REVIEW

Functional dyspepsia assessment - current diagnostic methods and new promising techniques

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ABSTRACT

Functional Dyspepsia (FD) is a disorder of gut-brain interaction (DGBI) characterized by chronic symptoms without an organic cause. Diagnosis follows the Rome IV criteria, requiring symptoms for at least six months. FD affects up to 20% of the population, significantly impacting the quality of life and healthcare systems. Upper gastrointestinal endoscopy is often performed to rule out organic disorders but has limited utility in typical FD cases. FD's etiology involves gastric motility alterations, dysbiosis, and immune and central nervous system dysfunction. This review summarizes FD diagnostic methods. A PubMed search was conducted using keywords: Functional Dyspepsia, Gastric Motility Assessment, ROME IV, and Gastric Emptying (GE). Relevant studies were manually reviewed, excluding those unrelated to FD or gastric motility assessment. Despite extensive research on organic gastrointestinal diseases, FD's pathophysiology remains unclear, necessitating further studies. Diagnostic methods include the rapid water and nutrient drink tests for assessing impaired gastric accommodation, hypersensitivity, and delayed gastric emptying. Drinking-ultrasonography and three-dimensional ultrasound evaluate gastric motor and sensory functions. MRI-based assessments provide detailed stomach volume and geometry insights. Gastric emptying scintigraphy and the 13C-gastric emptying breath test measure gastric emptying rates. High-resolution electrogastrography (HR-EGG) assesses gastric myoelectrical activity, while EndoFLIP measures sphincter function. Functional MRI and PET scans analyze brain activity related to FD symptoms.

These methodologies enhance the understanding and management of FD by providing objective measures of gastric motility, accommodation, and sensory function. The integration of these advanced techniques into clinical practice holds the potential to move beyond symptom-based diagnosis, allowing for a more precise, individualized approach to treatment. Standardizing these diagnostic modalities will be crucial in optimizing patient care and alleviating the burden of FD on healthcare systems.

KEYWORDS: functional dyspepsia; gastric emptying; gastroparesis; gut-brain interaction

1. INTRODUCTION

Functional Dyspepsia (FD) is a DGBI with chronic manifestations, without an identifiable organic cause. The current diagnosis relies on Rome IV criteria, stating that the onset of the symptoms should be at least half year earlier. The prevalence of uninvestigated dyspepsia (UD) is up to approximately 20% in general population, with a minority of UD patients frequently addressing to the outpatient care unit for persistent or recurrent symptoms [1-2]. Therefore, FD is a significant healthcare problem with serious impact on the quality of life of the patients and an important burden for the healthcare systems worldwide. According to the definition, to exclude an organic disorder, upper gastrointestinal endoscopy should be performed. However, recent studies showed that its utility in patients with typical symptoms is minimal and it should be restricted to people of older age or to those with warning signs [3]. Gastric motility, dysbiosis, central nervous system, immune and mucosal impairment are considered to be involved in the etiology of FD [4]. Symptoms of functional dyspepsia may result from disrupted gastric motility, such as poor fundic accommodation or delayed gastric emptying, altered gastric sensation, including hypersensitivity to gas and bloating, or inflammation in the stomach and duodenum [5]. Given the fact that nowadays lots of research concerning organic gastrointestinal diseases are available, we assume that gut-brain axis disorders should be studied more thoroughly to obtain a clear understanding of its etiology and pathogenesis. This will lead to an improvement in their management and indirectly improve the quality of life of the patients.

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To assists a better management of FD this review summarizes the available diagnostic methods useful in FD management and methods that are used in gastric motility assessment that can be useful in FD evaluation. FD is known to be associated with: impaired gastric accommodation; hypersensitivity to gastric distension; and delayed gastric emptying [6].

2. METHODS

A comprehensive literature search was conducted in PubMed to identify studies related to Functional Dyspepsia (FD) and gastric motility assessment. The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms, keywords, and Boolean operators to ensure a thorough review. The following search string was used: (''Dyspepsia''[MeSH] OR ''Functional Dyspepsia''[Title/Abstract]) AND (''Gastrointestinal Motility''[MeSH] OR ''Gastric Emptying''[MeSH] OR ''Gastric Emptying Test'' [Title/Abstract]) AND (''ROME IV''[Title/Abstract] OR ''ROME Criteria''[Title/Abstract]).

No restrictions were applied to language, article type, or publication year to maximize the scope of relevant studies. Filters were applied to exclude non-human studies.

Inclusion criteria: (1) Studies that specifically investigated functional dyspepsia (FD) and its association with gastric motility assessment. (2) Studies that used validated diagnostic criteria, such as ROME IV, to define FD. (3) Articles discussing gastric emptying tests, gastric accommodation assessment, or other gastric motility evaluation methods. (4) Original research articles, systematic reviews, and meta-analyses providing clinical data on FD and gastric motility.

Exclusion criteria: (1) Studies that did not focus on FD or gastric motility assessment. (2) Studies investigating dyspepsia of organic origin (e.g., peptic ulcer disease, gastroesophageal reflux disease (GERD), or malignancies). (3) Articles solely focused on animal models or in vitro studies. (4) Case reports, editorials, commentaries, and conference abstracts that lacked primary research data. (5) Studies that did not provide detailed methodology regarding gastric motility assessment techniques.

Additionally, the reference lists of all relevant articles were manually reviewed to identify further studies that met the inclusion criteria. Last search conducted: 20 July 2024.

3. CURRENT ASSESSMENT METHODS

3.1. Gastric emptying scintigraphy

Gastric emptying scintigraphy (GES) has been employed for more than 6 decades to assess the speed of gastric emptying and has been widely accepted as the primary diagnostic method for identifying both rapid and delayed gastric emptying. Current guidelines suggest performing a 4-hour GES when gastroparesis is suspected in individuals experiencing symptoms like premature fullness after meals, feeling excessively full after eating, nausea, vomiting, bloating, and/or abdominal discomfort [7]. While GES is frequently employed in clinical settings, its clinical value is debated due to various issues, including inconsistent results, poor correlation between symptoms and gastric emptying rates, limited predictive value, and its inability to forecast the response to prokinetic medications. Recent technological advancements and efforts to standardize testing procedures aim to enhance the reliability of GES results, to increase its practicality in clinical practice [8]. In their clinical trial, Camilleri et al. proved that the 320-kcal (with 30% fat) GES test offers a reliable diagnosis of gastroparesis or FD in over 85% of cases and is recommended as the preferred standard test for suspected gastric emptying disorders [9].

4. NEW TECHNIQUES IN FD ASSESSMENT

4.1. The rapid water drink test or the load test

The water drink test was initially developed as a provocative examination to investigate symptom patterns and the capacity to tolerate a specific volume of liquid in the stomach among patients with FD. In the initial implementation of the rapid drinking test, 24 FD patients and 24 appropriate healthy volunteers (HV) were instructed to freely consume noncarbonated water at room temperature within a 5-minute timeframe. Concurrently, upper gastrointestinal symptoms and the occurrence of gastric arrhythmias were documented using symptom assessment surveys and electrogastrography, respectively. Though the paper fails to mention the demographic data of the patients and the HV, the result show that the patients diagnosed with FD tolerated smaller amounts, and achieved elevated symptom ratings for feelings of fullness, satiety, bloating, and nausea [10].

Boeckxstaens et al. included 25 HV and 42 FD patients who ingested aliquots of 100 ml of water per minute until a discomfort score of 5 was attained on a 0 to 5 scale. Following each 100 mL intake and at 1- and 2-hours post-test completion, upper gastrointestinal symptoms were evaluated. Notably, men consumed significantly larger volumes of water compared to women. Additionally, FD patients exhibited lower tolerance for higher volumes and reported higher and more persistent symptom scores during the water drinking test in comparison to HV. The rapid water consumption test involving 100 mL of water per minute until reaching either the highest discomfort score or the maximum water intake within a 5-minute period is straightforward and appears to be replicable. However, it is susceptible to gender and possibly body mass index variations. The drawbacks of the rapid water drink test include its unphysiological methodology, the utilization of a noncaloric stimulus and the subject's awareness of the ingested volume [11].

4.2. Rapid nutrient drink test

In Boeckxstaens et al. study rapid nutrient drink test was also used to evaluate patients with FD. FD patients and HV consumed quantities of 100 ml of mixed nutrient drink, until a discomfort score of 5 was reached. The ingestion pattern was similar to the rapid water drink test. In this study, FD patients manifested lower tolerance to this test in comparison with HV, while also reporting higher and more persistent symptom scores during the drinking test. The volume intake registered in men was significantly greater then in women. These findings coordinate with those of the rapid water drink test, but the tolerated volume of nutrient drinks was notably less than that of water [11].

Similar studies were performed by Hjelland et al. and Abid et al. [12-13]. The results corelate to the ones in rapid water drink tests, but the tolerated volumes were lower. Although the 5-point scale is easy to use and relatable to the one in rapid water intake, volumes of tolerated mixed nutrient drinks were significantly lower. Also, the

reproducibility of the studies could be difficult due to the mixed nutrient drinks composition and their ingredients which are in constant improvement and modification. Given this fact, it could be difficult to reproduce, since there are limitations in finding a nutrient drink with the same composition as the one used in older studies.

4.3. Satiety drinking test and slow nutrient drink test

The initial presentation of a slow nutrient drinking test dates to a 1998 paper addressing impaired gastric accommodation in FD [14]. The satiety drinking test was designed to assess GA noninvasively. Patients consumed a liquid mixed nutrient drink administered through an infusion pump at a gradual, constant rate until they reached the maximum satiety score, denoted as a score of 5 out of 6 on a 0–6 satiety Likert scale [14]. This approach aimed to blind the patient to the ingested amount. In the initial report on the satiety drinking test, patients drank significantly less than HV. The outcome was associated with impaired gastric accommodation but not with a decreased rate of gastric emptying [15]. Notably, a study compared the outcomes of a slow nutrient and a slow water drinking test, both administered at a rate of 15 mL/min, in 20 FD patients and 20 HV, revealing considerably lower volume tolerance in the patient group [16]. To reveal the impact of variable caloric density (1.5–2.0 kcal/mL) in the satiety drinking test Tack et al. [15] demonstrated that even with an intake of higher caloric rates the satiety scores did not significantly differ. These observations indicate that the satiety drinking test is inherently driven by volume, aligning with its purpose to quantitatively assess gastric accommodation [15].

4.4. Comparison of gastric relaxation and sensory functions between functional dyspepsia and healthy subjects using novel drinking-ultrasonography test

Hata et al. conducted a study in order to assess gastric motor and sensory functions using a novel ultrasonography drinking test. In this article were included 20 HV and 26 FD diagnosed according to ROME III criteria [17].

The drinking-ultrasonography test was conducted after a minimum of 6-hour fasting period. Throughout the drinking phase, subjects consumed 200 ml of water at 2-minute intervals, repeated four times (totaling 800 ml). The test ceased when subjects felt unable to ingest more. Emptying period assessment occurred 5 and 10 minutes after consuming 800 ml or discontinuation, marking the ending of the test. The cross-sectional view of the proximal stomach was observed through extracorporeal ultrasonography, utilizing the 10th intercostal space with the spleen serving as an echo window. The maximum cross-sectional measurement of the proximal stomach was captured before water intake, after each 2-minute interval of water consumption, and 5 and 10 minutes post the completion of the drinking test. Following image freezing, the ultrasonography system was employed to delineate the mucosal surface of the gastric lumen, and the subsequent computation of the cross-sectional area was carried out. During the period of water consumption, abdominal symptoms were appraised on five occasions using the visual analog scale (VAS). Assessments were performed both prior to the test and directly following each water ingestion, utilizing pre-test measurements as the baseline. Participants were specifically inquired about any impediments in drinking attributed to symptoms such as abdominal fullness and epigastric pain. Throughout the test, individuals autonomously completed a questionnaire, utilizing a numerical scale that ranged from 0 (indicating no difficulty) to 10 (reflecting the utmost difficulty).

The results of the study showed that the average cross-sectional area of the fornix following the ingestion of 800 ml of water was notably reduced in the FD group (75.2 ± 19.0 cm^2) in contrast to the control group (98.5 ± 23.7 cm^2). The proportions of the fornix's cross-sectional area at 5 and 10 minutes were 81.7 ± 14.8% and 69.6 ± 15.7%, respectively, in the control group and 86.0 ± 25.2% and 77.5 ± 28.4%, respectively, in the FD group. While no statistically significant differences were observed ($p = 0.272$) between the two groups, the average value of the fornix's cross-sectional area in the FD group surpassed that in the control group, indicating a potential delay in emptying in individuals with FD. In the FD group, noticeable symptoms, such as abdominal fullness and epigastric pain manifested immediately upon commencing water intake, and the VAS score tended to be elevated compared to the HV. The VAS score exhibited a significant difference ($p < 0.01$) between the control and FD groups at each assessment point indicating heightened sensitivity in the FD group [17].

4.5. Functional magnetic resonance (positron emission tomography – PET, functional magnetic resonance imaging – fMRI)

Functional magnetic resonance imaging (fMRI) is a technique used to analyze regional alterations in oxygenation and blood flow within the brain. It detects changes in the volume of active brain regions through BOLD (blood-oxygenation-level-dependent) signals, which indicate the relationship between MRI signal intensity and blood oxygenation levels. Variations in these signals occur due to fluctuations in deoxyhemoglobin levels, which can originate from changes in cognitive states during tasks or during resting periods [18]. Patients diagnosed with FD exhibit diverse irregularities in certain specific brain regions. Vandenberghe and colleagues conducted a study [19] on FD patients utilizing gastric balloons and noted anomalous activity in several brain areas. These included the precentral gyrus (on both sides), the inferior frontal gyrus (on both sides), the central frontal gyrus, the superior temporal gyrus, both hemispheres of the cerebellum, and the inferior temporal gyrus on the left side.

Researchers also explored disturbances in the resting state of FD patients. Van Oudenhove et al. demonstrated that psychosocial factors play a role in abnormal brain activity during rest in FD patients. Their investigations revealed that the activity of the pregenual anterior cingulate cortex (pACC) and anterior middle cingulate cortex (aMCC) exhibited a negative correlation with anxiety levels, whereas activity in the dorsal part of the pons showed a positive correlation. Additionally, they found that a history of abuse was linked to distinct activity patterns in the insula, prefrontal cortex (PFC), hippocampus, and corpus callosum [20-21].

5. GASTRIC EMPTYING ASSESSMENT METHODS THAT CAN BE USED IN FURTHER FD STUDIES

5.1 Magnetic Resonance Imaging (MRI) based assessment of stomach volume, surface area and geometry in response to gastric filling and emptying

Given the fact that MRI scans offer a great amount of high-quality information regarding soft tissues and does not imply high invasivity or significant side effects and risks, certain methodologies that are useful in gastric motility assessment can be of great value in FD evaluation.

Bertoli et al. (2022) studied the utility of MRI in the assessment of stomach volume, surface area and geometry in response to gastric filling and emptying.

In the study data were obtained from 12 healthy subjects, normal-weighted, without prior history of gastric disorders or other diseases affecting the gastrointestinal (GI) function. None of the subjects was treated with any medication that could affect the GI system.

After a minimum fasting period of 6 hours (abstaining from both solids and liquids), a baseline scan (at t: −30 minutes) was conducted in a transversal plane with the subjects in a supine position. Following the meal ingestion, subjects underwent scans at five additional time points (0, 15, 30, 45, and 60 minutes) using the same sequence as the baseline scan. The model successfully captured variations in volume, surface areas, and wall tension distribution in the fundus, corpus, and antrum. Distinct patterns were observed for each compartment concerning the changes in gastric variables during filling and emptying. Wall tension was found to be unevenly distributed among different compartments, exhibiting diverse dynamic changes throughout the emptying phase. Additionally, during gastric filling, notable changes in volume and surface area were predominantly observed in the fundus, emphasizing its function as a reservoir for undigested food [22].

5.2 Carbon-gastric emptying breath test

The 13C-gastric emptying breath test (13C-GEBT) is a non-invasive technique employed for evaluating gastric emptying (GE) of both solid and liquid substances. It utilizes various labeled compounds, like 13C-octanoic acid or 13C-spirulina platensis for solids, and 13C-acetate for liquids, to monitor their passage through the gastrointestinal tract [23-25]. Using this, researchers and clinicians have the capability to indirectly determine the GE time, which offers valuable insights into the transit duration of ingested substances through the stomach and small intestine [26]. The actual ACG clinical guideline regards the GE breath test utilizing 13C-spirulin as a dependable method for assessing GE in patients suspected of gastroparesis (GP). Additionally, the test has obtained approval from the FDA [27]. In a study led by Szarka et al. [28] comprising 129 patients with suspected delayed gastric emptying (GE) and 38 controls, the pairing of breath samples taken at 45 and 180 minutes demonstrated 93% sensitivity in detecting accelerated GE. Meanwhile, the combination of samples collected at 150 and 180 minutes exhibited 89% sensitivity for identifying delayed GE.

5.3 Evaluation of gastric emptying in patients with gastroparesis by three-dimensional ultrasound

Though the studies below refer to gastroparesis patients, we assume that three-dimensional (3-D) ultrasound assessment of gastric emptying could also be useful in FD patients due to the involvement of altered motility in this pathology. In their study, Shi et al. (2021) used gastric ultrasonography assisted by virtual organ computer-aided analysis (VOCAL) to assess gastric emptying in patients with gastroparesis. Though the study does not properly refer to FD, given the fact that in both cases gastric emptying can be altered, we assume that the used methods could be useful in FD assessment. In the study, three groups were enrolled: 21 HV, 46 diabetic gastroparesis patients, and 22 post-surgical gastroparesis patients. 3-D ultrasonography was performed after at least 12 hours of fasting. The study design included an oral contrast agent.

Following the administration of 250 mL of contrast agent by mouth, gastric volume scans were performed at 2, 30, 60, and 90 minutes after meals. The acquisition and volume calculation of 3-D ultrasound (US) were conducted using the Voluson E8 ultrasound system (GE Healthcare, New York, USA) and the VOCAL software (GE Healthcare). At the same time, the 3-D model was used to capture images of the stomach in the long-axis, short-axis, and coronal planes. Subsequently, the VOCAL software integrated into the ultrasound system was activated, and gastric shape curves were manually outlined on the long-axis plane at a 15° rotation angle. After 12 sketches, the VOCAL software automatically generated a 3-D reconstruction of the stomach along with its volumetric measurement. The research provided statistically significant results, showing an important difference in gastric residual volume between HV and diabetic gastroparesis patients [29]. Given that the methodology used in the study was effective in assessing gastric emptying, we assume that it could also be informative for FD assessment. However, studies including FD patients should be conducted to validate this method for investigating FD patients.

5.4 High-resolution electrogastrography (HR-EGG)

High-resolution electrogastrography (HR-EGG) has gained recognition as a valuable non-invasive tool for assessing gastric motility in patients with gastroparesis. This technique enhances the ability to detect gastric myoelectrical activity with greater accuracy. Studies suggest that individuals with gastroparesis often exhibit altered electrical patterns, characterized by one- to two-cycles-per-minute rhythms and a decrease in normal three-cycles-per-minute EGG activity compared to healthy individuals. A prospective international study found that patients suffering from chronic unexplained nausea and vomiting (CUNV) displayed slow-wave abnormalities, including disruptions in initiation (such as unstable focal activities and stable ectopic pacemakers) and conduction (such as wave-front collisions, retrograde propagation, conduction blocks, and re-entry) across multiple frequency ranges. By incorporating spatial mapping, HR-EGG has shown potential in precisely identifying gastric hypomotility in gastroparesis. This advancement paves the way for a more targeted and personalized approach to treating patients with the condition [30-34].

While these assessments have proven effective for gastroparesis, their applicability in evaluating gastric motility in functional dyspepsia (FD) should also be explored through further research involving FD patients.

5.5 Endoluminal functional lumen imaging probe

The Endoluminal Functional Lumen Imaging Probe (EndoFLIP Impedance Planimetry System, Medtronic, Dublin, Ireland) is an innovative and highly advanced technology that has significantly improved the evaluation of gastrointestinal sphincters. This system features a specially designed balloon, maneuvered endoscopically, which is equipped with 16 strategically placed on a catheter. These sensors can accurately measure essential parameters of GI tract sphincters, including intraluminal pressure, diameter, cross-sectional area and distensibility [35]. Though the EndoFLIP is mostly used in gastroparesis assessment and pre- and post-gastric peroral endoscopic myotomy G-POEM assessment, we assume it could also be useful in FD assessment, especially in the postprandial distress syndrome form.

An overview of the diagnostic methods discussed in this study is shown in Table 1.

CONCLUSIONS

Functional Dyspepsia remains a complex disorder with multifaceted pathophysiology, necessitating a precise and multimodal approach for accurate diagnosis and management. While traditional methods such as gastric emptying scintigraphy and endoscopy provide limited utility in routine FD assessment, emerging techniques ranging from drinking tests and ultrasonography to high-resolution electrogastrography and functional imaging offer promising insights into gastric motility, accommodation, and gut-brain interactions. The integration of non-invasive, standardized diagnostic tools will not only refine FD classification but also pave the way for personalized treatment strategies. Future research must focus on optimizing these diagnostic

Table 1. Overview of diagnostic methods presented in the study.

Method	Description	Findings/Utility	Limitations	References
Gastric Emptying Scintigraphy (GES)	The standard test for assessing the rate of gastric emptying using radioactive markers.	Widely accepted and reliable for diagnosing gastric emptying disorders; effective for FD diagnosis.	Inconsistent results; poor correlation with symptoms; limited predictive value.	[7-9]
Rapid Water Drink Test	Patients consume water rapidly and symptoms are assessed.	FD patients show lower tolerance for water, higher symptom scores compared to healthy volunteers (HV).	Gender and BMI variations affect results; unphysiological methodology; awareness of volume ingested.	[10-11]
Rapid Nutrient Drink Test	Similar to the water drink test but with a nutrient drink.	FD patients have lower tolerance for nutrient drinks and higher symptom scores compared to HV.	Differences in nutrient drink composition can affect reproducibility.	[11-13]
Satiety Drinking Test and Slow Nutrient Drink Test	Gradual consumption of a nutrient drink until maximum satiety score is reached.	FD patients drink less than HV, indicating impaired gastric accommodation.	Results are volume-driven, and the methodology may be hard to reproduce due to variations in nutrient drink composition.	[14-16]
Drinking-Ultrasonography Test	Assessment of gastric motor and sensory functions using ultrasonography while consuming water.	FD patients show reduced cross-sectional area of the stomach and higher sensitivity scores.	Small sample size; limited to certain parameters of gastric emptying.	[17]
Functional MRI and PET	Analyzes brain activity and its correlation with FD symptoms using functional imaging techniques.	Detects abnormalities in brain regions related to FD; investigates the gut-brain axis involvement.	High cost and limited availability; requires further validation for clinical use in FD.	[18-21]
MRI-Based Assessment	Uses MRI to assess stomach volume, surface area, and geometry during gastric filling and emptying.	Provides detailed information on gastric motility and accommodation.	High cost and limited availability; small sample size of studies.	[22]
Carbon-Gastric Emptying Breath Test	Non-invasive test using labeled compounds to assess gastric emptying.	FDA-approved; reliable for assessing gastric emptying; high sensitivity in detecting delayed or accelerated emptying.	Limited research on its specific application to FD; primarily used for gastroparesis.	[23-28]
Three-Dimensional Ultrasound	Assessment of gastric emptying using 3D ultrasound after consumption of a contrast agent.	Effective in differentiating gastric emptying in healthy subjects vs. gastroparesis patients; potentially useful for FD assessment.	Limited research on FD patients; primarily studied in gastroparesis patients.	[29]
High-Resolution Electrogastrography (HR-EGG)	Non-invasive method to evaluate gastric myoelectrical activity.	Identifies irregularities in gastric slow waves; promising for personalized treatment in gastric hypomotility.	Primarily studied in gastroparesis; needs further research in FD patients.	[30-34]
Endoluminal Functional Lumen Imaging Probe (EndoFLIP)	Measures gastrointestinal sphincter parameters using a balloon-equipped catheter.	Advanced technology for assessing GI sphincters is potentially useful for postprandial distress syndrome in FD.	Primarily used in gastroparesis; needs further research in FD patients.	[35]

modalities and establishing evidence-based guidelines to enhance patient outcomes, ultimately reducing the burden of FD on healthcare systems worldwide.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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