OPINION

A Critical Review of the Current Clinical Landscape of Gastroparesis

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Abstract: Gastroparesis has emerged as a common gastrointestinal disorder over the past few decades. It has been questioned whether this increase in prevalence reflects a true epidemic or rather the mislabeling of a variety of entities of similar symptomatology accompanied by a delay in the emptying of a meal from the stomach on a radionuclide gastric emptying study. Several factors contribute to this diagnostic morass, including a failure to recognize other conditions with similar symptoms, the relative convenience and accessibility of gastric emptying tests, the pervasive presence of some delay in gastric emptying in a variety of functional gastrointestinal disorders, and the confounding effects of certain therapies (opioids in particular) on gastric emptying rates. As a consequence, the label gastroparesis is affixed to patients whose symptoms have little to do with the rate at which food leaves the stomach and initiates a misdirected course of treatment that includes prokinetics, gastric electrical stimulation, and surgery. This strategy has already led to several well-documented therapeutic failures. When evaluating patients with upper gastrointestinal symptoms, the many facets of gastric and duodenal physiology that could contribute to symptoms should be considered, and a rush to attribute them to delayed gastric emptying should be resisted, as the subset of patients with accurately diagnosed gastroparesis is small. This opinion piece critically reviews the clinical landscape of gastroparesis as well as attempts to outline what should and should not be defined as clinically important gastroparesis.

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Gastroparesis is defined as "a chronic symptomatic disorder of the stomach characterized by delayed emptying without evidence of mechanical obstruction."[1] Thus, 3 elements are central to the clinical diagnosis of gastroparesis: related symptoms, gastric emptying delay, and the absence of another organic explanation for the patient's symptoms (eg, obstruction). Of these criteria, the last is the easiest to fulfill; endoscopy and a variety of imaging techniques can detect relevant diseases of the stomach and small intestine with considerable sensitivity and specificity. However, other questions remain: what symptoms should lead clinicians to suspect gastroparesis? How is its presence best defined? How relevant is gastric emptying delay to symptom pathogenesis? Is gastroparesis a valid target for therapeutic interventions? Although gastroparesis appears to be easily diagnosed with a gastric emptying test, the condition continues to present a challenge, with affected patients seeming to rapidly progress along a path of increasing levels of intervention without much improvement in outcome. Meanwhile, clinical investigators struggle to understand how a delay in the emptying of the solid and/or liquid components of a meal can explain a myriad of symptoms, and clinicians attempt to untangle the many factors that could lead to gastroparesis. To patients, this poorly understood condition could be debilitating, as it disrupts aspects of their personal and social lives. Gastroparesis is not uncommon; hospitalization rates for individuals in whom this condition was either a primary or secondary diagnosis increased

significantly between 1995 and 2004,[2] and it now represents a significant burden for health care systems due to the extent of health care utilization involved.[1,3] A lack of specificity of symptoms attributed to gastroparesis (ie, early satiety, postprandial fullness, nausea, vomiting, upper abdominal pain[1]) and variations in the performance and interpretation of gastric emptying tests, together with a long history of therapeutic failures for drugs and other modalities designed to accelerate gastric emptying, call for a critical examination of the status of gastroparesis as a clinical entity.

History of Gastroparesis

Gastroparesis was first described among patients with type 1 diabetes and was typically complicated by end-organ complications such as nephropathy, retinopathy, and peripheral neuropathy.[4] Prior to the use of scintigraphy, diabetic gastroparesis appeared to be uncommon; Roon and Mason observed in 1972 that only 21 cases had been reported in the literature.[5] Features of autonomic neuropathy were usually prominent, and late postprandial vomiting of undigested food was characteristic and pathophysiologically resonant. Endoscopy or imaging modalities demonstrated a dilated stomach full of food, and a gastric emptying test expressed emptying times in hours rather than minutes. This scenario continues to be encountered, but it is an uncommon feature of type 1 diabetes. Indeed, in the Olmsted County survey, the cumulative incidence of gastroparesis was only 4.8% in patients with type 1 diabetes.[6] Although a much lower incidence (1%) was noted among patients with type 2 diabetes,[6] it is expected that most cases of diabetic gastroparesis will be found within this patient population due to the much larger and growing presence of type 2 diabetes. Additionally, the increase in availability of tests that measure gastric emptying rate, particularly scintigraphy, allowed for a larger number of symptomatic patients to be assessed; accordingly, the diagnosis of gastroparesis grew, especially among nondiabetic patients.

Although a host of endocrine, neurologic, metabolic, and rheumatologic conditions have been associated with gastroparesis,[7] idiopathic gastroparesis, which has no discernible cause, is the predominant diagnosis. For example, the Olmsted County study reports the incidence of gastroparesis among nondiabetic patients in the general population to be 1 in 1000 (0.1%).[6] Additional studies show a preponderance of idiopathic gastroparesis among patients.[8,9] Another study from Olmsted County suggests that the condition may have been underdiagnosed, noting a large discrepancy between the prevalence of diagnosed (by scintigraphy) gastroparesis (0.02%) and that of symptoms compatible with gastroparesis (1.8%).[10] This hypothesis is difficult to prove given the tenuous relationship that exists between symptoms and gastric emptying rate.

Outside of the aforementioned studies in which rigorous attention was paid to the definition of gastroparesis, it is our experience that the label of gastroparesis is loosely applied to a much broader and less clearly defined group of patients with unexplained nausea and vomiting.[11] The (mis)diagnosis of this condition leads patients down a therapeutic path from dietary adjustments, prokinetics, antiemetics, pyloric botulinum toxin injections, placement of gastrostomy and jejunostomy tubes, and implantation of gastric electrical stimulators to various surgical approaches.

Symptoms of Gastroparesis

The list of gastroparesis symptoms as proposed by a contemporary review includes bloating, early satiety, nausea, postprandial fullness, and vomiting.[1] Abdominal pain has also emerged as a common symptom.[12-14] In a large multicenter study conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), upper abdominal pain was rated as being moderate to severe by two-thirds of all patients surveyed and as the predominant symptom by one-fifth of all patients.[14] Moderate to severe abdominal pain was more common among patients whose gastroparesis was considered to be idiopathic and was significantly associated with the use of opiates, raising the question of how many diagnoses of gastroparesis are made in the context of opiate use. Pain was not associated with gastric emptying rate,[14] questioning the role of gastric motor dysfunction in its pathogenesis. Bloating is a more recent symptom described among patients with gastroparesis and, although common, was not linked to gastric emptying rate.[15] Abdominal pain and bloating are such ubiquitous symptoms among functional gastrointestinal disorders that their presence in gastroparesis may be a marker of a diffuse disorder of gut perception or a chronic pain syndrome rather than a motility problem.

Attempts to predict gastric emptying rate or a clinical response to agents that accelerate gastric emptying based upon the evaluation of symptoms have encountered several challenges. First, symptoms, either individually or collectively, have proven to be poor predictors of the presence of gastroparesis.[16-20] For example, delayed postprandial vomiting of an undigested meal has traditionally been associated with delayed emptying, whereas most patients diagnosed with gastroparesis describe immediate or very early vomiting in relation to a meal. It is physiologically challenging to reconcile this presentation with a disorder whose origins are based upon impaired stomach

emptying alone. Second, accelerated gastric emptying, described in some patients with type 2 diabetes, results in a similar array of symptoms as those described in gastroparesis.[21,22] Third, an examination of the history of purportedly prokinetic strategies in gastroparesis reveals much disappointment and frustration.[20,23] Specifically, whereas certain agents accelerated emptying but had no impact on symptoms, other agents ameliorated symptoms without an appreciable acceleration of gastric emptying rate.[24-26] The latter observation implies that the effects of these interventions on other mechanisms (eg, visceral sensation, fundic accommodation, pyloric distensibility, antral distension) might explain their impact on symptoms.[27,28] It may be conceded that although attempts to address these mechanisms have been reported, they have not been universally successful.[29,30] However, such efforts should not be abandoned; recent interest in the pylorus exemplifies the potential contribution of other phenomena to these symptoms.[31,32] Finally, the rush to implicate gastric emptying delay conceals a failure to carefully seek out other explanations for patients' symptoms. For example, is the symptom rumination or regurgitation instead of vomiting? Could symptoms be a manifestation of dumping syndrome? Does the symptom pattern fit with that of cyclic vomiting syndrome? The category of unexplained nausea and vomiting could also halt concentrated efforts to search for alternative explanations for a patient's presentation.

In order to provide a semiquantitative measure of symptom severity, the Gastroparesis Cardinal Symptom Index (GCSI) was developed as part of the Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity Index.[33] The GCSI is based on 3 subscales: postprandial fullness and/or early satiety, nausea and/or vomiting, and bloating, with scores ranging from 0 (no symptom) to 5 (very severe symptom) and with a 2-week recall period.[30] The GCSI also includes grades, with grade 1 (mild gastroparesis) representing symptoms that are relatively easy to control, and the ability of the patient to maintain weight and nutrition on a regular diet; grade 2 (compensated gastroparesis) representing moderate symptoms that are only partially controlled with the use of daily medications, and the ability of the patient to maintain nutrition with dietary supplements; and grade 3 (gastric failure) representing refractory symptoms that are not controlled, the patient having emergency department visits and/or frequent physician visits or hospitalizations, and/or the inability of the patient to maintain nutrition via an oral route. The validity and reproducibility of the GCSI have been established in gastroparesis,[34,35] and although the index correlated with the severity of gastroparesis grades clinically,[36] it did not correlate with gastric emptying delay and, in a population of patients with chronic nausea and vomiting, could not differentiate between patients with or without delayed gastric emptying.[37]

Gastroparesis Vs Functional Dyspepsia

The primary issue with gastroparesis is its similarity to functional dyspepsia (FD). FD is viewed as a sensorimotor functional disorder of the gastroduodenal region, defined, according to the Rome IV criteria, by the presence of 1 or more of the following: bothersome postprandial fullness, early satiation, epigastric pain, and/or epigastric burning. Additionally, there should be no evidence of a structural disease or disorder that could explain the symptom(s). FD symptom(s) should be present for 3 months with onset occurring at least 6 months prior to diagnosis. FD is divided into 2 subgroups: postprandial distress syndrome, which must include postprandial fullness and/or early satiation for at least 3 days per week for 3 months; and epigastric pain syndrome, which is characterized by epigastric pain or burning, or both, occurring at least once per week either postprandially or when fasting.[36] FD is common worldwide, with a prevalence in the general population ranging from 11% to almost 30%.[38,39]

Multiple factors are involved in the pathogenesis of FD, such as delayed gastric emptying, impaired gastric accommodation, and gastric and duodenal hypersensitivity to distention and other stimuli.[16,17,28,29,40,41] The main symptoms of gastroparesis, nausea (>91%) and vomiting (72%), are found in 10% to 50% of patients with FD[42-44]; additionally, testing revealed that approximately 30% of patients with FD also exhibit delayed gastric emptying,[16,20,28,38] making it challenging to differentiate FD from gastroparesis. Indeed, associations between gastric emptying rate and any individual symptom or symptom complex have been inconsistent.[42,43,45-48] In a large study including 864 patients with FD, no association was evident between epigastric pain, early satiety, nausea, or bloating and delayed gastric emptying; postprandial fullness alone correlated with delayed emptying.[46] In a study of 243 patients with idiopathic gastroparesis, severe delay in gastric emptying was associated with worse vomiting, more severe loss of appetite, and the overall severity of symptoms of gastroparesis.[49] A study of 266 patients with gastroparetic symptoms found that the severity of nausea or vomiting and postprandial fullness correlated with the severity of gastric emptying delay.[42] A study by the NIDDK gastroparesis study group reported that patients with chronic unexplained nausea and vomiting and normal gastric emptying were clinically indistinguishable from patients with gastroparesis.[37] Abdominal pain, the most predictive symptom of epigastric pain syndrome, is present in up to 90% of patients with gastroparesis, but does not correlate

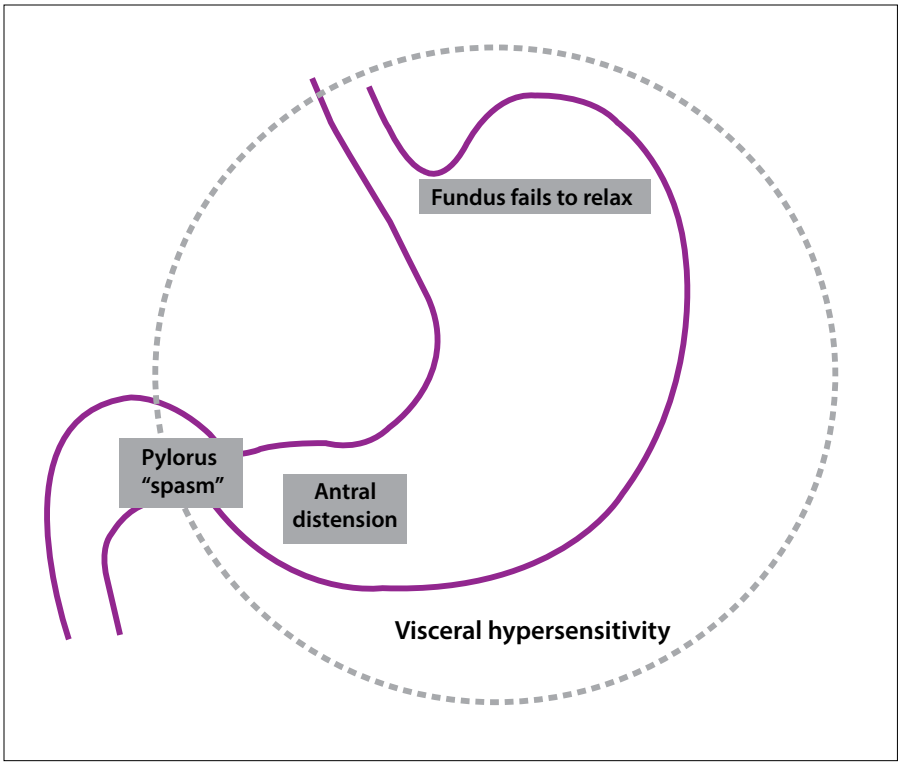

Figure. The pathophysiologic phenomena that contribute to symptoms in patients labeled as having gastroparesis may include:

Fundus fails to relax – loss of accommodation

Antral distension – if severe, could lead to pump failure

Pylorus "spasm" – recent studies suggest that loss of pyloric distensibility could cause a functional obstruction

Visceral hypersensitivity – a ubiquitous feature in many functional gastrointestinal disorders that could initiate or exacerbate symptoms

with gastric emptying rate.[13] Further, FD has correlated more closely with visceral hypersensitivity.[45]

It is evident that FD and gastroparesis share clinical characteristics that make differentiating the 2 conditions difficult. The Rome IV update proposed a separation of unexplained nausea and vomiting from FD.[38] These patients with unexplained nausea and vomiting are a major clinical challenge and their symptoms are not explained by delayed gastric emptying, although a gastroparesis diagnosis is usually given in this patient population.[37] The disparate and inconsistent findings from these studies suggest that gastric emptying alone is not the principal driver of symptoms in either FD or in most patients diagnosed with gastroparesis (however defined), and that other mechanisms may be relevant to individual patients or patient groups. For example, it has been observed that the symptom pattern in patients with idiopathic gastroparesis is determined more by proximal stomach dysfunction than by the severity of delayed emptying.[43] Similarly, among patients with FD and predominant pain, hypersensitivity to gastric distention appears to be the dominant finding.[45] Clinical research suggests that among the heterogeneous patient population bearing the label gastroparesis, there may be a small population with especially severe symptomatology in which the severity of gastric emptying delay may be predictive of poor outcome.[50] These patients may have a true diagnosis of gastroparesis.

Advances in Research

Pioneering research points the way to the presence of fundamental pathologic findings in gastroparesis that may shed more light on the pathophysiology of gastroparesis symptoms and provide a more appropriate label (Figure).[51-53] Employing full-thickness gastric biopsies, a loss of interstitial cells of Cajal (ICC) was identified as a common pathologic finding associated with delayed gastric emptying in diabetic, but not idiopathic, gastroparesis.[51] However, ICC or enteric nerve loss did not correlate with symptom severity.[51] In contrast, clinical severity and nausea were associated with a myenteric immune infiltrate among patients with idiopathic gastroparesis.[51] The number of CD206-positive macrophages correlated with the number of ICC, suggesting that these macrophages may exert a protective effect on ICC in the human stomach.[52] These studies offer hope for a future that is based on proven clinicopathologic correlations.

Tests

In most institutions, gastric emptying is evaluated by a scintigraphic assessment of gastric emptying rate performed in the nuclear medicine department. The American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine and Molecular Imaging recommend a standardized test with a technetium-labeled, low-fat, egg-white, albumin-based meal with

imaging at 0, 1, 2, and 4 hours after meal ingestion.[54] Based on a large multicenter study, gastric emptying is best defined as the retention of more than 10% of the radioisotope-labeled meal at 4 hours following meal ingestion.[55] Studies of shorter duration (eg, 90 minutes, 2 hours), although commonly performed, may be misleading and can cause an overdiagnosis of gastroparesis. Alternatives to scintigraphy include a breath test that involves the use of nonradioactive $^{13}CO_2$ bound to octanoic acid. Although this breath test is not widely used in the United States, results have been shown to correlate well with those of scintigraphy.[56-58] Gastric emptying may also be measured using a nondigestible wireless ambulatory capsule (SmartPill, Given Imaging).[59,60] The capsule technology has been approved by the US Food and Drug Administration for this application.

Conclusion

Gastroparesis is often inaccurately defined and misdiagnosed in patients whose symptoms have little to do with the rate at which the stomach empties its contents. A minority of patients with severely impaired gastric motor functions do have an inability of the stomach to empty, resulting in vomiting, weight loss, bezoars, and, in patients with diabetes, impairment of diabetic control; however, the majority of patients are mislabeled as gastroparetic. The temptation to rush to tests and the subsequent misdiagnosis deflect attention from gathering critical elements of the patient's history that may reveal other diagnoses (eg, rumination, dumping syndrome, cyclic vomiting syndrome, iatrogenic or central nausea) that may be more relevant and amenable to therapy. We propose that the symptom landscape that includes all patients who formerly would have been diagnosed with either FD or gastroparesis be revisited (using Rome IV criteria), and presentations that are clinically coherent and pathophysiologically convergent be identified. In the meantime, and with the exception of the aforementioned cases in which gastric emptying delay is clearly relevant, the term gastroparesis should be applied carefully, and symptoms such as unexplained nausea and vomiting should be thoroughly evaluated and defined. Gastroparesis and FD are equally valid terms when applied correctly; the challenge lies not in the terminology but in its usage. Mislabeling a patient as gastroparetic may prolong hospital stays, increase readmission rates, and increase utilization of ineffective and expensive interventions.

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