

Functional Dyspepsia: An Unresolved Issue

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Abstract

Functional dyspepsia (FD) is one of the commonest medical problems which affect the quality of life. Due to its global presentation variety of symptoms recorded, therefore no global consensus developed. The recorded symptoms of functional dyspepsia are nonspecific and the pathophysiology is diverse. The role of genetics in the susceptibility of FD is still not well established. The last Rome III criteria defined the FD as symptoms of epigastric pain or discomfort, early satiety and postprandial fullness with in the last three months with symptoms not less than six months. Patient cannot have any evidence of structural disease and predominant Gastro esophageal reflux symptoms. Failure to respond to 'test and treat approach' is also categorize as FD. A universally effective treatment for functional dyspepsia remains elusive. The purpose of this paper is to highlight the details in perspective of functional dyspepsia.

Keywords: Functional dyspepsia; Epigastric pain; Ischemic bowel disease

Introduction

Dyspepsia is a Greek word having two components 'Dys' means dysfunction and 'Pepsia' means related to digestion. The term was first used in mid-18th century and then it was used widely. It was thought to be a nervous disorder and is associated with hysteria and hypochondria. Historically the term 'dyspepsia' was used for a heterogeneous group of abdominal symptoms. The functional dyspepsia was defined as symptoms or set of symptoms related to the upper gastrointestinal tract without organic lesion. It is characterized by upper abdominal discomfort or pain, feeling of upper abdominal fullness, early satiety, belching and nausea. There is an overlap of symptoms, therefore a standardize definition that is acceptable to all populations remains controversial [1,2]. This review article highlights the different aspects of functional dyspepsia.

Prevalence of functional dyspepsia

The true prevalence of functional dyspepsia is difficult to determine in the population, due to difficulties in excluding organic disease in large number of people. The very few studies are country based, while majority of them are city or community based. In the USA (one institution based study) 29.2% of the general population have the problem of dyspepsia with reflux symptoms and 15% without reflux symptoms [3]. In the U.K (national based study) the prevalence of functional dyspepsia was 23.8% [4]. In a Norwegian (one municipality based survey) the dyspepsia was recorded in 14.7% [5]. In Japan (one city based study) the prevalence of functional dyspepsia recorded during the screening program of carcinoma of breast was recorded to be 17% [6]. In Balochistan a hospital based study revealed that the functional dyspepsia was recorded in 38.9%. [7] In Taiwan (health check attendees based study) the prevalence of functional dyspepsia recorded was 23.8% using Rome 1 criteria, while 11.8% using Rome II

criteria [8]. With the data that is available the true prevalence of functional dyspepsia globally is estimated between 11.5-29.2% [9].

The misconception about the dyspepsia is that it turns into cancer. It is estimated that 10% of all health care expenditure in the U.K go towards treating dyspepsia. In the USA the cost of treating the dyspepsia was more than 2 Billion Dollars/year. In USA an average patient cost \$ 698/year [10].

Demography of functional dyspepsia

Age: Majority of the surveys conducted to determine the prevalence of dyspepsia show no relation to the age. The previous record of functional dyspepsia in Balochistan showed the most common age group was 31-40 years [7]. The functional dyspepsia in Chinese population was recorded in majority of people between the ages of 41-50 years [11] In Japan the most common age group recorded was 50-59 years [6].

Gender: A study conducted in Balochistan showed males (77.9%) and females (22.1%) were suffering from functional dyspepsia [7]. Many studies all over the world revealed that there is predominance of female, who suffered from dyspepsia [4,12]. Studies conducted in Taiwan and Australia revealed that females were more sufferer of functional dyspepsia as compared to the male [8,12]. Why female gender is more prone to functional dyspepsia needs to be elaborated.

Ethnicity: Most of the studies in different parts of the world on dyspepsia were almost a single nation or ethnic group. No single nation or ethnic group found to have more predominance of functional dyspepsia. Future studies are needed to find the differences in functional dyspepsia between various populations will enhance the global understanding of the condition and better inference will be drawn [13].

Dietary factors: The different studies in different regions of the world revealed various dietary factors as an etiological cause of functional dyspepsia. In Chinese study bad dietary factors was the significant risk factor [11]. In an Indian study the consumption of

vegetables, meat, spicy food and fried food had no significant correlation [14]. In surveys conducted in USA and Western countries the excessive use of tea and coffee has not been related to the dyspepsia [3,15]. Canadian study revealed that heavy intake cola was associated with increase dyspepsia [16]. Still more studies are needed to establish the role of diet in dyspepsia.

Socioeconomic Status: A study conducted in the USA revealed a strong relationship among the low socioeconomic class, increase number of family members with high prevalence of functional dyspepsia [17]. Similar results were also recorded in studies of China [11]. In another study it was concluded that dyspepsia in population of developing countries is mostly organic, while functional dyspepsia is more prevalent in Western nations [18].

Clinical diagnosis of functional dyspepsia

The clinical diagnosis of functional dyspepsia has passed through different evolutionary phases. The clinical diagnosis from 18th century to till date is still under debate. Over the last 20 years the definition of functional dyspepsia changed many times.

Rome I committee in 1991, describe dyspepsia as persistent or recurrent upper gastrointestinal discomfort. It was further classified as:

Dyspepsia with identifiable cause such as chronic peptic ulcer, reflux esophagitis, upper gastrointestinal malignancy and Hepatobiliary disease.

Dyspepsia with an identifiable cause of uncertain origin such as H. pylori gastritis, duodenitis, idiopathic Gastroparesis, gastric dysrhythmias and small bowel dysmotility. Dyspepsia with no explanation identified.

In Rome I dyspepsia with no explanation identified was termed as 'Functional Dyspepsia'. It was further sub classified as

Functional dyspepsia as ulcer like: It is mainly characterized by epigastric discomfort or pain. This is usually associated with empty stomach. The upper digestive endoscopy reveals absence of ulcer.

Functional dyspepsia dysmotility like: It is characterized by sensation of epigastric fullness, early satiety, eructation. The digestive investigations will reveal the absence of lesion.

Functional Dyspepsia nonspecific type

The diagnosis was made by the presence of symptoms present over a period of 12 weeks.

In 1999, the Rome I criteria was revised and Rome II criteria was introduced. The clusters of symptoms in subtype were changed into one predominant symptom that is most bothersome. The purpose of this is to identify the cause and to focus on treatment.

Functional dyspepsia as ulcer like: The most bothersome symptom is epigastric pain

Functional dyspepsia dysmotility like: The most bothersome symptom is abdominal fullness, which is related to early satiety, bloating or nausea.

The diagnosis was made by the presence of symptoms over a period of 12 weeks in last 12 months period, which needs not to be continuous.

In 2006, Rome III criteria were formulated because there were certain draw backs in Rome I and Rome II criteria. The criteria for epigastric pain and discomfort were varying. Some patient with little pain had exaggerated feeling, while other patients did not. The concept of predominant symptoms as suggested by Rome II is easily picked by the patients due to predominance of more than one symptom. The Rome III criteria were formulated as

Bothersome post prandial fullness: Occurring after ordinary sized meal, atleast several times per week.

Early satiety: Finishing the regular meal early, at least several times per week.

Epigastric burning or pain: Pain in the epigastrium of at least moderate severity once a week. The pain is intermittent, not generalized, not radiating, and not relieved by passage of flatus and no association with Hepatobiliary symptom. No evidence of structural diseases, excluded by upper gastrointestinal endoscopy. The symptoms must be present at least three months with onset at least six months prior.

In Rome III criteria, the various presentations of patients were further classified which were labelled as functional gastroduodenal disorders. There was an overlap of symptoms of Gastro-Esophageal Reflux Disease (GERD) and Irritable Bowel Syndrome (IBS). Finally the Rome III criteria the term epigastric discomfort was replaced by the terms of post prandial fullness or early satiety. Later these collectively termed as 'post prandial distress syndrome'. The epigastric pain with its typical characteristic called as 'epigastric pain syndrome' [19-21]. It is finally concluded that it is a complex condition without organic lesion, characterized by upper abdominal discomfort or pain, feeling of upper abdominal fullness, early satiety, belching and nausea (Tables 1 and 2). The functional dyspepsia subgroups based Rome III criteria needs validation in Asia because of an overlap of symptoms of irritable bowel syndrome according to Asian consensus group [1].

Age > 50 years
Anorexia and weight loss
Dysphagia or odynophagia
Vomiting
Anaemia
Occult faecal blood
Jaundice
Failure of several treatments
Strong history of familial cancer

Table 1: Dyspepsia with definitive underlies organic disorder.

Peptic ulcer disease
Gastro-esophageal reflux disorder
Cholelithiasis or Choledocholithiasis
Acute or chronic pancreatitis
Gastric neoplasm

Carbohydrate malabsorption (lactose, sorbitol and fructose)
Intestinal parasites (Giardia, Strongyloides)
Drug induced dyspepsia (NSAIDs, antibiotics, iron supplement, acetylsalicylic acid)
Systemic disorder like diabetes mellitus, thyroid and parathyroid disorder and connective tissue disorder.
Ischemic bowel disease

Table 2: Differential Diagnosis of Functional Dyspepsia.

Genetics aspect of functional dyspepsia

A lot of studies had been done to establish the cause of functional dyspepsia. Various genetic factors like G-protein beta 3 (GNB3) subunit C825T, serotonin transporter promoter (SERT-P) gene polymorphism, IL-17F, migratory inhibitory factor (MIF), Catechol-o-Methyl transferase (COMT) Geneva 1158 met, 779TC of CCK-1 intron 1, cyclooxygenase (COX-1), transporter receptor potential cation channel subfamily v member1 (TRPV1), regulated upon activation normal T cell expressed and secreted (RANTES) polymorphism found to be associated with functional dyspepsia. However the role of genetic in the susceptibility of functional dyspepsia is inconsistent and not well established.

The role of G protein beta3 (GNB3) subunit C825T was first reported gene to be associated with functional dyspepsia in USA, Germany, Japan and Netherland, [22] however studies in Korea revealed no association of G-protein beta 3 (GNB3) subunit C825T with functional dyspepsia and irritable bowel syndrome [23]. A significant association between first degree relative with dyspeptic symptoms and functional dyspepsia was found [Odd ratio (OR)=1.8, 95%CI; 1.05-3.0]. Further an increase [Odd ratio (OR)=3.4, 95%CI; 1.0-11.5] of dyspepsia with positive family history of indigestion [24]. These data indicates that genetic factors are differently involved in functional dyspepsia between different populations.

The association between SERT polymorphism and functional dyspepsia was explored in two studies; however they showed no significant association between them [25,26]. It was observed that IL-17 and migratory inhibitory factor (MIF) have an important role in the inflammatory response to *H. pylori* and may affect the development of functional dyspepsia in *H. pylori* infected subjects but there was no association of 779TC of CCK-1 intron 1 polymorphism with functional dyspepsia in US community [25]. Similarly 1676T allele carriers of cyclooxygenase-1 (cox-1) was associated with developing gastric ulcer but not associated with functional dyspepsis [27]. NPY-399C/T is associated with stress response and emotions but no correlation was found with functional dyspepsia [28].

Further studies are needed to confirm these data and to determine how genetic factors influence the clinical manifestations of the functional dyspepsia.

Pathophysiology of functional dyspepsia

The exact pathophysiology of functional dyspepsia is unknown. However a variety of mechanism has been suggested as possible etiological condition.

Gastric motility abnormality

- **Antral hypomotility:** It accounts for 25-40% of gastric motility abnormalities.
- **Impaired gastric accommodation:** Gastric accommodation is a reflex adaptation of the proximal stomach in response to food. It is mediated by the vasovagal reflex. It is influenced by the eating, antral distension and duodenal exposure to food contents. Failed fundic accommodation (a stiff gastric fundus) was found in 40% of the patients [29].
- **Disordered gastric electrical activity:** It accounts for 30% of gastric motility abnormalities. An alteration in the mechanoreceptor in the wall of stomach results in disordered electrical activity.

Visceral sensory abnormalities

Reduced motor duodenal response

- Duodenal lipid hypersensitivity
- Hypersensitive to intraduodenal acid

Psychological factors

- Depression
- Anxiety
- Somatization

Diagnosis of functional dyspepsia

Prior to investigational workup, patients with upper abdominal discomfort (dyspepsia like symptoms) are called 'Uninvestigated Dyspepsia'. The following investigations are performed to reach the diagnosis of functional dyspepsia and possible etiological factors.

Upper G.I endoscopy: Patients without symptoms relief after 6-8 weeks therapy should undergo for endoscopic examination. Although it has no role in diagnostic and therapeutic management of functional dyspepsia except to exclude the structural abnormality. It is costly. The usual indications for endoscopy are 'Alarm Symptoms' (Table 3).

Age >50 years
Family history of gastrointestinal tract malignancy
Weight loss >10 %
G.I bleed
Progressive dysphagia
Odynophagia
Recurrent vomiting
Palpable tumor
Jaundice

Table 3: Alarm Symptoms (Red Flags).

Gastric ultrasonography: It demonstrates impaired gastric accommodation. An abnormal accommodation of food in the antrum of stomach as compare to the proximal stomach. The impaired accommodation of the stomach is due to vasovagal reflex, which involves nonadrenergic and noncholinergic pathways. On the other

hand it is not recommended without clinical or biochemical evidence of pancreatic or biliary disease.

Gastric Barostat studies: It denotes patient with functional dyspepsia have a lower sensitive threshold of distension for the barostat inside the proximal region of stomach or duodenum. Barotesting is the gold standard for diagnosing the visceral hypersensitivity, but it is invasive and uncomfortable. Gastric accommodation studies, by gastric barostat and specialized scintigraphic technique not recommended routinely measuring the gastric volume. 5HT₃ receptors might be involved in the abnormal distension of the stomach in response to the fatty infusion in the duodenum.

PH Studies: Acid secretion is normal in patients with functional dyspepsia.

Single photon emission tomography: It is used to assess the intragastric volume. It is a simple method. The radionuclide is taken once by mouth. The gastric emptying is quantified. The fasting compliance of fundus is normal in functional dyspepsia, while after taking food it is impaired in one third of the patients. The feedback mechanism of the duodenum is also impaired. The volume determined cannot reflect the muscle activity of the stomach. It is highly operator dependent technique. Gastric scintigraphy is usually recommended in refractory postprandial distress syndrome.

Duodenal infusion of lipid: The duodenal infusion of lipid provokes the early symptoms of gastric dilatation in patients of functional dyspepsia. It is relieved by cholecystokinin receptor antagonist (Loxiglumide). CCK-8 (Cholecystokinin octapeptide) is used instead of lipid infusion to provoke the symptoms in patients with functional dyspepsia, but this does not affect normal individuals.

H. pylori Detection: Patients with documented functional dyspepsia may have *H. pylori* induced gastritis in 30% of patients. There is no correlation between *H. pylori* and functional dyspepsia [29]. *H. pylori* detection is usually done by Urea breathe test and stool antigen test.

When these conditions are excluded through appropriate investigations the patient is diagnosed as a case of functional dyspepsia.

Treatment

Proton pump inhibitors (PPI): Acid suppression is the first line treatment to treat the functional dyspepsia even in the absence of *H. pylori*. In a meta-analysis study it was revealed that pain in the epigastrium was relieved but the other symptoms had not improved [30].

Histamine receptor blockers (H₂RB): In a meta-analysis study it was revealed that H₂ RB was superior to the placebo in the treatment of functional dyspepsia. Larger studies evaluating the dose and duration of therapy are needed to verify its effect. The benefit of epigastric pain relief was observed but it had no statistical significant [31].

Prokinetic agents: When delayed gastric emptying suspected prokinetic agents like Cisapride, Domperidone, Metoclopramide, Tegaserode (5HT receptor agonist) and Itopride (D₂ antagonist). The most commonly used is Domperidone in a dose of 10 mg three times a day. This may improve the symptoms even if the gastric emptying is normal. The reason needs more studies.

Antidepressant: Low dose tricyclic antidepressant therapy may be helpful in patients with difficulty in controlling symptoms. Low dose therapy of Imipramine 10 mg at night may have beneficial effects. The dose may increase to 50 mg. The exact mechanism how it is beneficial needs to be addressed.

H. pylori eradication treatment: Although the role of *H. pylori* in functional dyspepsia is not well established, however proton pump inhibitor is definitely better than placebo therapy in eradicating the *H. pylori*.

Erythromycin therapy: Erythromycin is a motilin agonist. It causes contraction of antrum and leads to emptying of the stomach. It is given in small dose of 100-150 mg thrice a day as orally in solution form or in injection. Initial therapy may help in improving symptoms but prolong use result in resistance. The Medicaid database study revealed that there was twice the risk of sudden cardiac death that uses Erythromycin as compare to those who are not using [32]. The data on clinical efficacy is still lacking due to lack of clinical trials.

Botulinum toxin injection therapy: Endoscopic injection of botulinum toxin into the pylorus improves the gastric emptying or symptoms of Gastroparesis. The response rate is 43% and it lasts about 5 months. However the safety of botulinum therapy is established but still more clinical trial are needed to prove its clinical efficacy in the treatment of Gastroparesis [33].

Visceral analgesia: Serotonin is a gut neurotransmitter. It reduces the gastric motility and induces satiety. Serotonin receptor antagonists are used to treat the functional dyspepsia. Somatostatin analogue Octerotide and Kappa receptor opioid agonist Fedotozine has been used in the treatment of functional dyspepsia but they were not found to be very effective. More studies are needed to prove its efficacy [34].

Herbal medicine: These are widely used in the community to treat dyspepsia. Iberogast is a herbal medicine containing extracts of nine plants including Iberis amara (Candytuft), Peppermint and Licorice used to treat dyspepsia. It relaxes the gastric fundus. In a double blind study it was proved to be effective [35]. Various other herbal and natural products are used for the treatment but the scientific proves are lacking.

Gastric electrical stimulation therapy: A subcutaneous electrical generator is surgically implanted with two electrical leads in the wall of antrum of the stomach. The low energy electrical stimulation leads to stimulation of afferent vagal pathway to the central nervous system and subsequent stimulation of the efferent pathway. The symptoms and quality of life was improved. The refractory cases of nausea and vomiting improved very much. However some patients required high electrical stimulation. The clinical trials are very few to establish the consensus [36].

Acupuncture: Three sessions per week for two weeks improved the symptoms of functional dyspepsia and quality of life.

Psychological therapies (selective serotonin reuptake inhibitor like Paroxetine, Venlafaxine), behavioural therapies (hypnotherapy) and complementary strategies have a beneficial role in the treatment of functional dyspepsia but trials needed to prove their effects.

The future prospects to treat functional dyspepsia under trials are neurokinin antagonist, corticotrophin releasing factor antagonist, opioid antagonist, Ghrelin and tetracyclic antidepressant (Mianserine). There is significant placebo response 40-60% in treating function dyspepsia.

Conclusion

Functional dyspepsia is a partially neglected entity because of absence of mortality. However the issues of quality of life and financial burden are not ignored. It is a fact that still in this modern era of technology the diagnostic and therapeutic options available for the treatment of functional dyspepsia are not up to the mark. The uses of different modalities of treatments are still not based on proven scientific basis. The quality of life is still an issue. The emerging theories and changing concepts of functional dyspepsia, we can say that “today’s wisdom may be the tomorrow’s folly”.

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