Future Directions in Functional Dyspepsia

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Introduction

Functional dyspepsia (FD) is being increasingly recognised as a common cause of chronic abdominal symptoms and represents a significant health care burden.1,2 There is lack of understanding of the patho-physiology of this condition that is recognized on the basis of symptoms that makes the diagnosis subjective, as well as controversy regarding the management of this condition. Although there has been considerable interest in recent years to study this syndrome, a clear understanding of its mechanism and treatment are still not available.

Pathophysiology

The pathophysiology of dyspepsia is unclear. Several symptoms and theories that have been put forward suggest multiple heterogenous mechanisms, some possibly inter-related and complex. Delayed gastric emptying, antral hypomotility and altered intestinal motility, decreased gastric accommodation, H. pylori infection, enhanced visceral sensitivity, abnormal duodenal sensitivity to acid, carbohydrate maldigestion, immune cell infiltration including mast cells and eosinophils, and psychological factors have all been identified in subgroups of patients with functional dyspepsia, albeit with much overlap.

Abnormal Gastric Motility

Abnormal mobility of the stomach and duodenum is suspected to underlie functional dyspepsia (FD), of which delayed-gastric-emptying variant has been the most commonly described as the most common variant.3 Other types of motor abnormalities seen in patients with FD include abnormal phasic fundic contractions, abnormal gastric myoelectrical rhythm, and antro-duodenal dysmotility.

Gastric scintigrams have shown that the distribution of ingested solid food in the stomach differ significantly between healthy subject and patients with FD. While most of the food accumulates in the fundus in healthy subjects, even in the upright position, it is seen to move down and collect in the distal stomach in patients with FD, suggesting impairment in accommodation reflex.4 The reasons for this difference are not clear and raise suspicion of the role of genetic factors.

Another important development in recent years has been the recognition of a distinct clinical entity called post-infectious FD. Besides H. pylori other microbial infections have also been implicated in pathogenesis of FD. The frequency of FD was found to be increased fivefold over controls at 1 year after acute Salmonella gastroenteritis.5 Further studies are needed to identify the underlying pathophysiology and risk factors, and define the long-term prognosis of post-infectious functional dyspepsia.

FD is commonly associated with chronic allergic disorders. Gastrointestinal symptoms are significantly more common in patients with asthma or allergic rhinitis.6 The underlying mechanism may be due to activated mast cells that increase excitability of enteric neurons leading to abnormal gut sensory and motor function.

A number of psychological and personality factors have also been observed, including somatization, depression, and anxiety as well as health-seeking behaviour. Till date it is still unclear whether these psychological factors are cause or effect of FD. Studies of the efficacy of psychological therapies in functional dyspepsia remain, to date, inconclusive.

Genetics and Functional Dyspepsia

There is growing evidence that genetic factors may contribute to the etiology and clinical manifestations of FD. They come from studies based on familial aggregation, twin studies and genetic epidemiological studies focusing on gene polymorphisms. Familial clustering is often seen and several genotype associations with FD have been reported6,9 although their phenotypic correlations have not been always consistent. The inconsistency might be explained by the differences in the genotype composition of populations in different countries with different racial groups or by varying environmental factors. Some of the candidate genes which have been studied so far include G-proteins, serotonin transporter protein, interleukin 17 (IL-17) and migratory inhibitory factor (MIF). The most robust association with functional dyspepsia has been reported with GNb3.10,11 However while interpreting the results of these studies it is important to note that they may not be applicable to all groups of populations as these studies come from specific countries and have been done on small numbers.

Another source of confusion is the varying inclusion criteria for these studies as the definition of FD has undergone considerable change from time to time and therefore may have included phenotypically different variants of FD. There have been no studies that have tried to look at pharmacogenetics and response to treatment. Also there is requirement for a genome wide association study for FD.

Treatment

Currently, the possibilities of pharmacological therapy for FD are somewhat limited. In the backdrop of a diagnosis based on only symptoms, wide phenotypic heterogeneity, and ill-understood patho-physiological mechanisms, several agents have emerged and quickly disappeared because of either side-effects or disappointing lack of effectiveness. Classically acid suppression, mucosal protective agents, prokinetics, anti-depressants and H. pylori eradication have been used for treatment. Most of these agents have either minimal or transient effect on FD. Moreover the number needed to treat (NNT) by these agents is usually high.12 Therefore there is a need to develop new drugs which target multiple pathways involved in pathogenesis of FD. Novel targets in the treatment of FD are impaired gastric accommodation and visceral hypersensitivity, and explore the use of fundic relaxants or visceral analgesics.

Newer Prokinetic Drugs

5 HT4, receptor agonists

Tegaserod, a partial 5-HT4 receptor agonist, was found effective in relieving symptoms in a large randomized controlled trial in women with dysmotility-like functional dyspepsia but had to be withdrawn from the market because of increased
incidence of cardiovascular ischemic events. Mosapride is now an established drug for functional dyspepsia in our country but in Europe it has failed to show efficacy over placebo. Prucalopride is a new drug of class of 5-HT4 receptor agonists known as benzofurancarboxamides. This drug is mainly used in chronic constipation and it enhances gastric emptying as well as small bowel and colonic transit and has been approved in Europe for the treatment of chronic constipation in women who fail to respond to laxatives. Its efficacy in dyspepsia is still uncertain.

Naronapride (ATI-7505) is derived from cisapride, with modifications aimed at eliminating the HERG channel and still uncertain.

for chronic constipation and there is currently no published information on their efficacy in FD.

The 5-hT1a receptor agonist buspirone, introduced originally as an anxiolytic drug, relaxes the proximal stomach in a dose-dependent manner. Newer members of this family like tandospirone, has shown improvement in upper abdominal pain and discomfort in placebo controlled trial. The improvement in anxiety scores did not differ between both treatment arms, suggesting that anxiolytic effects do not account for the therapeutic benefit. R137696, a novel 5-HT4 receptor agonist also initially showed a dose-dependent relaxation of the proximal stomach in healthy subjects that a subsequent Phase IIA study failed to substantiate in a group of 53 FD patients with impaired accommodation or hypersensitivity to gastric distension. Clonidine, which activates presynaptic inhibitory receptors on cholinergic nerve endings in the stomach, may improve gastric accommodation but has not been studied for functional dyspepsia till date.

**Acotiamide**

Acotiamide is a carboxamide derivative compound that acts by blocking presynaptic muscarinic (mainly M1 and M2) receptors on cholinergic nerve endings and thus blocks cholinergic negative-feedback inhibition. It also acts centrally through decreasing expression of neuropeptide U, GABA receptor and GABA transporter gene. In healthy volunteers, acotiamide 100 mg t.i.d. did not alter gastric emptying or nutrient tolerance. In patients with FD, acotiamide showed mixed results. In some studies where gastric emptying was measured by breath test, it showed no significant improvement while in an ultrasonography study it demonstrated enhanced gastric emptying. Gastric accommodation, on the other hand, was found to be enhanced by acotiamide (100 and 300 mg, respectively) as assessed with the barostat and ultrasonography. Extensive analysis showed improvements in the overall symptom score as well as specifically for symptoms of early satiety, upper abdominal bloating, postprandial fullness and nausea. The 50 and 100 mg doses showed significant improvement in some domains of the SF-36 quality of life questionnaire. In a small Phase IIA randomized controlled study in Japan, 127 FD patients were randomized into four groups: placebo, 50 100 or 300 mg of acotiamide t.i.d. for 4 weeks, in which the drug improved functional dyspepsia in doses of 100 and 300 mg. In a larger study from US, 404 patients who had not responded to a proton-pump inhibitor therapy were randomized to placebo, 300, 600 or 900 mg of acotiamide t.i.d. for 12 weeks. Acotiamide in dose of 300 mg dose was found to be effective in improving symptoms and quality of life, especially during the first 4 to 6 weeks. In two larger Phase II studies (evaluating 50, 100 and 300 mg) in Japan that enrolled 425 and 731 FD patients respectively, acotiamide marginally improved overall symptoms. As benefit was noted in symptoms of postprandial distress syndrome (PDS), a Phase III study was undertaken in Japan with focus meal-related FD symptoms (PDS). All these studies suggest that acotiamide provides symptomatic benefit in functional dyspepsia patients, and this beneficial effect is most consistently found with the 100 mg t.i.d., and primarily involves the PDS symptoms of postprandial fullness, early satiety and upper abdominal bloating. Overall, acotiamide may be the first drug to be approved for the treatment of FD.

Although nitrates, sildenafil and sumatriptan, can relax the proximal stomach, they seem less suitable for therapeutic application in FD. Visceral hypersensitivity is another attractive target for drug development. The principal drug classes under evaluation are neurokinin receptor antagonists and peripherally acting k-opioid receptor agonists (fedotozine). Also alternative therapies have recently shown some promise and include certain

Fundus Relaxant and Visceral Analgesic

**5-HT4 receptor agonists**

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herbal preparations (example Iberogast), psychotherapy, hypnotherapy and acupuncture. These novel approaches are in a nascent stage and data is limited. There is a need for large multicentric randomized controlled trials with these approaches to reach any definitive conclusion.

**H. pylori and Functional Dyspepsia**

Recent studies have suggested that a subset of patients develop FD after a gastrointestinal infection suggesting the concept of post-infectious FD. A number of trials have been published showing the high prevalence of H. pylori in patients with FD. H. pylori infection causes gastric mucosal inflammation leading to alterations in many cytokines and chemokines in gastric mucosa. For this reason, one of the major research interests has been to study the differences between H. pylori-associated dyspepsia and other FD. H. Pylori infection induces inflammatory changes in the gastric mucosa, in the gastric muscular layer as well as in the duodenum. However, most patients with H. pylori infection do not have symptoms. Therefore there is need to conduct further investigation about the true relationship between dyspepsia symptoms and H. pylori infection to determine when and how symptoms arise.

Presently FD is classified into two types based on symptoms into epigastric pain syndrome (EPS) and post-prandial distress syndrome (PDS). Some authors have proposed a new etiological classification for functional dyspepsia based on presence or absence of H. pylori infection. They suggest that as the management of patients with H. pylori and dyspepsia is different as compared to classical FD, it should be classified as a separate entity. However on the other side FD and H. pylori are so common that a lot of overlap may occur between these two conditions.

Another important aspect of H. pylori is whether dyspepsia should be an indication for eradication of this bacterium. There have been several studies trying to answer this difficult question with varying conclusions. It appears that H. pylori eradication therapy is effective only in a sub-set of population of FD who have the infection. A metaanalysis of randomized controlled trials showed that H. pylori eradication therapy appears to have a small but statistically significant effect in H. pylori associated dyspepsia. The efficacy of eradication therapy for dyspepsia in Asia is however expected to be different from those in Western countries, as prevalence rates in the population, cagA gene polymorphisms, levels of acid secretion in the stomach and the severity or pattern of gastritis differ vastly, further reducing the chances of a favourable outcome.

**Functional Dyspepsia: Research Design**

In spite of a plethora of published reports on the pathophysiology and treatment of FD, predictable effective therapy for this condition is still not available. This may represent several methodological shortcomings of trials including unclear underlying mechanisms, inaccurate classification of patients, failure to use appropriate patient response outcomes, and the absence of objective end-point in clinical protocols. Therefore there is a strong need to modify the clinical protocols. Firstly all the patients included in research trials should not only fulfil standardized validated criteria (like Rome 3), but should be further subdivided into the EPS and PDS. These two categories of FD have different pathophysiological mechanisms and therefore may differ with regard to treatment approaches.

Presently standard questionnaires are used to differentiate between the two types. However questionnaires alone may not always suffice. Theoretically, technologies now available, such as gastric emptying scans, magnetic resonance imaging, and single photon emission computed tomography (SPECT) that may further refine and help distinguish the FD subgroups. Another handicap is the lack of an objective instrument to assess the severity FD. There are many tools which may serve covariates in the assessment of outcomes based on patient responses. Important among these tests are nutrient drink test, gastric emptying by scintigraphy and gastric emptying by stable isotope breath test. Inclusion of these tests in clinical trials will add more objectivity and reproducibility to the symptom-based questionnaires that are being presently used.

**Conclusion**

Management of FD is a major challenge in today's medical practice. Despite recent studies on pathogenesis of this disorder, the exact mechanism is still not clear. Studying the pathophysiology may help understand the processes that underlie the patient's complaints although direct correlation to symptom severity may still remain a challenge. The role of subcategorization patients based on altered physiology, seems to be emerging, which may allow more accurate assessment of response to therapeutic agents. The development of pharmacological treatment for FD is challenging.

Further, end points of dyspepsia studies are difficult to define as measurements of outcome by current patient-reported questionnaires may not be sensitive enough to detect treatment efficacy despite validation. Complementary therapies such as herbal medicine and hypnotherapy require further validation.

**References**


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