DIABETIC GASTROPARESIS – DIAGNOSIS AND TREATMENT

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Abstract

Autonomic neuropathy is a disease of the autonomic nervous system affecting mostly the internal organs. In diabetes mellitus this is a frequent but undiagnosed complication. Digestive autonomic neuropathy can affect all the segments of the digestive tract, among which stomach resulting in diabetic gastroparesis. The clinical definition for gastroparesis is based solely on the emptying time of the stomach and not on other symptoms, and severity of symptoms does not necessarily correlate with the severity of gastroparesis. Therefore, some patients may have marked gastroparesis with few, if any, serious complications.

Treatment includes dietary changes, oral medications such as Metoclopramide, Cisapride, Erythromycin and Domperidone, implanted gastric neurostimulators, or botulinum toxin. This is a review of the main theraputic methods used nowadays in gastroparesis, along with clinical and diagnostic issues.

Keywords: diabetes mellitus, gastroparesis.

Gastroparesis is defined as the reduction in motor activity of antrum and fundus of the stomach, with gastric dysrrhithmia and pyloric spasm; it has an important impact on quality of life of the affected individual, but it is to often ignored by the clinician. The majority of cases are idiopathic, and long standing diabetes mellitus is responsible for about 25-30% of cases [1].

The exact onset of gastroparesis is hard to be established because the disease is asymptomatic in the first stages and for a long period of time, and the symptoms, when present, are highly uncharacteristic. The onset may be acute with symptoms mimicking pyloric stenosis. Its cardinal features include nausea, vomiting, bloating, early satiety and discomfort. Weight loss, dehydration, electrolyte disturbances and malnutrition may develop in severe cases [1,2,3]

Asymptomatic patients may present the association an insufficiently controlled disease with a higher incidence of hypoglycemic episodes secondary to unequal absorption of ingested food. Food retention results in acceleration of fermentation which can determine diarrhea and progressive weight loss [3].

There are periods free of symptoms, but gastroparesis is progressive, chronic and may be disabilitating. There is no clear association between length of disease and the onset of delayed gastric emptying [3,4].

According to Revicki DA, et al. [5] the assessment of severity is important for appropriate management. One method is the Gastroparesis Cardinal Symptom Index, which is a sum of 3 subscales (ranging from 1–3) for the three main symptom complexes: postprandial fullness/early satiety, nausea/vomiting and bloating.

The diagnosis of gastroparesis may be confirmed by demonstrating gastric emptying delay during a 4-hour scintigraphy (gastric emptying scintigraphy-GES) [3].

GES has emerged as the most widely used test for the assessment of gastric emptying. According to Szarka LA & Camilleri M, the typical indications for GES are: unexplained nausea, vomiting, and dyspeptic symptoms; assessment of gastric motility prior to fundoplication for GERD; assessment of gastric motility prior to surgical treatment in colonic inertia and to screen for gastroparesis in diabetic patients who are being considered for treatment with medication that may further delay gastric emptying [4,5,6].

Magnetic resonance imaging (MRI) has been studied in last years, but further validation is needed before MRI is ready for applications in clinical practice. Additional attributes, as compared to GES, are: the ability to resolve wall motion, and to assess extragastric organs, along with absence of radiation [6].

Functional ultrasonography is a relatively inexpensive, safe, noninvasive method to assess gastric emptying. Duplex Doppler techniques have been used to study transpyloric flow of liquid meals. In the future, 3D

ultrasonography could become the most convenient test, but it still needs further validation. So, nowadays GES remain the golden standard to assess gastric function, including in diabetes patients [6].

There is a proposed classification of gastroparesis severity which may be useful in the approach of a diabetes mellitus patient with gastrointestinal symptoms and in treatment decisions.

According to Abel et al [7] **grade 1** means *mild gastroparesis*, with symptoms relatively easily controlled, the patient is able to maintain weight and nutrition on a regular diet or minor dietary modifications alterations.

Grade 2 means *compensated gastroparesis*, with moderate symptoms and partial control with pharmacological agents. The patient is able to maintain nutrition with dietary and lifestyle adjustments, and requires rare hospital admissions

Grade 3 is *gastroparesis with gastric failure*. The patient has refractory symptoms despite medical therapy, has also the inability to maintain nutrition via oral route, and needs frequent hospitalizations.

<u>**Treatment**</u> consists in frequent, small meals and psychological support; also, several drugs are available, but with limited efficacy, like prokinetics and antiemetics which are the most wide-spread medicaments used [8,9,10].

Prokinetics (see also table 1)

Prokinetic agents most commonly used to treat gastroparesis include metoclopramide and erythromycin. Randomized clinical trials have shown a symptomatic benefit of these agents, as well as of cisapride and domperidone [11-19].

In general, as compared with placebo, these agents have increased gastric emptying by about 25 to 72% and have reduced the severity of symptoms by 25 to 68%. However, many of these trials were small, some were not blind, and some included patients with gastroparesis due to causes other than diabetes.

Cisapride (5-HT4 receptor agonist) proved itself very useful but it is associated with an increased risk of cardiac arrhythmia, including torsades de pointes; therefore it is currently unavailable in many countries, and is used only if other medications fail [10].

Metoclopramide is a dopamine receptor antagonist which is widely used, as well as domperidone. With metoclopramide, patients may develop tolerance over time and the side effects may limit its use in up to 30% of patients. Irreversible late dyskinesia is a serious side effect that occurs in 1–10% of patients treated for more than 3 months [20]. In one trial, metoclopramide and domperidone were equally effective in reducing symptoms, but side effects on the central nervous system (somnolence, mental function, anxiety, and depression) were more pronounced in patients receiving metoclopramide [13].

The efficacy of **domperidone** matches that of metaclopramide and cisapride [20] but its effect on solid-phase gastric emptying is lost by 6 weeks [8, 20]. Domperidone is not currently approved by the Food and Drug Administration (FDA) but is available, with approval by local institutional review boards, through an FDA investigational new drug application.

The efficacy of **erythromycin** in gastroparesis has not been fully demonstrated yet [20,21]. Erythromycin improves gastric emptying, but only a minority of patients will benefit with regard to symptoms amelioration [22]. Intravenous erythromycin (3 mg per kilogram of body weight every 8 hours by infusion) is more effective than placebo in relieving acute gastroparesis in hospitalized patients [23,24,25]

Muscarinic cholinergic agents (e.g., bethanechol), anticholinesterases (e.g., pyridostigmine), and the 5-hydroxytryptamine4 (5-HT4) agonist tegaserod may accelerate gastric emptying [7], but data from trials assessing effects on symptoms of gastroparesis are lacking.

Table 1. Prokinetics used in gastroparesis (after [10]).

Agent	Mechanism of action	Comments
Metoclopramide	Dopamine receptor antagonist, central/peripheral Also 5-HT3 antagonist Also 5-HT4 agonist	FDA approved for gastroparesis Central nervous system side effects in 20–30% Prokinetic and antiemetic properties
Erythromycin	Motilin receptor agonist	Gastrointestinal side effects in many patients: nausea/vomiting/abdominal pain Tachyphylaxis with long-term oral administration
Cisapride	5-HT4 receptor agonist Facilitates acetylcholine release Also 5-HT3 antagonist	Taken off market in March 2000 for prolonging QT interval Was only approved for nocturnal heartburn Currently not available as prescription in United States
Domperidone	Dopamine receptor antagonist peripheral	Prokinetic and antiemetic properties. Available in Europe/Canada/Mexico/New Zealand but not in United States
Tegaserod	5-HT4 partial agonist	FDA approved for irritable bowel syndrome, constipation predominant in women Improves gastric emptying, no data on symptoms
Bethanechol	Muscarinic receptor agonist	Increases amplitude of contractions, not peristalsis Not a true prokinetic agent

Antiemetic agents are helpful for the relief of symptoms. Commonly used antiemetic agents include prochlorperazine, trimethobenzamide, and promethazine. Phenothiazines may be administered as tablets, capsules, liquid suspensions, or suppositories or by injection. For patients with severe symptoms, suppositories or injectable forms may be more efficacious. Side effects from phenothiazines are common and include sedation and extrapyramidal effects [10,21].

Pain relief is sometimes required. There are no data from controlled trials to guide the choice of agent for use in patients with gastroparesis. Agents used in clinical practice include antidepressants (e.g., low-dose tricyclics or duloxetine) and pregabalin (approved for patients with diabetic neuropathy) [10,21].

Nutritional Support

The choice of nutritional support and its route of administration depend on the severity of disease. The indications for supplementation of enteral nutrition [7] include unintentional loss of 10% or more of the usual body weight during a period of 3 to 6 months, inability to achieve the recommended weight by the oral route, repeated hospitalization for refractory symptoms, interference with delivery of nutrients and medications, need for nasogastric intubation to relieve symptoms, and nausea and vomiting resulting in a poor quality of life [7].

Botulinium injections are thought to decrease pylorospasm and accelerate gastric emptying. However, a controlled trial showed no efficacy [26].

Gastric electrical stimulation proves itself useful in refractory cases [20], but this method is, at present, limited to a few centers. It involves the use of electrodes, usually placed trough laparoscopy in the muscle wall of the stomach antrum, connected to a neurostimulator in a pocket of the abdominal wall. In one controlled trial involving 33 patients with idiopathic or diabetic gastroparesis, electrical stimulation had no significant effect on symptoms overall, but reduced the weekly frequency of vomiting (P<0.05) [27]. The mechanism by which electrical stimulation improves symptoms is unclear. The use of different electrical settings for stimulation may improve clinical efficacy, but this suggestion requires further study [28].

In a large, heterogeneous series of patients with gastroparesis who were managed in a tertiary center, the majority (74%) required long-term prokinetic therapy [16]. The postsurgical group, and those with idiopathic gastroparesis associated with prominent abdominal pain or a history of physical or sexual abuse, were the most refractory to pharmacologic therapy.

Guidelines for management have been published by the American Gastroenterological Association [10] and the American Motility Society [7]; these guidelines predominantly reflect expert opinion, since there are only limited data from randomized trials to guide management.

The prognosis in diabetic gastroparesis has been assumed to be poor, but follow-up over at least a decade indicates that this is not necessarily the case, with no increase in mortality over patients with diabetes and a normal rate of gastric emptying [29]. Neither the rate of emptying nor symptoms changed markedly over a similar period [30].

Trimebutine (an endorphinic agonist) may also be used in gastroparesis due to its prokinetic activity [31].

References
1. Igaz P, Tulassay Z. Gastroparesis and its treatment options. Orv Hetil. 2008; 2; 149 (9):393-8.
2. Smith DS, Ferris CD. Current concepts in diabetic gastroparesis. Drugs. 2003; 63 (13):1339-58.
3. Vinik AI, Maser RE, Mitchell BD, et al. Diabetic autonomic neuropathy. Diabetes Care. 2003; 26: 1553–1579.
4. Moldovan C, Dumitrascu DL, Demian L et al. Gastroparesis in diabetes mellitus – an ultrasonographic study. Rom J Gastroenterol. 2005; 14 (1): 19-22.
5. Revicki DA, Rentz AM, Dubois D, et al: Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. Aliment Pharmacol Ther. 2003; 18: 141–150.
6. Szarka LA, Camilleri M. Clinical Imaging. Clin Gastroenterol Hepatol. 2009 7 (8): 823-27.
7. Abell TL, Bernstein RK, Cutts T et al. Treatment of gastroparesis: a multidisciplinary clinical review. Neurogastroenterol Motil. 2006; 18: 263–83.
8. Dumitrascu DL, Weinbeck M: Domperidone versus metoclopramide in the treatment of diabetic gastroparesis. Am J Gastroenterol. 2000; 95: 316–17.
9. De Block CE, De Leeuw IH, Pelckmans PA, et al. Current concepts in gastric motility in diabetes mellitus. Curr Diabetes Rev. 2006 Feb; 2 (1):113-30.
10. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association Technical Review on the Diagnosis and Treatment of Gastroparesis. Gastroenterology 2004; 127: 1592–1622.
11. Park MI, Camilleri M. Gastroparesis: clinical update. Am J Gastroenterol 2006; 101:1129-39.
12. McCallum RW, Ricci DA, Rakatansky H, et al. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care 1983; 6:463-7.
13. Patterson D, Abell T, Rothstein R, Koch K, Barnett J. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol 1999;94:1230-4.
14. Dutta U, Padhy AK, Ahuja V, Sharma MP. Double blind controlled trial of effect of cisapride on gastric emptying in diabetics. Trop Gastroenterol 1999;20:116-9.

15. Braden B, Enghofer M, Schaub M, Usadel KH, Caspary WF, Lembcke B. Longterm cisapride treatment improves diabetic gastroparesis but not glycaemic control. Aliment Pharmacol Ther 2002;16:1341-6.

16. Soykan I, Sarosiek I, McCallum RW. The effect of chronic oral domperidone therapy on gastrointestinal symptoms, gastric emptying, and quality of life in patients with gastroparesis. Am J Gastroenterol 1997;92:976-80.

17. Silvers D, Kipnes M, Broadstone V, et al. Domperidone in the management of symptoms of diabetic gastroparesis: efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. Clin Ther 1998;20: 438-53.

18. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol 1993; 88: 203-7.

19. Franzese A, Borrelli O, Corrado G, et al. Domperidone is more effective than cisapride in children with diabetic gastroparesis. Aliment Pharmacol Ther 2002; 16: 951-7.

20. Gumaste V, Baum J. Treatment of gastroparesis: an update. Digestion 2008; 78:173-79.

21. Camilleri M. Diabetic gastroparesis. N Engl J Med 2007; 356:820-9.

22. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. Am J Gastroenterol. 2003; 98: 259–63.

23. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. N Engl J Med 1990; 322:1028-31.

24. Dive A, Miesse C, Galanti L, et al. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. Crit Care Med 1995; 23:1356-62.

25. Fontana RJ, Barnett JL. Jejunostomy tube placement in refractory diabetic gastroparesis: a retrospective review. Am J Gastroenterol 1996;91:2174-8.

26. Arts J, Caenepeel P, Degreef T, et al. Randomised double-blind cross-over study evaluating the effect of intrapyloric injection of botulinum toxin on gastric emptying and symptoms in patients with gastroparesis. Gastroenterology 2005;128:A-81. abstract.

27. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 2003;125:421-8.

28. Abidi N, Starkebaum WL, Abell TL. An energy algorithm improves symptoms in some patients with gastroparesis and treated with gastric electrical stimulation. Neurogastroenterol Motil 2006; 18: 334-8.

29. Kong MF, Horowitz M, Jones KL, et al. Natural history of diabetic gastroparesis. Diabetes Care. 1999; 22: 503-7.

30. Jones KL, Russo A, Berry MK, et al. A longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus. Am J Med. 2002; 113: 449-55.

31. Dumitrascu DL. Therapy of functional gastrointestinal disorders, in DL Dumitrascu, L Nedelcu: Neurogastroenterology, Ed Med Univ Iuliu Hatieganu 2005