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AN UPDATE OF THE ALGORITHM FOR DIABETIC GASTROPAREIS MANAGEMENT

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Diabetic gastroparesis is defined as gastric emptying disturbance with associated upper gastrointestinal symptoms in the absence of gastric obstruction. It is one of the most severe complications of diabetes mellitus, affecting patients with uncontrolled, long-standing type 1 and type 2 diabetes. The pathogenesis of this gastrointestinal disease is complex involving vagal dysfunction, loss of interstitial Cajal cells, loss of neuronal nitric oxide synthase, oxidative stress and chronic hyperglycemia. The diagnosis and management might be challenging for the clinician. The gold standard of diagnosis is gastric emptying scintigraphy. Management should be multidisciplinary based on diet modifications, antiemetics, prokinetics, optimization of glycemic control. Novel promising therapeutic modalities include ghrelin receptor agonists and selective 5-hydroxytryptamine receptor agonists. Patients with severe symptoms may benefit of endoscopic intervention, gastric electrostimulation or surgical treatment. The aim of this review is to provide an update on the pathophysiology, clinical aspects, diagnosis and treatment advancements for diabetic gastroparesis. As the cellular and molecular changes that characterize this disorder are better understood, new opportunities for targeted treatment may emerge.

Keywords: diabetic gastroparesis; diabetes; gastrointestinal disease; Cajal cells.

GENERAL DATA

Diabetic gastroparesis (DG) is a digestive disorder characterized by delayed gastric emptying or intermittent slow evacuation, in the absence of a mechanical obstruction in the stomach resulting from long-standing poorly controlled type 1 (T1DM) or type 2 diabetes mellitus (T2DM).[1]

Gastroparesis is one of the most common complications of diabetes mellitus described since ancient times, being mentioned by Aretaeus of Cappadocia who at that time considered diabetes a digestive disorder. It was reported in the literature since the mid-1900s and it was first described by Rundles RW in 1945. The term gastroparesis diabeticorum was introduced by Paul Kassander in 1958.[2]

DG is a component of autonomic neuropathy what affects approximately 25–50% of the diabetic patients especially those with T1DM with poor glycemic control and those with T2DM with a progression of disease greater than 10 years, diagnosed with other microvascular complications such as retinopathy, nephropathy and neuropathy.[3]

The 10-year cumulative incidence of DG has been estimated to 5.2% in patients with T1DM and 1% in those with T2DM and the increasing prevalence of T2DM worldwide has led to larger number of patients with DG.[4]

The prevalence of DG is low, most of the patients may remain undiagnosed because the symptoms are present in only 5–12% of the patients with diabetes and it should be suspected in people with uncontrolled blood sugar levels. The prevalence and severity of symptoms suggestive of gastroparesis is increased especially in obese, elderly diabetic women with poor glycemic control.[5,6] DG may cause severe nutritional deficiencies being associated with increased morbidity and mortality. Early diagnosis of DG is necessary because the therapy based on strict blood glucose control, proper nutritional intervention, and administration of prokinetics usually lead to an improvement of the patient's clinical status.[6,7]

CHANGES AT THE CELLULAR AND MOLECULAR LEVEL

The main factors involved in the etiopathogenesis of DG are the following: vagal denervation of the stomach, altered contractility of smooth muscles, oxidative stress, loss of interstitial cells of Cajal which are the electrical pacemakers of the stomach, loss of expression of neural nitric oxide synthase in the myenteric plexus, chronic hyperglycemia. This contributes to the pathogenesis of gastroparesis by several mechanisms: activating the polyol pathway that stimulates the accumulation of sorbitol and fructose in Schwann cells and axons, increasing their osmolarity due to attracting water into the inner part of the cells, leading to the ballooning of these cells and finally to axonal degeneration and demyelination.[8,9] Furthermore, the non-enzymatic glycosylation of the proteins resulting in advanced glycation products stored in the vessel walls lead to thickening of the basement membrane, swelling of endothelial cells, the loss of pericytes, occlusion of the capillaries and degeneration of the vessels that supply the nervous tissue and finally generating ischemia and neuronal apoptosis. Moreover, chronic hyperglycemia is associated with increased oxidative stress, and the production of free radicals.[9,10] The mechanisms underlying DG include autonomic neuropathy, enteric neuropathy, abnormalities of the Cajal interstitial cell network, poor glycemic control with acute fluctuations, the use of incretin therapy, psychosomatic factors.[6] Women generally have a slower gastric emptying of solids and liquids. The explanation may be related to estrogen levels. During ovulation and pregnancy women tend to have reduced peristaltism and an increased incidence of constipation.[5,6] Acute glucose level fluctuations influence gastric motility. Sudden increases of blood glucose levels particularly in patients with T1DM result in delayed gastric emptying due to antral hypomotility. The main mechanism underlying this phenomenon is enteric neuronal apoptosis during hyperglycemic states. On the other hand, hypoglycemia stimulates the activity of the vagus nerve.[11]

In scientific researches, gastric biopsies taken from patients with idiopathic gastroparesis (IG) and DG were analyzed in light microscopy. Microscopic structural changes were highlighted in 83% of the patients. The main defects were the loss of Cajal interstitial cells and neuronal abnormalities, without possibility to distinguishing between the two diseases.[12] The samples were also examined in transmission electron microscopy that emphasized interstitial Cajal cells modifications, dilated and empty nerve endings, the presence of lamellar bodies and lipofuscin in the smooth muscle cells. The ultrastructural changes were more severe in patients with IG. The presence of a thickened basal lamina surrounding the smooth muscle cells and nerves was specific to DG, while IG was characterized by fibrosis particularly around the nerves. Identifying significant ultrastructural differences between DG and IG offers an open up into the pathophysiology as well as into potential targeted therapies.[13, 14]

PATHOPHYSIOLOGICAL MECHANISMS

The pathophysiology of DG involves neuronal changes, abnormalities in the structure and function of autonomic nervous system, smooth muscle cells and Cajal interstitial cells. Oxidative stress in diabetes seems to be incriminated in the pathogenesis of diabetic complications, including gastroparesis.[15] Recent studies have shown the potential role of macrophages as key cellular elements in the pathogenesis of DG. Macrophages are important for maintaining homeostasis and in the processes of defense against pathogens.[16] Heme oxygenase-1 is an enzyme present in a subset of macrophages and has been shown to be protective against oxidative stress. The activation of these macrophages with high levels of heme oxygenase-1 is protective against the development of delayed gastric emptying in animal models, while the activation of other types of macrophages is associated with neuromuscular cell injury.[17]

The Cajal interstitial cells represent the pacemaker cells of the gastrointestinal tract. They are modified smooth muscle cells that generate and propagate slow waves, determining the muscle membrane potential. Abnormal slow wave activity has been described in diabetic gastroparesis due to Cajal cell morphofunctional damages.[18]

The loss of vagus nerve function is an important pathophysiological factor in gastroparesis because due to vagal disfunction gastric emptying is delayed, the pyloric relaxation and antral contraction are reduced.[9] There have also been studied the genetic factors that may determine susceptibility to gastroparesis. A long repeat polymorphism in the heme oxygenase has been shown to be a risk factor for the development of gastroparesis.[19]

CLINICAL ASPECTS

The symptoms are not proportional to the severity of the disease, as there are asymptomatic patients with gastroparesis and subjects with a noisy clinical picture, in whom the gastric evacuation is unchanged. Gastric emptying may be surprisingly normal in some dyspeptic patients with longduration diabetes and delayed in asymptomatic T2DM patients.[20] In a study that included patients with T2DM, the prevalence of the specific symptoms of gastroparesis was 10.8%.[21] The main symptoms were: pirosis, abdominal pain, nausea, vomiting undigested food, early satiety, postprandial fullness, abdominal bloating, loss of appetite, weight loss, anorexia, diarrhea or constipation, tendency to hypoglycemia due to delayed emptying of the stomach. There are many risk factors that can aggravate the symptoms of diabetic gastroparesis for example: quantitatively abundant, unfractionated meals, high-fat foods, dietary fibers, solid foods, dehydrated foods and carbonated drinks. If ingested food stagnates for a long time in the stomach, it favors bacterial overpopulation by fermentation and can compact to form solid masses called bezoars.[22, 23] Certain medications can worsen the symptoms, for example glucagon like peptide-1 receptor agonists (GLP-1 RA), amylin, opioids, anticholinergics, tricyclic antidepressants. GLP-1 RA may exacerbate patients' symptoms because they slow down gastric emptying and decrease appetite and for this reason, the use of this group of medication is not recommended for patients with gastroparesis.[21]

Other factors that may worsen the symptoms are advanced age, the association of hypertension, dyslipidemia, smoking, alcohol consumption, associated psychiatric disorders such as anxiety or depression. Delayed gastric emptying may result in wide glycemic fluctuations, poor nutrition and dehydration, what it can lead toto frequent hospitalizations and poor quality of life.[23, 24]

DIAGNOSIS DIFFICULTIES

Diagnosing DG in some cases may be difficult because the symptoms can be easily confused with those of other gastroenterological conditions.[2] On the barium X-ray normally the stomach should be empty, with no food leftovers after 12 hours of fasting.[21] Gastric emptying scintigraphy is the gold standard for the diagnosis of gastroparesis, it measures the rate of gastric emptying at baseline (after meal ingestion) and at one, two and four hours after food intake and if there is greater than 60% retention at two hours or more than 10% retention at four hours the diagnosis of gastroparesis is confirmed.[25] The gastric emptying breath test measures the rate of gastric emptying that is reflected by breath excretion of carbon dioxide. Wireless motility capsules have the advantage of visualizing the mucosa of the entire small intestine, completing the picture offered by the classic upper digestive endoscopy but the gastrointestinal endoscopy should be done in order to make sure that nothing is physically blocking the movement of food from the stomach to the small intestine. The presence of remaining food in the stomach after a fasting period is highly suggestive for gastroparesis. Gastric manometry allows the measurement of the electrical activity of the stomach. Abdominal ultrasound may be useful for differential diagnosis (gallbladder disorders, pancreatitis).[21, 26]

The main step for the certainty diagnosis is to firstly exclude the existence of a mechanical obstruction that can cause upper gastrointestinal symptoms: partial or complete bowel obstruction, gastric outlet obstruction, gastric cancer, pyloric stenosis.[27] There are several other diseases that may mimic the symptomatology of gastroparesis, such as: peptic ulcer disease, gastroesophageal reflux, Celiac disease, Crohn’s disease, chronic pancreatitis, chronic uremia, hypercalcemia, hypokalemia, postsurgical vagotomy, metabolic disorders, autoimmune and connective tissue disorders, central nervous system lesions, eating disorders, pregnancy, but and use of certain drugs that can slow down gastric emptying (anticholinergics, calcium channel blockers, octreotide).[28] Hyperparathyroidism, Addison's disease, hypothyroidism can determine symptoms similar to those occurring in diabetic gastroparesis.[29]

THE IMPACT OF THE PROGRESSION OF DIABETIC GASTROPARESIS

This includes esophagitis, volume depletion with acute renal failure, electrolyte disturbances, severe dehydration and malnutrition. Gastroplegia is the major consequence that appears due to complete gastric denervation that leads to the acute expansion of the stomach causing a clinical picture suggestive of a mechanical obstruction (vomiting, absolute food intolerance).[28] Gastroesophageal reflux disease is often associated with gastroparesis and the Mallory-Weiss syndrome occurs due to chronic nausea and vomiting. If food stagnates for a long time in the stomach it will lead to the formation of bezoars due to the overpopulation of the food with bacteria. Bezoars are solid masses that can cause nausea, vomiting and gastric obstruction by blocking the passage of food from the stomach into the duodenum.[30, 31]

Hyperglycemic emergencies including diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome appear more frequently in patients with gastroparesis. According to studies patients with T1DM and DG were fourfold more often hospitalized due to diabetic ketoacidosis than patients with T1DM without gastroparesis. These patients have an impaired quality of life due to frequent hospitalizations, persistent symptoms and complications and if is associated with anxiety and depression may have a significant impact on the self-management of diabetes leading to fluctuating blood glucose levels. [32]

THE MANAGEMENT OF GASTROPARESIS

Management of patients should be multidisciplinary, with close collaboration between different medical specialties: gastroenterologist, diabetologist, nutritionist, surgeon, radiologist and psychologist. Therapeutic management depends on the severity of the pathological condition, the ability to maintain adequate nutrition and response to therapy. In mild to moderate forms of DG treatment consists of diet modification, avoidance of exacerbating agents and prokinetics medications to enhance gastric peristalsis, antiemetics to control nausea, antibiotics to avoid bacterial overpopulation and insulin therapy to control glucose levels.[33, 34] Compensated DG is associated with moderately severe symptoms, partially controlled by medication, changes in diet and lifestyle, and hospitalization which is rarely required. In patients with severe forms (with malnutrition, cachexia, with frequent hospitalizations, and multiple complications) refractory to dietary and drug therapy, intravenous fluid administration, enteral or parenteral nutrition and endoscopic or surgical treatment are recommended.[35]

The main therapeutic target is to improve gastric evacuation and maintain normal blood glucose levels. Controlling factors that may aggravate the symptomatology of diabetic gastroparesis includes the optimization of the blood glucose levels and serum electrolyte levels, adequate nutritional support and symptomatic therapy.[33]

GLP-1 RA such as liraglutide, dulaglutide, semaglutide and amylin agonist (pramlintide) that are used for T2DM treatment can exacerbate symptoms of delayed gastric emptying; on these patients it is recommended to avoid these type of medication.[34,36]

The management of gastroparesis includes nutritional recommendations, glycemic control, pharmacological therapy and supplementary therapeutical options as follows.[36]

NUTRITIONAL INTERVENTIONS

The treatment typically starts making changes of the patient's diet which is often effective: avoiding spicy, acidic, fatty foods. Patients are advised to eat smaller and more frequent meals, four to five meals per day, consume food that are low in fat and in soluble fiber, with avoidance eating food that are high in fiber such as whole grains, vegetables.[37,38] Those with severe symptoms may require enteral or parenteral nutrition. In severe cases with involuntary weight loss, enteral nutrition can be done via a jejunostomy tube. Patients may develop dehydration, electrolyte disturbances, hypovitaminosis and nutritional deficiencies that must be balanced with supplemental hydration and nutrition.[38] For patients who take mealtime rapid- or short-acting insulin it is recommended to inject prandial insulin after meals to prevent postprandial hypoglycemia. Patients who require frequent blood glucose monitoring they need to use continuous blood glucose monitoring systems, thus reducing the risk of hypoglycemia. Smoking and alcohol consumption should also be avoided.[37, 39]

GLYCEMIC CONTROL

Optimal glycemic control is associated with improvement of symptomatology. It has been demonstrated that elevated blood glucose levels directly interfere with normal evacuation of food from the stomach. The majority of patients with T2DM and gastroparesis require insulin therapy as oral antidiabetics cannot be absorbed adequately and some drugs are associated with gastrointestinal side effects such as metformin, GLP-1 RA or increase the risk of hypoglycemia such as sulfonylureas. In patients with gastroparesis risk of postprandial hypoglycemia is higher because carbohydrate absorption is delayed. In order to prevent postprandial hypoglycemia are recommended administering rapid-acting insulin after meals, multiple intakes of small foods, frequent, small doses of prandial insulin with aggressive glycemic monitoring.[36,40] A good glycemic management often involves customizing insulin delivery using basal-bolus insulin and technology, including sensor-augmented pumps and continuous glucose monitoring systems particularly in patients with T1DM.[41]

The term gastric hypoglycemia is used for patients with hypoglycemia that appears due to gastroparesis and should be taken into account when we are making the differential diagnosis with patients who have poorly controlled diabetes. An interesting phenomenon described is the turnover of symptoms (their appearance and disappearance over time) which, according to some studies, is common in patients with DG.[42]

PHARMACOLOGICAL THERAPY

First of all, it is recommended to discontinue drugs that might delay stomach emptying: opioids, anticholinergics, tricyclic antidepressants, GLP-1RA, pramintide, calcium channel blockers. The drugs more frequently used are prokinetics (for example: metoclopramide, domperidon, cisaprid, erythromycin, betanecol) and antiemetics agents (for example: ondansetron and dimenhidrinat). These drugs do not improve gastric emptying but they improve the symptoms.[43, 44] Metoclopramide is the only one approved by Food and Drug Administration (FDA) for the management of gastroparesis, but it is not recommended to use for more than 3 months due to the serious adverse effects risk such as: extrapyramidal signs, acute dystonic reactions, parkinsonism, late dyskinesia.[45] Metoclopramide nasal spray (Gimoti) was approved by FDA in June 2020 for the treatment of gastroparesis. It can be systemically absorbed by avoiding the passage through a poorly emptying stomach, thus ensuring the delivery of a therapeutic dose even during episodes of vomiting and it is useful in avoiding hospitalizations.[46] Other therapeutic agents that can improve symptoms by increasing gastric emptying and can be used in the treatment of DG are domperidone, a dopamine 2 receptor antagonist, erythromycin, a macrolide antibiotic and motilin agonist, and cisapride, a 5-hydroxytryptamine receptor agonist. There are studies in progress with motilin receptor agonists, ghreline agonists and new type 4-5-hydroxytryptamin receptor agonists.[47] There are ongoing studies that included patients with DG treated with subcutaneously administered ghreline receptor agonist called relamorelin which significantly increases gastric motility and improves symptoms and the quality of life of the patients.[48–51]

NON-PHARMACOLOGICAL THERAPEUTIC OPTIONS: ENDOSCOPIC TREATMENT, GASTRIC ELECTROSTIMULATION, SURGICAL TREATMENT, ALTERNATIVE THERAPIES

The surgical interventions at the level of the pylorus aim to solve the pyloric spasm by injecting botulinum toxin, dilating the pylorus, respectively stent implantation at this level.[36, 43] The endoscopic injection of botulinum toxin into the pylorus in order to keep it open is effective in accelerating gastric emptying, but it provides an improvement in symptoms for a period of only 3 months.[52] Gastric endoscopic pyloromyotomy is usually practiced in patients with refractory gastroparesis and the favorable evolution after this intervention was demonstrated in several studies. [53.54] Surgical treatment is recommended for refractory cases of gastroparesis. There are several surgical approaches that can be tried: pyloroplasty, gastrojejunostomy, total gastrectomy or gastric bypass. Patients who performed laparoscopic gastric sleeve had a significant improvement in symptoms and quality of life.[36,55] In 2000, FDA approved the use of gastric pacemaker that reduces symptomatology, improved nutritional state after 6 months and increases the quality of life. This stimulator uses a device that emits high-frequency electrical pulses to the smooth muscles of the stomach that appears to interfere with sensory transduction to the brain.[56, 57]

Considering that many patients are looking for alternative methods of treatment, acupuncture it can be one of the options. A Cochrane analysis of 32 heterogeneous revealed the improvement of symptoms only in the short term and only in combination with gastro kinetic drugs.[58]

CONCLUSIONS

DG is a severe complication of diabetic autonomic neuropathy that impairs quality of life and increases morbidity and mortality. The identification, diagnosis and treatment of DG continue to remain a challenge for the medical practitioner due to the ineffectiveness of the current perspective in improving the patient's clinical condition. The multidisciplinary approach and the implementation of individualized strategies based on the knowledge of pathological mechanisms are the cornerstone in obtaining favorable results in patients with gastroparesis. In the future, as the cellular and molecular changes are deciphered, new pharmacological agents, but also medical devices with advanced technology will open up, targeting the deficits that need to be corrected.

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