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Diabetic gastroparesis – from diagnosis to gastric electrical stimulation treatment

Dijabetička gastropareza – od dijagnoze do električne stimulacije želuca

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Abstract. The most common known underlying cause of gastroparesis is diabetes mellitus. General symptoms and signs include nausea, vomiting, bloating and early satiety. The diagnosis of diabetic gastroparesis (DGP) is closely made based on clinical history, exclusion of gastrointestinal obstruction by endoscopy and abdominal ultrasound, and confirmation of delay in gastric emptying by gastric emptying scintigraphy. First-line interventions for DGP are dietary modifications and prokinetic-antiemetic therapy. In cases resistant to maximal medical therapy, gastric electrical stimulation is indicated.The aim is to alleviate both the severity and frequency of symptoms, improve gastric emptying, ameliorate patient's nutritional status and to optimize glycemic control.

Key words: diabetes mellitus; electrical stimulation therapy; gastroparesis; scintigraphy

Sažetak. Šećerna bolest je najučestaliji poznati uzrok gastropareze. Uobičajeni simptomi su mučnina, povraćanje, nadutost i rano postizanje sitosti. Postavljanje dijagnoze dijabetičke gastropareze (DGP) temelji se na kliničkoj prezentaciji bolesti, otklanjanju mogućnosti opstrukcije endoskopskim ili ultrazvučnim pregledom te na potvrdi usporenog pražnjenja želučanog sadržaja uz pomoć nalaza scintigrafije pražnjenja želuca. Prve terapijske odrednice za DGP su dijetoterapija te uvođenje prokinetika i antiemetika u kroničnu terapiju. Električna stimulacija želuca indicirana je u slučajevima rezistentnim na maksimalnu medikamentoznu terapiju. Cilj je ublažiti intenzitet i učestalost simptoma, poboljšati pražnjenje želuca i nutritivni status pacijenta te optimizirati kontrolu glikemije.

Ključne riječi: električna stimulacija; gastropareza; scintigrafija; šećerna bolest

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ABBREVIATIONS

DGP – diabetic gastroparesis; DTPA – diethyltriamino pentaacetic acid; FDA – Food and Drug Administration;GCSI – Gastroparesis Cardinal Symptom Index; GEMS – Gastric Electrical Mechanical Stimulation Study; GES – gastric electrical stimulation; IGF-1 – insulin-like growth factor 1; LEHR – low-energy high-resolution; MBq – milibecquerel; 99mTc – technetium-99m; USA – United States of America; WAVESS – Worldwide Anti-Vomiting Electrical Stimulation Study

INTRODUCTION

Gastroparesis is defined as a chronic motility disorder characterised by objectively delayed gastric emptying in the absence of any mechanical obstruction. The average time it takes the healthy stomach to empty half of its contents into the small intestine is approximately 60 to 100 minutes, while patients with gastroparesis have emptying times with a half-life from just over 100 to >500 minutes[1]. Hence, patients who suffer from this disease often report a significant reduction of their life quality[2]. The incidence of gastroparesis is not known precisely, but it is estimated to affect about 4 %–5 % of the entire population[3].

ETIOPATHOGENESIS OF GASTROPARESIS

Idiopathic (36 %), diabetic (29 %) and postsurgical (13 %) etiologies include the majority of all gastroparesis cases[4,5]. Idiopathic gastroparesis, as the most common form of gastroparesis, refers to a symptomatic patient from delayed gastric emptying with no detectable primary underlying abnormality. The pathogenesis of postsurgical gastroparesis is known and it is based on vagal nerve disruption or interference[6-8]. On the contrary, the exact mechanism of diabetic gastroparesis (DGP) is unknown, but several contributing factors have been suggested: hyperglycemia, vagal dysfunction, loss of neural nitric oxide synthase expression in the myenteric plexus, oxidative stress with loss of upregulation of protective enzymes, loss of interstitial cells of Cajal with resultant gastric arrythmia and delay in gastric emptying, smooth muscle atrophy and loss of insulin-like growth factor 1 (IGF-1), and last but not least, loss of macrophages expressing heme oxygenase-1[9]. Rare causes of gastroparesis also could be Chagas disease, hypothyroidism, hyperparathyroidism, hypoparathyroidism, collagen vascular diseases, some neurological conditions like Parkinsonism or medication[4,10].

DIABETIC GASTROPARESIS

Diabetic gastroparesis, as the complication of diabetes, was first reported in 1958[11]. Typically, it develops after at least 10 years of previously diagnosed diabetes mellitus, and this group of patients in most cases already has evidences of autonomic dysfunction[12,13]. Nevertheless, at the population level 5 % of type 1 and 1 % of type 2 diabetes patients have both a delay in gastric emptying and the presence of typical DGP symptoms[10,13]. The disease affects females more than males in approximate 4:1 ratio[8,13]. There are two possible explanations for the gender differences. One explanation is the fact that gastric emptying in female gender is on average slower than in males[12]. The other possible explanation is based on recent animal data which pointed that the effect of diabetes mellitus on the enteric nervous system is more expressed in females[14,15].

Diabetic gastroparesis can cause a wide variety of symptoms. Early in the course of the disease symptoms may be minimal, but as the dysfunction upwards they become more common. General symptoms and signs include nausea, vomiting, bloating, postprandial fullness, upper abdominal pain and finally weight reduction.

Clinical manifestations and diagnosis

In order to exclude other disorders that may mimick DGP (rumination syndrome, superior mesenteric artery sindrome, cyclic vomiting syndrome and bulimia nervosa), the diagnosis of gastroparesis is closely made based on typical clinical history, exclusion of gastrointestinal obstruction by endoscopy and abdominal ultrasound, and confirmation of delay in gastric emptying[13,16]. DGP can cause a wide variety of symptoms[13,17]. Early in the course of the disease

Table 1. Review of gastroparesis cardinal symptoms index (GCSI) (Adapted from reference 20)

	None	Very mild	Mild	Moderate	Severe	Very severe
1. Nausea	0	1	2	3	4	5
2. Retching	0	1	2	3	4	5
3. Vomiting	0	1	2	3	4	5
4. Stomach fullness	0	1	2	3	4	5
5. Not able to finish a normal-sized meal	0	1	2	3	4	5
6. Feeling excessively full after meals	0	1	2	3	4	5
7. Loss of appetite	0	1	2	3	4	5
8. Bloating	0	1	2	3	4	5
9. Stomach or belly visibly larger	0	1	2	3	4	5

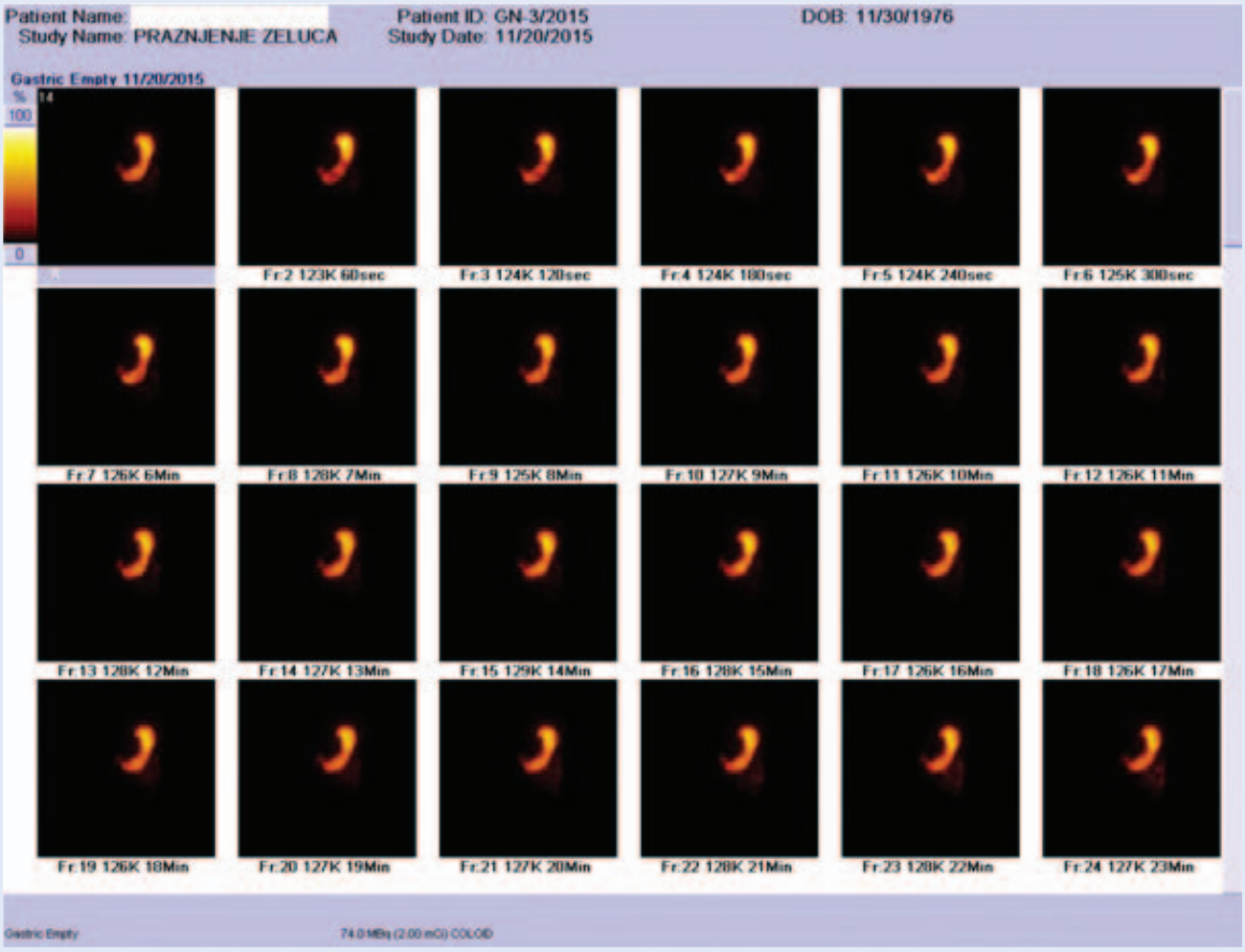

Figure 1. Gastric emptying scintigraphy – the gold standard for measuring gastric emptying

symptoms may be minimal, but as the dysfunction upwards they become more common. However, several symptoms do not always correlate to measures of gastric emptying[18]. General symptoms and signs include nausea, vomiting, bloating, postprandial fullness, upper abdominal pain and finally weight reduction[19]. There is a variety of scoring systems for symptoms of gastroparesis, but the most commonly used system is the Gastroparesis Cardinal Symptom Index (GCSI), which is a validated scoring system. The GCSI consists of nine symptom severity items that cover the following domains: nausea/vomiting (3 items); fullness/early satiety (4 items); and bloat-

ing (2 items). Symptoms are rated by the patients among the choices: none (0), very mild (1), mild (2), moderate (3), severe (4) and very severe (5) (Table 1). The GCSI total score equals the sum of the nausea/vomiting, bloating and fullness/early satiety subscales divided by 3[20]. After gastrointestinal obstruction is ruled out by endoscopy and abdominal ultrasound, gastric emptying scyntigraphy – gold standard for measuring gastric emptying, is performed[21]. In our Clinical Hospital Centre gastic emptying study (Figure 1) is usually performed after labelling the liquid meal, Alitraq® (Abbot, USA) with 74 MBq 99mTc DTPA (diethyltriamino pentaacetic acid) radiopharmaceutical. Content of one Alitraq® package is dissolved in 250 ml of water, resulting in the volume of 300 ml. One third of the content, 100 ml is used per patient and mixed with 74 MBq of DTPA prepared earlier according to the manufacturer's instruction. Patients are asked to drink the glass containing labelled meal with the straw, taking care to avoid possible contamination. Immediately after that, patients are positioned in semi recumbent position with the gamma camera detector placed over the region of abdomen, parallel to the surface of the body. Images are collected during 120 minutes, 60 s per frame in a matrix 128 × 128, zoom 1.0, with one detector Siemens Diacam gamma camera equipped with low-energy high-resolution (LEHR) collimator. Acquired images are firstly inspected visually, and then analyzed with Siemens Icon software package for Gastric emptying, with region of interest drawn over the gastric activity. Generated time activity curves are analyzed for the time needed for complete emptying or the estimate; emptying half time and time delay until emptying begins (retention time).

Therapeutic options

The aim of DGP treatment is to alleviate both the severity and frequency of symptoms, improve gastric emptying level, ameliorate the patient's nutritional status and to optimize glycemic control. First-line interventions for DGP are dietary modifications accompanied with or without medical therapy[18]. According to nutrition guidelines 4-5 small, low-fat, low-fiber meals a day are recommended, since both fat and fiber can lead to delay in gastric emptying. Small meal size is preferred, because stomach may only empty up to 2 kcal/min[5]. In diabetics, normal glycemic control with diet and hypoglycemic drugs are of high importance, as improvement of hyperglycemia can accelerate gastric emptyng. DGP medical therapy may include several medication classes-prokinetics, antiemetics and pain modulation therapies[13]. Mostly used prokinetic agents in DGP treatment are: antidopaminergic prokinetics (metoclopramide, domperidone) and motilin receptor agonists which include the macrolide antibiotics, with erythromycin as the classic agent used. Of the prokinetic agents, only metoclopramide is USA Food and Drug Administration (FDA) approved medication for the treatment of gastroparesis for no longer than a 12-week period[18]. Nevertheless, since DGP is a chronic disease, it is often prescribed indefinitely on 'as required' basis. Motilin agonist-erythromycin is usually not used as a first-choice prokinetic due to antibiotic resistance and tachyphylaxis[13]. To conclude, there is a little evidence that prokinetic agents may improve glycemic control through improved gastric emptying[22]. In drug-resistant cases, mechanical steps in therapy such as endoscopic pyloric botulinum toxin injection, gastric electrical stimulation (GES), gastrectomy and gastrostomy or jejunostomy may need to be considered[5,23].

Gastric emptying scintigraphy has been considered as gold standard in gastric emptying measurement due to its physiologic, quantitative and non-invasive nature.

GASTRIC ELECTRICAL STIMULATION

When it comes to gastric electrical stimulation, three principal methods are currently available: low-frequency/high energy GES with long pulse stimulation, high-frequency/low energy GES with short pulse stimulation and neural sequential GES. Low frequency/high energy GES is currently not suitable for implantation, because of heavy batteries and variable effect od gastroparesis symptoms, while neural sequential GES is not even used in humans at the moment[24]. Finally, high frequency/low energy GES, also known as

Enterra (Medtronic, Minneapolis, MN, USA) Therapy, is currently the only GES principal method suitable for human implantation[25]. It delivers impulses at high frequency/low energy (short pulses) at around 12 pulses per minute through pacemaker and consequently stimulates the gastric emptying. The exact mechanism is not well understood yet, but initial studies suggest that it may induce descending noxious inhibitory control by the brain via vagal afferent nerves from the stomach[13,26].

Enterra Therapy implantable system consists of two unipolar intramuscular leads and a neurostimulator that uses mild electrical stimulation of the lower stomach (antrum) to reduce drug-resistant nausea and vomiting associated with gastroparesis of diabetic or idiopathic origin.

The Enterra system consists of a neurostimulator implanted beneath the skin, usually in the lower abdominal region and two leads. The leads are implanted via laparotomy or laparoscopy into the stomach wall muscle layer 1-2 cm apart at greater curvature of the stomach, 10 cm proximal to the pylorus[27]. An upper endoscopy is performed to ensure that there is no penetration of the wires through the mucosa into the stomach lumen. The neurostimulator is programmed to specific parameters established on earlier canine and human studies[28,29]. It delivers low-energy, high frequency stimuli and has a battery life of 5-10 years, depending on the pulse parameters used[30]. When the battery life is over, the pulse generator is replaced by local intervention.

The experience of gastric pacing was obtained through 2 multicenter trials, the Gastric Electrical Mechanical Stimulation Study (GEMS)[31] and the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS)[32]. GEMS was an open-labeled which has documented improvement in both specific and global gastroparesis symptoms and gastric emptying, while WAVESS was a controlled double-blind sham stimulation trial that reaffirmed the efficacy of GES[4]. Afterwards, GES has been aproved by the FDA (Enterra Therapy, Medtronic, Minneapolis, MN, USA) for patients with diabetic or idiopathic gastroparesis resistant to drug therapy.

About 10 % of patients develop GES complications: infections, electrode dislodgement, wire breakage, penetration of the stomach and intestinal obstruction. Due to complications surgical intervention with removal of the device needs to be performed[33]. However, GES does seem to offer significant improvement in life quality and in the severity and frequency of symptoms to a subset of patients. Still, more multicenter long-term controlled studies will be necessary for GES to be ready for its prime time.

CONCLUSION

The rising rates of diabetes mellitus will inevitably result in increasing the incidence of diabetic complications, including gastroparesis. Most therapeutic options available to treat DGP are less than ideal and patients usually require their combination depending on the severity of their condition. Hence, further research isneeded for better understanding of the pathogenesis of DGP, which may lead to improved treatment options. However, gastric electrical stimulation with Enterra system is at this point definitely the most efficient therapeutic solution, when dietary modifications accompanied with medical prokinetic and antiemetic agents fail to showsatisfying results.

Conflicts of interest statement: The authors report no conflicts of interest.

REFERENCES

1. Ross J, Masrur M, Gonzalez Heredia R, Elli EF. Effectiveness of Gastric Neurostimulation in Patients With Gastroparesis. JSLS 2014;18:1-6.
2. Talley NJ, Locke GR, Lahr BD, Zinsmeister AR, Tougas G, Ligozio G et al. Functional dyspepsia, delayed gastric emptying and impaired quality of life. Gut 2006;55:933-9.
3. Hasler WL. Gastroparesis: symptoms, evaluation and treatment. Gastroenterol Clin North Am 2007;36:619-47.
4. Gumaste V, Baum J. Treatment of Gastroparesis: An Update. Digestion 2008;78:173-9.
5. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol 2013;108:18-38.
6. Jung HK, Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Szarka LA et al. The incidence, prevalence and outcomes of patients with gastroparesis in Olmsted County, Minessota from 1996 to 2006. Gastroenterology 2009;136:1225-33.

7. McCallum R, Lin Z, Wetzel P, Sarosiek I, Forster J. Clinical response to gastric electrical stimulation in patients with postsurgical gastroparesis. Clin Gastroenterol Hepatol 2005;3:49-54.
8. Timratana P, El-Hayek K, Shimizu H, Kroh M, Chand B. Laparoscopic Gastric Electrical Stimulation for Medically Refractory Diabetic and Idiopathic Gastroparesis. J Gastrointest Surg 2013;17:461-70.
9. Kashyap P, Farrugia G. Diabetic Gastroparesis: what we have learned and had to unlearn in the past 5 years. Gut 2010;59:1716-26.
10. Parkman HP, Camilleri M, Farrugia G, McCallum RW, Bharucha AE, Mayer EA et al. Gastroparesis and functional dyspepsia: excerpts from AGA/ANMS meeting. Neurogastroenterol Motil 2010;22:113-33.
11. Kassander P. Asymptomatic gastric retention in diabetics (gastroparesis diabeticorum). Ann Intern Med 1958;48:797-812.
12. Bharucha AE, Camilleri M, Forstrom LA, Zinsmeister AR. Relationship between clinical features and gastric emptying disturbances in diabetes mellitus. Clin Endocrinol (Oxf) 2009;70:415-20.
13. Vanormelingen C, Tack J, Andrews CN. Diabetic gastroparesis. British Medical Bulletin 2013;105:213-30.
14. Gangula PR, Maner WL, Micci MA, Garfield RE, Pasricha PJ. Diabetes induces sex-dependent changes in neuronal nitric oxide synthase dimerization and function in the rat gastric antrum. Am J Physiol Gastrointest Liver Physiol 2007;292:725-33.
15. Gangula PR, Sekhar KR, Mukhopadhyay S. Gender bias in gastroparesis: is nitric oxide the answer? Dig Dis Sci 2011;56:2520-27.
16. Fukami N, Anderson MA, Khan K, Harrison ME, Appalaneni V, Ben-Menachem T et al. The role of endoscopy in gastroduodenal obstruction and gastroparesis. Gastrointest Endosc 2011;74:13-21.
17. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. Gastroenterology 2011;140:101-15.
18. Alam U, Asghar O, Malik RA. Diabetic Gastroparesis: Therapeutic Options. Diabetes Ther 2010;1:32-43.
19. Camilieri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms and magement of diabetic gastroparesis. Clin Gastroenterol Hepatol 2011;9:5-12.
20. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ et al. Development and validation of patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. Aliment Pharmacol Ther 2003;18:263-83.
21. Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Maurer AH et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. Am J Gastroenterol 2008;103:753-63.
22. Intagliata N, Koch KL. Gastroparesis in type 2 diabetes mellitus: prevalence, etiology, diagnosis and treatment. Curr Gastroenterol Rep 2007;9:270-79.
23. Camilieri M. Clinical practice. Diabetic gastroparesis. N Engl J Med 2007;356:820-9.
24. Bortolotti M. Gastric electrical stimulation for gastroparesis: a goal greatly pursued, but not yet attained. World Journal of Gastroenterology 2011;17:273-82.
25. Lal N, Livemore S, Dunne D, Khan I. Gastric Electrical Stimulation with the Enterra System: A Systematic Review. Gastroenterol Res Pract 2015; Forthcoming.
26. Hasler WL. Methods of gastric electrical stimulation and pacing: a review of their benefits and mechanisms of action in gastroparesis and obesity. Neurogastroenterol Motil 2009;21:229-43.
27. Soffer E. Gastric Electrical Stimulation for Gastroparesis. J Neurogastroenterol Motil 2012;18:131-7.
28. Familoni BO, Abell TL, Nemoto D, Voeller G, Johnson B. Efficacy of electrical stimulation at frequencies higher than basal rate in canine stomach. Dig Dis Sci 1997;42:892-7.
29. Familioni BO, Abell TL, Voeller G, Salem A, Gaber O. Electrical stimulation at a frequency higher than basal rate in human stomach. Dig Dis Sci 1997;42:885-91.
30. McKenna D, Beverstein G, Reichelderfer M, Gaumnitz E, Gould J. Gastric electrical stimulation is an effective and safe treatment for medically refractory gastroparesis. Surgery 2008;144:566-74.
31. Abell T, Van Cutsem E, Abrahamsson H, Huizinga JD, Konturek JW, Galmiche JP et al. Gastric electrical stimulation in the tractable symptomatic gastroparesis. Digestion 2002;66:204-12.
32. Abell T, McCallum R, Hocking M, Koch K, Abrahamsson H, Leblanc I et al. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 2003;125:421-8.
33. Maranki J, Parkman HP. Gastric electrical stimulation for the treatment of gastroparesis. Curr Gastroenterol Rep 2007;9:286-94.