

# Diabetic Gastrointestinal Neuropathy: Elusive Diagnosis and Difficult Treatment

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**Abstract:** Diabetic Gastrointestinal Neuropathy is an elusive diagnosis and often overlooked. The affected patients do not connect the symptoms with diabetes and undergo a painstaking and expensive search for other disorders of the digestive tract. Diabetic Gastrointestinal Neuropathy additionally causes a baffling glucose instability that further aggravates the condition. The treatment is difficult. The less severe cases respond to prokinetic treatment, but when the disease is advanced the only available therapy is the insertion of a pacemaker.

**Keywords:** Diabetic gastrointestinal neuropathy, glucose variability, gastrointestinal pacemaker.

## INTRODUCTION

Diabetic gastrointestinal neuropathy is a frequent condition present in nearly 50% of the diabetic population [1] both type 1 [1, 2] and type 2 [3], but unfortunately, rarely recognized. The medical literature on this topic is rather limited. A search of PubMed for the term “diabetic Gastroparesis” returned 587 papers, with 125 being reviews. The affected patients do not connect the symptoms with diabetes and undergo a painstaking and expensive search for other disorders of the digestive tract. Diabetic Gastrointestinal Neuropathy also causes a baffling glucose instability that further aggravates the condition. The treatment is difficult. The less severe cases respond to prokinetic treatment, but when the disease is advanced the only available treatment is the insertion of a pacemaker.

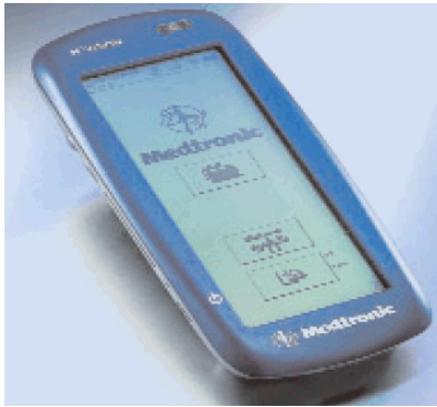
## PATHOPHYSIOLOGY AND SYMPTOMS

The signs and symptoms vary from the full blown picture that clinches the diagnosis to the most elusive one. Esophageal dysfunction may cause heartburn, anol reflux, dysphagia. The gastric involvement may impair gastric acid secretion and interfere with the motility to the extreme degrees of gastroparesis diabeticorum. Among the symptoms are early satiety, nausea, anorexia, vomiting, epigastric discomfort and bloating which are easily dismissed or attributed to drugs. In this condition there may be emesis of undigested food. Most commonly extreme irregularity and unpredictable fluctuations of the blood glucose [4] due to the erratic absorption of food may appear. In the extreme states the life of the patient is miserable with wasting and loss of weight. Often the symptoms are elusive and the outstanding manifestation is a mindboggling glucose instability with unexpected peaks at any time of the day and unexplained

and unpredictable hypoglycemic episodes that impact on the life of the patient and his family [5]. Hypoglycemia is a serious limiting factor for the intensive treatment of hyperglycemia at any age [6, 7]. Beyond its ravaging consequences GI neuropathy may be a marker of other neuropathies and diabetic complications. Furthermore, the frequent vomiting causes alteration in absorption of nutrients and additional damage to the body. Recent data suggest that a delayed radionucleotide gastric emptying study predicts increased mortality in diabetic patients with symptoms of gastroparesis, [8] irrespective of the cardiovascular involvement [9].

Diabetic gastropathy is a heterogenous syndrome, and the diagnosis is not straightforward. The term should probably be revisited [10]. The emptying of liquids behaves unpredictably [11-13] and the ingestion of solid meals appears to be more consistently delayed [14] with retention in the proximal stomach [15]. There is no Gold Standard for the diagnosis, and this has hampered the definitive evaluation of the impact of this complication and its treatment. Another complicating factor is the behavior of the gastric motility according to the blood glucose level. In healthy subjects the rate of gastric emptying is slower during experimental hyperglycemia [16-18]; the reverse is also true because in the experimental setting in type 1 diabetics solid and liquid foods are apparently absorbed more rapidly during hypoglycemia [19]. While this behavior is entirely consistent with an attempt to modulate the blood glucose level, all these data were obtained in different populations and under different conditions and should be replicated with the actual technology. Moreover it is yet to be demonstrated that these responses obtained in an acute setting hold true also in the chronic state, since the limited data we have argue against this mechanism [20, 21]. It is not known if and to what degree autonomic neuropathy may interfere with these processes. The knowledge of these mechanisms and their derangements is of the outmost relevance to the treatment of diabetes mellitus because a correct match between food

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**Fig. (1).** The device in its typical presentation (courtesy of Medtronic Inc).

absorption and insulin or oral euglycemic agents has a key role in maintaining a normal blood glucose level. Another key aspect not solved is the role of the nutrients in modulating the intestinal motility which could concur to determine the characteristic glycemic response to food we know as the glycemic index.

It is also possible that gastric neuropathy is due to an intestinal myopathy possibly associated to the dysfunction of the local nerve plexus, although this is based on conflicting results [22, 23]. In summary, many factors influence the gastric emptying, the most prominent being loss of the interstitial pacemaker cells of Cajal, disturbed neurotransmission and altered hormonal environment [24].

#### **MEDICAL TREATMENT AND GASTRIC ELECTRIC STIMULATION**

The first line treatment for gastroparesis is made of prokinetics and antiemetic drugs. The former ones are metoclopramide, which is endowed with CNS side effects as dosage increases, and domperidone. Erythromycin also belongs to this category but usually induces tachyphylaxis leading to its abandonment. Antiemetics include phenothiazines, antihistamines and serotonin antagonists, and can be given alone, but often are added to prokinetics. All of these drugs are used empirically and are not expected to be highly effective. In alternative low-dose tricyclic antidepressants can be used when nothing helps. Even pyloric injections of botulinum toxin may be chosen to induce muscle paralysis and pylorospasm relief in extremely refractory cases, but their usefulness is debatable [25-28].

The introduction of Prucalopride [29], a new, selective 5-HT<sub>4</sub> agonist and enterokinetic, for the treatment of constipation in women elicited some hopes, but there are at present no data on its efficacy.

When no medical treatment strategy helps Gastric Electric Stimulation (GES) may be attempted. This technique makes use of an implantable stimulator, like the Enterra® Therapy, Medtronic Inc., MN, USA, which has been approved by the US FDA for the treatment of severe and refractory gastroparesis (Figs. 1, 2). High frequency GES delivers a high-frequency (12 cpm), low-energy signal in short pulses and must be distinguished from “gastric pacing” that delivers high-energy stimuli at a frequency slightly above that of the intrinsic slow wave activity. The

higher-frequency stimulus does not entrain slow waves or reverse underlying slow wave dysrhythmias. Stimulating wires attached to the electric stimulator - which is positioned in a subcutaneous abdominal pouch - are sutured into the gastric muscle along the greater curvature during laparoscopy or laparotomy. This procedure is expected to nearly normalize stomach motility and relieve patients' symptoms. Its effects seem to be promising as successful results have been reported in as many as 50% to 80% cases, although the ability to promote gastric emptying through enhanced motility was relatively low. An explanation may be that gastric stimulation of vagal afferents may be able to suppress the vomiting centers in the brain [27, 30-32].



**Fig. (2).** Site of insertion of Enterra.

According to a review published by the American Gastroenterological Association (AGA) in 2004 GES is an emerging treatment for diabetic refractory gastroparesis which seems to promote gastric emptying of liquids better than of solids. In long-term follow-up this tool yielded a reduction in the mean vomiting frequency from 25 to 6 times per week with an associated improvement in quality of life, improved nutritional parameters and decreased requirements for supplemental feedings [33]. Unfortunately some open-label studies have not confirmed this benefit [34]. Because of potential advantages the gastric electric neurostimulator was granted humanitarian approval from the FDA for the

treatment of chronic, refractory nausea and vomiting secondary to idiopathic or diabetic gastroparesis. Some complications have been reported, mainly infections necessitating device removal in approximately 5%–10% of cases. According to the AGA further investigation is needed to confirm the effectiveness of gastric stimulation in long term blinded studies. The key questions needing answer are which patients are likely to respond, the optimal electrode placement, and the optimal stimulation parameters, none of which had been rigorously evaluated (American Gastroenterological Association Technical Review on the Diagnosis and Treatment of Gastroparesis) [35] and still have not been so far.

This is the reason why other experiments have been performed during the last few years, including the one by Lin's group [36] who retrospectively reviewed all patients undergoing GES implantation at the University of Kansas Medical Center (KUMC) from 1998 to 2002, to analyze the effects of GES on symptoms, health-related quality of life (HQOL), nutritional status, GE, and the degree of glucose control in 48 diabetic patients who had medically refractory gastroparesis and at least 12 months of follow-up available. In agreement with previous studies on GES in gastroparesis [37-40] they confirmed that GES by a permanently implantable system (Enterra Therapy) significantly reduced severity and frequency of all upper GI symptoms assessed, including vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain, with all subscores significantly reduced at 6 and 12 months of GES. The authors argue that the statistical significance of the results, which were also accompanied by a significant improvement in the HQOL (Health-Related Quality of life) evaluated using the previously validated SF-36 questionnaire, might depend on the larger database available for analysis in their study [41]. They also emphasize that, although GES does not correct other comorbidities of underlying diabetes, clearly makes life more functional on both mental (MCS) and physical (PCS) levels for the majority of patients. The significant reduction in HbA1c levels combined with the reduction in days of hospital stay was their major finding. In fact, by controlling nausea and vomiting and thus stabilizing food intake and maximizing the glucose/insulin relation, better diabetes control was achieved. The absence of nausea and vomiting could allow those patients to be candidates for renal and pancreas transplantation in the future because they can absorb the oral immunosuppressant agents needed to prevent organ rejection. In addition, the economics of fewer hospitalizations and the accompanying substantial savings emphasize another parameter of long-term outcome and quality of life [42]. Despite all these positive aspects, the method has also some deficiencies: the median gastric retention measured by a standardized 4-h scintigraphy of a solid meal was not significantly reduced at 12 months, indicating no special association between changes in symptoms and GE. The fact that other papers reported a significantly improved GE with the majority of gastroparesis patients (67%), getting back to normal levels and reversing gastric dysrhythmia with enhancement of the gastric slow waves [43], might depend on different stimulation parameters used. This suggests that in the future different stimulation parameters will be needed to reverse dysmotility in DGP. In Lin's study in patients with long-term diabetes

[44], the major adverse event related to GES therapy was postoperative infection, which often required the device to be removed. There was a significant relation between the risk of death and duration of diabetes ( $P < 0.02$ ): the mean duration of diabetes for the four patients who died in their study was 25.3 years, substantially higher than in the survivors (12 years) or those that deceased in another study discussed above [39]. Without taking into account open label studies, often claiming an impressive success rate, even as high as 97% improvement in more than 80% of patients [39], a randomized, double-blinded, multicenter clinical trial, later transformed into an unblinded cross-over trial (Worldwide Antivomiting Electrical Stimulation Study [WAVESS]) confirmed significant improvement in gastrointestinal symptoms. This study was limited to some extent as it recruited fewer patients than intended (33, when powered for 80) and only showed improvement in weekly vomiting frequency during the randomization phase [45]. Overall the various studies published during the last ten years or so did not use the same methods to quantify symptoms, so it is extremely difficult to draw sound undebatable conclusions. Moreover the Enterra settings in terms of frequency, energy and on/off periods were not always reported and in some cases success was claimed in nonresponders after adjustment of the frequency and energy delivered by the device. Thus it is difficult to draw straightforward conclusions on the overall efficacy of Enterra, especially as the mentors of this technique claim that in nonresponders (who usually have painful gastroparesis and make use of narcotics) good results may be obtained by adjusting voltage, frequency and on/off periods of stimulation [46]. Positive results have been undoubtedly obtained in the vast majority of cases reported in the literature.

In 2009 O'Grady, *et al.* tried to summarize the current evidence for the efficacy of high-frequency GES in the treatment of gastroparesis, by conducting a comprehensive literature review and a meta-analysis of selected published studies from January 1992 to August 2008. They included as sources Medline, EMBASE, Google Scholar, ISI Proceedings, the Cochrane Library, and online registers of controlled clinical trials on implanted high-frequency permanent GES devices and, because of the limited numbers of controlled clinical trials, took into account 13 non-controlled observational studies. They excluded publications reporting duplicate outcomes from a previous study and small case series. Post-GES measures demonstrated a consistent and significant benefit over baseline measures for both vomiting severity score and nausea severity score; SF-36 PCS and MCS Quality of Life measurement outcomes, which were available from four studies, demonstrated consistent and highly significant improvements post-GES compared with baseline values; moreover, prior to GES, against a total of 96 patients requiring enteral or parenteral nutritional support at baseline, only 21 still required it after GES.

On the other hand, the natural history of gastroparesis remains poorly understood [47], and even patients with longstanding disease may spontaneously improve with standard medical care alone. Another issue in relation to study design is the potential confounding effect of concurrent pharmacological therapy, in particular opiate use, which is present in some of the studies included in this meta-

analysis. Opiates may cause complex gastric dysrhythmias, slow gastric emptying, and exacerbate gastroparesis-related symptoms: one study included reported that 45% of the patients were narcotic dependent prior to device implantation and were actively weaned, with variable success, after the institution of high-frequency GES [48]. Thus it possible that symptom improvement might have resulted from the reduction in narcotic dosage rather than the implementation of high-frequency GES. Moreover, the non-responders to GES may have had their devices removed, or may have declined to participate in post-treatment evaluations, leading to a greater representation of responders in the summary statistics. Meanwhile, research continues into other methods of gastric stimulation, and these also hold some promise for the treatment of gastroparesis as shown, for example, by multichannel gastric pacing accelerating gastric emptying in a canine model [49]. There is therefore need to improve the efficiency and protocol designs of such treatments before they become routine procedures.

A major consideration arises from McCallum report on 55 cases of diabetic GP treated with Enterra undergoing a controlled, prospective, multicenter cross-over study [50]: the rapid and significant induction of symptom improvement in the first 6 weeks was sustained despite a period of up to 3 months with the device off. Therefore, the carryover effects of neuro-stimulation may persist and remain effective over a number of weeks to months, thus allowing the authors to hypothesize that the initial 6-week stimulation period rendered the subsequent double-blind data null.

A follow-up study with a different design has therefore to be suggested to address these other potential explanations for various studies' results and, in light of data suggesting the possibility of longterm carryover effects of the therapy, a cross-over design probably should be avoided. These results support the efficacy of Enterra therapy for severe diabetic gastroparesis patients failing medical therapy but also suggest that more research is needed to address the remaining questions about study results. In particular, the most meaningful design is a parallel study design with subjects randomized at the time of surgery to implant the Enterra device to either on or off for a 3- to 6-month time period. This would address previous study concerns.

**CONCLUSIONS**

Other mechanisms of action that could be hypothesized for high-frequency GES include gastric fundic relaxation, an action on the autonomic nervous system, and release of GI hormones, including ghrelin. Activation of central control mechanisms for nausea and vomiting in the brain stem and central nervous system by stimulating afferent pathways is the most unifying theory, but as yet there are no supporting data. GES might in fact increase vagal function, also resulting in increased fundic accommodation and possibly decreased sensitivity to distention [51]. Although these hypotheses might fit some of the observations, it is important to note that there is still no evidence that the vomiting center function is actually altered, and the relationship between the described changes and symptom relief requires more study. Most patients who respond to GES do so fairly soon after implantation of the device. This has led to the proposal that temporary endoscopic placement of stimulation leads in the

stomach can be used to predict response to the permanent device. The choice of the current parameters used in GES was partly based on battery considerations. Better methods to detect the underlying electrical signal including mucosal EGG might clarify the role of EGG as well as predict response to GES.

According to some authors, the fact that Enterra Therapy provides a modicum of relief to this group of patients who are at the 'end of their rope' is an argument in favor of its effectiveness [45]. Clearly, even with gastric neurostimulation some patients will continue to live with crippling symptoms. Enterra Therapy is not meant to be a substitute for other treatments – patients may still require antiemetics, pain medication, anxiolytics and antidepressants, as well as dietary support, possibly with jejunal enteral feedings and psychosocial support. Patients require constant follow-up. Any physiological or psychological stress may cause recurrent symptoms, and bridging the patient through these periods requires knowledge of inciting factors and their interventions. However, the pros and cons need to be viewed in terms of the present disease burden and the lack of effective treatments (Tables 1 and 2). Additionally, there are other types of gastric neurostimulation, with placement of electrodes endoscopically or *via* a gastrostomy. These techniques may hold promise. In fact, there are a few studies available aiming to improve the technique of gastric neurostimulation and there still seems to be a need for randomized double blinded controlled clinical trials. These will be helpful in elucidating properly the contribution of confounding factors to the gastroparesis puzzle.

**Table 1. Main PROS of GES**

(Near) normalization of stomach motility
good gastric emptying of liquids
vomiting rate decrease
relief of nausea, early satiety, bloating, postprandial fullness
early improvement (by 6 weeks) with sustained effect
improved quality of life
improved nutrition
reduction in HbA1c levels
decrease in hospitalization days

**Table 2. Main CONS of GES**

uncertain patient selection criteria
poor definition of optimal electrode position
need to define best on/off periodicity
unknown optimal stimulation parameters
partial emptying of solids
some persistence of vomiting
possible infections causing device removal / death (rare)
poor understanding of the natural history of gastroparesis
Potential confounding effect of concurrent pharmacological therapy

**DISCLOSURE**

This paper was solicited by the interest of the authors in this field. There is no conflict of interests to declare.

**ABBREVIATIONS**

AGA	=	American Gastroenterological Association
FDA	=	Food and Drug Administration
GI	=	Gastrointestinal
GES	=	Gastric Electric Stimulation
KUMC	=	Kansas Medical Center
HRQL	=	Health-Related Quality of Life

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