Diabetic gastroparesis – from diagnosis to gastric electrical stimulation treatment

Sanja Klobučar Majanović1*, Marko Zelić2, Andrej Belančić3, Neva Girotto4, Vanja Licul5, Davor Štimac5

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
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. Hence, patients who suffer from this disease often report a significant reduction of their life quality. The incidence of gastroparesis is not known precisely, but it is estimated to affect about 4 %–5 % of the entire population.

ETIOPATHOGENESIS OF GASTROPARESIS
Idiopathic (36 %), diabetic (29 %) and postsurgical (13 %) etiologies include the majority of all gastroparesis cases. 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. 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 arrhythmia 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. Rare causes of gastroparesis also could be Chagas disease, hypothyroidism, hyperparathyroidism, hypoparathyroidism, collagen vascular diseases, some neurological conditions like Parkinsonism or medication.

DIABETIC GASTROPARESIS
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.

Diabetic gastroparesis, as the complication of diabetes, was first reported in 1958. 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. 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. The disease affects females more than males in approximate 4:1 ratio. 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. 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.

Clinical manifestations and diagnosis
In order to exclude other disorders that may mimic DGP (rumination syndrome, superior mesenteric artery syndrome, 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. DGP 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. However, several symptoms do not always correlate to measures of gastric emptying. General symptoms and signs include nausea, vomiting, bloating, postprandial fullness, upper abdominal pain and finally weight reduction. 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 bloating. General symptoms and signs include nausea, vomiting, bloating, postprandial fullness, upper abdominal pain and finally weight reduction. 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 bloating.
Gastric emptying scintigraphy has been considered as gold standard in gastric emptying measurement due to its physiologic, quantitative and non-invasive nature.
Enterra (Medtronic, Minneapolis, MN, USA) Therapy, is currently the only GES principal method suitable for human implantation. 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.

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. 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. It delivers low-energy, high frequency stimuli and has a battery life of 5-10 years, depending on the pulse parameters used. 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) and the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS). 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. 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. 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 is needed 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 show satisfying results.

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

REFERENCES