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Diabetic gastroparesis: a disease for which long-term therapeutic benefits are difficult to obtain

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Abstract
The pathophysiology of diabetic gastroparesis (DGP), a common complication in diabetic patients, is not fully known. Its development has been linked to several causes, including hyperglycaemia, vagal nerve dysfunction, aberrant Cajal's interstitial cell network (ICC), lack of nerve nitric oxide synthase (nNOS) expression in the intermuscular plexus, and hormonal alterations in the gastrointestinal tract. Glucose management, diet control, gastric stimulants, anti-emetic medications, *Helicobacter pylori* eradication, stomach electrical stimulation, and surgery are the main current treatments. These methods, however, could have unfavourable consequences. By examining recent studies and literature reviews, we outline the state of the study on diabetic gastroparesis in this paper. **(Endokrynol Pol 2024; 75 (2): 148–158)**

Key words: *diabetic gastroparesis; pathogenesis; treatment strategy; adverse effects*

Introduction

Diabetic gastroparesis (DGP), a term first coined by Kassander in 1958, is a common and remote complication in patients with diabetes mellitus [1]. It is characterized by delayed gastric emptying in the absence of evidence of mechanical obstruction. Typical symptoms include early satiety, nausea, vomiting, abdominal distention, and epigastric pain [2]. Up to 50% of individuals with long-term type 1 and type 2 diabetes have delayed stomach emptying [3]. A cross-sectional US study that examined the medical records of more than 3 million diabetic patients found that type 1 DGP prevalence was 4.6% and type 2 DGP prevalence was 1.3% [4, 5]. Furthermore, the severity of delayed gastric emptying was found to be positively correlated with symptom severity [6]. The symptoms associated with DGP not only impair the quality of life but also contribute to anxiety and depression [7]. In recent years, the prevalence of diabetes mellitus has also led to an increasing prevalence of DGP. The pathogenesis of DGP is complex. Currently, both domestic and foreign treatments primarily aim to alleviate the clinical symptoms. However, there are not enough focused and efficient therapy approaches. Nevertheless, research into the pathophysiology and potential treatments has made some headway in recent years. Researchers are actively exploring targeted treatment strategies for DGP. The management of DGP has greatly benefited from the combination of several disciplines, including gastroenterology, endocrinology, and neurology. These advancements can be summarized as follows.

Aetiology and pathogenesis

The process of gastric emptying involves coordinated interactions among exogenous nerves, the enteric nervous system (ENS), smooth muscle cells (SMC), and ICC within the myenteric and intermuscular layers of the stomach, as well as coordination between different parts of the stomach and feedback loops between the small intestine and the stomach [8]. Prior to gastric emptying into the duodenum, food is stored in the gastric fundus through gastric conditioning, which is regulated by vagal innervation. Vagal fibres and endogenous cholinergic neurons regulate sinus contraction. Nitrogenergic neurons are responsible for pyloric sphincter relaxation and gastric peristaltic activity. Additionally, ICC and other fibroblast-like cells, which function as pacemakers, mediate gastric excitatory and inhibitory impulses within the pacemaker of the gastrointestinal muscle [9]. Therefore, hyperglycaemia, vagal nerve dysfunction, abnormalities in the Cajal interstitial cell network, deletion of nerve nitric oxide synthase (nNOS) expression in the intermuscular plexus, and gastrointestinal hormonal changes promote the development of DGP [10].

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Table 1. *Results in a hyperglycaemic state*

Hyperglycaemic state	Mechanisms	Results
Acute, severe hyperglycaemia	Decreased incidence of migrating motility complex (MMC) and reduced plasma gastric motility levels	Delayed gastric emptying and gastric rhythm disturbances
AGEs	Impaired structure and function of gastrointestinal nerves, intestinal contractile dysfunction	Delayed gastric emptying, neuropathy
Inflammatory reaction	Induces osmotic stress, inflammatory changes, and damage to the small blood vessels that supply the nerves	Neuropathy
H. pylori colonization	Increased prevalence of gastrointestinal symptoms in H. pylori-positive patients	Delayed gastric emptying, bloating, vomiting, abdominal pain, constipation, and diarrhoea

AGEs — advanced glycation end products

Hyperglycaemic state

A large cross-sectional analysis demonstrated a significant association between long-term glycaemic control and gastric motility disorders, revealing that increased gastric retention scores were linked to higher glycated haemoglobin (HbA_{1c}) levels [11]. Patients with poor glycaemic control were found to be 2.7 times more likely to develop gastric bradycardia compared to those with good glycaemic control [12]. A gastric rhythm analysis indicated that gastric rhythm disturbances were also observed in normal subjects when their blood glucose levels exceeded 220 mg/dL [13]. Acute, severe hyperglycaemia has been shown to delay gastric emptying in both healthy individuals and type 1 diabetic patients [14]. This delay may be attributed to the decrease in the incidence of migrating motility complex (MMC) in the stomach and the reduction in plasma gastric motility levels, ultimately resulting in delayed gastric emptying [15]. The hyperglycaemic state leads to the diversion of excess glucose molecules into alternative metabolic pathways such as polyols and hexosamine. These glucose molecules can bind to fats or proteins, leading to the formation of advanced glycation end products (AGEs), which contribute to neuronal radical and oxidative damage, thereby impairing the structure and function of gastrointestinal nerves and causing intestinal contractile dysfunction [16]. Hyperglycaemia induces osmotic stress, inflammatory changes, and damage to small blood vessels that supply the nerves, further contributing to neuropathy in diabetic patients [17]. Additionally, hyperglycaemia is considered a susceptibility factor for *H. pylori* colonization [18]. *H. pylori*-positive patients exhibit a higher prevalence of gastrointestinal symptoms, including bloating, vomiting, abdominal pain, constipation, and diarrhoea. Therefore, in a hyperglycaemic state, both pyloric contraction and sinus motility are reduced, resulting in delayed gastric emptying [10]. The combination of inflammation and stress on neural and cellular rhythms within the gastrointestinal tract, along with the catalytic effect of *H. pylori*, contributes to delayed gastric emptying (Tab. 1).

Vagal nerve dysfunction

The vagus nerve, a component of the parasympathetic nervous system, plays a crucial role in regulating stomach excitability and inhibition. Dysfunction of the vagus nerve is associated with more severe upper gastrointestinal symptoms and delayed gastric emptying [19]. A controlled clinical study demonstrated that patients with diabetic gastroparesis had twice the prevalence of proximal gastric dysmotility compared to healthy controls [20]. When food enters the stomach, a relaxation reflex occurs to accommodate the ingested food or liquid. Stretching of the oesophagus and stomach triggers a vasovagal reflex, resulting in relaxation of the base and upper parts of the stomach body. This relaxation allows food to enter the stomach without increasing gastric pressure. In diabetic patients, increased hypoxia, blood glucose levels, and oxidative stress directly and indirectly contribute to neurological dysfunction. This dysfunction is caused by impaired paracord barrier function, impaired myelin, reduced antioxidant capacity, and decreased axonal nerve trophic support [21]. A study investigating the electrophysiological properties of the insula, which stimulates and records the perception of oesophago-gastro-intestinal symptoms and function, confirmed reduced oesophageal hypersensitivity and vagal tone in patients with diabetic gastrointestinal lesions [22]. Early observations of diabetic gastroparesis have also revealed vagal dysfunction through reduced pancreatic peptide responses and decreased gastric secretion during sham feeding [23]. Consequently, when food is ingested but gastric regulation is impaired – which means vagal neuropathy, which leads to decreased pyloric relaxation, impaired sinus contraction, and impaired sinus-pyloric coordination — patients may experience symptoms including early satiety, nausea, vomiting, and abdominal distension [24].

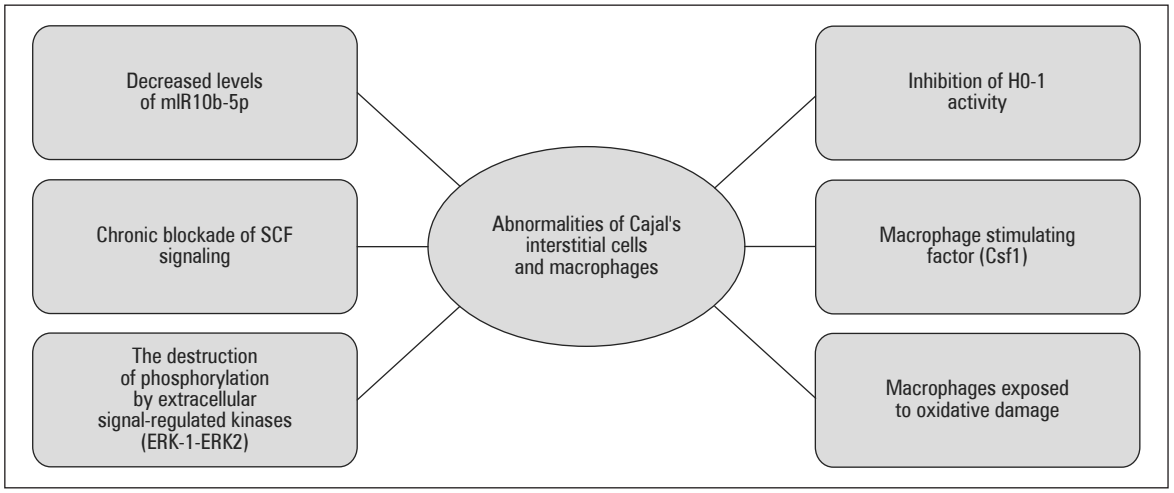

Figure 1. *Causes of abnormalities in Cajal's interstitial cells and macrophages. SCF — stem cell factor*

Abnormalities of Cajal's interstitial cells and macrophages

Within the gastrointestinal tract, Cajal's interstitial cells (ICC), situated between nerve endings and smooth muscle cells, serve as pacemakers and mediators, transmitting electrical signals from nerves that regulate smooth muscle contraction. The intricate interactions between smooth muscle, ICC, and the intestinal and extraintestinal nervous systems are responsible for regulating gastric emptying [25, 26]. The ICC network, characterized by the expression of c-Kit, generates electrical waves that depolarize the smooth muscle cell (SMC) membrane, leading to the emptying of gastric contents. A balanced presence of macrophages within the muscle layer and intermuscular plexus, many of which express anti-inflammatory proteins like M2 macrophage CD206 and hypohaemoglobin oxygenase-1 (HO-1), plays a crucial role in maintaining ICC function [8]. Consequently, abnormalities in ICC and macrophages are associated with abnormal increases in gastric slow waves, delayed gastric emptying, worsening clinical symptoms, and poor symptomatic response to gastric electrical stimulation (GES) [2].

Studies suggest several potential causes of ICC loss. Insulin and insulin-like growth factor (IGF-1) receptors, found in gastric smooth muscle cells of patients with diabetic gastroparesis, promote the production of essential cytokines for the development and maintenance of ICC. Decreased levels of miR10b-5p in diabetic patients have been shown to reduce c-kit expression, resulting in the loss of crucial cytokines and indirectly affecting ICC development and maintenance [27, 28]. Inhibition of HO-1 activity in mice with normal gastric emptying has been observed to lead to deficient c-Kit expression and diabetic gastroparesis. Chronic blockade of SCF signalling via anti-c-Kit antibodies through the c-Kit receptor disrupts and eventually leads to the loss of inter- and intramuscular ICC networks, resulting in the impairment of slow-wave electrical responses and electrical stimulation responses [27]. Increased levels of oxidative stress, stemming from deficiencies in CD206 and HO-1 in M2 macrophages, have been identified as another potential cause of ICC loss [29]. Additionally, phosphorylation of extracellular signal-regulated kinases (ERK1-ERK2) involved in glucose oxidative metabolism has been shown to activate and downstream affect ETV1, thereby increasing c-Kit expression and promoting accelerated gastric emptying [30]. Knockdown of macrophage stimulating factor (Csf1) has also been demonstrated to reverse the decrease in ICC and restore normal gastric emptying. Moreover, macrophages, when exposed to oxidative damage, have been found to produce the soluble factors interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α), which are detrimental to the ICC network [31]. This further suggests that macrophage abnormalities are associated with the development of diabetic gastroparesis due to ICC damage (Fig. 1).

Absence of neurotype nitric oxide synthase (nNOS) expression in the intermuscular plexus

The enteric nervous system (ENS) serves as the autonomic nervous system within the gastrointestinal tract wall and plays a crucial role in maintaining normal intestinal function, including motility and secretion [32]. The neural network of the ENS consists of excitatory (cholinergic) and inhibitory (nitrogenergic) motor neurons, primary afferent neurons, and interneurons. Excitatory motor neurons stimulate muscle contraction by releasing neurotransmitters such as acetylcholine and substance P, while inhibitory neurons induce muscle relaxation through the re-

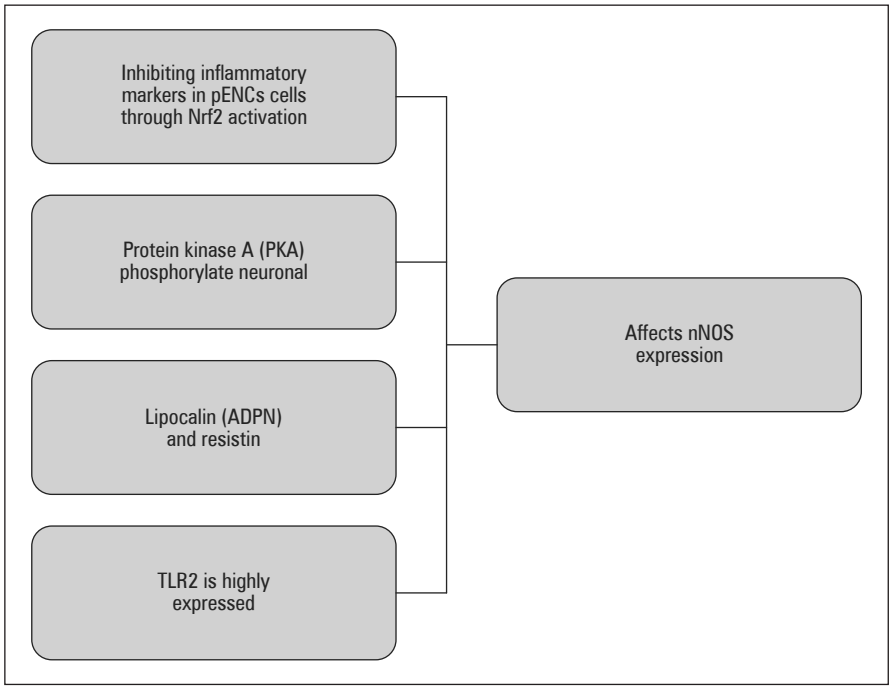

Figure 2. *Factors affecting the expression of nerve nitric oxide synthase (nNOS). pENC — primary enteric neuronal crest cells; Nrf2 — nuclear factor erythroid 2-related factor 2; TLR2 — toll-like receptor 2*

lease of nitric oxide (NO), adenosine triphosphate (ATP), and vasoactive intestinal peptides [33, 34]. Pathological alterations in these pathways disrupt the control of motility in the gastrointestinal tract, leading to delayed emptying, impaired regulation, and disturbances in gastric rhythm. In particular, inhibitory nNOS plays a crucial role in regulating smooth muscle, including pyloric relaxation and peristalsis in the small intestine [1, 35].

Animal studies using rat models of spontaneous and streptozotocin (STZ)-induced diabetes have shown impaired gastric relaxation as well as reduced nNOS expression and activity in the intermuscular plexus of the intestine [36]. Consequently, impairment or absence of the nitric oxide pathway may result in pyloric spasm, preventing the pylorus from relaxing while the gastric sinus contracts, ultimately impairing gastric emptying [15]. On the other hand, there are several pathways that influence nNOS expression. Studies have demonstrated that inhibiting inflammatory markers in primary enteric neuronal crest cells (pENCs) through nuclear factor erythroid 2-related factor 2 (Nrf2) activation can restore nNOS expression in the gastrointestinal tract of mice with diabetic gastroparesis and alleviate delayed gastric emptying [37, 38]. Protein kinase A (PKA) promotes ileal relaxation in mice by phosphorylating neuronal nitric oxide synthase [35, 39]. Additionally, lipocalin (ADPN) and resistin in white mouse adipocytes upregulate nNOS expression and increase the proportion of nNOS-positive neurons in the intestinal plexus, thereby maintaining relaxation of the gastric fundus [34]. The gram-positive receptor TLR2, highly expressed on colonic enteric neuronal precursor cells (ENPC) in mice, induces the formation of new nNOS-rich neurons upon activation, further contributing to the maintenance of gastrointestinal nerve function [32]. Thus, nNOS is a critical factor influencing gastrointestinal nerve function (Fig. 2).

Gastrointestinal hormones

Following the digestion of food in the stomach, gastric motility is regulated by waves of contractions known as migrating myoelectric complexes (MMC). MMC is comprised of 3 phases, and numerous gut hormones influence MMC. Gastrin, produced by M cells in the intestine, activates the second phase of MMC and promotes gastric emptying. The hunger hormone ghrelin, synthesized by ghrelin-producing cells in the stomach's fundus, stimulates appetite and enhances gastric motility [40]. Glucagon-like peptide 1 (GLP-1), secreted by L cells in the intestinal mucosa, reduces glucagon levels, stimulates insulin release, and inhibits gastric emptying [41–43]. Glucose-dependent proinsulin, mainly produced by K cells in the intestinal mucosa, promotes insulin release [44]. Peptide tyrosine (PYY), produced by L cells in the distal intestinal mucosa, inhibits gastric emptying. Cholecystokinin (CCK) is synthesized by

I cells in the small intestinal mucosa and is involved in the release of appetite suppressants. CCK inhibits pancreatic secretion and gallbladder contraction when fatty acids and monoglycerides enter the duodenum and jejunum, thereby limiting gastric emptying [45, 46]. Gastrin, produced by G cells in the duodenum and gastric sinus, increases gastric motility and stimulates gastric acid secretion. Consequently, any factor that influences the secretion of gastrointestinal hormones can impact gastric emptying.

Others

DGP is not only associated with diabetes but also to various neurological disorders such as Parkinson's disease, connective tissue disorders like scleroderma, endocrine disorders, and medication side effects such as opioid analgesics, tricyclic antidepressants, or anticholinergics [47]. Among these, studies have reported a high prevalence of opioid use (up to 40%) in gastroparesis in the United States, and both endogenous and exogenous opioids have been found to be associated with pyloric constriction or delayed gastric emptying [48]. Moreover, a retrospective study has indicated that mortality in DGP patients is related to systemic inflammation and coagulation dysfunction [49], although further investigation is required to understand the specific mechanisms. Additionally, some studies suggest a potential association between DGP and the role of *H. pylori* in inducing systemic inflammation because there is a higher proportion of *H. pylori* infection in DGP patients and a greater prevalence of gastrointestinal symptoms, although the symptoms can be relieved by *H. pylori* eradication [50]. However, these findings need to be validated through further analysis of larger sample sizes.

Diagnosis method

Due to the lack of unique symptoms, there are currently no consensus criteria for diagnosing DGP. The diagnosis is typically based on associated symptoms and delayed gastric emptying without objective evidence of mechanical gastric outlet obstruction. Gastroscopy is recommended for all patients to rule out mechanical obstruction. Gastric scintigraphy and 13C-breath testing are generally considered the preferred methods for assessing gastric emptying. However, a large prospective study validating wireless motion capsules in patients with diabetes demonstrated their reliability in assessing gastric emptying in patients with DGP. The study showed a very high interobserver correlation, superior even to scintigraphy [51, 52]. Functional luminal impedance planimetry (FLIP) has recently emerged as a tool to evaluate pyloric sphincter function. FLIP involves using a 240-cm catheter with a bag attached to its distal end, which is positioned in the pylorus through an endoscope. The bag is gradually filled to predefined volumes, and parameters such as cross-sectional area (CSA), pouch pressure, and distensibility index (P-DI) are recorded to assess pyloric function. Some studies have indicated a correlation between FLIP findings and symptoms of gastroparesis and gastric emptying [48]. However, the impact of gastric filling and the use of anaesthetics on FLIP detection have not been thoroughly studied. Furthermore, normal and pathological values for FLIP parameters require further confirmation [53]. Therefore, the current diagnostic modalities for assessing gastric emptying include gastric scintigraphy, 13C-breath testing, and wireless motion capsules.

Treatment

The therapeutic goals for DGP involve delaying disease progression, alleviating symptoms, managing complications, and restoring function. Treatment approaches are determined based on the underlying pathogenesis, pathophysiological changes, and contributing factors.

Diet

Dietary interventions play a crucial role in managing DGP. The following dietary recommendations are suggested:

— eating smaller portions more frequently throughout the day can help alleviate symptoms and promote better gastric emptying;
— certain foods can impede gastric emptying and exacerbate symptoms;
— it is advisable to avoid carbonated beverages, alcohol, and smoking, because they can cause bloating and reduce sinus contraction, respectively;
— foods that are high in fibre and fat can slow down gastric emptying, so it is beneficial to moderate the intake of these foods to improve symptoms.

Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are types of carbohydrates that tend to ferment in the colon, leading to bloating and discomfort. Avoiding FODMAP-containing foods may help alleviate bloating symptoms in DGP patients [54].

Blood glucose control

As previously mentioned, hyperglycaemia induces an inflammatory state and oxidative stress in the body, which can affect gastrointestinal hormones and gastric electrical rhythm, ultimately leading to impaired gastric emptying. Therefore, achieving optimal blood glucose control is crucial to reducing acute symptoms and improving gastric emptying in DGP patients. It serves as an important prerequisite for the treatment of DGP.

Drugs

Facilitation

Dopamine D2 receptor antagonists (metoclopramide with domperidone): Metoclopramide, the only Food and Drug Administration (FDA)-approved drug for short-term DGP treatment, blocks D2 and 5-HT3 receptors in the central chemoreceptor trigger zone, exerting an antiemetic effect. It also blocks D2 receptors in the intestinal wall and stimulates the presynaptic terminals of 5-hydroxytryptamine receptor 4 (5-HT4) receptors, leading to the release and amplification of acetylcholine. This results in increased lower oesophageal sphincter and gastric tone, producing a prokinetic effect [55]. Domperidone, another dopamine D2 receptor antagonist, improves gastric emptying and significantly alleviates symptoms such as postprandial satiety, early satiety, nausea, and vomiting [56]. 5-HT4 agonist (procalcitonin): procalcitonin is a highly selective 5-HT4 agonist that interacts with 5-HT4 receptors in the gastrointestinal tract. It promotes acetylcholine release from the gastrointestinal plexus, leading to increased lower oesophageal sphincter pressure and contraction of the gastric sinus, jejunum, and duodenum [9]. It has shown effectiveness in a small, randomized, placebo-controlled trial [57]. Ghrelin agonist: ghrelin, a peptide hormone released from gastric mucosal endocrine cells, acts as a ligand for growth hormone pro-secretory receptor 1a. It enhances gastrointestinal motility by stimulating vagal signals and directly affects gastrointestinal motility within the enteric nervous system or central nervous system by crossing the blood-brain barrier. Ghrelin agonists have demonstrated significant improvement in symptoms such as abdominal pain, nausea, early satiety, and vomiting in patients [58]. Gastrin receptor agonist: whole genome sequencing (WGS) studies in patients with DGP have identified gastrin receptors as important therapeutic targets for gastromotility disorders [59]. Erythromycin, a gastrin receptor agonist, has shown efficacy in improving gastric motility and gastroparesis symptoms with short-term treatment [60]. Other investigational agents, including selective 5-hydroxytryptamine agonists such as buspirone, ghrelin agonists like relamorelin (a growth hormone-releasing peptide agonist administered via subcutaneous injection), and gastrin receptor agonists such as camicinal, need further experiments to verify their effectiveness.

Antiemetic

Anti-emetic agents are an important component of managing patients with DGP, especially considering that the severity of vomiting is often higher in diabetic patients compared to those with idiopathic gastroparesis [61]. Several types of antiemetics are commonly used: 5-HT3 receptor antagonists (ondansetron) and type 1 histamine receptor antagonists (e.g. diphenhydramine); these drugs inhibit receptors in the vagal afferent nerve and chemoreceptor trigger zones, providing antiemetic effects without affecting gastrointestinal motility [62]. Phenothiazines (e.g. prochlorperazine and chlorpromazine): these drugs inhibit D1 and D2 receptors in the brain, leading to antiemetic effects [54]. Neurokinin-1 (NK-1) receptor antagonists (e.g. aprepitant): they reduce nausea and vomiting by inhibiting substance P in the terminal area [63]. Mirtazapine (an antidepressant) has central adrenergic and 5-hydroxytryptaminergic activity. In an open-label study, it demonstrated improvements in nausea, vomiting, and anorexia in patients with DGP [64].

Other drugs

Bicyclic amines and scopolamine, through their anticholinergic action, relax intestinal smooth muscle and are used to treat mild pain in patients with diabetic gastroparesis. Tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and nortriptyline are commonly used in clinical practice for pain modulation. At low doses, they can also reduce symptoms of nausea and vomiting [65]. Acotiamide, a muscarinic antagonist, acts as a fundus relaxant. By increasing acetylcholine levels, it produces a prokinetic effect through sinus contraction [66]. Etifoxine and *Lactobacillus* supplementation: based on recent studies on the intestinal flora, some researchers have suggested that etifoxine or supplementation with *Lactobacillus* strains, which aim to restore the physiological microbiota, may improve gastrointestinal (GI) symptoms. However, more research is needed to understand the mechanisms involved in this area [67]. Synthetic cannabinoids such as dronabinol and nabilone are approved for the treatment of nausea and vomiting associated with chemotherapy. In a recent population-based study, one-third of patients with GI symptoms reported active use of cannabinoids, and most of them experienced symptom improvement [68]. Inhibition of smooth muscle contraction by intramuscular injection of botulinum toxin can provide temporary relief of delayed gastric emptying and associated symptoms, particularly in cases where delayed emptying is due to pyloric spasm [9]. These therapeutic approaches still require extensive animal and human studies to determine their exact efficacy in patients with DGP. Certain areas remain controversial and unclear.

It is worth noting that among the gastrointestinal hormones that affect gastric emptying, GLP-1 has been shown to delay gastric emptying and thus lower blood glucose, and long-term glucose control is associated with a lower incidence of gastroparesis [69]. Thus,

recent guidelines strongly recommend glucagon-like peptide 1 receptor agonists (GLP-1Ras) as the first injectable glucose-lowering therapy in type 2 diabetes mellitus (T2DM), indicating that this choice is preferable to basal insulin therapy because of its clinical benefits (efficacy in lowering HbA_{1c} with additional weight loss) without the risk of hypoglycaemia [70]. However, given the effect of GLP-1RAs on gastric emptying, the use of GLP-1RAs in diabetic gastroparesis is a matter of concern, with studies suggesting that short-acting agonists appear to have a substantial and sustained effect on slowing gastric emptying, while the acute effects of long-acting agonists on gastric emptying diminish with continued use [71–74]. Another study investigating the effects of GLP-1 agonist therapy on gastric emptying in diabetic patients with and without gastroparesis showed that GLP-1RAs significantly delayed gastric emptying in patients without or with mild gastroparesis, without worsening gastric emptying in patients with overt gastroparesis [75]. Therefore, it may be prudent to consider the use of long-acting GLP-1RAs in patients with pre-existing diabetic gastroparesis, an issue that warrants further investigation and study.

REVIEW

Gastric electrical stimulation

Gastric electrical stimulation (GES) involves the use of electrical stimulation to activate and restore myoelectric activity in the gastric sinus, ultimately improving gastric emptying [76]. This treatment was approved in 2000 by the FDA under the Humanitarian Use Device Exemption for refractory gastroparesis and DGP. GES can be delivered through percutaneous high-frequency, low-energy electrical stimulation using electrodes on the smooth muscle wall of the gastric sinus or through high-energy, low-frequency stimulation via a permanent pacemaker inserted by dissection to entrain the gastric slow wave at a rate of 3 cycles per minute (cpm) and induce subsequent contractions [77]. Studies on gastric electromechanical stimulation have shown a 90% reduction in the frequency of nausea and vomiting after 11 months in patients who received percutaneous or permanent GES devices [78]. Diabetic patients have demonstrated a greater reduction in Gastroparesis Cardinal Symptom Index (GCSI) scores and significant relief from nausea and vomiting compared to those with idiopathic gastroparesis. However, strict adherence to the indications for GES is crucial [79]. It is typically reserved for patients whose symptoms are unresponsive to oral medications despite strict glycaemic control, significantly impacting their quality of life and nutritional status. Additionally, there is a need for comparative studies to evaluate the efficacy of GES in comparison to other surgical treatments and to account for placebo effects [80]. Therefore, further research is necessary to validate the development of this treatment modality.

Surgery

Surgical interventions for gastroparesis include pyloric botulinum toxin injection, pyloric stenting, pyloric balloon dilatation, pyloromyotomy (POP), and percutaneous endoscopic gastrostomy (G-POEM). While certain studies have demonstrated significant symptom improvement with surgical treatment, there is a limited availability of controlled trials with larger sample sizes to assess the complications and long-term outcomes associated with these surgical approaches [81].

Limitations of Western medical treatment

Side effects and adverse effects of drug therapy

Metoclopramide: due to its ability to cross the blood-brain barrier, metoclopramide can cause side effects such as somnolence, restlessness, hyperprolactinaemia, and tardive dyskinesia [55]. Tardive dyskinesia has a prevalence ranging from 1% to 15% with metoclopramide use [82]. Additionally, a large cohort study showed an increased risk of Parkinson's disease in newly diagnosed diabetic patients with prolonged metoclopramide treatment, regardless of duration exceeding 3 months [83]. There are significant duration-response and dose-response effects. As a dopamine receptor antagonist, domperidone blocks D2 receptors in the chemoreceptor trigger zone, providing antiemetic effects. It also has prokinetic effects in the proximal stomach and duodenum by blocking D2 receptors in the enteric nervous system. The most common side effects of domperidone are cardiac, including QT interval prolongation and arrhythmias [56]. TCAs such as amitriptyline and nortriptyline are used for pain relief. However, they may cause side effects such as dry mouth, dry eyes, and urinary retention [54]. Erythromycin is a ghrelin receptor agonist, but its long-term use is limited due to the risk of prolonging the QT interval and inhibiting the cytochrome P450 system, which results in bacterial resistance, rapid allergy, and sudden cardiac death [40]. Ghrelin receptor agonists, including relamorelin, are still under investigation. In a phase 2 study, relamorelin was associated with side effects such as headache, worsening diabetes, hyperglycaemia, urinary tract infections, headache, dizziness, and diarrhoea in 5% of the treatment group [84]. Other new therapeutic agents, such as 5-hydroxytryptamine receptor agonists and fundus relaxants, require further studies to evaluate their long-term use in gastroparesis. Some experimental studies have shown a reduction in Gastroparesis Cardinal Symptom Index (GCSI) scores, but more research is needed to establish their safety and efficacy.

Limitations of gastric electrical stimulation and surgical treatment

While GES is a common treatment for refractory gastroparesis, it is associated with post-treatment complications. Studies have shown that up to 20% of patients experience serious long-term complications, including infection, migration of the device and/or wires, gastric perforation, erosion, and chronic pain [85]. The severity of clinical symptoms is positively associated with the occurrence of these complications [86]. Further research is needed to better understand and address these complications. Pyloric botulinum toxin injections have shown short-term improvement in symptoms such as vomiting, nausea, postprandial fullness, and bloating. These injections are often associated with accelerated gastric emptying. However, the existing studies are retrospective and open with small sample sizes, mainly focusing on the physiopathological status of the pylorus before and after treatment. More extensive studies are necessary to evaluate the long-term efficacy and safety of this treatment [48]. Case reports have shown that pyloroplasty and gastric myotomy can have long-term efficacy in improving symptoms and enhancing the quality of life for patients. However, surgical treatments carry the risk of complications such as leakage, bleeding, wound infection, ulceration, peritoneal effusion, and fibrosis at the pyloromyotomy site. These complications may lead to constriction and narrowing of the pyloric ring and a recurrence of symptoms. Strict indications and close postoperative monitoring are necessary to identify and manage these potential complications [23, 87–89] (Tab. 2).

Table 2. *Mechanisms and side effects of common treatment modalities*

Treatment		Rationale	Results	Adverse Effects
Gastric stimulants	Dopamine D2 receptor antagonists	Blocks D2 receptors in the central chemoreceptor trigger zone	Antiemetic; increased lower oesophageal sphincter pressure and gastric tone	Somnolence, restlessness, hyperprolactinaemia, tardive dyskinesia, QT interval prolongation and arrhythmias
	5-HT4 agonist (procalcitonin)	Interacts with 5-HT4 receptors in the gastrointestinal tract; promotes acetylcholine release from the gastrointestinal plexus	Increased lower oesophageal sphincter pressure and the contraction of the gastric sinus, jejunum, and duodenum	Diarrhoea, headache and abdominal cramps
	Ghrelin agonist	Stimulates vagal signals	Enhances gastrointestinal motility	Headache, worsening diabetes, hyperglycaemia, urinary tract infections
	Gastrin receptor agonist	Agonist of the gastrin receptor	Improves gastric motility and gastroparesis symptoms	Prolongs the QT interval and inhibits the cytochrome P450 system, have the risk of bacterial resistance, rapid allergy, and sudden cardiac death
Antiemetic	5-HT3 receptor antagonists	Inhibit receptors in the vagal afferent nerve and chemoreceptor trigger zones	Anti-emetic	Diarrhoea, rash, acute dystonic reaction, hypokalaemia, electrocardiographic changes, etc
	Type 1 histamine receptor antagonists	Block receptors in the vagal afferent nerve and chemoreceptor trigger zones		Sedation, drowsiness, fatigue, weakness, dizziness, dry mouth, and even blurred vision; constipation; difficulty urinating
	Phenothiazines (e.g., prochlorperazine and chlorpromazine)	Inhibit D1 and D2 receptors in the brain		Dizziness, generalized weakness, dyskinesia, blurred vision, diplopia, and other symptoms of excessive CNS depression
	NK-1 receptor antagonists (e.g., aprepitant)	Inhibiting substance P in the terminal area		Loss of appetite, diarrhoea, abdominal pain, constipation, fatigue, weakness, mild headache, dizziness, debility, low blood pressure, bone marrow suppression, coughing, dehydration, etc., severe with Stevens-Johnson syndrome
	Mirtazapine (an antidepressant)	central adrenergic and 5-hydroxytryptaminergic activity		Increased appetite and weight gain. Drowsiness, sedation, isolated mania, convulsive seizures, tremors, myalgias, etc.

→

Table 2. *Mechanisms and side effects of common treatment modalities*

Treatment		Rationale	Results	Adverse Effects
GES		GES activates and restores myoelectric activity in the gastric sinus	Improve gastric emptying	Infection, migration of the device and/or wires, gastric perforation, erosion, and chronic pain
Surgical interventions	pyloric botulinum toxin injection, pyloric stenting, pyloric balloon dilatation, POP, and G-POEM		Accelerates gastric emptying and improves symptoms	Leakage, bleeding, wound infection, ulceration, peritoneal effusion, fibrosis at the pyloromyotomy site, and potential constriction or narrowing of the pyloric ring

5-HT — 5-hydroxytryptamine receptor; NK-1 — neurokinin-1; CNS — central nervous system; GES — gastric electrical stimulation; POP — pyloromyotomy; G-POEM — and percutaneous endoscopic gastrostomy

Conclusion

In summary, DGP is a common complication in diabetic patients. Its symptoms are non-specific, and diagnosis can be complicated. A full understanding of its pathogenesis is still lacking. However, recent research conducted by numerous scholars both domestically and internationally has contributed to a better recognition of its pathogenesis and improved diagnostic methods for delayed gastric emptying. The treatment of DGP currently lacks targeted drugs and mainly focuses on symptomatic relief. While these approaches can provide short-term improvement in clinical symptoms, the long-term benefits are limited, and adverse reactions can occur with drug therapy, gastric electrical stimulation, and surgical interventions. Consequently, a complete cure of the disease remains challenging. Therefore, further exploration of the pathogenesis and the search for more effective treatment options are essential to enhance long-term symptom management and improve patients' quality of life.

Authors' contributions

J.Z.: conceptualization, investigation, writing — original draft; L.R.: writing — review and editing; C.Z.: review and editing. All authors read and approved the final manuscript.

Conflict of interest

The authors disclose no conflicts.

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