

## **GASTROPARESIS DIAGNOSIS, ETIOLOGY AND TESTING**

Gastroparesis is a syndrome where an individual has objective or laboratory documented delayed gastric emptying of food from the stomach to the small intestines in the absence of any mechanical obstruction or blockage in the Gastrointestinal (GI) tract. Symptoms of Gastroparesis include early satiety, nausea, vomiting, bloating and abdominal distension, upper abdominal pain and at times anorexia. Postprandial fullness is often noticed, and patients cannot finish a good portion of their meal. Abdominal pain is variable. These symptoms of Gastroparesis may be nonspecific and can mimic other structural diseases of the upper GI tract including peptic ulcer disease, small bowel obstruction, partial gastric obstruction, gastric cancer, and pancreatic and biliary disorders. Many of these diseases are anatomical. Gastroparesis is a physiologic disorder.

There are disorders which can have identical symptoms to Gastroparesis, but objective diagnostic testing does not demonstrate delayed gastric emptying. We term these Gastroparesis-like disorders. These disorders may have normal or accelerated gastric emptying the later of which is seen with dumping syndrome. Functional dyspepsia may accompany these disorders. It is important to make the differentiation objectively whether there was delayed gastric emptying or not since drug therapy and general treatment oftentimes differs. For Gastroparesis, the symptoms above justify a gastric emptying test. However the diagnosis of Gastroparesis is specific to delayed gastric emptying, objectively documented by one of several tests. These tests will be discussed below.

There are disorders, including gastritis secondary to *Helicobacter pylori* infection, which also may occur and give identical symptoms to Gastroparesis with normal or accelerated gastric emptying. It also should be noted that the sensation of postprandial fullness, a sensation which occurs after even eating a little of a meal, correlates better with delayed gastric emptying than the upper abdominal pain and bloating which are more nonspecific.

Gastroparesis especially acute exacerbations of flare-ups have been increasing. Between the years 1995 and 2004, one study documented a 158% increase in hospitalizations. Some of the increased incidences could be explained by increased recognition and expedient testing. It is estimated that over four million Americans have Gastroparesis. The female to male ratio is 4:1, or possibly even higher. Some have postulated there is a hormonal mechanism that may be involved in the sex differential.

In summary, the diagnosis of Gastroparesis is made based on a combination of symptoms, absence of a structural abnormality or blockage, or gastric outlet obstruction or ulceration, and objectively documented delay in gastric emptying by a gastrointestinal laboratory test. Again, we stress accelerated gastric emptying and functional dyspepsia or even normal gastric emptying with dyspepsia with identical symptoms in those patients with Gastroparesis can occur, and it is very important to document delayed gastric emptying because selective therapy with medications or new therapies and devices, such as promotility enhancing drugs or

gastroesophageal stimulators (gastric-type pacemakers) may be indicated for one disorder and not the other.

Tertiary referral centers that would see high volumes of patients with Gastroparesis have in one study of 146 patients identified the etiology to be as follows: 36% were idiopathic, that is the cause of Gastroparesis was not known; 29% were diabetic, which could be either type 1 or type 2 diabetes; 13% were due to post-gastric surgery (these include bariatric surgery, partial gastrectomies, surgery for peptic ulcer disease with Vagus Nerve injury, and surgery for reflux esophagitis, so call Nissen); 7.5% were due to Parkinson's disease; 4.8% due to collagen vascular disorders the most common usually be scleroderma; 4.1% due to a disorder known as intestinal pseudo-obstruction; and 6% were due to other varied causes. Therefore, the two major causes are idiopathic or unknown, and diabetic with the third most common cause being Gastroparesis due to various upper GI-type surgical procedures. One should check for the presences of diabetes in patients who present with Gastroparesis with hemoglobin A1c test and a fasting blood sugar or a postprandial blood sugar. Also, one should check for thyroid disease. Prior history for gastric or bariatric surgery should be taken and sought after also. Also, autoimmune disorders should be ruled out especially collagen vascular diseases. Neurological diseases also need to be ruled out such as Parkinson's disease.

Some patients with Gastroparesis report having a viral illness just prior to the episode. These patients many times will improve over time. However, there is a subset of patients who may not improve over time especially if the virus is an Epstein-Barr virus, a Cytomegalovirus, or a Herpes Zoster virus. These types of viral infections can have protracted Gastroparesis courses in which the patients do not respond over time. Gastroparesis has also been reported in HIV patients.

Medications can also cause delay in gastric emptying and producing Gastroparesis syndrome. These especially include narcotic and anticholinergic agents (including antidepressants). There are also diabetic agents that belong to the class of GLP-1 and Amylin analogues, and these need to be excluded. Diabetic medications commonly implicated include Exenatide, which is a GLP-1 analogue, and Pramlintide. So, antirejection medicines such as Cyclosporine can also cause Gastroparesis. Narcotics are a common culprit. Alcohol can potentiate or cause Gastroparesis. Many anticholinergic agents such as those found in antidepressants whether they are SSRI, SNRI or tricyclics, calcium channel blockers, blood pressure medicines such as Clonidine, dopamine agonists, such as those used for Parkinson's disease (Sinemet), histamine-H2 receptor antagonist, Lithium, nicotine, Progesterone, and proton-pump inhibitors can also be implicated. Medicines used as antispasmodic agents such as Bentyl may also potentiate Gastroparesis. An estimated 1/4 to 1/2 of patients with type 1 diabetes and 1/4 of patients with type 2 diabetes demonstrate some degree of Gastroparesis. Patients diagnosed with Diabetes, usually have other end-organ abnormalities as well, including of the eye, heart, brain or kidneys which accompanies the Gastroparesis also. There is a subgroup of patients who develop Gastroparesis immediately after Cholecystectomy. There is a subset of patients who have gastroesophageal reflux disease and nonulcer dyspepsia associated with Gastroparesis. In

addition to Parkinson's disease, we have also seen cases of Gastroparesis as directed result of Multiple Sclerosis, Cerebral Palsy, and other neurological disorders.

Some cases of Gastroparesis are associated with abnormal autonomic function, which is general and some specific which we call Abdominovagal dysfunction. The latter can be tested with Postprandial Pancreatic Polypeptide blood tests.

Symptoms in Gastroparesis are not specific for any specific etiology and no significant overlap. However, patients with Idiopathic Gastroparesis have more early satiety and abdominal pain. This abdominal pain is usually induced by eating, can be nocturnal or it can interfere with sleep. However, it can occasionally be chronic. Patients with diabetic Gastroparesis usually have more nausea and vomiting than abdominal pain or early satiety. Blood sugar control is important in treating Gastroparesis symptoms in patients with diabetes.

Type 1 and type 2 diabetes are known to damage the Vagus Nerve. The Vagus Nerve, the major portion of the Parasympathetic nervous system outside the brain is known to control the GI tract. Parasympathetic insufficiency, including that found in Diabetic and Cardiovascular Autonomic Neuropathy are highly associated with Gastroparesis. Many of the viruses that we have discussed, including HIV, can also damage the Vagus Nerve. Many postviral infections which lead to Gastroparesis are known to cause a cholinergic dysautonomia due to abnormality of either the Vagus Nerve or the Autonomic Enteric system within the GI tract. The Parasympathetic nervous system is also known as the Cholinergic nervous system because Acetylcholine is its primary neurotransmitter.

This is a complicated area. The Vagus Nerve is very susceptible (exposed and vulnerable to insult) as it is the longest cranial nerve in the body and is responsible for many functions. As one of its functions, the Vagus Nerve transmits impulses to the stomach and intestines to modulate motility through peristalsis. More Vagal activity increases peristalsis and less Vagal activity decreases peristalsis. When the Vagus Nerve is damaged, transfer of food from the stomach to the small intestines is reduced because the muscles (peristalsis) will not operate properly. Injury to the Vagus Nerve, therefore, can impair gastric emptying.

One needs to differentiate Rumination Syndrome and other eating disorders including Anorexia Nervosa and Bulimia from Gastroparesis when evaluating patients with nausea, vomiting, abdominal pain and abdominal bloating. In Rumination Syndrome, there is abnormal contraction of the abdominal musculature and individuals regurgitate their own food within a short period of time after eating, usually within 15 minutes. With Gastroparesis, usually symptoms of vomiting occur an hour or more after eating. Also, patients who are on chronic cannabinoid agents have a syndrome (Cannabinoid Hyperemesis) which can mimic Gastroparesis when they have a significant amount of vomiting (known as hyperemesis). When they have these symptoms, people should stop using cannabinoid agents.

Interestingly, cannabinoid agents can also be useful in treating nausea from Gastroparesis; therefore, there is a fine line between when they are used for treatment and when they can

cause excessive vomiting. We believe this line is crossed, and patients are at risk for Cannabinoid Hyperemesis if they are found to demonstrate a dysautonomia called Parasympathetic Excess and they consume high doses of cannabinoid agents. Different patients are susceptible to different affects from cannabinoid agents. Cyclic vomiting syndrome also can mimic Gastroparesis. It occurs for several days and usually every several months in individuals where they go into phases for three or four days where nausea and vomiting occurs in a protracted fashion. These are difficult disorders to treat pharmacologically and usually are not associated with delayed gastric emptying as seen in Gastroparesis. Many times, alternative therapies, such as acupuncture, meditation, yoga and relaxation techniques are useful in treating these disorders.

As mentioned, abnormalities of the Autonomic Nervous System (ANS) are implicated in causing delayed gastric emptying in patients with Gastroparesis. Injury to the Vagus Nerve is a very common cause, whether by virus, Bariatric or upper abdominal surgery. In an elegant work [1], measures of Cardiovascular Autonomic Neuropathy (CAN) were used as a surrogate for a marker of GI-autonomic neuropathies. These tests can routinely be performed, noninvasively, in the office setting. These tests oftentimes involve calculations from changes in heart rate responses with a cardiogram in relation to one's respirations. CAN, gastric-autonomic neuropathy and peripheral neuropathy are all closely related to abnormalities in the R-R interval series on the electrocardiogram. The R-R interval series is known as a measure of Heart Rate Variability (HRV).

The R-R interval is the distance between two EKG complexes. This variation is especially correlated when the variation is calculated during deep breathing (paced breathing at 6 breathes per minute). This is a good indicator of Diabetic Neuropathy when abnormal. Also, the Vagal cholinergics are affected to a greater degree in a diabetic Gastroparesis patient than idiopathic Gastroparesis patient. Surgical patients usually have the Vagal Nerve effected by the surgical procedure and therefore were excluded from the above study [1]. Because there is such a high prevalence of Vagal cholinergics affected with diabetic Gastroparesis, this may explain why gastric pacemakers, or so called gastroesophageal stimulators are more useful in diabetics than idiopathic Gastroparesis patients. We will discuss gastroesophageal stimulators in part II in these Gastroparesis communications. Therefore, Vagal tone abnormalities may not be a universal mechanism for Gastroparesis and are seen more often in Diabetics and also in Bariatric patients who may have injury to the Vagus Nerve and in some postviral states.

Neural GI motor function is a coordination of the Parasympathetic and Sympathetic (P&S) branches of the ANS. Also, there is a coordination of neurons and pacemaker cells in the gastric mucosa known as the interstitial cells of Cajal within the stomach and small intestine and smooth muscles of the gut. Elegant studies with gastric biopsies have shown abnormalities in these different types of cells. There is a very complex coordination involving the various branches of the Autonomic Nervous System with these cells in the gastric mucosa, which contributes to many of the abnormalities seen in patients with Gastroparesis. ANS dysfunction is usually caused by impaired neural transmission with increases in oxidative stress. Also, there is documented loss of insulin-like growth factors and also direct damage to the interstitial cells

of Cajal. In our latest text on autonomic dysfunction and mitochondrial dysfunction, we implicate oxidative stress to neurons in the P&S nervous system as being a major mechanism in causing disruption of the Autonomic function in patients who develop Dysautonomia. Future studies will need to be done to see which patients with Gastroparesis will benefit most from balancing abnormalities of autonomic testing, which we routinely do in the office setting. Many times, this is done on a trial by error basis based on the data we obtain with these noninvasive tests which involve HRV with EKGs and respiratory monitoring, and having patients breathe at a certain respiratory rate and making calculations.

The most reliable test to diagnose Gastroparesis is the gastric emptying study. This measures gastric retention at four hours after ingesting a solid meal. There is a standardize protocol where one ingests a radiolabeled meal and assess emptying at one and two hours up to four hours. The emptying phase of solids is usually linear after initial lag phase. Gastroparesis due to motility disorders or neuropathic disorders will cause slow gastric emptying. By definition, a patient with Gastroparesis must have delayed gastric emptying for which there are set standard definitions of how much of the radionuclide meal is left behind and not moving into the small bowel after four hours.

Another test used to assess gastric emptying is one which will show a change in acid to gastric pH once food goes into the small intestine. There is usually a rise in the pH of approximately three points when this happens, and we can time approximately when this happens and can assess whether gastric emptying is delayed, normal, or even rapid. The apparatus used is known as the Smart Pill and is known as a Wireless Motility Capsule (WMC). WMC is highly correlated with the gold standard of Gastroparesis, the gastric emptying study. There are other imaging modalities which are not routinely used, such as upper GI Barium studies and Single-Photon Emission Computed Tomography (SPECT). Another test that is occasionally used is a breath test, which is very noninvasive and avoids radiation. Breath tests use Carbon-13 labeled radioisotopes and the early arrival of an increased quantity of Carbon-13 compared to Carbon-12 that is measured in the breath gives an indication of how early or delayed ingested food particles containing these nuclear carbon atoms is being measured. A delay in measuring C-13 with a breath test is indicative of Gastroparesis. There are standards that have been developed with this which also correlates with the gold standard, the Scintigraphic Gastric Emptying Study.

With these tests, it is important to note that patients should restrain from taking any medicines that increase motility or decrease motility in the GI tract. Also, patients should normalize their blood sugar as best as possible, since high sugars above 275 can make a gastric emptying test more abnormal. Medications which can slow gastric-emptying, are antidepressants, anticholinergics, narcotics and so forth. Medicines that can increase gastric-emptying time should also be avoided. Most medicines should be stopped at least 48 hours before any diagnostic test assessing gastric motility. We like to stop most of these medicines at least three days prior, or 72 hours.

Occasionally, non-diabetics will have a negative gastric emptying study and no evidence of delayed emptying, but when a liquid gastric emptying study is done it will be abnormal. It

appears that in these cases, the liquids and not solid intake can be more sensitive in these non-diabetic patients. It is important that a skilled Enterologist read and interpret these tests in conjunction with a Radiologist. The Radiologist can comment on whether the test shows delayed, normal, or accelerated gastric emptying (the latter usually seen in dumping syndrome, which is not a Gastroparesis syndrome). However, a Radiologist cannot interpret the patient's clinical symptoms or medications prescribed, if they have not examined the patient or if they do not know the patient's history. Therefore the clinician is most important in knowing these data and the basis for ordering for the test.

Therefore, in summary, there are three major tests that are used to document delayed gastric emptying: 1) the Scintigraphic Gastric Emptying Test using solids with a standard meal with eggs and toast is the one most conventional, 2) the Wireless Motility Capsule motility test which assesses pH and other data after a capsule is ingested, and 3) the Carbon-13 breath test which is done with a radionuclide Carbon labeled tracer in a solid meal. The advantage of the breath test is it is noninvasive and requires no radiation or imaging but does require special equipment in a very rigid protocol.

Patients with Gastroparesis have significant morbidity and may even have mortality if they do not get nutrition and lose weight from not eating properly. This can be a very serious condition. They need to be carefully monitored by a Gastroenterologist who specializes in motility for the most part. It would also be advantageous to have a physician, whether a Cardiologist, Neurologist or Endocrinologist experienced in autonomic dysfunction, since there are some generalized autonomic disorders that can be improved with proper balance of the ANS (the P&S nervous systems). As we discussed, proper P&S balance helps Gastroparesis respond favorably as well.

In Part II, we will discuss various treatment algorithms and approaches to the patient with Gastroparesis. We will discuss diet, exercise, and pharmacology used to treat Gastroparesis. Treatment may also include some novel interventions that are invasive, whether they be gastric pacemakers or surgical and some research medicines. In Part III, we will discuss Gastric-Dumping syndrome and other gastric and intestinal motility disorders as they relate to the ANS.

Lastly, occasionally, one will need an interventional Radiologist or a surgeon to evaluate patients especially those who have chronic symptomatic Gastroparesis or who are refractory to drug treatment. Occasionally surgical options may include (1) a Jejunostomy tube for feeding, (2) a Gastrostomy tube for stomach decompression, and (3) Pyloroplasty for gastric emptying. However, these are a really last resort techniques, which will be discussed in Part II, and we will also discuss gastric stimulators and pacemakers.

## REFERENCE

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1 Mohammad MK, Pepper DJ, Kedar A, et al. Measures of Autonomic Dysfunction in Diabetic and Idiopathic Gastroparesis. *Gastroenterology Res.* 2016; 9(4-5): 65–69. doi:10.14740/gr713w.