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REVIEW

Visceral hypersensitivity and electromechanical dysfunction as therapeutic targets in pediatric functional dyspepsia

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Abstract

Functional gastrointestinal disorders (FGID) are common clinical syndromes diagnosed in the absence of biochemical, structural, or metabolic abnormalities. They account for significant morbidity and health care expenditures and are identifiable across variable age, geography, and culture. Etiology of abdominal pain associated FGIDs, including functional dyspepsia (FD), remains incompletely understood, but growing evidence implicates the importance of visceral hypersensitivity and electromechanical dysfunction. This manuscript explores data supporting the role of visceral hypersensitivity and electromechanical dysfunction in FD, with focus on pediatric data when available, and provides a summary of potential therapeutic targets.

Key words: Motility; Visceral hypersensitivity; Functional dyspepsia

Core tip: Functional dyspepsia (FD) is a common disorder of upper gastrointestinal symptoms in adults and children. Etiology and mechanisms of FD are complex, and improved understanding could help direct therapy. Visceral sensitivity and intestinal electromechanical function both are demonstrated to be altered in some FD patients and are potential targets for treatment. Limited studies in pediatric FD are available, but available evidence supports adult data that targeting visceral hypersensitivity and electromechanical dysfunction is warranted, particularly in the context of the biopsychosocial model. Future studies in pediatrics are needed to determine optimal therapy and appropriate patient application.

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INTRODUCTION

Functional gastrointestinal disorders (FGIDs) account for more than 80% of chronic abdominal pain complaints in children. Although additional studies are needed, pediatric FGID prevalence and impact are described broadly in North America[1,2] and Europe[3,4], and with increasing recognition in other parts of the world[5-7]. The impact of pediatric FGIDs on patients and health-care systems cannot be overstated. In one epidemiologic study, 38% of school-aged children in the United States reported abdominal pain weekly and 24% reported abdominal pain persisting for more than 8 wk[8]. Further, FGIDs frequently are associated with somatic symptoms[9], decreased quality of life[10,11], psychological comorbidities[12], and school absenteeism[8]. Consequently, the burden on public health care[13] and associated financial costs are enormous[14,15].

In the late 1950s, Apley and Naish described an entity of recurrent abdominal pain (RAP)[16]. RAP was defined

by 3 or more bouts of pain severe enough to interfere with activities and occurring over at least a 3 mo period. Children with a wide variety of clinical presentations and etiologies were included under the single entity of RAP. This entity was rendered inadequate for clinical practice due to broad inclusivity. Over the past decade there was an effort to reclassify RAP into discrete groups that are known as FGIDs. FGIDs are defined by symptom-based clinical criteria set forth by an expert panel generally referred to as the Rome Committee. The committee met for the third time in 2006 (Rome Ⅲ) to update the criteria[17]. Rome Ⅲ defines abdominal pain associated FGIDs in children as pain occurring at least weekly for longer than 2 mo and without identifiable biochemical, structural, or metabolic abnormalities to explain symptoms. However, abdominal pain associated FGIDs are diagnosed even in the absence of laboratory, radiologic, and endoscopic testing, or in the presence of mild chronic inflammation of the intestinal mucosa[18,19]. Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are among the most common pediatric FGIDs[20]. FD is diagnosed in children by: (1) upper abdominal pain or discomfort several times a week or more often; (2) upper abdominal pain or discomfort longer than 2 mo duration; (3) pain "sometimes" or less relieved by defecation; and (4) pain "once in a while" or less associated with a change in stool form or frequency. FD is differentiated from IBS in that IBS pain can be upper or lower abdomen, is more often relieved with defecation, and is often associated with change in stool form or frequency. Although distinctions are made within the criteria, it is debatable whether the two disorders are truly distinct in etiology or mechanism and ultimately may be symptom-defined diagnoses sharing a common underlying pathophysiology[21,22].

In adults, FD is further delineated by two subtypes: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). PDS is defined by the presence of upper abdominal fullness or early satiety after normal size meals, whereas EPS is defined by predominance of epigastric pain or burning. PDS and EPS are not included within the pediatric FD symptom definition due to lack of supportive evidence in children. However, subsequent to Rome Ⅲ, evidence emerged that adult subtypes also may be relevant in the pediatric population. For example, children with PDS-type symptoms have been found to have increased anxiety[23,24], a phenotype demonstrated in adults with PDS[25].

FD, as true of other FGIDS, is considered to be etiologically multi-factorial. The biopsychosocial model proposes contributions from and interactions between biologic, psychologic, and social systems. Factors within any of these systems may initiate, exacerbate or alter the course of the pain syndrome. In addition, adverse events early or later in life may lead to brain-gut axis changes, including long-term alterations in visceral electromechanical function, sensitivity, immunity, and brain-gut stress response. Examples of early adverse events span the biopsychosocial spectrum to include infection[26], inflammation, surgery[27,28], abuse[29], and wartime exposure[30].

We previously reviewed the role of inflammation (specifically eosinophils and mast cells) in pediatric FD[31]. In this companion review, we explore the role of visceral hypersensitivity and gastrointestinal electromechanical dysfunction in generation and maintenance of FD symptoms or subtypes, as well as their potential as therapeutic targets. Although they will generally be treated as separate entities in this discussion, visceral sensation, motor function and inflammation interrelate and should be considered as such when pursuing patient diagnosis and treatment.

VISCERAL HYPERSENSITIVITY

Visceral sensory output from organs (*e.g.*, intestine, bladder) to the central nervous system occurs continuously. Signals result from stimuli including hollow organ distension, inflammation, traction on the mesentery, and ischemia. Normal physiologic function of the visceral organs, including gastrointestinal distension and contraction, is typically nonpainful. However, the subjective interpretation may change due to increased frequency or amplitude of the visceral stimulus, or increased sensitivity to a typically painful (hyperalgesia) or nonpainful (allodynia) stimulus. Visceral hypersensitivity may result from alterations in the peripheral or central nervous system and has complex but increasingly understood etiology[32]. Human and animal studies have identified numerous contributing factors to this alteration, with visceral hypersensitivity now considered one of the central mechanisms of FGIDs.

Visceral hypersensitivity in FD may result in early satiety, abdominal pain, and nausea. Results from pediatric and adult investigations strongly suggest that sensory thresholds in FD patients are different than in subjects with other intestinal disorders and healthy controls. Visceral hypersensitivity was studied in 11 FD, 8 IBS and 11 FD-IBS overlap adults utilizing gastric and rectal barostats[33]. FD patients had predominant gastric (91% of subjects) over rectal (18%) hypersensitivity, IBS patients had only rectal (75%) hypersensitivity, and overlap patients had hypersensitivity to both (82% gastric, 91% rectal). Findings from this study suggest that hypersensitivity in FD may be localized to the stomach. However, other studies have failed to demonstrate these location-specific findings[34,35]. Differences in findings across studies may be related, at least in part, to heterogeneity in patient selection and/or in hypersensitivity definition.

Assessment of visceral hypersensitivity

Visceral sensitivity of the intestine is measured using a variety of methods in clinical studies. Patients undergo specific interventions, then either subjective pain reports or objective clinical data (*e.g.*, biometrics, functional brain imaging) are collected and analyzed. Tests utilized include water load, balloon distension, and inflammatory/nociceptive challenge. In many studies, tests of visceral sensitivity are conducted in a multimodal design, both to

determine correlation and to validate outcomes. Water load testing requires subjects to drink a maximal amount of water in a brief discrete time period (typically 5 min). Outcomes include subjective symptoms and quantity of water ingested. Balloon distension of hollow organs, including gastric barostat, measures distension thresholds and corresponding signs and symptoms. Of note, balloon distension also is used in animal models of visceral pain, with electromyographic recording included as an additional objective outcome. Inflammatory/nociceptive challenges directly stimulate intestinal mucosal sensory nerves by application of a chemical (*e.g.,* acid or lipid) and measuring subjective pain thresholds. Both water load and balloon distension tests are affected by gastric accommodation and emptying, further demonstrating that separating sensation from function is a practical but artificial distinction.

Water load test: The water load test is advocated as a means of identifying patients with visceral hypersensitivity. Although the water load test may not be useful for identification of pediatric FD due to suboptimal sensitivity, children diagnosed with FD often have abnormal test results[36]. In a controlled study by Schurman *et al*[36], 68 pediatric patients with FGIDs and 26 healthy children completed the Behavioral Assessment Scale for Children-Self-Report Form (BASC-SR) and underwent a rapid water load test (maximal tolerable volume within 3 min). Children with FD, with or without corresponding IBS, had lower water consumption than healthy controls. This was not true of children with IBS only. Using the 10th percentile for water volume consumption in the control group as a lower limit of normal, the water load test had 28% sensitivity and 100% specificity in identifying patients with the diagnosis of FD as determined by the clinician. Consistent with the biopsychosocial model, self-reported anxiety was negatively correlated with volume of water intake; however, it accounted for only 6% of the variance.

A variation on the water load test measuring satiety was evaluated in 28 pediatric patients diagnosed with FD using Rome Ⅲ criteria[37]. Participants drank a liquid meal at a constant rate and repeatedly scored satiety until reaching maximal possible score or 5 min time. Total intake volume was decreased in dyspeptic patients compared to healthy controls. Another study of 15 adolescents with FD who consumed a liquid meal at a constant rate to maximal tolerable volume found no statistical difference in total ingested volume or time to satiation compared to controls[38]. However, total volume was over 10% less and time to satiation over 20% sooner in FD subjects. Additionally, postprandial nausea and bloating were greater in dyspeptics, with 7/15 subjects reporting postprandial pain scores > 99th percentile of scores for healthy adolescents. Of note, in a study of 101 children with functional abdominal pain that utilized multiple validated questionnaires in addition to a water load test, children believing they could modify their own pain (high problem-focused pain efficacy) had decreased visceral sensitivity compared to those who perceived little control over pain[39]. Although the direct application to children with FD is unclear given different inclusion criteria, findings support consideration of visceral sensitivity to gastric distension as a possible pathophysiologic mechanism and, further, the potential beneficial role of CNS-mediated inhibition.

Measures of visceral sensitivity are studied more extensively in adult patients with FGIDs including FD. While water load testing in adults with FD has yielded similar results[40-44] to those reported above for pediatric studies, studies in adults contain expanded data investigating other upper GI conditions, demographic and psychosocial factors, and liquid composition. In one study of adults, patients with FD (n = 59), GERD (n = 101), and ulcer (n = 55) all demonstrated decreased maximal ingested volume of water over 5 min compared to 30 healthy controls[45]. Although this again supports visceral sensitivity mechanisms, it also raises concern regarding the specificity of the water load test as an assessment for FD. Strid *et al*[43] evaluated 35 FD adults and 56 controls. Depressed mood and poor overall health correlated with lower tolerated volumes in FD patients only, again reinforcing the brain-gut connection/biopsychosocial model and the useful but artificial construct of measuring visceral sensitivity in isolation. In contrast, Jones *et al*[44] found no correlation between psychological measures and specific water load test outcomes. Composition of the liquid also appears to affect the postprandial symptom profile in FD. Lee *et al*[46] compared 30 adults with FD to 12 healthy controls and found that symptoms of bloating and abdominal pain within 30 min following ingestion were greater in FD patients after a nutrient drink as compared to water, while there was no symptom difference between the two liquids in healthy controls[46]. Interpretation of liquid loading needs to take into consideration the psychologic state of the subject and the nutrient content of the ingested liquid.

Gastric barostat: Barostat testing is the traditional "gold standard" for evaluating mechanical hypersensitivity in adults. In FD, the evaluation utilizes balloon distension of the fundus and subjective scoring of discomfort. Hoffman *et al*[47] found that FD children had abdominal discomfort at lower gastric distension pressures compared to healthy young adults. This is consistent with a separate study utilizing barostat testing in which visceral hypersensitivity was identified at a higher frequency in children with RAP as compared to healthy controls[48]. The RAP group likely included children with FD as well as other abdominal pain disorders.

Gastric barostat studies in adult FD generally replicate, and also extend, pediatric findings. Evaluation of 8 dyspeptic adults found lower sensation threshold to gastric distension compared to controls, although maximal tolerated distension pressure and volume were similar[49]. These 8 patients had not previously consulted health care

professionals regarding symptoms, suggesting that visceral hypersensitivity to balloon distension is independent of referral bias and certain psychosocial characteristics (such as high anxiety regarding symptoms). FD patient heterogeneity was demonstrated in two other studies, however, suggesting that sensitivity to balloon distension is not universal. Specifically, relative pressure (intraballoon pressure/intraabdominal pressure) to produce discomfort was abnormal in only 37% of 160 consecutive patients with FD when compared to 80 healthy controls and gastric hypersensitivity was found in only 44% of "pain-predominant" and 25% of "discomfort-predominant" FD adults[50]. Hypersensitivity to balloon distention is enhanced in the postprandial state in FD patients (but not controls) and correlates with preprandial sensitivity, impaired accommodation, and the severity of meal-related symptoms[51]. Taken together, studies suggest that mechanical hypersensitivity may be associated with an increased prevalence of postprandial pain.

Duodenal infusion: Although chemosensitivity has not been evaluated in children with FD, adults with FD have demonstrated increased symptoms to both duodenal[52] and gastric[53] acid infusion. Duodenal acid infusion has most often been associated with nausea but also bloating and pain[52,54-56]. Duodenal acid infusion decreases antral motility and alters response to balloon distention[46,55]. In a study of adults with FD, Feinle *et al*[57] showed that duodenal lipid exposure affects gastric sensitivity to balloon distension supporting the effect of lipids and cholecystykinin on visceral sensitivity. Lipid infusion, but not glucose infusion, enhances perception to gastric distention and lipid infusion is associated with nausea[58]. In addition to mechanical sensitivity, chemosensitivity represents another potential therapeutic target.

Mechanisms of hypersensitivity

Visceral hypersensitivity is a complex process which may occur both within the CNS and at the level of the peripheral nervous system. Mechanisms of increased visceral sensitivity to balloon distension have been studied extensively in animal models[59,60] and in several cohorts of adults with FD, but have not been reproduced in dyspeptic children. Neuroimaging studies conducted in adults with FD support the presence of abnormal CNS processing of pain signals as compared to controls and in FD patients with hypersensitivity as compared to FD patients with normal sensation[61,62]. Vandenberghe *et al*[63] postulated that intense stimulation of low threshold multimodal afferent pathways, as opposed to sensitization of nociceptive pathways, occurs in hypersensitive FD adults. Their conclusion is based on studying 48 FD adults (hypersensitive, n = 20) in whom non-pain symptoms were induced at similar distending pressures that resulted in pain. At a peripheral level, hypersensitivity may be induced by a number of factors, including alterations in mediator release (*e.g.*, serotonin) or receptors (*e.g.*, 5-HT or TRPV1), inflammation, or the stress response.

Serotonin (5-HT) is abundant throughout the intestine and is an important neurotransmitter within the brain and the GI tract where it plays a key role in the regulation of motility and sensation. The effects of serotonin are modified by 5-HT receptors and its reuptake controlled by SERT. In adults with FD, plasma levels of 5-HT are decreased in the basal and postprandial states[64]. This has not been studied directly in children with FD; however, gastric 5-HT content and SERT mRNA do not differ between children with FD and controls[65]. Due to its important role in sensation, serotonin (broadly or specific serotonin receptors) represents a potentially important treatment target.

Transient receptor potential (TRP) channels survey the gastrointestinal contents for chemicals ingested, produced within the gastrointestinal tract (including those produced by the microbiome), and/or generated by inflammatory responses[66]. TRP vanilloid type 1 (TRPV1) is a polymodal nociceptor on GI afferent neurons and is the specific sensor for capsaicin. Based on oral capsaicin capsule titration, the majority of adults with FD demonstrate visceral chemosensitivity involving TRPV1 pathways[67-69]. Repeated ingestion of capsaicin in healthy volunteers initially increases symptoms, but after 4 wk decreases symptoms through desensitization of both chemo- and mechanoreceptors[70]. The effects on sensitivity appear to be dependent on length of exposure. In healthy volunteers with 7 d exposure, chemoreceptors remain sensitized while threshold of mechanoreceptors to distention decreases[71]. TRPV1 potentially plays a key role in chemosensation and possibly mechanosensitivity; as such, TRPV1 may represent another therapeutic target.

Inflammation and stress have been implicated in the pathophysiology of visceral hypersensitivity in FD. Consistent with the biopsychosocial model, electromechanical dysfunction may also be influenced by anxiety and the stress response. Anxiety is the most highly implicated psychological contributor to the development and maintenance of FGIDs including FD. Approximately 50% of children and adolescents with FD demonstrate elevated anxiety scores[72]. Anxiety can trigger the stress response which is mediated primarily through the release of corticotrophin releasing hormone (CRH) from the hypothalamus. The stress response results in physiologic effects relevant to FGIDs including inflammation (particularly mast cell activation), sympathetic nervous system activation, altered gastric accommodation, gastric dysmotility, and visceral hypersensitivity. CRH also alters central processing of nociceptive messages. The effects of CRH on hypersensitivity and electromechanical dysfunction may be direct and mediated *via* CRH1 and CRH2 receptors. Downstream effects of CRH-induced mast cell activation and mediator release can stimulate afferent nerves signaling pain, sensitize afferent nerves resulting in visceral hypersensitivity, and alter electromechanical function. In adults with FD, hypersensitivity is associated with mast cell degranulation after balloon distention of the proximal stomach[73].

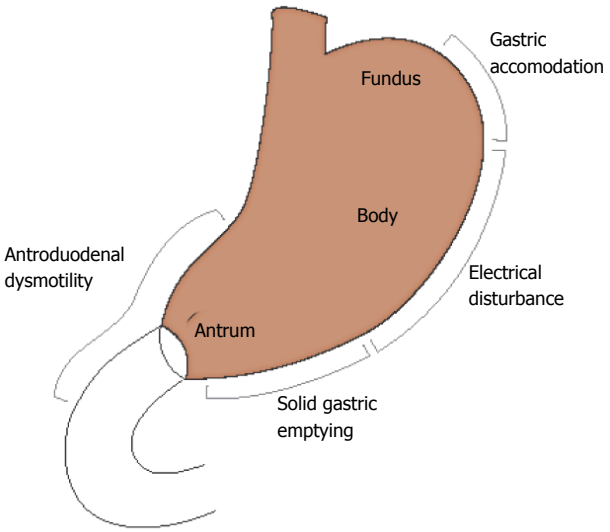

Figure 1 Overview of electromechanical disturbances in functional dyspepsia.

ELECTROMECHANICAL DYSFUNCTION

Visceral hypersensitivity undoubtedly has a role in dyspeptic symptoms, but it is identified in only a fraction of patients diagnosed clinically with FD. In contrast, disordered accommodation, delayed gastric emptying, gastric electrical rhythm disturbances, and altered antroduodenal motility are all physiologically relevant and common in FD (Figure 1). As reviewed by Azpiroz *et al*[74], gastric motor function is interdependent on visceral sensation and is a complex function affected by both tonic and induced stimuli. Understanding physiologic abnormalities in specific disorders such as FD can guide effective therapy.

Assessment of electromechanical dysfunction

Motor function of the stomach and duodenum is a coordinated activity meant to prepare food for digestion and initiate passage through the small intestine. The stomach serves as a reservoir for ingested food and functions to grind food and then provide passage to the intestine at a rate appropriate for effective nutrient absorption. In the interdigestive period, gastroduodenal motility is modulated by the migrating motor complex (MMC) which is a multiphase action propagated from the gastric antrum into the small intestine controlled by the enteric nervous system, central nervous system, and intestinal regulatory hormones. Gastroduodenal motility depends on prandial state, food composition, presence and type of inflammation, distal intestinal motor function, and both motor and autonomic neural input. Symptoms related to altered gastroduodenal motor function may include abdominal pain, nausea, vomiting, and early satiety and can occur due to rapid[75] or delayed gastric emptying, or altered proximal stomach accommodation with normal gastric emptying. Gastroduodenal mechanical function can be measured with a variety of tools including scintigraphic or breath gastric emptying study (GES), gastric barostat, antroduodenal manometry (ADM), and electrogastrography (EGG) as well as newer studies including single-photon emission computed tomography (SPECT), and the wireless motility capsule (WMC). Each test measures related but different aspects of physiology including compliance, accommodation, contractility, coordination, and propagation as highlighted below.

Gastric emptying

Pediatric studies have identified abnormal gastric emptying in FD. In a study of 15 FD adolescents using the ^{13}C-*s platensis* breath test, gastric emptying of solids was significantly delayed[38]. Solid-phase delays were similarly identified in 26% of dyspeptic children when evaluated with the ^{13}C-octanoic breath test[37]. Emptying function has also been evaluated in pediatric dypeptics with scintigraphy using 99mTc-sulfur colloid and a standard meal[76]. Although a majority of the 57 patients had normal gastric emptying at 2- and 4-h post meal, abnormalities of rapid (20%) and slow (20%) gastric emptying were observed. Symptoms did not correlate with emptying rates in these children. Another study utilizing scintigraphy demonstrated delayed solid emptying in 47% of patients, but again there was no relationship between emptying and symptom severity[77]. In contrast, Devanarayana *et al*[78] recently used antral ultrasound to correlate gastric emptying after a liquid meal with symptoms in pediatric dyspeptics. Forty-one FD patients had delay in both gastric emptying rate (% change in antral cross sectional area from 1 to 15 min post ingestion) and antral motility index (product of contractile amplitude and frequency) compared to healthy controls. Severity of symptoms correlated negatively with gastric emptying rate (r = -0.35), but not with other measures of motility. Gastric emptying appears to have no relationship to satiety in children[37]. Delays in gastric emptying may also be affected by concurrence of constipation in pediatric dyspepsia[79]. FD patients with constipation had longer gastric emptying times than FD patients without constipation, and treatment with lactulose over 3 mo resolved the difference.

Abnormal gastric emptying by scintigraphic evaluation has been demonstrated in a significant proportion of adults with FD[80-82] although findings may be affected by the modality of measurement as well as meal volume and contents[83]. In adults, there have been no reproducible relationships between impaired emptying and specific symptoms. Some studies have revealed no or only weak associations with symptoms[84-86]. Other studies have reported variable and highly inconsistent associations with nausea, vomiting, postprandial fullness, and bloating with both positive and negative relationships with regard to pain[87-91]. Postprandial fullness and nausea, and severe early satiety have been reported with delayed liquid emptying[88,90].

Gastric accommodation

Gastric accommodation, the ability of the proximal stomach to relax and serve as a reservoir for food, is implicated as a motor abnormality responsible for symptoms in some dyspeptic patients[92]. Impaired accommodation

has been associated with early satiety in some but not all studies[84,91,93]. Assessment of accommodation can be conducted with gastric barostat, ultrasound, MRI, and SPECT. Gastric emptying and water-load capacity are certainly affected by accommodation, but neither is a specific measure of fundic relaxation. Impaired accommodation was demonstrated in pediatric RAP patients assessed by 2-dimensional ultrasound[94]. Participants, most of whom had dyspeptic symptoms, had decreased proximal stomach saggital area and increased rate of proximal stomach emptying after a liquid meal when compared to healthy controls. A similar assessment of RAP patients utilized 3-dimensional ultrasound to assess antral relaxation and gastric distribution of ingested liquids[95]. Participants demonstrated decreased postprandial proximal filling (accommodation) and altered liquid distribution favoring the distal stomach despite no difference in gastric emptying rate. Ultrasound evaluation of children with FD also showed increased antral distension after a mixed solid-liquid meal, but without specific evaluation of the proximal stomach[96]. Adolescents with FD also have a lower postprandial gastric volume change than healthy adults when assessed by SPECT[38]. No MRI studies of gastric function in pediatric FD patients have been published.

In adults with FD, decreased gastric accommodation and abnormal gastric volumes are widely demonstrated using barostat[90,97,98], ultrasound[99,100], SPECT[80,101,102], and MRI[83]. Accommodation defects have been reported in 40% of adults with FD as assessed by barostat and in 47% as assessed by SPECT[93,101]. It is less clear whether symptoms are associated with abnormal accommodation or gastric volumes[91] and whether newer imaging modalities such as MRI will consistently support these findings[103].

Electrogastrography

Electrogastrography (EGG) is a noninvasive method to evaluate gastric myoelectrical activity. It can assess rhythmic gastric slow waves associated with frequency and propagation of contractions, as well as superimposed activity (spike/second) indicative of antral contractility. Cutaneous abdominal electrodes are utilized to obtain raw data, then computer analysis is performed to determine targeted values for comparison. Normative data are considered similar in children, adolescents, and adults[104], but not in neonates or toddlers[105].

Children with FD have abnormal EGG compared to healthy children, indicating underlying myoelectrical dysfunction. Chen *et al*[106] assessed 15 pediatric patients with FD compared to 17 healthy controls using surface electrodes. Children with FD had a lower percentage of slow waves and more time with no rhythmic activity in fasting and fed states. In the postprandial state, frequency of gastric slow waves also increased less in subjects than controls although measures of contractility (power) were similar. In an independent study of 30 children with FD, EGGs were abnormal in 50% and correlated with symptom severity[77].

Electrogastrogram abnormalities in adults with FD are similar to those described in children[42,107]. Patients with abnormal EGG also had higher postprandial pain scores, and patients with a history of vomiting had more frequent fasting bradygastria and fewer normal slow waves. This symptom correlation suggests clinical relevance of EGG abnormalities and is consistent with other data correlating EGG and symptoms in pediatric FD[106,108]. However, the role of EGG abnormalities as a therapeutic target remains to be established.

Antroduodenal manometry

Antroduodenal manometry also demonstrates abnormal motility in children with FD[109]. A study of 34 children and 35 adults with FD found a majority with abnormal motility with a neuropathic pattern observed most commonly[110]. Several studies of antroduodenal motility also demonstrate abnormalities in adults with FD[111,112], but symptoms, intestinal dysmotility, and gastric emptying delays are not clearly correlated[112]. The relationship between motility studies is made even less clear in that a study of 31 adults with FD showed abnormal EGG was not associated with concurrent abnormalities in antroduodenal manometry[113], and available pediatric data supports this concept[114]. The clinical significance of altered antroduodenal motility, particularly as a therapeutic target, is not established.

Wireless motility capsule

The WMC shows promise as a relatively noninvasive, clinically relevant measure of gastrointestinal motility[115]. It is used to study prokinetic medication efficacy[116] and to describe an adult irritable bowel syndrome cohort[117]. Data is not yet available in adult or pediatric dyspeptics, but an initial study suggests the WMC is a sensitive detector of motor abnormalities in pediatric patients with upper gastrointestinal symptoms[118].

Mechanisms of electromechanical dysfunction

The specific cause of electromechanical dysfunction in FD is unclear, but may be related to immune activation[119]. Inflammation is implicated as a contributor in dyspepsia-associated dysmotility[31,120]. However, this effect appears to require specific inflammatory pathways. For example, EGG abnormalities in children and adolescents with FD are independent of chronic gastritis, but associated with antral mast cell and eosinophil density[121,122]. Likewise, in children with FD, increased antral mast cell density is associated with slower gastric emptying[121].

As alluded to previously, the stress response also has effects on electromechanical function. Experimentally induced stress has been shown to increase symptoms and inhibit normal postprandial EGG responses in some, but not all studies[123,124]. Stress is shown to impair accommodation and to decrease gastric emptying[125,126]. The effect on gastric emptying appears to be mediated primarily *via* CRH receptors.

THERAPIES FOR PEDIATRIC FD

Proper identification of functional dyspepsia using symptom based criteria (Rome Ⅲ) is the first step in treatment. Diagnostic and screening tests to evaluate for diseases with similar symptoms are sometimes important, but not necessary for FD diagnosis. Providing a named diagnosis (*i.e.,* FD) and the expectation of treatment success potentially increases the treatment response rate. Importantly, the placebo effect may be particularly strong in children with FGIDs and should be considered when interpreting efficacy of studied interventions[127].

Reassurance and education regarding FGIDs is imperative. Validating that subjective symptoms are real and putting them in the context of the biopsychosocial model aids in directing effective treatment and provides hope for patients and families. Visceral hypersensitivity and electromechanical dysfunction represent potential targets, but patients may be more effectively managed if underlying factors (such as inflammation, anxiety, *etc.*) are considered in the treatment plan. Treating FD, like other FGIDs, in the conceptual framework of the biopsychosocial model necessitates inclusion of both medical and psychological interventions. Effective medical therapy targeted to the specific pathophysiologic mechanism is preferred, but symptom-based therapy may also be useful. Although we will discuss medications in the context of their most likely target, it should be noted that visceral sensation, motor function, and inflammation do not exist in a vacuum; many medications exert an effect on more than one domain of sensation and mechanical function.

Targeting visceral hypersensitivity

Treatment of visceral sensitivity related to distension in FD has focused largely on antidepressant therapy, including tricyclic antidepressants (TCAs), selective serotonin uptake inhibitors (SSRIs), and related medications. Antidepressants may have primary effects on comorbid anxiety/depression that secondarily alter symptom perception, coping skills, arousal thresholds, and/or sleep quality. Alternately, they may affect functional gastrointestinal pain through central nervous system analgesia or a direct effect on gastrointestinal tract sensitivity. Serotonergic neurons have a role in gastrointestinal pain as discussed above, but antinociceptive effects of these medications cannot always be dissociated from their influence on motility and, in some cases, may be integral to effective treatment[128]. For example, TCAs slow gastric emptying and small bowel transit in healthy patients[129,130], but do not affect SPECT-determined gastric accomodation or outcomes of the nutrient drink test, except for post-satiation nausea[129]. Similarly, SSRIs shorten small bowel transit time in healthy patients, but do not clearly decrease gastric sensitivity or compliance[131,132]. Treatment with TCAs, SSRIs, and related medications must be carefully weighed against potential adverse effects, including cardiac dysrhythmias, suicidality, and anticholinergic effects, and monitored to minimize these relatively rare, but potentially life-threatening issues.

Several studies have investigated whether TCAs, SSRIs, and related medications alter visceral sensitivity and overall symptoms in adult FD. Data in healthy adult volunteers demonstrate no change in tolerated gastric volume in the nutrient drink test after a short treatment course with desipramine (TCA) or escitalopram (SSRI)[133]. Although total symptom scores induced by the nutrient drink test were influenced, treatment effects were nullified in multivariate analysis considering age, gender, BMI, and baseline scores. Fluoxetine (SSRI) improved symptom scores in depressed adults with FD[134], but non-depressed subjects had no change in symptom scores and EGG measures were similar across all groups. Sertraline (SSRI) similarly failed to alter global symptoms or quality of life in adults with FD[135]. Finally, a randomized clinical trial (RCT) of venlafaxine, a medication with combined SSRI and selective norepinephrine reuptake inhibition (SNRI), demonstrated significant patient dropout due to medication adverse effects and no differences in symptom scores, health-related quality of life, anxiety, or depression[136]. Taken together, current evidence does not support a strong direct effect of SSRIs or TCAs on visceral sensitivity in adults. The potential role of these medications in treatment of visceral hypersensitivity, as well as gastroduodenal motility, may be further clarified by an international multicenter placebo-controlled RCT currently underway to compare escitalopram to amitriptyline in adults with FD. This trial has completed enrollment and data collection for the primary outcome of global symptom score, and also is assessing solid gastric emptying, liquid nutrient drink test, and SPECT (http://clinicaltrials.gov, NCT00248651).

Limited data exists regarding treatment of pediatric FD with TCAs and SSRIs, and studies typically include a mixed cohort of FGIDs. A double-blind placebo-controlled RCT of amitriptyline (TCA) in 33 pediatric patients with IBS treated for 8 wk demonstrated improvement in QOL and some IBS-associated symptoms[137]. Symptom improvement was limited to very specific symptoms (*i.e.*, right lower quadrant pain) and the reason for such specificity is not clear. Amitriptyline also was studied in 90 pediatric FGID patients in a multicenter double-blinded placebo-controlled RCT[138]. Few patients were diagnosed with FD (8% placebo, 13% amitriptyline), but primary outcome of symptom relief was not different when analyzed by diagnosis. No difference in symptom relief, depression, or functional disability was noted, although anxiety was decreased in subjects receiving treatment. Notably, at least "fair" improvement in pain relief was seen in greater than 2/3 of subjects receiving placebo. A retrospective study of 98 pediatric FGID patients (n = 16 with FD) treated with TCAs found greater than 75% symptom response rate in all FGID subtypes, but limitations include lack of validated outcome measures, blinding, and control subjects[139]. A 12-wk open label study of citalopram (SSRI) in 25 pediatric patients with RAP identified improvement in global symptoms, so-

matic symptoms, anxiety, and functional impairment[140]. There are no published placebo-controlled RCTs of SSRIs for treatment of pediatric FGIDs in general or FD in particular. Given the questionable efficacy in adults with FD, SSRIs should not be viewed as first-line therapy, if at all, in pediatric FD.

In addition to mechanosensitivity, visceral chemosensitivity may represent a valid therapeutic target. Lipid sensitivity may be addressed through diet modification, but there have not been any studies demonstrating long-term benefit from low fat diets. Acid sensitivity may be addressed more directly through acid reducing medications. Acid-suppressive therapy with histamine-2 receptor antagonists (H2RA) and proton-pump inhibitors (PPI) improve pain in adults with FD[141-143]. PPI therapy may be more effective than H2RA[144], but studies typically have a mixed cohort without control for presence of *H. pylori* infection, gastroesophageal reflux disease (GERD), or both. A randomized, controlled trial in adults found that PPI therapy improved symptoms only in FD patients with concurrent heartburn[145]. Whether the therapeutic benefit is related to acid hypersensitivity is not clear as these medications may be treating a component of acid mucosal injury or co-morbid GERD, or may also improve dyspeptic symptoms related to delayed gastric emptying[146]. Still, acid reduction therapy remains the most common treatment prescribed empirically by pediatric gastroenterologists for FD in children[147]. In children with abdominal pain, famotidine has demonstrated superiority to placebo in global improvement, and additional benefit is noted in children with FD[148]. In a large pediatric cohort, omeprazole had no benefit over ranitidine or famotidine in the relief of pain, nausea, or vomiting[149]. Although acid suppression appears promising, the specific mechanism of action in FD remains unclear.

Treatment of visceral chemosenstivity in FD also has targeted specific nociceptors including TRPV1. As described earlier, healthy adults ingesting capsaicin achieve desensitization following initial increase in symptoms, and FD adults may have increased chemosensitivity to TRPV1 agonists. A double-blind, placebo-controlled trial of red pepper powder in 30 FD adults demonstrated efficacy in decreasing overall symptoms, epigastric pain, and epigastric fullness within 3 wk[150]. Although some initial discomfort occurred in treatment group patients, only two discontinued the study due to severe pain or burning. Capsaicin or other TRPV1 agents have promise in FD patients with demonstrated chemosensitivity.

Targeting electromechanical dysfunction

Therapies for electromechanical dysfunction in FD can be broken down into those targeting gastric motility/emptying and those targeting gastric accommodation. Therapies to increase gastrointestinal motility and emptying have met with mixed results for FD. A meta-analysis of 1844 adult patients with FD and 1599 controls found that prokinetics were effective in decreasing symptoms[151]. The authors importantly note that most studies of prokinetics assess short-term efficacy only. Interestingly, a separate analysis of studies including measures of symptom improvement and gastric emptying found no correlation between the two, suggesting that alternate effects of prokinetics are responsible for symptom improvement[152].

Prokinetics evaluated in adults include agents primarily targeting 5-HT (5-HT_3 antagonists and 5-HT_4 agonists), dopamine, and motilin receptors. Cisapride, a 5-HT_4 receptor agonist, demonstrated symptom reduction in adults with FD in one meta-analysis, but potential bias and inclusion of specific FD-subtypes may affect applicability of findings[153]. In pediatric patients with dyspepsia it may normalize gastric myoelectric activity[154], but data on clinical effects is not available. Cisapride and newer 5-HT_4 receptor agonists regulate intestinal motility through effects on enteric cholinergic neurons, enhancing gastric emptying and accomodation, as well as potentially modulating visceral sensitivity[155,156]. Although cisapride was withdrawn from the United States and European markets due to concern for potentially fatal cardiac arrythmias, it is not clear that these effects are common in otherwise healthy children[157] and the medication can still be used in limited capacity with close supervision. Another serotonergic/anti-dopaminergic compound, levosulpiride, has demonstrated noninferiority to cisapride[158] with safety and efficacy confirmed in an open-label trial of 279 adults with FD[159]. A selective 5-HT_4 agonist and 5-HT_3 antagonist (mosapride) has shown mixed results in FD symptom improvement[160-162]. Cinitapride, a relatively new 5-HT_4 receptor agonist/dopamine-2 receptor antagonist, was demonstrated to relieve symptoms and reduce symptom severity as well as domperidone in a double-blind phase Ⅲ RCT[163]. There is a lack of pediatric data regarding agents targeting 5-HT receptors.

Metoclopramide is a dopamine antagonist with a long history of use in FD as an effective promotility agent that reduces dyspeptic symptoms[164,165], but adverse effects may include irreversible extrapyramidal symptoms. There is evidence that metoclopramide liquid formulation may actually be more effective than the tablet[166]. Domperidone, a dopamine-2 receptor antagonist that does not cross the blood-brain barrier, is shown to improve symptoms in adults with FD[167] though it may be less effective when compared to cisapride[168,169]. Domperidone is currently available for pediatric patients only as an investigational new drug for compassionate use. Itopride, which is anti-dopaminergic and inhibits acetylcholinesterase, did not have promising results in a phase Ⅲ trial in adults[170], but a meta-analysis that included a heterogenous patient population with potential comorbid disease (*i.e.*, *H. pylori*) suggests that it may be effective in symptom reduction[171]. A lack of proven efficacy and significant potential side effects should limit the long-term use of metoclopramide in pediatric FD.

Erythromycin activates antral and small intestinal motilin receptors, and may have differential physiologic effects in children with underlying gastrointestinal dis-

orders, including FD[172]. Erythromycin in adults with FD improved bloating and gastric emptying of liquids and solids, but did not affect meal related symptom severity[173]. The motilin agonist ABT 229 provided no symptom improvement in adults with FD[174]. Another motilin agonist, mitemcinal, showed promise in relieving gastroparesis-associated symptoms in adult diabetics[175]. Efficacy in a subset of those patients with lower body mass index and hemoglobin A1C suggests a role in nondiabetics with upper gastrointestinal symptoms[176]. Motilin receptor agonists are known to decrease gastric accommodation and compliance[177,178] and are susceptible to tachyphylaxis, both factors that may contribute to limited efficacy in FD.

Actiomide is a novel agent that has minimal interaction with serotonin and dopamine receptors. It affects gastrointestinal motility in adult FD, including improving accommodation and gastric emptying[179], through muscarinic receptor inhibition. This, in turn, increases acetylcholine release and inhibits its degradation. Elimination of meal-related symptoms, and improvement in symptom subgroups and quality of life was demonstrated in a phase Ⅲ clinical trial in Japan[180] . Phase Ⅲ trials are currently in preparation in the US and Europe.

Gastric accommodation represents another potential therapeutic target within the broad category of electromechanical dysfunction. Buspirone, a $5HT_{1a}$ receptor agonist, increased accomodation and decreased symptom severity, postprandial symptoms, and liquid gastric emptying rate, but did not specifically affect gastric sensitivity to distension by barostat in adults with FD[181]. Tandospirone, a partial $5HT_{1a}$ agonist similar to buspirone, also improved symptom scores in FD adults, but had no effect on early satiety implicating central anxiolytic effects rather than altered gastric accommodation[182]. Sumatriptan is another $5HT_1$ receptor agonist that alters gastric size in dyspeptics, but specific mechanical effect and association with symptom improvement remains unclear[93,183]. A subset of FD patients also showed improvement in nausea and accommodation when treated with ondansetron, a $5HT_3$ antagonist, but mechanical and clinical effects were disassociated[184]. Tegaserod, a partial $5HT_4$ receptor agonist, is shown to enhance gastric accommodation and two large randomized trials showed significant symptom relief compared to placebo[185]. Paroxetine, an SSRI, has been shown to enhance gastric accomodation in healthy volunteers but has not been studied in FD[186].

Cyproheptadine is efficacious in improving symptoms in children with FD[187]. As an antagonist of serotonin, histamine H1, and muscarinic receptors, it is possible that physiologic effects are due to increased gastric accommodation or decreased gastric hypersensitivity to distension. In a retrospective open-label study of 80 children, Rodriguez *et al*[187] showed FD-symptoms significantly improved in 33 (41%) and resolved in 11 (14%) with very good medication tolerance even in nonresponders. It was previously found to be effective in a RCT of children with functional abdominal pain[188].

Complementary therapies such as ginger[189,190], peppermint oil[191], and iberogast[192], may also have a role in the treatment of FD. Ginger enhances gastric emptying in healthy volunteers and adults with FD but had no impact on FD symptoms[193,194]. In healthy volunteers, peppermint oil enhances gastric emptying without effects on sensitivity or accomodation[195,196]. It was effective for irritable bowel syndrome in children, but has not been specifically studied in FD[191]. Iberogast (STW 5), an herbal preparation, improves symptoms in FD, but there is not clear data determining whether effects are directly mediated by acceleration of gastric emptying or an alternate mechanism[192,197].

Non-medication treatments

Gastrointestinal motility can also be influenced by mechanical devices including the gastric electrical stimulator. The device utilizes electrodes implanted into the antrum to deliver high frequency, low amplitude stimulation. Adult studies show the device decreases symptom severity and improves quality of life[198] and findings were recently replicated in pediatric trials[10,199]. The study of 24 pediatric FD patients included those who did not improve with conventional medical therapy and most underwent temporary endoscopic gastric pacemaker placement to assess for symptom improvement prior to implantation of the permanent device[10]. Most patients showed significant gastrointestinal symptom improvement, as well as improved quality of life and global health scores.

Given the interaction between the stress response, visceral hypersensitivity, and electromechanical dysfunction, non-medication treatment of stress and anxiety likely have a role in the management of these patients.. Psychological and relaxation interventions studied in children with FGIDs include cognitive behavioral therapy, gut-directed hypnotherapy[200,201], yoga[202], and biofeedback-assisted relaxation therapy (BART)[203]. Children receiving a standardized course of targeted medication plus BART demonstrated better outcomes including decrease in pain intensity, decrease in pain episode duration, and global pain improvement as compared to children receiving only the medication component.

This gives rise to the hope that treatments addressing multiple, complementary targets within the biopsychosocial model can improve outcomes for children with FD, although further research needs to be done with multiple-component treatments to determine optimal combinations for individual children.

CONCLUSION

FGIDs, including functional dyspepsia, are incompletely understood despite high prevalence and significant impact on patient quality of life and healthcare costs. FGIDs are best approached utilizing a biopsychosocial model in which all relevant factors (biologic, psychologic and social) are identified and targeted in treatment. As

mechanisms of disease are further investigated, both in laboratory and clinical models, opportunities arise to target therapies. In addition to inflammation (addressed elsewhere), visceral hypersensitivity and gastrointestinal dysmotility are pathophysiolgic alterations that may respond to directed treatment. Despite limited evidence in children, the role of pharmacologic agents within a broader biopsychosocial treatment context remains promising.

There remains a need for placebo-controlled trials of therapy targeting visceral hypersensitivity and electromechanical dysfunction in children with FD. Likewise, there is a need to better understand the diagnostic and prognostic utility of various tests of upper intestinal sensory and mechanical function including visceral sensitivity, accommodation, and gastric emptying. Application of knowledge from placebo-controlled trials and specific tests of function may improve directed medical therapy for children with FD.

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