Diabetic Gastroparesis II – its interest

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Abstract

Gastrointestinal (GI) function is controlled by the intrinsic nervous system (the enteric plexuses - the little digestive brain) and the extrinsic nervous system (sympathetic and parasympathetic). Gastrointestinal symptoms in patients with Diabetes mellitus (DM) can affect the entire digestive tract. Diagnosing how it affects the autonomic nervous system (SNA) in patients with diabetes, particularly in relation to GI function, is a very difficult task because it is usually asymptomatic or has no specific symptoms.

The prevalence of Diabetic Neuropathy is highly variable, and depending on the series, it can be debilitating and difficult to treat.

The authors present a short review of the theme, emphasizing the importance of the study of Diabetic Gastroparesis (GPD), as this can help the doctor and the patient choose the most appropriate insulin regime and the best time for its administration. According to studies carried out, the most important points of treatment are good glycemic control, associated with hygiene and dietary measures.

Key Words: Diabetes mellitus, Autonomic Neuropathy, Diabetic Gastroparesis, Gastric Scintigram, Prokinetic agent, Gastric pacemaker.

Introduction

Diabetes mellitus plays a major role among systemic diseases which affect the central nervous system (SNA). Gastrointestinal effects on the SNA are difficult to diagnose in the diabetic population, as they are generally asymptomatic or manifest through non-specific symptoms.

In 1958, Kassender recognized, for the first time, asymptomatic gastric retention in diabetic patients, referring to it as *Gastreoparesis diabeticorum*. Since the term was first coined, it has been used to define gastric retention, whether symptomatic or asymptomatic.

Epidemiology

According to the American Diabetes Association (ADA), the prevalence of diabetic sympathetic neuropathy is highly variable, ranging from 1.9% to 90%, depending on the diagnostic exams used.[1] From a review of some published articles, it is concluded that around 50% of patients with diabetes have delayed gastric emptying, and more than three quarters report at least one symptom of GI, generally obstipation.[2]

Some of the series studied estimate a prevalence of gastroparesis of around 30% in type 2 diabetics, and between 40% and 50% in type 1 diabetics.

Generally, it is a late finding in the type 1 diabetic population, but it can be detected early in patients with type 2 diabetes.

In fact, gastrointestinal symptoms are common among diabetics. Feldman and Schiller report the presence of at least one GI symptom in 76% of the patients referred to a Diabetes clinic.[3] In a second study, Clouse also identifies the presence of GI symptoms in 20% of diabetics of the General Clinical Research Center.[3] However, in the Rochester Diabetic Neuropathy Study, only 1% of diabetics had symptoms of gastroparesis, and only 0.6% had night-time diarrhea.[3]

Paradoxically, a study by Olmsted County demonstrated lower prevalence of heartburn in a study of a population of type 1 diabetics. There are two possible reasons for this: the presence of vagal neuropathy reduces the sensation of heartburn; on the other hand, decreased use of NSAIs in these diabetics, at the recommendation of clinics (due to the risk of nephropathy) decreases the frequency of this symptom.[4]

However, it is important to remember that the high prevalence of functional GI pathologies in western civilizations, such as irritable bowel syndrome, chro-

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nic constipation or functional dyspepsia, can confuse the estimate of the presence of diabetic gastroparesis based on symptoms alone.[3]

Physiopathology

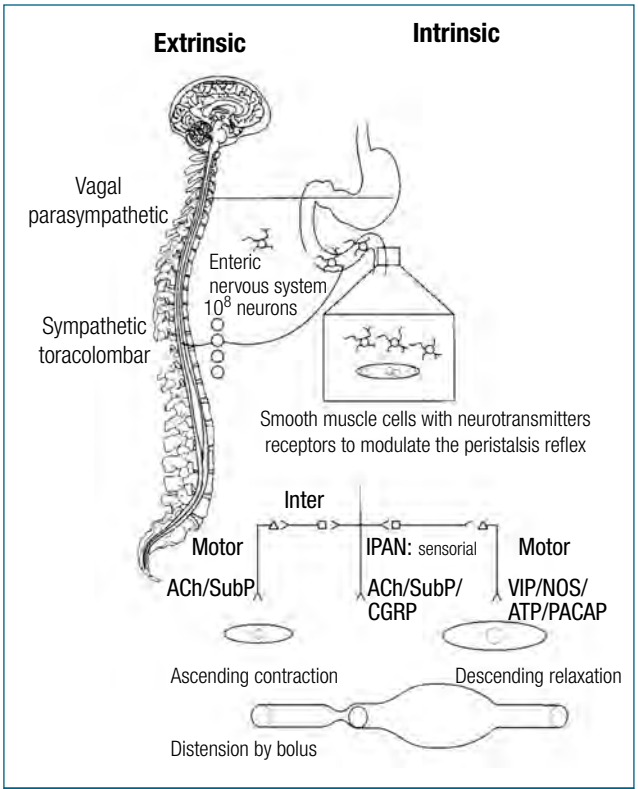
GI function is controlled by the intrinsic nervous system (enteric plexus – the little digestive brain) and by the extrinsic or autonomous nervous system, (sympathetic and parasympathetic). The lesions can affect both the afferent and efferent fibers of the sympathetic and parasympathetic SNA. Any part of the digestive tract can be affected, from the esophagus to the anus.

Various mechanisms explain the different signs and symptoms of GI dysfunction *(Fig. 1)*. Vagal dysfunction is probably associated with gastric stasis of solid foods. Alterations in intrinsic control are mainly the job of the cells of Cajal, in relation to regulation of GI motility.[5]

The intrinsic electrical activity of the stomach produces action potentials that lead to contractions known as "slow waves". These "slow waves" are generated at a frequency of three cycles per minute, originating in a focus that functions like a "pacemaker" located next to the transition from the fundus to the body, in the greater curvature of the stomach. The "slow waves" are produced by the cells of Cajal, and are transmitted slowly from cell to cell. The entire process is controlled by the intrinsic or enteric nervous system, which is modulated by the sympathetic and parasympathetic extrinsic nervous system. Gastric motor activity is also influenced by various nucleopeptides and hormones, such as gastrin, cholecystokinin and motilin, among others.[2] Usually, the combination of the various processes leads to complete gastric emptying between 90 and 120 minutes after ingesting food.

Clinical Presentation

GPD can manifest through non-specific signs and symptoms which appear in insidious form, such as: anorexia, postprandial effusion, early satiety, nausea and vomiting, epigastralgia, gastric gurgling by stasis, alterations in intestinal transit (diarrhea/obstipation) or weight loss *(Fig. 2)*. However, in the majority of these cases, the gastroparesis is clinically silent; even so, in its more severe forms, it represents the most debilitating of all the gastrointestinal complications of diabetes.



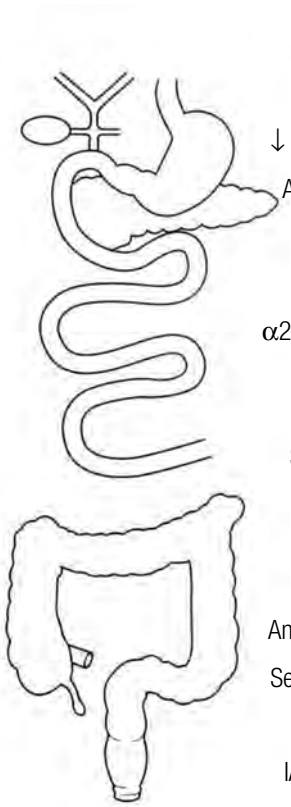
Control of gastrointestinal motility.

FIG. 1

Diagnosis

Effective gastric emptying is a determining factor for adequate metabolic control. Its investigation is essentially the result of the degree of suspicion on the part of the doctor. Its confirmation requires documentation of the delayed gastric emptying by diagnostic methods, and the preferred exam for this purpose is the scintigram.[6] This exam involves ingesting a meal, preferably solid, which is marked by radioactive isotopes.[7,8] Gastric images are produced, in which the proportion of radioisotope retained in the stomach from 2 to 4 hours is analyzed, enabling normal function to be distinguished from the presence of gastroparesis with a sensitivity of 90% and specificity of 70%.[3] However, there is a lack of consensus in relation to the scintigraphy technique, on what constitutes normal standard values.

There are other, recently used non-invasive tests, although these are little publicized in Portugal; examples include the Acetaminophen Absorption Test and the Octanoic Acid Breath Test. Acetaminophen is a



Diabetes GI manifestations	Associated diseases	Clinical presentation
↓ gallbladder motility		Gallbladder lithiasis
Antral hypomotility	Exocrine pancreatic insufficiency	Gastric stasis, bezoars
Pylorus Spasm		
↓ Tonus		Steatorrhea diarrhea
α2 – adrenergic in the enterocytes	Celiac sprue	
Small bowel (SB) dysmotility	Bacterial proliferation SB	Gastric stasis or SB
		Or SB quicker transit time
Colon dysmotility	Bile acids malabsorption	Constipation or diarrhea
Anorectal dysfunction		Diarrhea or incontinence
Sensorial neuropathy		
Neuropathy		
IAS – sympathetic		
EAS - pudendum		

Forms of gastrointestinal manifestation of diabetes and their clinical presentation.

FIG. 2

compound which is weakly absorbed at gastric level, and its absorption is preferably duodenal. It therefore enables gastric emptying and duodenal absorption to be assessed. The absorption curve is plotted based on seriate blood samples. However, it is a test which lacks specificity, and therefore it is not commonly used in clinical practice. The Octanoic Acid Breath test, however, appears to be more promising in the diagnosis DPG. It uses a standard reference consisting of a biscuit (for example) enriched with 13C, a stable isotope which binds to the octanoate, a medium chain triglyceride. After ingestion and gastric emptying, the 13C-octanoate is absorbed by the small intestine and quickly metabolized by the blood, after which the 13CO2 is exhaled. The measurement of 13CO2 contained in the expired air by means of mass spectrometry enables the average gastric emptying time to be indirectly estimated. This exam should involve lower costs, for which reason it could become the screening test of choice for DGP. However, it presents some limitations in patients with emphysema, cirrhosis, celiac disease or pancreatic insufficiency, all of which can influence the test results.[8,9]

Increasingly less used nowadays, radiography with barium swallow is a less sensitive method of measuring gastric emptying, as it is difficult to quantify the fraction of food retained in the stomach, and because barium is not a "physiological meal". Barium retention in the stomach after 6 hours, or very low or reduced emptying of the barium swallow in the first 30 minutes, is suggestive of gastroparesis. The great value of this test is the possibility of excluding certain lesions of the mucosa or the presence of extrinsic mechanical compression.

Gastroduodenal manometry is a technique which enables the internal pressure in the stomach and intestine to be determined. According to the physiopathology, referred to above, antral hypomotility is an important cause of motor dysfunction and increased gastric emptying time.

Upper Digestive Endoscopy should precede any investigation of suspected gastroparesis, and is important for excluding any organic pathology of the esophagus or stomach, such as gastroduodenal ulcer, gastritis, gastric neoplasm, pyloric stenosis, and esophageal candidiasis, among others, which could explain the patient's clinical condition.

Differential diagnosis

The differential diagnosis of DGP is extensive. Around 76% of diabetics report digestive complaints.[10] In the interview, the patient should be asked about use of drugs such as: antidepressants, anticholinergic agents, atropine, lymph node blockers, beta-adrenergic ago-

TABLE I

Pathophysiology of diabetic gastroparesis

Autonomic neuropathy (Vagal)
Intrinsic neuropathy: Excitatory and inhibitory nerves Interstitial cells of Cajal
Acute increase in glycemia
Psychosomatic factors

nists and vincristine. Gastroparesis can be observed in breast, bronchial or esophageal carcinomas, when they affect invading the vagus nerve.[11] It can also form part of a paraneoplastic syndrome of the carcinoid tumors and small cell lung carcinoma.

Any pathology involving neuromuscular dysfunction of the gastrointestinal tract can cause gastroparesis. Sclerodermia, amyloidosis and hypothyroidism can result in delayed gastric emptying, as well as chronic obstipation, intestinal dysmotility or pseudo-obstruction. There are many possible causes of delayed gastric emptying; however, the most frequent etiologies are associated with diabetic or idiopathic neuropathy, or post-surgical situations.[2]

Complications of DGP

The most frequent complications are:

- Poor metabolic control of diabetics.
- Formation of bezoars due to delayed emptying of indigestible particles.
- Acute gastric dilation during episodes of ketoacidosis, sometimes requiring nasogastric aspiration.
- Esophageal candidiasis in 15% of cases, probably by stasis and gastroesophageal reflux secondary to the DGP.
- Gastroesophageal impactation
- Other direct or indirect complications, such as: gastric emphysema, incorrect absorption of drugs, worsening of emesis in pregnancy, weight loss, malnutrition, and aspiration penumonias.[10]

Treatment

Strict glycemic control, associated with dietary measures, is the starting point for the treatment of DGP. Treatment should include dietary changes, with emphasis on light, frequent meals and the use of liquid supplements. A diet low in residues is recommended,

TABLE II

Differential diagnosis of DPG

Idiopathic gastroparesis
Metastatic tumors that affect the vagus nerve
Visceral paraneoplastic neuropathy
Medications that slow down gastric emptying
Multiple sclerosis
Local herpes zoster
Cranial traumatism
Medullobastoma of the posterior fossa
Myotonic dystrophy
Amyloidosis
Post-radiotherapy gastroparesis
Thyrotoxicosis
Post acute viral disease gastroparesis
Gastric ischemia
Anorexia nervosa
Progressive systemic sclerosis
Dermatopolymyositis
Chronic idiopathic digestive pseudo-obstruction
Bulimia

to avoid the formation of bezoars. While on one hand, all diabetics should divide up their meals into smaller portions, which helps ensure good metabolic control and prevent/treat the DGP, on the other hand, diabetics are asked to reduce their ingestion of fibers, which are an important element of the diet.

The use of prokinetics is indicated in patients who show clinical signs of delayed gastric emptying, despite having achieved good metabolic control. Prokinetic agents used in the treatment of diabetic gastropathy are methoclopramide, domperidone, cisapride and erythromycin.

Methoclopramide was one of the first drugs to be used to treat DGP. At a dose of 10mg every 30 minutes before meals, it presents antiemetic properties, stimulates the release of acetylcholine in the myenteric plexus, and is a dopaminergic antagonist. It acts by coordinating pyloric relaxation, duodenal peristalsis and contraction of the smooth gastric muscle, accelerating gastric emptying. However, due to its side effects on the Central Nervous System, it should not be used in chronic form. Side effects include irritability, drowsiness, myoclonias, galactorrhea and

extrapyramidal manifestations.

Doperidone, a selective dopamine antagonist which has the advantage that it practically does not pass through the hematoencephalic barrier, causes less adverse effects than metoclopramide. Its administration can improve gastric emptying; however prolonged use – for more than 30 days - reduces its effectiveness, although some action continues in the proximal stomach, facilitating the emptying of liquids.[12]

Cisapride increases GI motility by simulating the release of acetylcholine in the myenteric postlymph node neurons. It regulates the antral activity, in fasting or with food, accentuates antral-duodenal coordination, and activates small intestine motility. Various studies have demonstrated the superiority of cisapride over metoclopramide as an accelerator of gastric emptying (this drug was recently withdrawn from the market in Portugal, due to the risk of heart rate dysfunction).[13]

Some antibiotics appear to be of interest in this context, one example being erythromycin, which has a powerful effect on stimulating the GI motilin receptors, with demonstrated effectiveness in the acceleration of gastric emptying. In acute cases it may be administered endovenously (250 mg for 20 min every 8h), although its continued use could cause tachyphylaxia.[14,15]

Tegaserod is the most recent prokinetic agent approved by the US Food and Drug Administration, and is indicated for the treatment of obstipation associated with Irritable Bowel Syndrome. It is a selective 5-HT_4 receptor agonist. Studies on animals and humans have effectively demonstrated its activity in the motor stimulation of the digestive tract. More recent studies demonstrate the benefit of its administration in patients with gastroparesis, improving the symptoms and gastric emptying time. The recommended dose of this drug is 6mg in two daily doses, taken orally. Tegaserod does not have antiemetic properties; therefore it should be administered in combination with an antiemetic.[16]

All the drugs used so far in clinical practice appear to have limited benefit, and there is currently no specific drug indicated in the international guidelines, for the treatment of DGP.[15,17,18]

Other therapeutic alternatives currently under investigation include Sildenafil and injectable Botulinic Toxin A, both of which are potentially effective in relaxing the pylorus. Preliminary studies suggest transitory effectiveness in the alleviation of symptoms in diabetic and idiopathic gastroparesis after administration of Buotulinic Toxin. However, further studies are necessary in this field.[16,19]

In more severe cases which are resistant to medical treatment, or with prolonged and frequent exacerbations, one option is surgical treatment. Other available options are enteral or parenteral nutrition and nutrition by jejunostomy.

The gastric pacemaker is a promising alternative. The device is implanted subcutaneously in the abdominal wall during laparotomy or laparoscopy, and electrodes are placed on the smooth muscle, approximately 9.5 to 10 cm from the pylorus, along the greater antral curvature. Its placement is indicated in cases where the symptoms of DGP persist for more than 1 year, where the DGP is resistant to medical treatment, and where there is abnormal gastric retention (>60% in 2h, >10% in 4h with a low-calorie meal). The use of the gastric pacemaker reduces the number of hospitalizations and healthcare costs, as well as improving the quality of life of these patients.[15,16,20]

Conclusion

Retention of foods in the stomach causes delayed absorption of carbohydrates, leading to delayed hyperglycemia peaks, which may result in a lack of synchrony between the ingestion of foods and the administration of insulin. For this reason, study of DGP can assist the clinic and the diabetic patient, in the choice of the most appropriate insulin scheme, and the most appropriate timing of its administration.

The authors also highlight that DGP is infrequent in the absence of clinically detectable neuropathy. Knowing that DGP is part of the context of Autonomic Neuropathy, the clinic should investigate the possible presence of cardiovascular and genitourininary neuropathy. The prevalence of DGP is highly variable, depending on the series. However, its impact on autonomic dysfunction with repercussions on mortality is undeniable.[7]

According to the literature review, in terms of prognosis, the presence of DGP *per se* is not associated with a higher risk of mortality. However, gastroparesis, whether symptomatic or asymptomatic, has a major impact on the patient's daily life, affecting the glycemic profile and preventing adequate metabolic control.

As is evident, DGP does not occur in isolation in

DM. Therefore, besides affecting the patient's quality of life, there is no doubt that in clinical practice, it will indirectly lead to early mortality. ■

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