DOI: https://doi.org/10.22516/25007440.561

Review article

Current diagnosis and treatment of gastroparesis: A systematic literature review

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Citation:
Mayor V, Aponte D, Prieto R, Orjuela E. Current diagnosis and treatment of gastroparesis: A systematic literature review . Rev Colomb Gastroenterol. 2020;35(4):471-484. https://doi.org/10.22516/25007440.561

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Received: 07/05/20
Accepted: 16/09/20

Abstract

Normal gastric emptying reflects a coordinated effort between different regions of the stomach and the duodenum, and also an extrinsic modulation by the central nervous system and distal bowel factors. The main events related to normal gastric emptying include relaxation of the fundus to accommodate food, antral contractions to triturate large food particles, the opening of the pyloric sphincter to allow the release of food from the stomach, and anthropyloroduodenal coordination for motor relaxation. Gastric dysmotility includes delayed emptying of the stomach (gastroparesis), accelerated gastric emptying (dumping syndrome), and other motor dysfunctions, e.g., deterioration of the distending fundus, most often found in functional dyspepsia. The symptoms of gastroparesis are nonspecific and may mimic other structural disorders.

Keywords

Gastric emptying, Gastroparesis, Gastric dysmotility.

INTRODUCTION

Gastric emptying depends on the coordinated activity between different areas of the stomach and the duodenum. This process is extrinsically modulated by the central nervous system (CNS) and by factors occurring in the distal intestine. Gastroparesis is a chronic symptomatic disorder consisting of delayed gastric emptying without mechanical obstruction being present. Its main causes are of endocrine, neurological and metabolic origin, and the most frequent clinical entity is diabetic gastroparesis. Symptoms are variable and may overlap with other gastrointestinal diseases. Patients with gastroparesis suffer from nausea, vomiting, early satiety, anorexia, weight loss, and epigastric pain (1). Different diagnostic techniques and therapeutic approaches have been proposed over time. Therefore, this systematic review aims to describe the current relevant literature on the different diagnostic options and therapeutic approaches to gastroparesis. A summary of what is known to date about gastroparesis, with an emphasis on its etiology, pathophysiology, and current definitions is performed prior to describing how the review was conducted and the results retrieved. With that in mind, the findings retrieved from the studies included in the review regarding contrast radiography techniques, gastric emptying scintigraphy, drugs affecting gastric emptying, gastroparesis breath test,

electrogastrography, antroduodenal manometry, ultrasonography, magnetic resonance imaging and positron emission computed tomography are presented in this paper. Furthermore, dietary treatment, pharmacological treatment (anti-5-hydroxytryptamine3 [anti-5HT3], anti-D 2, peptide agonists associated with gastric emptying, antidepressants, and macrolides), gastric electrical stimulation and surgical approaches are also described.

WHAT IS KNOWN ABOUT GASTROPARESIS?

The main causes of gastroparesis are of endocrine, neurological and metabolic origin. It usually occurs in diabetic patients, after undergoing surgeries involving vagotomy and by unknown causes (idiopathic gastroparesis) (**Table 1**). Symptoms are variable and include nausea, vomiting, early satiety, anorexia, weight loss, and epigastric pain (1).

Pathophysiological alterations in patients with gastroparesis are associated with (**Figure 1**):

1. Impaired gastric accommodation caused by loss of gastric inhibitory peptides or vagus nerve damage.
2. Depletion of interstitial cells of Cajal in diabetes cases and post-infection lesions, resulting in arrhythmias (e.g., tachygastria and ectopic pacemakers, associated with nausea and vomiting).
3. Abnormal smooth muscle contractions due to altered function of the neurons of the enteric nervous system.
4. Atrophy or fibrosis of the smooth muscle.
5. Altered release of gastrointestinal peptides (motilin, ghrelin, and pancreatic polypeptide, which facilitate gastric motility).
6. Pyloric sphincter dysfunction and the concept of *pyloric spasm* (2).

Patients with gastroparesis have nonspecific symptoms that can simulate those of structural disorders such as ulcer-opeptic disease, partial gastric or intestinal obstruction, gastric cancer, and pancreatic biliary disorders. Symptoms of gastroparesis and functional dyspepsia also overlap; the latter is characterized by experiencing chronic or recurrent discomfort in the upper abdomen, although many people report dysmotility together with nausea, vomiting, and early satiety, and some subgroups of patients experience delayed gastric emptying (3, 4).

The correlation of symptoms with delayed gastric emptying is variable in diabetic gastropathy, idiopathic gastroparesis, and functional dyspepsia cases. Recent studies have reported that early satiety, postprandial fullness, and vomiting predicted delayed gastric emptying in patients with functional dyspepsia (3, 4). In addition, a feeling of fullness and meteorism have been found to predict delayed gastric emptying in patients with diabetes (5, 6).

Table 1. Reversible causes of gastroparesis

Etiology	Examples
Pharmacological	A. Commonly prescribed medications: - Anticholinergics, PPIs - Calcium channel blockers - Cyclosporine - Exenatide - Pramlintide - Lithium - Octreotide B. Controlled substances: - Narcotics
Mechanical	Superior mesenteric artery syndrome Median arcuate ligament syndrome Median arcuate ligament syndrome
Metabolic	Neuromyelitis optica with aquaporin-4 autoantibodies (astrocytic water channels)
Psychiatric	Anorexia nervosa Bulimia nervosa
Endocrine	Hypothyroidism Adrenal insufficiency Diabetes mellitus
CNS disorders	Multiple sclerosis Parkinson's disease
Paraneoplastic	ANNA-1, sometimes called *anti-Hu*

ANNA-1: type 1 anti-neuronal nuclear antibodies; PPI: Proton pump inhibitors.

Patients with functional dyspepsia show exaggerated sensitivity to gastric distension, which suggests the contribution of afferent neuron dysfunction to the pathogenesis of the symptom. Also, in diabetic patients with symptoms of dyspepsia, gastric distension causes nausea, meteorism and marked abdominal discomfort. It is believed that these symptoms may be caused by sensory nerve dysfunction in these patients (7, 8).

In up to half of patients undergoing routine examinations such as upper gastrointestinal (GI) endoscopy or gastrointestinal endoscopy (GE) and laboratory tests, the identification of organic or biochemical abnormalities that easily explain gastroparesis symptoms is not possible. In most adults, gastroparesis is idiopathic. Complications associated with this disease may include Mallory-Weiss tears, bezoar formation, malnutrition, aspiration pneumonia, and electrolyte disorders (3, 4).

These so-called functional gastrointestinal disorders are highly prevalent, misunderstood, and have a great health care and socioeconomic impact. Therefore, it is important

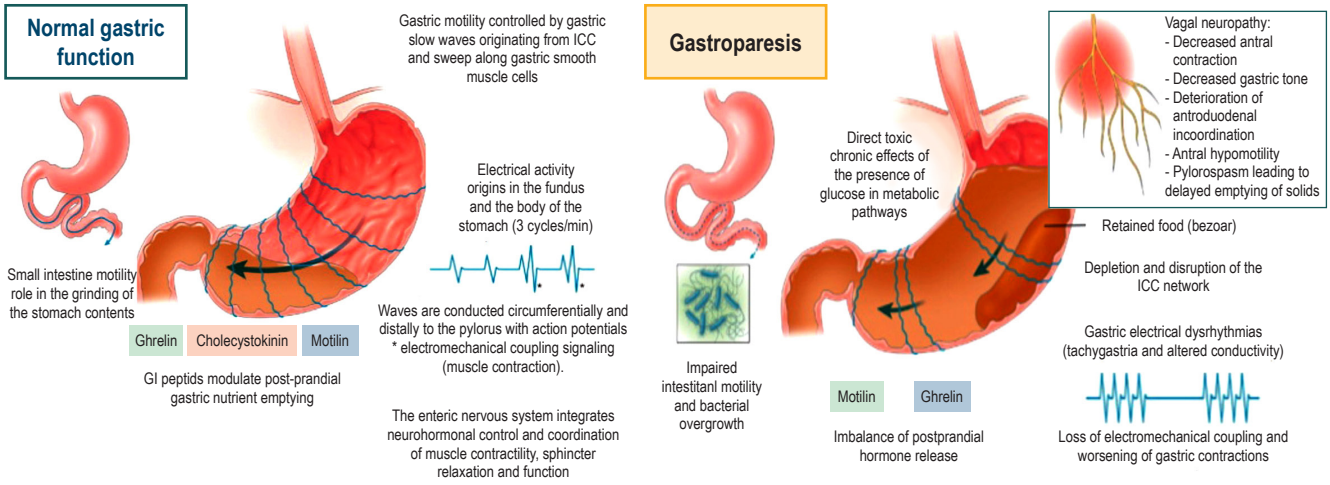

Figure 1. Gastroparesis pathophysiology. ICC: Interstitial cells of Cajal. Adapted from: Reddymasu SC, Sarosiek I, McCallum RW. Severe gastroparesis: medical therapy or gastric electrical stimulation. Clin Gastroenterol Hepatol. 2010;8(2):117-24.

to understand their possible diagnostic and therapeutic options (9).

Gastrointestinal and non-gastrointestinal disorders may be accompanied by gastroparesis, such as gastroparesis associated with gastroesophageal reflux disease (GERD) and generalized disorders of gastrointestinal motility.

Gastroparesis associated with GERD

Rates of up to 40% of gastroparesis prevalence have been described in patients with GERD, although other studies have reported occurrence rates of only 10% (10). The pathophysiology of delayed gastric emptying in patients with GERD is not clear. It is believed that distended gastric stasis may promote transient lower esophageal sphincter relaxation with subsequent gastroesophageal acid reflux (10). Recent studies suggest that delayed emptying of the proximal stomach, but not of the entire stomach, can be correlated with esophageal acid exposure, so performing gastric scintigraphy in patients with GERD symptoms refractory to acid suppressor therapy is considered appropriate (11).

Generalized disorders of gastrointestinal motility

Chronic intestinal pseudo-obstruction

It is a syndrome with recurrent symptoms that suggest intestinal obstruction without mechanical cause. Imaging findings in patients with chronic intestinal pseudo-obstruction include luminal dilatation with air-fluid levels throughout the small bowel. This disorder can be caused by several systemic diseases such as scleroderma, amyloidosis, myxedema, long-term diabetes *mellitus*, and the paraneoplastic complications most commonly observed in small cell lung carcinoma.

Myopathic and neuropathic chronic intestinal pseudo-obstruction are the two main types of this disease, and they can be differentiated by means of small intestine manometry. In myopathic form, contractions of low amplitude with normal coordination are observed. In neuropathic type, the amplitude of contractions is normal, but their morphology is disorganized, including disruption of phase III activity, bursts of non-propagating activity during fasting, and failure to achieve conversion from the fasting to the postprandial fed motor pattern. In the case of pseudo-obstruction of paraneoplastic origin, a variety of autoantibodies may be detected, such as ANNA-1 or anti-Hu antibodies, among others (12).

Constipation

A study found that 19% of patients with primary constipation had delayed gastric emptying. Another study conducted in patients with irritable bowel syndrome reported that delayed emptying of solids occurred in 64% of them, especially in those with predominating constipation. This fact has major implications for treatment, as patients with chronic severe constipation and proximal colonic dysmotility do not respond satisfactorily to surgical treatment (subtotal colectomy) (13).

Nongastrointestinal disorders

The most relevant nongastrointestinal disorders associated with delayed gastric emptying are ischemic gastroparesis, gastroparesis associated with a malignancy, chronic pancreatitis, kidney failure, and infectious causes of gastroparesis.

Ischemic gastroparesis

Patients with chronic atherosclerosis may experience episodes of gastric ischemia that may manifest as gastritis, ulcers, or gastroparesis. Diagnosis is made by angiography, and revascularization is considered the treatment of choice because it usually improves gastric emptying and corrects gastric dysrhythmias (14).

Gastroparesis associated with a malignancy

Gastroparesis has been described in patients with esophageal, gastric, pancreatic, breast and lung carcinoma. Although its pathophysiology is unknown, it has been attributed to paraneoplastic effects, neural invasion, or side effects of chemotherapy. In gastric cancer cases, tumor infiltration of the wall may alter the coordination of the neuromuscular function.

Cases of gastroparesis have been reported after radiation therapy to the abdomen and during chemotherapy (15), as well as after bone marrow transplantation and celiac plexus blockage to treat chronic pain in pancreatic cancer (16).

Chronic pancreatitis

A study found that 44% of patients with chronic pancreatitis of the accessory pancreatic duct had delayed gastric emptying. It was also considered that some of the abdominal pain, nausea and vomiting episodes in these patients may be due to gastroparesis (17).

Kidney failure

The intensity of symptoms such as nausea, vomiting, anorexia, and early satiety observed in patients on hemodialysis patients has been correlated with the degree of delayed gastric emptying (18). Other studies have also reported that delayed gastric emptying of solids in patients with kidney failure is correlated with changes in nutritional status biochemical indicators (19).

Infectious causes of gastroparesis

Delayed gastric emptying may occur in patients with acute viral infection caused by herpes zoster virus, Epstein-Barr virus, cytomegalovirus (CMV), rotavirus, and parvovirus-like agents such as norovirus.

In almost all cases, the delay in gastric emptying is transient and resolves over time after recovering from the viral infection. Although reports are largely anecdotal, a small number of these patients develop chronic symptoms (20).

CMV gastroenteritis occurs most commonly in immunocompromised people, particularly in transplant patients. In these cases, GI endoscopy usually shows large gastric folds and gastric inflammation, including acute superficial gastritis, ulcers, and duodenal erosions. Viral cultures of gastric biopsy specimens and histological evidence of CMV inclusions in the gastric mucosa usually allow confirming the diagnosis.

Delayed gastric emptying occurs in one third of HIV-positive people, particularly in those with advanced HIV disease, defined by a low CD4 cell count, significant weight loss, and enteric infections (21).

The effects of *Helicobacter pylori* on gastric motor function have been controversial. Few works suggest an association with gastroparesis (22), and in almost all studies, an association between active *H. pylori* infection and delayed gastric emptying or functional dyspepsia has not been found. Only one study reported the low prevalence of *H. pylori* infection and its relationship with reactive gastropathy (23).

Gastrointestinal motility and sensitivity disorders can be identified in tests such as esophageal manometry, acid perfusion test, gastric emptying scan, sphincter of Oddi manometry, colonic transit measurements, and anorectal manometry.

The clinical practice guidelines for the management of gastroparesis in adults published in 2013 recommend restoring fluids and electrolytes and providing nutritional support, preferably through the oral route (1). Pharmacological treatment is used in conjunction with diet therapy to improve gastric emptying and achieve relief of symptoms of associated gastroparesis. Prokinetic agents are usually the first-line pharmacological treatment and work by increasing gastrointestinal motility. In contrast, metoclopramide oral solution at the lowest effective dose is the drug of choice in patients who do not respond to treatment with prokinetics. Other pharmacological recommendations include oral administration of erythromycin to improve gastric emptying and antiemetics, and the use of agents alleviating symptoms associated with gastroparesis, or tricyclic antidepressants for the treatment of refractory nausea and vomiting. Neither antiemetics nor tricyclic antidepressants improve gastric emptying time and are only recommended, under certain conditions, as pharmacological treatment of gastroparesis in adults (2).

DATA COLLECTION

A search was conducted in the PubMed database using the MESH terms "gastroparesis" AND "gastric empathy" AND "diagnosis and treatment". The search yielded 618 results. After duplicates were removed, the following inclusion criteria were applied as search filters: systemic review articles, meta-analysis, case reports, and randomized and non-randomized clinical trials conducted in humans older than 18 years published in Spanish or English between January 2000 and December 31, 2016. Studies conducted in animals, or in participants under 18 years, written in languages, and published in different dates were excluded.

In total, 240 articles were retrieved from the search conducted in PubMed after applying the search filters. Then, we carried out a systematic reading of their abstracts, and those considered to be the most relevant for the purposes of this review were selected for full analysis (71 articles) (**Figure 2**).

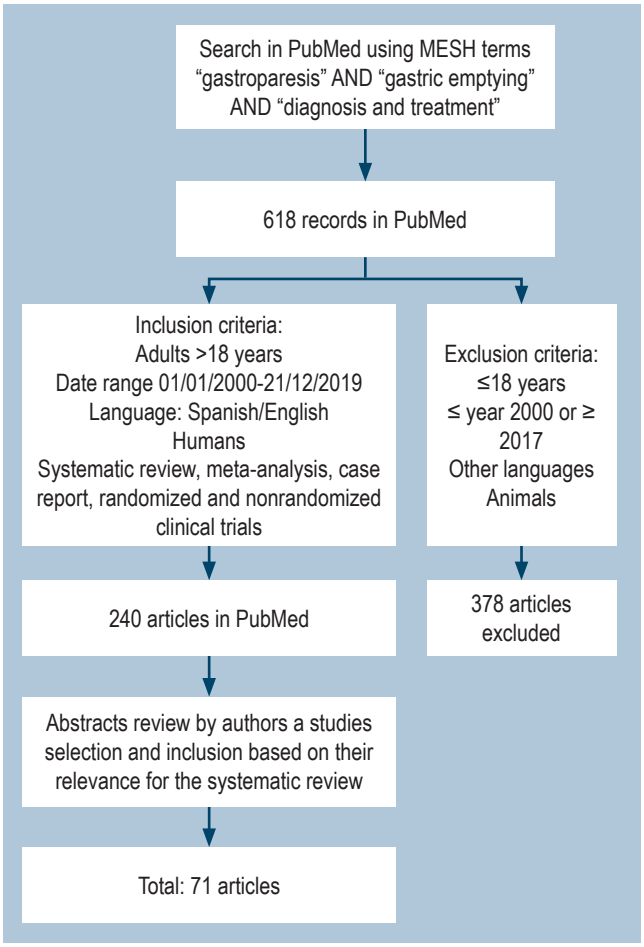

Figure 2. Data collection process

RESULTS

Based on the above, the following information regarding the current diagnosis and treatment of gastroparesis in adults was obtained.

Diagnosis

Gastroparesis is diagnosed in symptomatic patients in whom delayed gastric emptying is confirmed and after ruling out other causes.

Upper digestive tract endoscopy and imaging studies of the upper digestive tract must be performed to rule out pyloric stenosis, neoplasms, or active ulcerative disease in the antrum, pylorus, or duodenum. Endoscopy is more sensitive than barium x-ray to detect mucosal lesions, although double-contrast techniques improve the sensitivity of imaging studies (24).

A contrast x-ray of the small intestine is performed in patients with resistant symptoms and which the origin of symptoms seems to be the small intestine (e.g., extensive distension, steatorrhea, and fecal emesis), or in patients with evidence of dilated small bowel loops on a simple x-ray. When an upper gastrointestinal tract x-ray is requested, a gastrointestinal transit test may be requested; in this test, barium contrast medium is administered orally to dilute lesions in the small intestine. This imaging study allows the accurate detection of a high-grade obstruction of the small intestine, it usually provides adequate assessment of the terminal ileum, and may rarely suggest superior mesenteric artery syndrome. On the other hand, enteroclysis (small bowel enema), which is performed after a nasoduodenal or orogastric tube is placed, provides double-contrast imaging and is more accurate for detecting small lesions of the intestinal mucosa, medium to intermediate-grade obstructions, and small bowel neoplasms. Finally, a contrast (oral and intravenpus) computed tomography may also be useful for the detection and location of an intestinal obstruction.

Once a mechanical condition of the stomach and small intestine is ruled out, the gastric emptying rate of solids is usually determined by scintigraphy. An abnormal gastric emptying test result suggests, but does not confirm, that symptoms are associated with gastroparesis. When gastric emptying is normal, other causes should be considered. However, in symptomatic patients with normal gastric emptying, it is not possible to rule out a disorder of motor gastric function because regional gastric abnormalities, which include impaired fundic accommodation or gastric and electrical dysrhythmias, may be accompanied by symptoms (25).

Other complementary tests to confirm delayed gastric emptying include thyroid function tests to rule out hypothyroidism, and hemoglobin A1c test (HbA1c) to estimate long-term blood glucose regulation in diabetic patients. Moreover, based on the findings related to the current disease, the patient's history, and physical examination, autoimmune tests, neuromuscular disease studies, or paraneoplastic phenomena will be considered. Once other causes are ruled out, idiopathic gastroparesis is diagnosed (26, 27).

Several methods have been proposed for quantifying gastric emptying, gastric motor function and myoelectrical activity, including contrast imaging techniques, gastric emptying scintigraphy, gastroparesis breath test, electro-

gastrography, antroduodenal manometry, ultrasonography, magnetic resonance imaging, and positron emission tomography.

Contrast imaging techniques

Upper gastrointestinal series with barium contrast is not a sensitive method for measuring gastric emptying, because it is difficult to quantify the relative fraction of contrast passing through the intestine and because barium is not a physiological test meal. However, it may suggest gastroparesis due to poor gastric emptying, gastric dilation, and presence of retained food or a bezoar. Lack of, or very little, barium emptying at 30 minutes and gastric barium retention at 6 hours suggest gastroparesis (28).

The relevance of barium X-ray is based on the exclusion of mucosal lesions and mechanical gastric outlet obstruction.

Gastric emptying scintigraphy

Gastric emptying scintigraphy of a solid-phase meal is considered the gold standard for diagnosing gastroparesis because it quantifies the emptying of a physiological caloric meal. The measurement of solid-meal gastric emptying is more sensitive to detect gastroparesis because fluid emptying may remain normal even in patients with advanced delayed gastric emptying. Liquid-phase emptying studies are most commonly performed after gastric surgery in cases where rapid emptying syndrome is suspected. The usefulness of gastric scintigraphy to guide treatment and predict clinical response has been discussed (29). In this regard, some clinicians have proposed performing a dual-phase study of solid and liquid emptying in patients who underwent gastric surgery to establish whether symptoms are caused by delayed solid emptying or by rapid fluid emptying (30).

For solid-phase gastric emptying scintigraphy studies, almost all imaging studies centers use an egg sandwich labeled as having sulfide colloid and technetium-99m (^{99m}Tc) as a test meal (24). More recently, a technique consisting of using egg whites as a meal and performing scans immediately after meal ingestion and at 1, 2, and 4 hours has been proposed to provide a degree of standardization among imaging centers (31). This test meal has a very low-fat content and, in theory, could provide results that differ from conventional foods. Regardless of the food being used, cooking the radiotracer with it is necessary to ensure the attachment of the radioisotope during the solid-phase study. Gastric emptying scintigraphy should be prolonged at least two hours after eating.

However, even if scintigraphy is prolonged for this period, there may be significant day-to-day variability (up to 20 %) in gastric emptying rhythms. The test is less safe for shorter times due to the larger variations of normal gastric emptying. Some researchers recommend prolonging the scan for 4 hours to improve accuracy to establish the presence of gastroparesis (32, 33).

The simplest method for interpreting this gastric emptying imaging study is to report the percentage of retention at defined times after eating (usually 2-4 hours). It is also possible to estimate half gastric emptying times; however, extrapolation of the emptying curve of an individual in which 50% of the food consumed is not emptied during the actual imaging time may provide an inaccurate estimation of gastric emptying half-time (34).

Patients should discontinue medications that may affect gastric emptying for an appropriate period based on the biological half-life of the drugs prior to undergoing the scitigrapgy (**Table 2**). Most medications will take 48 to 72 hours to be eliminated from the body.

When symptoms are severe, serotonin receptor antagonists, such as ondansetron, may be administered before performing gastric scintigraphy, since they have little effect on gastric emptying (32). Also, hyperglycemia (glucose > 270 mg/dL) delays gastric emptying in diabetic patients. Thus, gastric emptying scintigraphy may be postponed until relative euglycemia is achieved, so that a safe estimation of the emptying parameters without the presence of an acute metabolic alteration is obtained (35, 36). Premenopausal women have slower gastric emptying than men.

Gastroparesis breath test

To measure gastric emptying, breath tests using a non-radioactive carbon isotope (^{13}C) have been validated; this isotope is administered together with a solid food meal attached to a medium-chain triglyceride called *octanoate* (37). In other studies, this isotope has been bound to acetate or algal protein (38). After ingestion and through gastric emptying, these substances are absorbed into the small intestine and metabolized to $^{13}CO_2$, which is expelled by the lungs during breathing. Measuring $^{13}CO_2$ levels allows the assessment of solid-phase gastric emptying. The octanoate breath test has yielded reproducible results that correlate with gastric emptying scintigraphy findings (37); however, it is necessary to validate these tests in patients with emphysema, cirrhosis, celiac disease, or pancreatic insufficiency since octanoate metabolism may be altered in these patients (38).

Electrogastrography

This study is carried out by attaching skin electrodes to the abdominal wall at the level of the stomach. It records gastric myoelectrical activity, known as *slow wave*, which is responsible for controlling the maximum frequency and amplitude of distal gastric contractions. Consumption of any meal increases the amplitude of the electrogastrography signal, which has been associated with an increase in antral contractility or mechanical distension of the stomach (39).

Table 2. Drugs that affect gastric emptying

Gastric emptying retardants
- Opioid analgesics
- Anticholinergic drugs
- Tricyclic antidepressants
- Calcium channel blockers
- Progesterone
- Octreotide
- PPIs and H2 receptor blockers
- IFN-α
- L-DOPA
- Fiber
- Sucralfate
- Aluminum hydroxide antacids
- β agonists
- Glucagon
- Calcitonin
- Dexfenfluramine
- Diphenhydramine
- Alcohol
Gastric emptying accelerators
- Prokinetic drugs
- Metoclopramide
- Erythromycin/clarithromycin
- Cisapride
- Domperidone
- Tegaserod
- β agonists

PPI: Proton pump inhibitors; IFN-α: Interferon alfa.

Electrogastrography test quantifies the dominant frequency and regularity of gastric myoelectric activity, the percentage of time during which abnormal slow wave rhythms exist while fasting and after ingestion and assesses the increase in signal amplitude after a meal (40).

Electrogastrography is considered abnormal when dysrhythmias occur for more than 30% of the recording time, or when consumption of a meal does not cause an increase in signal amplitude (39).

This test is considered complementary to gastric emptying scintigraphy in the management of patients with resistant symptoms, suggestive of an upper gastrointestinal motility disorder (39).

Antroduodenal manometry

Gastric motor activity depends on the state of fasting or ingestion and is specific to each of them. The interdigestive pattern (fasting) consists of three cyclical phases known as *the migratory motor complex* (MMC), which occurs every two hours unless interrupted by an intake. Phase I is a period of motor latency, followed by a period of intermittent phasic contractions (phase II). Phase III consists of a burst of regular rhythmic contractions that spread from the antrum to the proximal small intestine; during this phase, dietary fibers and non-digestible solids are removed from the proximal intestine.

Antroduodenal manometry evaluates gastric and duodenal motor function in both fasting and postprandial periods. It can be performed for short periods of 5 to 8 hours but is usually carried out on an outpatient basis for a period of 24 hours, in which symptoms are correlated with abnormal motor patterns. Its use is especially indicated in patients with motor dysfunction with unexplained nausea and vomiting, patients with gastric or small bowel stasis, and patients with chronic intestinal pseudo-obstruction (41, 42).

In cases of gastroparesis, antroduodenal manometry may show a decrease in the frequency or strength of antral contractions and detect most phase III complexes in the duodenum. In some people, it is possible to observe an increase in tonic and phasic activity of the pylorus (pylorospasm) or irregular bursts of small intestine contractions.

Myopathic disorders, such as scleroderma or amyloidosis, produce low amplitude rhythmic contractions, while neuropathic conditions are characterized by normal-amplitude contractions with abnormal propagation, including loss of intestinal phase III, random bursts of activity and lack of conversion to the fed pattern after consuming a meal. Therefore, antroduodenal manometry makes it possible to differentiate the cause of gastroparesis between these two etiologies.

Also, antroduodenal manometry is a useful test for diagnosing rumination syndrome or hidden mechanical intestinal obstructions, where two characteristic motor patterns are observed: cluster postprandial contractions lasting more than 30 minutes and separated by a period of quiescence (> 8 seconds), or simultaneous summation suggesting a common cavity phenomenon of a dilated segment of the intestine (42).

Some studies suggest that findings in antroduodenal manometry influence less than 20% of therapeutic decisions in patients with dysmotility syndromes (43).

Other motor gastric function tests

Ultrasonography

Transabdominal ultrasonography measures various parameters of motor gastric function. Serial changes in the antral cross-sectional area may provide a gastric emptying rate, which is considered complete when the antral area returns to the baseline level when fasting. Ultrasonography has also been used to measure the accommodation of the proximal stomach. Duplex ultrasonography can quantify the transpyloric flow of the liquid gastric content. Unfortunately, determining gastric emptying through ultrasound depends on the operator of the test and this test has been proved to be safe only to measure fluid emptying rates (44).

Magnetic resonance imaging

Stomach emptying and accommodation can be measured through magnetic resonance imaging using transaxial abdominal studies every 15 minutes. Magnetic resonance imaging allows differentiating between the gastric volume of a meal and the total gastric volume and determining gastric secretion rates. This is a non-invasive study that does not cause irradiation, but it is limited by the availability of equipment, the time required for its interpretation, and cost-related issues (44).

Proton computed tomography

Radionuclide imaging of the stomach wall has been used as a non-invasive measurement of gastric adaptation after intravenous injection of ^{99m}Tc pertechnetate, which is located in the gastric mucosa, and the subsequent performance of imaging studies using single photon emission computed tomography (45).

General measures

The treatment of gastroparesis has two main objectives: to identify and treat its cause, and to treat associated symptoms. This requires correcting hydroelectrolytic and nutritional deficiencies, modifying the diet and using prokinetic drugs that stimulate gastric motor activity, antiemetics to treat nausea and vomiting, and psychotropic agents to minimize symptoms. Although narcotic analgesics can improve abdominal pain rapidly, their chronic use can cause delayed gastric emptying, nausea, and vomiting, as well as dependence, which should be avoided. Total parenteral nutrition, although used in some refractory patients, has been associated with infections and thrombosis.

Similarly, lifestyle habits should be modified, and comorbidities should be monitored. This is the case of diabetic patients with gastroparesis, who usually have labile diabetes with long periods of significant hyperglycemia, since the latter delays gastric emptying, even when there are no fixed gastric motor deficits, and is likely to be mediated by reduced phasic antral contractility and induction of pyloric pressure waves (34, 46). It should also be noted that the intake of high amounts of alcohol tends to decrease antral contractility and impair gastric emptying (47), as well as smoking (48).

Dietary aspects

Gastroparesis can cause food aversion, poor oral intake, and consequent malnutrition. A study conducted in patients with diabetic gastroparesis and idiopathic gastroparesis found that 194 of them (64%) had calorie deficit diets, and only 5 patients (2%) followed the diet suggested for patients with gastroparesis. Deficiencies were evident in several vitamins and minerals. Patients with idiopathic disorders were more likely to have diets deficient in vitamins A, B_6, C and K, iron, potassium, and zinc than those with diabetes (49).

Patients who had a calorie deficit diet were characterized by having the most severe symptoms (abdominal distension and constipation). In addition, according to a multivariate logistic regression analysis, patients attending a nutritional consultation increased the chances of meeting total daily energy needs (*Odds ratio* [OR]: 1.51; $p = 0.08$) (46).

Pharmacological treatment

Prokinetics are considered the first-choice medication to treat patients with gastroparesis, although evidence of its efficacy is limited. A meta-regression analysis of the association between symptom improvement and frequency through performed based multiple studies about gastroparesis did not find a significant correlation between these two aspects (50).

Metoclopramide

Metoclopramide was approved to treat gastroparesis by the United States Food and Drug Administration (FDA) in 1979 and remains the first-line medication for the treatment of these patients. This drug acts as a prokinetic due to its antagonistic effect on dopamine receptor 2 (D_2R), promoting gastric emptying and binding to the 5-Hydroxytryptamine receptor 4 (serotonin 5-HT4) to stimulate the cholinergic nerve pathways in the stomach (51). Physiologically, it accelerates intestinal transit by increasing the tone and amplitude of gastric contractions, it increases the pressure of the lower esophageal sphincter, and it

improves antro-pyloro-duodenal coordination. Moreover, this antiemetic agent provides relief through central and peripheral dopamine receptors antagonism (52).

Parkman *et al.* (53) evaluated the efficacy of using metoclopramide nasal spray (10 or 20 mg) and tablets (20 mg) 4 times a day in 89 diabetic patients with symptoms suggestive of gastroparesis. Symptoms improved with the three nasal spray therapy modalities, showing better tolerance and similar or higher efficacy than the tablet-based treatment. Furthermore, in a multicenter study conducted in the United States, 285 diabetic patients with gastroparesis (82.5% with type 2 diabetes) were randomly assigned to a 4-week placebo or metoclopramide therapy consisting of oral administration (nasal spray) of 10 mg or 14 mg, 3 times a day 30 minutes before meals (54). In the subgroup analysis, females undergoing spray-based metoclopramide therapy showed a significantly greater relief of symptoms (52). It should be noted that nasal spray administration does not eliminate the possibility of neurological adverse effects.

Domperidone

This drug exerts its prokinetic effect by acting as a dopamine D2 receptor antagonist, thus improving antrum and duodenum contractions and, in turn, peristalsis. It also has antiemetic properties because it crosses the blood-brain barrier and acts on chemoreceptors located in the fourth ventricle (55).

In a double-blind, randomized, multicenter clinical trial comparing the use of domperidone 20 mg with metoclopramide 10 mg in patients with diabetic gastroparesis, a similar efficacy was found between both groups in terms of reducing the onset and severity of symptoms such as nausea, vomiting, early satiety, swelling, and distension. However, there was a significantly greater reduction in mental acuity in patients who were administered metoclopramide for 4 weeks. Moreover, fewer central neurological adverse effects (drowsiness, anxiety, depression, and acathisia) were observed after 2 and 4 weeks of follow-up in the domperidone group. In addition, domperione has no cholinergic activity (56).

Cisapride

Cisapride promotes the release of acetylcholine into the myenteric plexus of the intestine and indirectly stimulates gastrointestinal motility. It acts as a 5-HT4 receptor agonist and a 5-HT3 receptor antagonist, which contributes to the release of acetylcholine and its subsequent prokinetic effects. Unlike metoclopramide, it has no CNS effects due to its lack of antidopaminergic activity (57).

Although it was approved by the FDA for treating nighttime heartburn in patients with gastroesophageal reflux, a few studies have reported improved gastric emptying of both solids and liquids after single or repeated doses of cisapride (58). Some studies have shown that improvement in gastric emptying does not necessarily translate into a relief of symptoms (58), while others report that using this drug has not benefits in the treatment of gastroparesis. On the contrary, pharmacological surveillance after its commercialization has identified several cases of cardiac arrhythmia and sudden death, as this drug acts directly on the potassium channels of the heart, prolonging the QT interval and predisposing patients to the development of ventricular arrhythmias (59).

Other drug options

There are other types of prokinetic medications that are being used as attractive options for treating gastroparesis, including 5-HT receptor agonists (tegaserod and mosapride), dopamine receptor antagonists (levosulpiride), cholecystokinin receptor antagonists (dexloxiglumide), and motilin receptor agonists (mitemcinal [GM-611]. For example, levosulpiride, which has both antiemetic and prokinetic effects, can relieve symptoms and accelerate gastric emptying in diabetic patients with gastroparesis (60).

Ghrelin receptor agonists are a new class of prokinetics (61, 62). Oral administration of TZP-102, which was initially used in Phase IIb controlled trials conducted in in patients with type 1 or type 2 diabetes with clinical signs of gastroparesis and gastric emptying retardation, has been evaluated (61). Gastric emptying at baseline and at week 12 showed differences between the groups, but this study had some limitations including the permission of concomitant use of antiemetics and opioid analgesics, and the mismatch between symptom responses (62).

Relamorelin is another ghrelin receptor agonist that is administered subcutaneously. It has been reported that it improved gastric emptying and reduced symptoms severity in a pilot trial conducted in 10 patients with type 1 diabetes. It is currently in Phase II testing (63).

Psychotropic agents have also been used to treat patients with gastroparesis. Based on the assumption that visceral hypersensitivity contributes to the onset of symptoms, psychotropic drugs, especially tricyclic antidepressants, are often used in this setting, although evidence of their efficacy is unconvincing (64).

The efficacy of antidepressants to treat patients with dyspeptic symptoms, including those with delayed emptying, was also addressed in a placebo-controlled multicenter trial using amitriptyline and escitalopram (65). Said study included 292 patients with functional dyspepsia treated at 8 centers in the United States and who were randomly assigned to 12 weeks of treatment at night with placebo or with amitriptyline 50 mg or escitalopram 10 mg. Gastric emptying rate

was obtained at baseline and relief of symptoms of functional dyspepsia was assessed weekly. Response rates, defined as adequate symptoms relief for at least 5 of the last 10 weeks in the trial, were 40%, 53% and 38% for placebo, 53% for amitriptyline, and 38% for escitalopram (65).

Gastric electrical stimulation (GES)

The GES system has been approved by the FDA to treat patients who fail to respond or cannot tolerate medical therapy. This device consists of two electrodes that deliver low-energy, high-frequency pulses and are implanted in the muscle layer of the greater curvature, 9 or 10 cm from the pylorus, through laparotomy or laparoscopy. Leads are connected to a pulse generator, which is implanted subcutaneously into the abdominal wall (**Figure 3**).

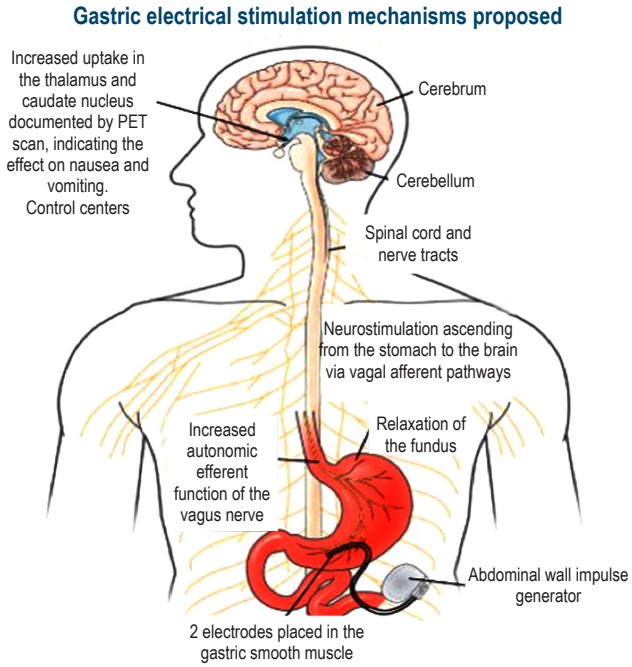

Figure 3. Gastric electrical stimulation device. PET: Positron emission tomography. Adapted from: Reddymasu SC, Sarosiek I, McCallum RW. Severe gastroparesis: medical therapy or gastric electrical stimulation. Clin Gastroenterol Hepatol. 2010;8(2):117-24.

Electrical stimulation at a 10% higher rate than that of the intrinsic slow wave initiates and establishes the passage of gastric myoelectric activity with long-lasting high-energy pulses (66).

The main effect of GES is increasing vagal activity based on the sympathetic-vagal relationship, which causes better fundal accommodation and improves food intake and storage capacity.

PET scans show increased activity in the thalamus and caudate nuclei after chronic therapy with GES. The device stimulates the projection of vagal afferent pathways to the nucleus of the solitary tract in the dorsal spine and the thalamus through reticular formation, achieving better control of symptoms.

A study showed efficacy of GES in 20 of 26 patients, with decreased nausea and vomiting at 3 and 6 months (67). In this research, gastric neurostimulation promoted gastric emptying of fluids but not of solids. Another study, a randomized, double-blind clinical trial conducted in 33 patients with chronic gastroparesis that was first controlled with made-up stimulation for two months and followed by an open-label phase in which the device was activated for one year, reported that Improvement was observed mainly in patients with diabetic gastroparesis, being higher than the improvement observed in the idiopathic gastroparesis group (68). Long-term follow-up over one year showed a decrease in mean vomiting frequency (25 to 6 times per week), with a concurrent improvement in quality of life. Subsequent studies have described improvements in nutritional parameters and reduced supplementary feeding requirements (69).

If GES is combined with pyloroplasty to accelerate gastric emptying, better results are achieved.

Surgery and endoscopic interventions for the management of gastroparesis

Surgery is often considered the last resort treatment in severe, drug-resistant gastroparesis, and few studies reporting results in this regard are available (70).

In a prospective study conducted in 35 patients (86% women) who underwent total or near-total laparoscopic gastrectomy for treating gastroparesis symptoms that did not respond to prokinetic and antiemetic therapies, being the most common reflux, nausea, and abdominal pain, surprisingly, 46% of them had previously undergone pyloromyotomy, 54% had undergone fundoplication, and 23% had undergone GES treatment. Follow-up at 6 months showed that surgery significantly improved nausea, abdominal distension, and burping, while no significant effect was observed in relation to pain (71). These studies on surgical management of gastroparesis report favorable results, but they have been conducted in an uncontrolled environment, with a relatively short follow-up time.

Taking into account the existing relevant literature, surgical management of gastroparesis must be considered with caution and temporary nasointestinal tube feeding can be used to evaluate the tolerance to nutrients that enter the small intestine rapidly (70).

DISCUSSION

The concept of *gastroparesis* still deals with the lack of association of symptoms with delayed gastric emptying. Based on recent studies, factors involved in its pathophysiology include pyloric resistance and increased duodenal contractility alteration. Studies on its pathophysiology confirm the importance of neuropathy and inadequate glycemic control as a long-term risk factor in the pathogenesis of gastroparesis in patients with type 1 diabetes. Loss of interstitial cells of Cajal, perhaps mediated through a M2 macrophage-deficiency, can be a key event at the cellular level.

The role of dietary therapy is under study, and a series of cases reporting favorable outcomes with surgical or endoscopic interventions have been published.

This paper reviews the available evidence on gastroparesis to provide clear and updated information about its diagnosis and treatment options. As stated above, there are several tests to assess patients with suspected gastroparesis. Gastric dysmotility treatments are based on dietary, pharmacological, and surgical therapies that relieve symptoms and maintain adequate nutrition.

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