and somatisation are more common in patients with functional dyspepsia. Acute mental stress may induce antral hypomotility, gastric hypersensitivity or inhibition of gastric emptying associated with early satiation, nausea, and vomiting (3,8,17). ❑

RECENT ADVANCES IN THERAPY

Therapy in functional dyspepsia should be individualized. Patient reassurance for the benign condition of the disease is essential for maximized the placebo effect of the medication. Similar with other functional disorders, the placebo effect of the therapy is high (between 20-60%) (18). Some general dietary recommendations are useful: ceasing consumption of alcohol, coffee and spicy foods, repeated small low-fat meals, and stopping smoking (7).

Investigating and treating *H. pylori* infection represents the first gesture to recommend according to Maastricht III Consensus in populations with high *H. pylori* prevalence (such as Romania). *H. pylori* eradication can induce sustained remission in a subgroup of patients according to a Cochrane meta-analysis and several other studies (2,19).

In patients with absence of *H. pylori* infection first line therapy to recommend is acid suppression with PPI or anti-H2 receptors drugs. A Cochrane meta-analysis showed a benefit of anti H2 receptors drugs over placebo with a number needed to treat (NNT) of 7 (5). Other meta-analysis proved also the PPI therapy benefit (19). Some of the patients with functional dyspepsia may in fact have gastroesophageal reflux diseases but they will benefit, from the anti-secretory therapy (3, 20, 21).

Prokinetic drugs have long time been used for treatment of functional dyspepsia. Metoclopramide, domperidon and cisapride showed some marginal benefits. However, new drugs are needed due to limited benefit and recognized

side effects (22, 23). D2 antagonist levosulpiride showed to be at least as efficient as cisapride in treating functional dyspepsia. Motilin agonist erythromycin increase gastric emptying rate but tachyphylaxis and recognized side effect limit its use. Sumatripan or buspirone, 5HT1 receptor agonists may induce gastric fundus relaxation but contradictory data on the clinical benefits still exist (3,8).

Association with psychiatric disorders such as anxiety or depression suggests a possible positive effect of antidepressant drugs. Amitryptiline has been used in low doses and showed a marginal benefit in terms of symptoms but not on visceral hypersensitivity (3,8).

Tegaserod and mosopride, 5HT4 agonists represent the present hope in improving the management of these patients. Tegaserod have been proved to be beneficial in female FD patients. However, the efficacy of mosopride was similar with Famotidine in elevating FD symptoms. CCK1 receptor antagonist dexloxiglumide, k-agonist fedotozide, tachikinin NK 1 antagonist aprepitant, phosphodiesterase 5 inhibitor sindenafil are new drugs on trial for functional dyspepsia patients (3,8). ❑

Conclusion

New recently launched diagnostic criteria (Rome III) are believed to better characterize the functional dyspepsia. Several possible pathophysiological mechanisms seems to be involved in functional dyspepsia : *H. pylori* infection, delayed gastric emptying, altered gastric electrical activity and antral hypomotility, impaired gastric accommodation and unsuppressed phasic fundic contractility, disturbed brain-gut interactions, altered bacterial flora, alteration of gastrointestinal hormones, psychosocial factors. The therapy implies *H. pylori* infection eradication, the use of proton pomp inhibitors and prokinetic drugs associated with psychological therapy in severe cases.

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