MICROVASCULAR COMPLICATIONS—NEUROPATHY (D ZIEGLER, SECTION EDITOR)

Diabetic Gastroparesis: Functional/Morphologic Background, Diagnosis, and Treatment Options

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Abstract The regulation of gastrointestinal motility mainly involves the smooth muscle, neural (extrinsic and intrinsic), and hormonal elements, the glial cells, and the interstitial cells of Cajal. An orchestrated function of all these components is required for the appropriate propulsive movement of the food in the gastrointestinal tract. Gastroparesis, a pathological slowing-down of gastric emptying, is a result of the damage to the tissue elements involved in the regulation of motility. Gastroparesis is one of the well-known complications of long-standing diabetes mellitus. Although it is rarely a life-threatening complication, it has a deteriorating effect on the quality of life, leads to unpredictable oscillation of the blood glucose level, and increases the time required for the absorption of food and medicines. This review describes the clinical characteristics of diabetic gastroparesis and summarizes the organic and functional motility abnormalities caused by this complication. Finally, the currently available and potential future therapeutic approaches are summarized.

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Abbreviations

ADRA1D	Alpha-1-adrenergic receptor gene
AGE	Advanced glycation end products
CCK	Cholecystokinin
CYP2D6	Cytochrome P450 2D6
FDA	Food and Drug Administration
GCSI	Gastroparesis Cardinal Symptom Index
GI	Gastrointestinal
GIP	Gastric inhibitory peptide
GLP-1	Glucagon-like polypeptide-1
ICC	Interstitial cells of Cajal
IGF-1	Insulin-like growth factor-1
KCNH2	Potassium voltage-gated channel, subfamily H [eag-related], member 2
NK-1 receptor	Neurokinin-1 receptor
nNOS	Nitric oxide synthase
NOD	Non-obese diabetic
NO	Nitric oxide
OEP	National Health Insurance Fund Administration
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders Quality of Life
PEJ	Percutaneous endoscopic jejunostoma
SCF	Stem cell factor
VIP	Vasoactive intestinal polypeptide
5HT receptor	5-hydroxytryptamine receptor
^{99m}Tc	Metastable nuclear isotope of technetium 99

Introduction

The mixing and the propulsive movement of liquid and solid food arriving into the esophagus and the lower parts of the gastrointestinal (GI) tract require the well-coordinated work of five basic tissue elements: smooth muscle, extrinsic and intrinsic neurons, glial cells, hormonal elements, and the interstitial cells of Cajal (ICCs). Damage to any of these elements leading to an imbalance of the neuromuscular unit will deteriorate the propulsive movement of food to some extent. The degrees to which these elements are involved determine the degree and nature of the functional disorder. The stomach, positioned in the upper tract of the GI system, has a unique role in the processing of food, since it accommodates to the volume of the aliments, stores them, grinds them into small pieces, and transmits the food toward the duodenum. Under physiological conditions, the movement of low-calory liquid food, especially water, toward the duodenum depends on its volume and the pressure pump function of the stomach [1]. Low-calory solid food (such as bread) spends 20–30 min in the stomach, while a continuous peristaltic movement starts at the mid-upper corpus of the greater curvature of the stomach, spreads toward the antral region (usually 3–5 times per minute) [2], and presses the pieces of food to the almost closed pylorus. This way, the stomach comminutes the solid food and makes it accessible to the digestive enzymes. Hyperosmotic, acidic, or nutrient-rich food makes stomach emptying much slower [3].

The over-slow emptying of solid food from the stomach for a nonmechanical reason is defined as gastroparesis [4]. The etiology of the disease is complex, but in approximately 30 % of the cases it is caused by long-term diabetes. Gastroparesis was one of the first complications of diabetes described [5], and some ancient doctors, such as Aretaeus of Cappadocia, thought that diabetes was a disease of the stomach. The etiology of gastroparesis cannot be identified in about a third of the cases [6]. The symptoms in all cases are chronic and recur frequently [7], including epigastric burning sensation, bloating, early satiety, abdominal discomfort, nausea, and vomiting. In approximately 90 % of the cases, the first symptom of diabetic gastroparesis is continuous nausea of fluctuating intensity. Eighty percent of the patients complain of bloating, and about 60 % present early satiety [6]. Gastroparesis develops in only 5 %–12 % of patients with diabetes [8], although previous studies reported a higher incidence [7]. Diabetic gastroparesis occurs more frequently in women, in obese patients with poor glycemic control, and in patients where other complications of diabetes have already appeared. Nonetheless, an obvious relationship between the higher glycated hemoglobin (HbA1c) level and the development and severity of gastroparesis has not been clearly established [9]. Another typical characteristic of gastroparesis is the fact that the severity and nature of the symptoms do not correlate linearly with the extent of the slowdown; therefore, analysis of the complaints alone is not sufficient for the diagnosis of impaired motility of the stomach [10]. Furthermore, a normal gastric motility rate does not exclude the possibility that the complaints originate from motility disorders, while a slower gastric motility is not always associated with symptoms [11]. It is important to emphasize that the only manifestation of gastroparesis in some patients without GI symptoms is poor glycemic control, whereas in other cases, the completely opposite phenomenon may be experienced: the presence of obvious symptoms are not related to dysglycemia [12]. Due to delayed food absorption, postprandial hypoglycemia might be a characteristic feature of gastroparesis among insulin-treated diabetic patients. Although slower stomach emptying in a case of long-standing diabetes mellitus rarely leads to life-threatening complications and does not increase mortality [13], it increases the risk of an electrolyte imbalance, as well as hypo- or hyperglycemia. Gastroparesis should also be considered as the underlying mechanism among patients thought to have brittle diabetes.

As in various other areas of medicine, the severity of the disease may be characterized by different scoring systems. In clinical practice, the Gastroparesis Cardinal Symptom Index [14] and the Patient Assessment of Upper Gastrointestinal Disorders Quality of Life [15] questionnaire are used. Further investigations are required to test whether these questionnaires are sufficiently valuable to guide the proper therapeutic approach or how well these scores lead to an estimate of the prognosis of the gastric complication.

Motility Disorders in Diabetic Gastropathy

Approximately 18 % of diabetic patients display some kind of upper GI symptoms [16]. The connection between symptoms and motility disorders related to gastroparesis is rather poor [17, 18]. An increased rate of stomach emptying is a characteristic finding in patients with a relatively short diabetes history (less than 2 years) and without the signs and symptoms of diabetic neuropathy [19]. Faster than normal stomach emptying can be observed even in long-term type 1 diabetes mellitus [12]. In animal models, insulin therapy in a subtherapeutic dosage normalized increased stomach emptying [20]. The most important consequence of faster gastric emptying in clinical practice is sudden postprandial hyperglycemia shortly following food intake. It is also possible that this increased rate of stomach emptying is a preliminary phase of later slower stomach emptying [21].

Diabetic gastroparesis involves a severe delay of stomach emptying of both solid and liquid food [22]. In a survey, type 2 diabetic patients with delayed emptying were older, had higher body mass index, and exhibited more intensive nausea and early satiety, as compared with type 1 diabetic patients

with impaired gastric motility [23]. Several functional changes can be found in the background of slower stomach emptying [21–24]. However, acute and chronic hyperglycemia have different effects on stomach motility.

In healthy volunteers, severe artificial hyperglycemia causes slowing-down of the emptying of nutrient-containing liquid and solid food [25]. In type 1 diabetic patients with diabetic autonomic neuropathy, hyperglycemia increases the frequency of rhythmic activity in the stomach, resulting in tachygastria [26]. Obvious deleterious effects of hyperglycemia cannot be confirmed on ICCs (cells generate and propagate electrical activity in the stomach and the GI tract) [27]. Interestingly, in type 1 diabetic patients without autonomic neuropathy, the stomach emptying can be significantly decreased even if the postprandial blood glucose elevation does not exceed the physiological range [28].

Chronic hyperglycemia in diabetes can also be responsible for all of the above-mentioned motility disorders. However, it is important to consider that diabetes is associated not only with elevated blood glucose levels, but additionally with an absolute or relative absence of insulin. The importance of this phenomenon is revealed by in vitro experimental data demonstrating the deteriorating effect of the absolute absence of insulin on stomach ICCs and the smooth muscle cells [27]. In general, slower movement of solid food from the stomach in diabetes is more frequent than slower movement of liquids. The impaired pyloric pressure pump function also has an effect on solid food emptying [29], and the dilatation of the distal stomach also relates to the antral hypomotility [30]. The decreased smooth muscle contraction might be explained by smooth muscle myopathy [27, 29] and/or inappropriate function of the stomach pacemaker activity and leads to disturbances of the coordination of electromechanical coupling [31]. It is probably important that the slow waves of the stomach generated by the ICCs are modified by a number of factors, such as the sympathetic–parasympathetic balance, eating, and medicines. Any disturbance in these factors can worsen the effectivity of the peristalsis [18].

The reasons for the discrepancy between the symptoms and detectable motility disorders are not clear; a possible explanation is the viscero-sensory functional defect related to diabetic autonomic neuropathy. The increased activity or sensitivity of these neuronal systems in the proximal stomach might explain the generation of nausea, vomiting, early satiety, and epigastrial pain experienced in type 1 diabetic patients without substantial motility disorders [32].

Cellular-Level Changes in Diabetic Gastroparesis

The morphological background of diabetes-related GI complications is still not clear. Various factors can damage different tissues, including hyperglycemia and an absolute or

relative lack of insulin. The increase in mitochondrial superoxide activity caused by the increased glucose burden can be an important factor in the development of chronic morphologic complications of diabetes [33]. The increased oxidative stress-related decrease in nitric oxide (NO) concentration, together with the reduced activity of heme oxygenase, is an important feature of the pathogenetic background at the cellular level [34]. Carbon monoxide (produced by heme oxygenase) has a protective effect on the ICCs [35].

Histological changes in long-standing diabetes can also be studied. In a human investigation in antrum samples, mild lymphocytic infiltration in the myenteric plexus was a characteristic finding of diabetic gastroparesis [36]. Significant reductions in the numbers of neuronal elements and the ICCs in the antrum wall were detected [37]. In another investigation, the loss of neuronal elements was proven in diabetic samples from the mucosal layer [38]. In a larger study [39], the most frequent abnormality was damage to or loss of the ICCs and the decrease in the number of NO synthase (NOS)-positive neurons. However, the loss of the NOS-positive neurons was more characteristic for idiopathic gastroparesis. Electromicroscopic investigations detected a significant increase in the amount of connective tissue. Overall, the most characteristic histopathological change in diabetic gastroparesis is the loss of or damage to the ICCs. The pathophysiologic steps leading to ICC damage are complex. The ICCs are very sensitive to the lack of insulin, despite the absence of insulin receptors and insulin-like growth factor-1 (IGF-1) receptors on these cells [40]. The explanation of this paradoxical situation was provided by experiments [41] that revealed that the smooth muscle cells of the stomach have insulin and IGF-1 receptors and these cells produce the stem cell factor (SCF) that is essential for the development and maintenance of the network of ICCs. The smooth muscle atrophy that develops in the lack of insulin is responsible for the decreased production of SCF and, hence, for the damage to the ICC network [27, 40]. The exact mechanism of ICC damage is still not clear, and several questions remain to be answered [42, 43]. The most characteristic histological findings and symptoms of diabetic gastroparesis are listed in Tables 1 and 2.

Table 1 Histological findings in diabetic gastroparesis in human investigations

Reductions in the numbers of neuronal elements (especially nitric oxide synthase positive neurons)

Damage or loss of interstitial cells of Cajal in the myenteric or intramuscular layer (most characteristic finding)

Increase in the amount of connective tissue

Abnormal immune infiltrate (CD45- and CD68-positive cells)

Smooth muscle atrophy

Table 2 Symptoms and sign of diabetic gastroparesis

Nausea (in about 90 %, the first symptom)

Bloating (80 %)

Early satiety (60 %)

Abdominal discomfort or pain

Vomiting

Epigastric burning sensation

Poor control of blood sugar

Poor appetite and weight loss

Role of Neuropathy in the Pathogenesis of Gastroparesis

The Contribution of Impaired Autonomic Function to the Development of Delayed Gastric Emptying

The motor, secretory, and sensory functions of the stomach may all be altered when the balance is impaired between the intrinsic enteral and the extrinsic (parasympathetic [vagal] and sympathetic [mesenteric] fibers} autonomic neuronal systems [24]. The parasympathetic regulation can exert both excitatory and inhibitory effects, while the sympathetic input is generally inhibitory, with the exception of its propulsive influence on the lower esophageal sphincter [44]. In accordance with the previous description, GI autonomic neuropathy is the result of a complex pathophysiological process that involves organic and functional impairments of the neuronal cells and a progressive imbalance of various autonomic regulations. The changes include reduced numbers of ICCs, extrinsic autonomic neurons, and smooth muscle cells with altered inhibitory neurotransmission [29]. In patients with diabetic gastroparesis, a reduction in the intraneuronal levels of NO has also been observed [45]. It is assumed that the leading pathophysiologic abnormality is the impairment of parasympathetic function in autonomic neuropathy. Sham feeding-induced gastric acid production or pancreatic polypeptide response to hypoglycemia is decreased in diabetic patients as well. Since both the gastric secretory function and pancreatic polypeptide secretion are under vagal control, these observations support the role of parasympathetic damage in the development of diabetic gastroparesis [46, 47]. The long-term diabetic exposure is one of the most important risk factors of autonomic neuropathy, as indicated in the EURODIAB IDDM study [48]. The progression of the impaired gastric emptying seems to be slower than the progression of the autonomic neuropathy [49]. Besides the chronic metabolic exposure, acute hyperglycemia can also alter GI vagal functions [50]. Moreover, current hyperglycemia affects parasympathetic cardiac functions even in healthy subjects, pointing to the importance of the physiological condition of all those factors that possibly affect the vagal control in the regulation of gastric emptying [51]. The emptying of the stomach might

be slower when the balance between the excitatory and inhibitory regulations of the autonomic system becomes disturbed [52]. Parasympathetic function becomes abnormal earlier during the progression of autonomic neuropathy than does the sympathetic function, leading to weakening of the excitatory parasympathetic innervation of the stomach and a relative strengthening of the inhibitory sympathetic effects [53]. The alteration in the sympathetic function can also have detrimental effect on gastric emptying.

Several important processes are regulated by the sympathetic nervous system, which may also partially affect the gastric motility (visceral reflexes, nausea, vomiting, and abdominal pain). Despite the well-known general consequences of the parasympathetic and sympathetic impairments, it is still not clear how these alterations act directly on the motility of the stomach in diabetic patients. Besides the normal extrinsic autonomic neuronal functions, intact central neuronal regulation is also mandatory for the integrity of gastric emptying. Abnormal visceral hypersensitivity as a result of an altered afferent central function is a newly documented source of various digestive symptoms that are responsible for an impaired quality of life [54]. In line with this, a recent study demonstrated altered central sensory processing in diabetic patients with upper abdominal symptoms [55]. A few clinical observations suggest the role of the central neuronal system in the regulation of certain visceral functions, including gastric motility [56]. The severity of the autonomic neuronal damage in humans is not yet measurable directly; therefore, reproducible and sensitive cardiovascular and sensory tests are applied to estimate the neuronal dysfunctions in patients with abnormal gastric emptying or GI symptoms. In some of these tests, correlations have been found between neuropathy and stomach motility. The overall autonomic neuropathy score calculated from cardiovascular reflex tests correlated positively with the scintigraphic gastric emptying rate of solids in patients with long-standing type 1 diabetic patients [57]. Two heart rate tests of the five cardiovascular tests consistently correlated with the emptying of an isotope-labeled solid meal from the stomach in long-standing type 1 diabetes [52]. These heart rate tests, the heart rate response to deep breathing, and the Valsalva maneuver are regarded as sensitive indicators of the parasympathetic function that become abnormal during the early course of neuropathy. These data support the hypothesis that the insufficiency of the excitatory effect of the vagal nerve on the postprandial phase of the stomach functions leads to delayed emptying in type 1 diabetic patients with long duration. Reduced heart rate variability, a well-known indicator of the autonomic dysfunction, was associated with GI complaints in diabetic patients with sensorimotor neuropathy, suggesting a concomitant role of various manifestations of neuropathy in the pathogenesis of digestive complications [58]. Although several studies have documented correlations between neuropathy tests and gastric emptying, numerous

other studies did not discern any relationship [59]. This might be explained in terms of the restricted methodology of the measurement of the complex GI neuronal dysfunctions, the heterogeneity of the tests applied in the various studies, and the importance of pathophysiological factors other than neuropathy in the pathogenesis of gastroparesis.

The Role of Nitric Oxide Synthase in the Development of Diabetic Gastroparesis

The NOS-positive neurons identified in the GI tract have a crucial role in the inhibitory regulation of the motility functions and, hence, in the relaxation of the different sphincters. It has been confirmed in animal models that inhibition of neuronal NOS results in slower stomach emptying. Human investigations have revealed that the endogenous NO inhibits the propulsive movement in the stomach [60]. The clinical observation that diabetic gastroparesis predominantly affects women might be related to the fact that impairment of the nitrergic system is more pronounced in females [61]. It has been revealed in animal models that the number of NOS-positive neurons decreases in diabetes and, in parallel with the loss of these neurons, the regulation of pyloric relaxation, just as the antral tone deteriorates. Early treatment with insulin led to rearrangement of the presence of NOS-positive neurons and their synthetic function [20]. A possible future therapeutic approach may be to transplant stem cells that can differentiate into NOS-positive enteral neurons [62].

The Role of Enteral Hormones in the Development of Diabetic Gastroparesis

The role of these hormones in the pathomechanism of diabetic gastroparesis is still controversial. The effects of the hormones that stimulate (e.g., serotonin, gastrin, acetyl choline, motilin, and substance P) or inhibit (NO, vasoactive intestinal peptide, cholecystokinin, gastric inhibitory polypeptide or glucose-dependent insulinotropic peptide, secretin, glucagon-like peptide) gastric emptying can be deteriorated either by the glycation of these hormones or their receptors or through the loss of the function of their target organs. One of the most frequently investigated enteral hormone is GLP-1, since dipeptidyl-peptidase-IV inhibitors and GLP-1 analogues and agonists are increasingly more widely used in clinical practice. The consequences of elevations or reductions of this peptide in diabetes have been analyzed, and an association was proven between the effect of GLP-1 on gastric emptying and the elevation of postprandial glucose levels [63]. Ghrelin has also been a target molecule in recent investigations. Although in a species-specific manner, ghrelin promotes the antro-pyloric coordination and can thereby improve stomach emptying [64, 65]. Ghrelin receptors are located in the highest concentrations on antral and duodenal neurons, with decreasing amounts toward the distal regions [66]. Accordingly, it can be assumed that ghrelin has effects on vagal nerves [67], and the connection between neuropathy and enteral neurons is also indicated [68]. The multiple aspects of the effects of enteral hormones can be further exemplified by the fact that some of the enteral hormones (GLP-1, peptide YY, and gastrin) promote the survival of the pancreas beta cells, which can have a beneficial influence on GI function [69].

The Role of Enteric Glial Cells on the Development of Motility Disorders in Diabetes Mellitus

Enteric glial cells (EGCs) outnumber the enteral neurons in a ratio of 2:1. In view of the close anatomical and functional connection between enteric neurons and EGCs [70, 71], it can be assumed that damage to these cells plays an important role in the diabetes-related impairment of the enteric nervous system and, hence, in motility disorders. However, this close neuron–glia connection complicates the separate in vivo investigation of these cells. Conditional ablation of the EGCs induces changes in the neurochemical coding of enteric neurons, which may be responsible, in part, for the reduced gastric emptying and intestinal transit [72]. In an in vitro study, viral targeted ablation of EGCs increased the level of neuronal death in the presence of oxidative stress because the neuroprotective effects of the EGCs via their release of glutathione were missing [73]. Oxidative stress also activates mechanisms that result in glia-mediated inflammation that causes secondary neuronal damage [74]. The complex role of EGCs in diabetes-related gastric motility disorders has not yet been clearly identified, but their potential targeted influence may open up new therapeutic approaches.

Diagnosis

Scintigraphic Gastric Emptying Procedure

The standard method for the diagnosis of diabetic gastroparesis is the scintigraphic evaluation of stomach emptying. Recent developments in ultrasonography make this technique too suitable for the evaluation and diagnosis of impaired gastric emptying. In clinical practice, when GI symptoms appear, patients should undergo routine gastroscopy, during which the possibility of slower stomach emptying may be suspected.

The standardization of the scintigraphic measurement of stomach emptying has raised a number of questions, since numerous factors influence gastric emptying [75]. The rate of gastric emptying is frequently defined by using ^{99m}Tc-sulfur

colloid-containing eggs. During the procedure, the imaging is carried out at minute intervals while the patient is lying in supine position. Medicines that affect the gastric motility have to be avoided for at least 72 h before the investigation. The blood glucose level must be kept in a narrow range during the procedure (between 4 and 10 mmol/l; 72–180 mg/dl for 2–4 h). The diagnosis of gastroparesis can be established if 60 % or more of the activity of the isotope remains in the stomach 2 h after the test meal ingestion or if at least 10 % of the initial activity is still detected after 4 h. The diagnostic steps for evaluating diabetic gastropathy are shown in Fig. 1.

Investigation of Gastric Emptying by Ultrasonography

The evaluation and follow-up of gastric emptying by ultrasonography is a convenient noninvasive method. An experienced physician visualizes the structure of the gastric wall by means of ultrasonography and can gain information about the intragastric dispersion of solid food, the accommodation of the stomach, the number of antral contractions, and the transpyloric flow of chopped food [76]. Ultrasonography provides more details of the stomach motility than does scintigraphy, and its sensitivity and specificity might be comparable to those of the isotope-labeling technique [77]. Through the use of 3-D techniques, the gastric volume changes over time can be evaluated more exactly, and the correlation between the findings of this technique and those of scintigraphy becomes more pronounced [78].
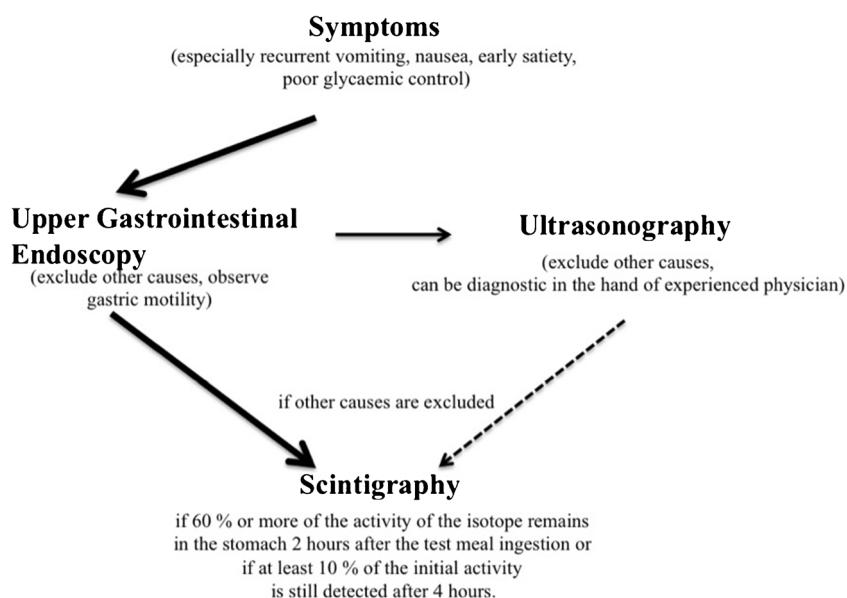
Therapeutical Approaches

In everyday practice, the available therapeutic approaches focus on the symptoms; no causal therapy is yet available, although stem cell replacement therapy (so far carried out only in animal experiments) raises the hope of long-term causal therapy.

The most important treatment option is still optimal glycemic control. Gastric motility disorders and the different stages of glucose metabolism mutually affect each other from several respects. Better glycemic control can improve the motility disorders, which creates an opportunity for stabilizing the blood glucose fluctuations. Adherence to the recommended diet is a crucial point of the treatment. Patients with diabetic gastroparesis should eat small meals, and eating is recommended 6–8 times a day. Solid food should be comminuted as much as possible. Meat containing large amount of dietary fibres or fatty acids should be avoided. Postprandial glucose level in patients with diabetic gastroparesis can be successfully decreased only if the suggested dietary rules are strictly observed [79].

The use of medication to treat diabetic gastroparesis is rather complicated. Prokinetic drugs seem to be right choices, since they improve gastric motility and promote the emptying of carbohydrates, ensuring better conditions of absorption in the small bowel. On the other hand, there is very little evidence that the improvement of motility achieved with these drugs stabilizes glycemic control [19]. Metoclopramide, a peripheral dopamine-2 receptor antagonist and, in part, an agonist of the peripheral serotoninergic 5-hydroxytryptamimne-4 (5-HT4) and vagal and brainstem 5-HT3 receptors, has combined effects (the increase of gastric contractility and the improvement of the relaxation of the pyloric sphincter and the bulbus, moderate nausea, and vomiting via affecting central dopaminergic receptors) and seemed to be promising medication for the treatment of diabetic gastroparesis [80], but its long-term efficacy has not been proven [81], and it has no obvious positive effect on the symptoms of diabetic gastroparesis and glucose metabolism

Fig. 1 Diagnostic steps for evaluating diabetic gastropathy. If symptoms (especially recurrent vomiting and nausea) are present, gastroscopy must be completed. It can exclude other causes of gastroparesis and can raise the possibility of motility disorder. An experienced physician can diagnose gastroparesis with ultrasonography. On the other hand, for the time being, scintigraphy is the most exact diagnostic step for evaluating gastroparesis. Note that other causes have to be excluded before the diagnosis is established

Symptoms
(especially recurrent vomiting, nausea, early satiety, poor glycaemic control)

Upper Gastrointestinal Endoscopy
(exclude other causes, observe gastric motility)

Ultrasonography
(exclude other causes, can be diagnostic in the hand of experienced physician)

if other causes are excluded

Scintigraphy
if 60 % or more of the activity of the isotope remains in the stomach 2 hours after the test meal ingestion or if at least 10 % of the initial activity is still detected after 4 hours.

[82]. Since diabetic gastroparesis is a chronic disease, the medicine is usually used for long-term treatment in clinical practice, although its effectivity diminishes with time and side effects become more frequent and pronounced. Some genetic factors have been reported to influence the effectiveness of the drug (polymorphisms in the potassium voltage-gated channel, subfamily H [eag-related], member 2, and the alpha-1-adrenergic receptor genes); the side effect is predicted by the polymorphism of the CYP2D6 and serotonin 5-HT4 receptor genes [83].

Another prokinetic drug for the treatment of diabetic gastroparesis is domperidone. This drug has a similar effect to that of metoclopramide, but its side effects are not so frequent, because it has no central effect, except for an elevation of the prolactin level. However, sudden cardiac death occurred more frequently among the patients treated with domperidone than among the controls. The explanation was based on the prolongation of the QTc interval [84]. Careful usage of this drug is required from health-care professionals. Domperidone is not currently a legally marketed drug or approved for sale in the U.S.

Erythromycin is an effective motilin receptor agonist [85]. Other macrolides, such as azithromycin, also improve the antroduodenal contractions [46]. Azithromycin does not participate in significant drug–drug interactions and may be of greater clinical importance in the treatment of gastroparesis [86]. The down-regulation of motilin receptors frequently leads to tolerance (tachyphylaxis). Macrolides also have a QT-prolonging effect, and some investigations have also shown an increase in sudden death following the application of this drug [87]. Administration of macrolides with the indication of motility enhancement is limited, with the exception of acute exacerbations, when they are administered intravenously.

Alpha-lipoic acid is an effective agent in the pathogenetically oriented treatment of diabetic neuropathy [88], and its beneficial effects on the cardiovascular manifestations of autonomic neuropathy have been proved [89]. These data may support the theory that the autonomic neuronal fibers that are responsible for gastroparesis might respond to alpha-lipoic acid treatment, but no studies have yet been organized to explore this possible effect. As benfotiamine blocks the four hyperglycemia-induced pathways, it exerts an antioxidative effect, resulting in an improvement in painful neuropathy [90]. This effect might theoretically be utilized in the treatment of GI neuronal dysfunctions, but no clinical observations have been published to confirm this hypothesis yet.

Some promising motility-enhancing drugs have appeared in the experimental phase recently [46], and the modulation of the effect of ghrelin, regulating food intake and gastric emptying in healthy subjects, seems to be also a promising approach [91, 92]. Further investigations are required to find their place in clinical practice.

Selective substance P receptor (NK-1 receptor) agonist aprepitant effectively moderates the complaints in diabetic gastroparesis [93]. In most countries, aprepitant is registered only for the treatment of chemotherapy-related nausea. The effectiveness of other antiemetics, such as ondansetron or promethazine, has not yet been proven in the treatment of diabetic gastroparesis [46], and their use is therefore not recommended.

Nonpharmacological Treatment of Diabetic Gastroparesis

The currently available medicines are not suitable for recovery of the physiological pattern of gastric motility. Moreover, they cannot treat the gastroparesis itself, and they do not have long-term efficacy against the symptoms. Surgical, endoscopic (botulinum toxin injection and percutaneous endoscopic jejunostomy), electric stimulatory possibilities (gastric electrical neurostimulation and gastric electrical pacing), and even acupuncture for the treatment of the disease have been tested, but none of these methods became a part of the routine clinical practice [94–99].

Conclusion

Gastroparesis is a well-known but difficult-to-treat complication of long-standing diabetes mellitus. Its exact pathomechanism is still not known, although more and more data become available as regard to the complex mechanisms in the background of this complication. Unfortunately, no uniquely effective medical or other treatment is available for influencing the disease, but some promising techniques (such as stem cell replacement or gastric pacing) and new drugs (e.g., ghrelin agonists) raise the possibility that successful treatment options will become available in the near future.

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