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EDITORIAL

Reassessment of functional dyspepsia: A topic review

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Abstract

Dyspepsia itself is not a diagnosis but stands for a constellation of symptoms referable to the upper gastrointestinal tract. It consists of a variable combination of symptoms including abdominal pain or discomfort, postprandial fullness, abdominal bloating, early satiety, nausea, vomiting, heartburn and acid regurgitation. Patients with heartburn and acid regurgitation invariably have gastroesophageal reflux disease and should be distinguished from those with dyspepsia. There is a substantial group of patients who do not have a definite structural or biochemical cause for their symptoms and are considered to be suffering from functional dyspepsia (FD). Gastrointestinal motor abnormalities, altered visceral sensation, dysfunctional central nervous system-enteral nervous system (CNS-ENS) integration and psychosocial factors have all being identified as important pathophysiological correlates. It can be considered as a biopsychosocial disorder with dysregulation of the brain-gut axis being central in origin of disease. FD can be categorized into different subgroups based on the predominant single symptom identified by the patient. This subgroup classification can assist us in deciding the appropriate symptomatic treatment for the patient.

Key words: Dyspepsia; Epidemiology; *H pylori*; Subgroups; Cholecystokinin; Visceral hypersensitivity; Psychosocial; Central receptors; Therapy

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Functional dyspepsia (FD) is a heterogeneous disorder of yet unknown etiology. It is commonly encountered both in the primary practice as well as the gastroenterological outpatient clinic. Though never life threatening, FD has important social and economic implications. It is an important cause of job absenteeism and a major burden on health care services. The review article by Sanjiv and Goh[1] in this topic highlights reported that 20% of patients would have consulted either a general practitioner or a gastroenterologist, 50% would be on medications most of the time, 30% would have days off work or schooling and there is a definite reduction in the quality of life. They also maintain that proper epidemiological studies on dyspepsia is plagued with problems without agreed definitions on "dyspepsia", but the recent definition based on the Rome II working committee report has helped. It is also important to distinguish between the patients who present with dyspepsia that is uninvestigated (UD) and the true functional dyspeptics. Prevalence rate of UD varies across the world depending on the definition of dyspepsia used. When Rome II criteria were used, studies showed that approximately 25% of people in the community complain of UD. For FD the rates are still quite variable depending on the geographical background, varying from 11.5% to 29.2%.

Majority of patients with a diagnosis of FD continue to be symptomatic over long period of time despite periods of remission. Approximately one-third of the patients lose their symptoms spontaneously. Only some dyspeptics present for medical care, in the United States and United Kingdom 1 in 4 will consult but the figure is higher in Australia. Severity of pain and anxiety over the possibility of serious diseases are factors associated with consulting behaviour. In their review the authors also considered various risk factors that may be associated with UD or FD. It appears that being a female and having underlying psychological disturbances will predispose one to having FD. On the other hand, smoking, caffeine intake, poor socioeconomic status and NSAID (non-steroidal anti-inflammatory drugs) ingestion placed one at risk from developing UD.

Does the ubiquitous bacterium, *Helicobacter Pylori* (*H pylori*) have any role to play in FD? Most authors will agree that the evidence is still unclear and most *H pylori* eradication trials in FD have been badly designed and gave conflicting results. However in the reviews by both O'Morain and Malfertheiner[2,9], evidence were provided of well conducted randomized control trials and meta-analysis, showing a small but significant effect in eradicating *H pylori* in dyspeptic patients. O'Morain further suggested that *H pylori* associated dyspepsia is related to acid secretion. *H pylori* infection resulted in increased fasting and post-prandial serum gastrin levels and decreased gastric mucosal levels

of somatostatin. Of more significance is the fact that these abnormalities were corrected following eradication therapy. Furthermore, an intravenous infusion of gastrin-releasing peptide causes a six-fold increase in acid secretion in *H pylori* peptic ulcer patients, a four-fold acid increase in *H pylori* FD patients and a two-and-a-half fold increase in asymptomatic *H pylori* infected individuals, compared to asymptomatic controls without *H pylori* infection.

Most authors would agree that, *H pylori* when discovered needs to be eradicated to prevent gastric ulcer and reduce the risk of gastric cancer. It will be interesting to see in the long term, if the eradication of *H pylori* does any harm. Recently it has been suggested that eradicating the bacteria in susceptible individuals, may predisposed them to develop reflux oesophagitis , which can lead to Barrett's oesophagus and oesophageal carcinoma. Whether it is cost-effective to conduct a "test and treat" or "search and treat" strategy and on which population is still debatable. A lot of it will depend on the resources available to the individual community.

Interestingly, it has also been reported that *H pylori* FD patients are less likely to show evidence of dysmotility or delayed gastric emptying. However it has consistently been shown that approximately 50% of FD patients have some kinds of gastric motility disorder, the most common of which is delayed gastric emptying. Doubts still remain as to the relationship between gastric dysmotility and dyspeptic symptoms. Symptoms may be caused as a direct result of the abnormal motility or arises secondarily from the effect of the abnormal gastrointestinal propulsion, or a combination of both.

The subdivision of dyspepsia into subsets according to symptoms clusters remain controversial but are widely practiced[3]. Two main subgroups were widely recognized: "ulcer-like dyspepsia" and "dysmotility-like dyspepsia". Ulcer-like dyspeptic patients usually complain of upper abdominal pain while dysmotility-like dyspeptic have symptoms very suggestive of impaired gastroduodenal motility. However it has now being realized that the subgroup classification according to symptom clusters suggested thus far is of no clinical utility. More recent suggestions for a new classification is based on the most bothersome or prominent symptom presented by the patient. Newer trials seem to support the existence of such grouping in that severe postprandial fullness and vomiting were independently associated with delayed gastric emptying, while impaired gastric accommodation is linked to early satiety. Furthermore response to proton-pump inhibitors was better in the subgroup of patients with epigastric pain rather than discomfort. However there is also published data that does not agree with the above mentioned observation. This new sub-grouping will need to be assessed further before it can be widely used. Patients who have heartburn as their predominant symptoms are generally accepted to have gastro-oesophageal reflux disease and not dyspepsia. They may have erosive or non-erosive oesophagitis and even "functional heartburn". Similarly patients with lower gastrointestinal symptoms probably fall in the domain of irritable bowel syndrome (IBS) rather than FD.

A "hypersensitive" gut is now considered as the main pathophysiological factor underlying the functional bowel disorders. Patients suffering from the irritable bowel syndrome (IBS) have a lower threshold for pain especially during endoscopy and digital examination. Similarly FD patients demonstrate an increased sensitivity to gastric distension at lower distending pressures when compared to normal healthy controls. Other investigators have also shown that patients with FD respond abnormally to an infusion of lipid into the duodenum. The observed abnormality was due to the effect of CCK released locally causing gastric sensorimotor dysfunction. CCK's influence is exerted either locally on CCK mucosal receptors or at a distance on CCK receptors located on sensory afferent fibers or CCK receptors located in central circuits of the CNS. However it is also conceivable that the effect of the CCK is not from the increased level of circulating CCK but rather due to an altered response of the CCK receptors. In this respect we have demonstrated that FD patients respond abnormally to an infusion of CCK octapeptide[5]. CCK infusion reproduced the dyspeptic symptoms which can be blocked by atropine and loxiglumide. End organs (sensory receptors) present in the mucosa, muscle layer or serosa may respond abnormally (hypersensitive) to an external stimuli. The enhanced sensory perception may also result from an alteration of ascending sensory afferent neurons (vagal or spinal afferents) and perhaps from central amplification of visceral signals. Interestingly the presence of CCK receptors has also been demonstrated at all the above sites.

Keohane *et al*[4] suggested in their review that apart from visceral hypersensitivity, visceral hyperalgesia and viscero-somatic referral also play important roles in FD. In viscero-somatic referral the offending stimulus will elicit pain at a site distant from the site of application. Visceral hyperalgesia is the phenomenon whereby the application of an ordinary innocent stimuli result in pain. Hyperalgesia consists of both peripheral and central components, initiation and continuance of which contribute to the observed altered sensations that is so prominent in FD. It is possible that an acute visceral insult may recruit or sensitize sensory receptors or fibers, which even after the insult has subsided, will result in long term consequences of sensory-motor disturbances so characteristic of FD. It is proposed that altered mucosal mechano- or chemoreceptor may contribute to an exaggerated response to the CNS, when exposed to the presence of normal food content. Conceptually CCK and serotonin will be released from endocrine cells in the presence of normal luminal contents, which then act on their respective receptors to generate an abnormal response which when presented to a normal functioning CNS may be interpreted as inappropriately painful.

The CNS-ENS (brain-gut axis) interaction is vital in the pathophysiology of FD. As suggested by O'Mahony *et al*[5] and Chua[6] in their review, the dyspeptic symptoms may result from altered interactions at any level of the brain-gut axis. The CNS plays a central role in conducting and processing visceral signals. Alterations in brain processing of pain, perception and affective responses may be important in the pathogenesis of dyspeptic symptoms. The finely regulated motor, sensory and secretory activities of the GI tract are coordinated by the interactive actions between the CNS, autonomic system (sympathetic and parasympa-

thetic) and the ENS. Both the central serotonergic (5HT) and adrenergic (AD) systems play important roles in this interaction.

Central serotonergic pathways are important in the control of nociception. Depending on the receptor subtype activated, the response could be pro or antinociceptive. The antinociceptive effects of serotonin are dependent on noradrenaline being release by the serotonin. Similarly central adrenergic receptors play an essential role in the regulation of gastrointestinal motility. Activation of central alpha-2 (NAD) receptors mediates the inhibition of GI function. NAD neuronal input to the paraventricular and supraoptic nuclei in the hypothalamus arises from cell groups in the brainstem, all of which receive directly or indirectly visceral sensory input from the vagus and glossopharyngeal nerves. The paraventricular nucleus has output nerves to the brainstem and spinal cord which are important in regulating feeding and GI function.

Peripherally serotonin is well recognized for its effects on GI motility and secretion. Whether central serotonergic systems play the same role remains unclear. 5HT neurons in the pons and medulla contribute to the innervations of the paraventricular nucleus which influence autonomic and neuroendocrine function. The paraventricular nucleus also projects to the dorsal motor nucleus where vagal efferent neurons that control the stomach are located. Interestingly it has been shown that hypersensitive central 5HT receptors are associated with delayed gastric emptying and an abnormal response to CCK-8 infusion in FD. Furthermore the dyspeptic symptoms in FD can be reproduced by the CCK-8 infusion. The hypersensitive CCK receptors as mentioned earlier, under physiological condition of CCK release, may be stimulated and activate a vago-vagal reflex pathway that results in GI sensory-motor dysfunction and feeding abnormality.

FD has been shown to demonstrate hypersensitive central 5HT receptors while their central alpha-2 (NAD) receptors appear to be down regulated. Serotonergic and noradrenergic pathways may have opposite effects on feeding behavior and GI sensory-motor function. NAD stimulation of the paraventricular nucleus elicits feeding behavior that can be antagonized by local pretreatment with serotonin. The anorexic effect of CCK is dependent on central serotonergic pathways. It is possible that both the serotonergic and noradrenergic pathways may mediate the CCK effect in FD in an antagonistic way, serotonergic pathways being excitatory while the noradrenergic pathways are inhibitory. The observed sensory-motor abnormalities may be the result of a final pathway that originated in the sensitized peripheral receptors and afferent vagal pathway, modulated centrally, and the efferent pathways from the dorsal motor nucleus results in perturbation of peripheral GI function.

A biopsychosocial model to explain FD has been proposed, whereby biological, psychological and social factors interact to account for patient's symptoms, behavioral response and disease outcome. The brain gut axis plays a central role in mediating this interaction. FD can then be seen as a result of dysregulation of intestinal motor, sensory and CNS activity, resulting from interruptions at some level of the brain gut axis.

Stress, a commonly seen factor in precipitating symptoms in FD, may aggravate symptoms by its effects on the CNS. Acute or short term stress may result in delayed gastric emptying or other sensory-motor disturbances which are present in FD. Psychosocial factors as suggested by Dinan *et al*[7] in this topical review may be implicated in the predisposition, exacerbation and perpetuation of functional bowel disorder (FBD) including FD. Different types of stressors may play different roles in the pathophysiology of FBD. Early life stress and acute life-threatening situations are strong risk factors for developing FBD in the genetically predisposed individual, later on in life. Other stressors occurring throughout life transiently may cause intermittent changes in the stress response so as to cause symptoms exacerbation. Conceivably, psychological stress may affect peripheral sensory-motor function through an effect on central processing circuits. Similarly physical stress such as infection and trauma may contribute to and aggravate symptoms, and in the vulnerable to perpetuate symptoms.

Corticotrophin-releasing factor (CRF) has long been believed to have a physiological role in the mediation of CNS response to stress. CRF is also involved in reactions that coordinate and modulate the autonomic, behavioral, and visceral responses of the CNS to stress. Dinan *et al* suggested that CRF may act via central connections known as the emotional motor system (EMS). Ascending monoaminergic projections and circulating glucocorticoids has a feedback control on output fibers from the EMS that modulate a peripheral response which involves the neuroendocrine, autonomic and endogenous pain control pathways.

A number of psychological factors have been linked to FD. These includes psychological stress, personality traits, social support, life-events and life-stresses including abuse and bereavement. Barry *et al* have elegantly debated through each factors and their association to FD in their comprehensive review. The suggestion that psychological morbidity and social stressors merely motivating health care seeking measures has been challenged.

Similar to patients with FD, individuals with IBS have a higher rate of psychiatric comorbidities. The two entities though regarded as separate disorders have many similarities and overlapping symptoms. Both seem to have a genetic predisposition, prior infection or inflammation may contribute to its pathophysiology, while stress, life events and history of previous abuse play important roles in the progress and manifestation of these two chronic diseases. It is relatively easy for IBS patients with upper abdominal pain to be misdiagnosed as FD. This problem seems to be greater in Asia as Asians tend to present more commonly abdominal pain, according to Gwee *et al*[8]. In his review, one important reason for differentiating IBS from dyspeptic symptoms is to avoid unnecessary surgery. In patients with concomitant FD and IBS (FD-IBS), the risk of cholecystectomy is much higher compared to either FD or IBS alone. One interesting fact highlighted by Gwee *et al* is the observation that overlapping FD is more commonly seen in IBS with constipation. Moreover delayed gastric emptying has been reported in IBS patients with concomitant FD but not in those with IBS alone. Further-

more it has been shown that dysmotility-type FD is more likely to be associated with constipation type IBS. Though impaired accommodation to a meal is as prevalent in FD alone compared to FD-IBS, visceral hypersensitivity is significantly higher in FD-IBS patients. Post infectious IBS has generally being accepted as an entity while recent reports also suggested that FD could develop post-infection with delayed gastric emptying and impaired accommodation. The infectious agent could be viral in origin while a recent study reported dyspeptic symptoms post salmonella gastroenteritis.

FD does coexist with IBS and a substantial proportion of FD patients will evolve into IBS with time. Whether it is important to differentiate between FD and IBS remain to be seen. Clinically it is common practice to use combination treatment for both, suggesting that perhaps considering them as a single disorder may be more practical.

The response to drug treatment remains variable and uncertain. Monkemuller *et al*[9] in their review suggested an approach that deals with patients' predominant symptom. If the predominant symptom is epigastric pain or presence of gastroesophageal reflux, then an acid suppressive therapy should be considered with the proton-pump blockers. If *H pylori* is present, it should be eradicated. If the main symptom suggest dysmotility type FD then prokinetic agents can be considered. Cisapride and domperidone has been widely used and quite effective, until cisapride was removed due to cardiac side-effects. Other prokinetics such as erythromycin, tegaserod and alosetron has produced inconsistent results. Newer agents including itopride hydrochloride (ganaton) and mosapride may provide better results. A recent multicentre randomized controlled trial was published in the NEJM by Holtman et al showing the effectiveness of Itopride in relieving symptoms in FD. Loxiglumide, a CCK receptor antagonist has been shown in a small study to be effective in dysmotility-like dyspepsia, but this needs to be repeated in a bigger randomized controlled study. Antidepressants like the serotonin re-uptake inhibitors (SSRI) and amitryptalline will be useful in treating FD with psychological overlays. The success of this treatment strategy may also be attributable to the effects of these drugs on central pathways. The SSRIs act on central as well as peripheral 5-HT receptors while amitryptalline effects may be *via* central alpha-2 receptors. Hypnotherapy is effective in IBS but its role in FD remains to be seen. It is not widely available and very time consuming. Most studies looking at drug therapy in FD are plagued by the high placebo response. This could be accounted for by the significantly greater attention and time given to the patient by the researchers, with the attending investigations carried out per study protocol which could alleviate to a certain degree some of the anxiety, uncertainty or fear which the patients may have.

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