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Diabetic Gastroparesis: A Narrative Review of a Neglected Complication

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Abstract

Diabetic gastroparesis is a form of autonomic neuropathy resulting in a complication of diabetes mellitus and characterized by delayed gastric emptying. The prevalence is estimated to be 5% among type 1 diabetics and 1% among type 2 diabetics. It is most commonly seen in people who have had diabetes for 10 years and have already developed other microvascular complications. The pathophysiology of diabetic gastroparesis is complex and not yet fully understood, but it is believed to involve several interrelated factors. One of the main contributing factors is damage to the nerves (diabetic neuropathy) that control the muscles of the stomach and intestines. This can lead to abnormal contractions and motility in the stomach, resulting in delayed gastric emptying and associated symptoms. The cardinal symptoms of gastroparesis include nausea, vomiting, postprandial fullness, early satiety, bloating, upper abdominal pain, and in severe cases, anorexia, and weight loss, with a characteristic cyclic pattern with periodic exacerbations. The diagnosis typically involves a combination of medical history, physical examination, and laboratory tests (i.e., scintigraphy, capsule endoscopy, and/or electrogastrography). The main targets of the management of gastroparesis include symptomatic control, correction of nutritional deficiencies, and maintenance of optimal weight. Pharmacological therapies aim to improve symptoms and include prokinetics, motilin agents, ghrelin agonists, 5HT4 receptor agonists, antiemetics, and neuromodulators. In order to ensure the successful management of diabetic gastroparesis, it is essential to achieve adequate glucose control with dietary and insulin intake modifications. Endoscopic therapies can be an effective alternative when conservative measures have failed to improve symptoms. Overall, diabetic gastroparesis is a debilitating and progressive disease that significantly affects a patient's quality of life and has limited treatments. This narrative review provides an updated overview of the medical approach to this multifaceted condition.

Keywords: Diabetic gastroparesis; Diabetes mellitus; Diabetic enteropathy; Diagnosis gastroparesis; Treatment gastroparesis

Abbreviations: DGp: Diabetic Gastroparesis; DM: Diabetes Mellitus; GI: Gastrointestinal; NIDDK: National Institute of Diabetes and Digestive and Kidney disease; GLP-1: Glucagon-like Peptide 1; EGG: Electrogastrography; 5-HT4: Serotonin Type 4 Receptor; 5-HT3: Serotonin Type 3 Receptor; US: United States; FDA: Food and Drug Administration; CSII: Continuous Subcutaneous Insulin Infusion; CGM: Continuous Glucose Monitoring; GES: Gastric Electrical Stimulation

Introduction

Diabetic gastroparesis (DGp) is a complication of diabetes mellitus (DM) characterized by delayed gastric emptying without mechanical obstruction [1]. Although a high prevalence of gastroparesis has been reported in type 1 diabetics (40%) and type 2 diabetics (10–20%), these studies are from tertiary academic medical centers where the prevalence is expected to be higher than the general population. The community prevalence is estimated to be ~5% among type 1 diabetics, and 1% among type 2 diabetics [2]. Several factors, such as extrinsic (i.e., sympathetic and parasympathetic) and intrinsic (i.e., enteric) neuromuscular dysfunctions, hyperglycemia, and hormonal disturbances, have been associated with gastrointestinal (GI) sensorimotor dysfunctions in DM [3]. The clinical presentation of gastroparesis includes nausea, vomiting, abdominal pain, early satiety, postprandial fullness, bloating, and, in severe cases, weight loss. Patients may experience epigastric distention or tenderness on a physical exam [1]. Gastroparesis is diagnosed by demonstrating delayed gastric emptying in a symptomatic patient after the exclusion of other potential etiologies of symptoms and obstruction with endoscopy or radiologic imaging. The current diagnostic method of choice is the scintigraphic measurement of the emptying of solids [4].

Dietary modifications and pharmacologic treatment with prokinetics to increase gastric motility form the mainstay of treatment. Newer therapies, including motilin receptor agonists, ghrelin receptor agonists, and neurokinin receptor antagonists, are currently being investigated. Transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy provide mechanical options for intervention, and surgical interventions in severe, intractable gastroparesis include laparoscopic pyloroplasty or gastrectomy [5]. Gastroparesis is a prevalent and debilitating complication of diabetes. It can cause significant physical, emotional, and financial burdens on affected patients. The aim of this narrative review is to offer a comprehensive overview of diabetic gastroparesis and to examine treatment strategies determined by the level of severity in order to improve the understanding of this commonly underdiagnosed condition.

Epidemiology

Gastroparesis, a form of autonomic neuropathy, is most commonly seen in people who have had diabetes for 10 years and have already developed other microvascular complications [6]. Previous studies have reported variable estimates of diabetic gastroparesis incidence depending on the clinical setting. However, as of 2020, the estimated prevalence of diabetes is about 536.6 million worldwide. Type 1 DM represents between 5 and 10% of all types of diabetes. Therefore, there are higher numbers of people with type 2 DM suffering from gastroparesis [7]. Well-conducted studies regarding the prevalence of gastroparesis, using both the presence of symptoms along with demonstrable delayed gastric emptying diagnosed by gastric emptying scintigraphy, are lacking. Only one population-based study from Olmsted County, Minnesota, has addressed the prevalence of gastroparesis using these criteria. Jung and colleagues used a medical record linkage system to identify community residents with gastroparesis based on strict definitions, including the presence of typical symptoms of up to 3 months and documented delayed gastric emptying on either endoscopy or upper gastrointestinal endoscopy. Based on these criteria, they identified 83 patients with a definite diagnosis of gastroparesis and a further 44 with probable gastroparesis. They reported a prevalence of definite gastroparesis per 100,000 persons of 37.8 in women (95% CI 23.3–52.4) versus 9.6 in men (95% CI 1.8–17.4) [8]. The reasons for the female preponderance remain unknown. Even in people with diabetes without clinical gastroparesis, gastric emptying is slower in women than men. It is not clear whether there is an ethnic predisposition for diabetes-related gastroenteropathy. Diabetic gastroparesis is less common in children, given that a longer duration of diabetes and hyperglycemia predicts DGp [9]. In a cohort of mostly type 1 diabetics followed in Australia over a period of approximately 25 years, DGp was not associated with a poor prognosis or with increased mortality when corrected for autonomic neuropathy and HbA1c [9].

Pathophysiology

Diabetic gastroparesis is a medical condition characterized by delayed gastric emptying and abnormal motility of the stomach in patients with diabetes mellitus [10,11]. The pathophysiology of this condition is complex and not yet fully understood, but it is believed to involve several interrelated factors. One of the main factors contributing to diabetic gastroparesis is damage to the nerves that control the muscles of the stomach and intestines [12]. This damage, known as diabetic neuropathy, is caused by high levels of glucose in the blood over time, which can damage the nerves that control the gastrointestinal tract [12,13]. This nerve damage can lead to abnormal muscle contractions and motility in the stomach, resulting in delayed gastric emptying and associated symptoms.

In addition to nerve damage, diabetic gastroparesis is also associated with abnormalities in the secretion and action of various hormones involved in the regulation of digestion [8,14]. For example, patients with diabetic gastroparesis may have reduced levels of the hormone motilin, which plays a key role in the regulation of gastric motility. Other hormones, such as ghrelin and cholecystokinin, may also be affected in diabetic gastroparesis [14,15]. Furthermore, inflammation and oxidative stress have also been implicated in the pathophysiology of diabetic gastroparesis. High levels of inflammation and oxidative stress in the stomach can lead to damage to the nerves and

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muscles, further contributing to delayed gastric emptying and other symptoms [16]. Overall, the pathophysiology of diabetic gastroparesis involves complex interactions between nerve damage, hormonal imbalances, inflammation, and oxidative stress [17,18]. Understanding these underlying mechanisms is important for the development of effective treatments for this condition.

Clinical Presentation

The diagnosis of diabetic gastroparesis is not usually straightforward because while some patients may be asymptomatic or have mild symptoms, particularly during the early phase, others present with extensive and incapacitating symptoms. The cardinal symptoms of gastroparesis include but are not limited to nausea, vomiting, postprandial fullness, early satiety, bloating, upper abdominal pain, and in severe cases, anorexia, and weight loss, with a characteristic cyclic pattern with periodic exacerbations. Although 72% of patients with gastroparesis report abdominal pain, it is still considered under-reported [2,19]. Patients may present with epigastric distention and tenderness on the physical exam [20]. According to the National Institute of Diabetes and Digestive and Kidney disease (NIDDK) gastroparesis registry, symptoms begin at a later age in patients with Type 2 DM (49±11 years) than in patients with Type 1 DM (34±10 years). The average duration of symptoms prior to the diagnosis of gastroparesis was 6 years in Type 1 DM and 4 years in Type 2 DM; vomiting was the most predominant symptom in these patients [3].

Patients that use insulin as their treatment for diabetes mellitus may present with hypoglycemia caused by a mismatch between slowed food absorption (due to the delayed gastric emptying) and continuous insulin absorption; among asymptomatic patients, erratic glycemic control, especially early postprandial hypoglycemia, maybe the only sign of gastroparesis [21]. Furthermore, patients with diabetic gastroparesis are at a higher risk of developing cardiovascular diseases, hypertension, and retinopathy. Therefore, they may also present with symptoms relating to these conditions [22]. In addition, certain antidiabetic medications, such as glucagon-like peptide 1 (GLP-1) receptor agonists, can exacerbate symptoms of diabetic gastroparesis by reducing gastric emptying and appetite and increasing glucose-dependent insulin secretion [21].

Diagnosis

Gastroparesis is a debilitating progressive disease that significantly affects a patient's life quality with limited and challenging treatments available [23]. The diagnosis of this complex condition typically involves a combination of medical history, physical examination, and laboratory tests. Besides typical symptoms (i.e., nausea, vomiting, and abdominal pain), the accurate diagnosis of gastroparesis often requires tests such as scintigraphy, capsule endoscopy, and/or electrogastrography (EGG). The gold standard for diagnosis with a 90% sensitivity is the scintigraphic assessment of solid emptying over four hours [23,24]. Scintigraphy, also known as a gastric emptying study, involves eating a meal charged with a contrast agent, which is radiologically tracked as it moves through the digestive system [24]. The stomach takes up this radiopharmaceutical and emits gamma rays, which a gamma camera can detect. The patient will typically consume a test meal containing the contrast agent and then lie down under the gamma camera, which will take images of the stomach at regular intervals over the course of several hours [25,26]. These images can show how quickly the stomach empties and help diagnose and assess the severity of diabetic gastroparesis. Standardized biscuit enriched with a 13C-enriched substrate is another valuable test for measuring solid-phase gastric emptying [25]. When metabolized, the proteins, carbohydrates, and lipids of the Spirulina platensis or the medium-chain triglyceride, octanoate, increase respiratory 13CO2, measured by isotope ratio mass spectrometry, allowing for estimation of gastric emptying [27,28]. Generally, a gastric emptying study using scintigraphy is considered a safe and non-invasive procedure. The amount of radiation used in the test is minimal and not regarded as harmful [28]. However, it is essential to note that this test involves radiation exposure that can harm a developing fetus or infant and is contraindicated during pregnancy or breastfeeding [29]. In summary, scintigraphy is a safe and non-invasive test that can provide valuable information about the function of the stomach in patients with diabetic gastroparesis and should be considered a first-line tool for diagnosis [29,30].

Another valuable diagnostic test for gastroparesis is capsule endoscopy. This non-invasive diagnostic procedure involves swallowing a small, pill-sized capsule that contains a camera and a light source [31,32]. The capsule is designed to travel through the digestive system and take pictures of the inside of the gastrointestinal tract, including the esophagus, stomach, and small intestine [32]. Capsule endoscopy can be used to diagnose gastroparesis by examining the stomach and small intestine for signs of delayed gastric emptying, such as the presence of undigested food or other material. The images captured by the capsule can also help identify any underlying structural abnormalities or damage to the GI tract that may contribute to gastroparesis. Overall, it is a safe and effective tool that can provide valuable information about the gastrointestinal tract in patients with gastroparesis [30,32].

Lastly, electrogastrography could serve as an aid for the diagnosis of gastroparesis. EEG is a non-invasive diagnostic test used to evaluate the electrical activity of the muscles in the stomach [33]. The test involves placing electrodes on the surface of the skin of the abdomen to record the electrical signals generated by the stomach muscles during the digestive process [34]. In gastroparesis, the regular electrical activity of the stomach muscles may be disrupted, leading to delayed

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gastric emptying and associated symptoms such as nausea, vomiting, and abdominal pain [25,33,34]. EGG can detect abnormalities in the stomach's electrical activity, including tachygastria (abnormally fast electrical activity) or bradygastria (abnormally slow electrical activity), which may be indicative of gastroparesis. During an EGG, the patient is typically asked to fast for a period before the test and may be given a meal or liquid to consume before the recording [23,28,33]. The test involves placing several small electrodes on the surface of the skin of the abdomen, which is connected to a recording device [24,34]. The recording device then records the electrical signals generated by the stomach muscles as the patient digests the meal or liquid. EGG is a safe and non-invasive test that can be useful in diagnosing gastroparesis and evaluating the effectiveness of treatments for this condition [34]. However, it is important to note that EGG is not a definitive diagnostic test for gastroparesis. Other tests, such as gastric emptying studies or capsule endoscopy, may be needed to confirm the diagnosis [32-34].

Medical Treatment

The main targets of therapeutic management of gastroparesis are symptom control, correction of nutritional deficiencies, maintenance of optimal weight, and identification and treatment of causes of delayed gastric emptying when possible [35]. In mild disease, maintaining oral nutrition is the goal of therapy. In severe gastroparesis, enteral or parenteral nutrition may be needed [2]. As gastric emptying of liquids is often preserved in gastroparesis, increasing the liquid nutrient component of a meal is effective. Small, low-fat, low-fiber meals, 4 – 5 times daily, are appropriate [2,36]. Foods that are spicy, acidic, and fatty should be avoided or minimized because they may worsen symptoms; with a similar impact, carbonated beverages can aggravate gastric distention [6]. Alcohol and tobacco smoking should also be avoided because both can modify gastric emptying [2,6]. Patients with gastroparesis may develop electrolyte abnormalities and nutrient and vitamin deficiencies for which supplemental hydration and nutrition may be recommended [2,37].

The use of pharmacological therapies is mainly to help improve a patient's symptoms. Some of the agents used are prokinetics, motilin agents, ghrelin agonists, 5HT4 receptor agonists, antiemetics, and neuromodulators [35]. As a group of medications, prokinetics have the most substantial clinical trials, and overall evidence suggests that they provide symptomatic benefits [37,38]. For all the medications, the recommendation is conditional for using treatment over no treatment to improve gastric emptying. The two prokinetic medications with the most significant number of individual clinical trials for gastroparesis are metoclopramide and domperidone [38]. Metoclopramide, a dopamine D2 receptor antagonist, has antiemetic and prokinetic properties [35]. It is the only medication available for the treatment of gastroparesis in the U.S., but, despite the chronicity of the condition, its use is restricted by the FDA to 12 weeks to avoid extrapyramidal symptoms, which include pseudo parkinsonism, akathisia, and acute dystonic reactions [38,39]. These side effects often respond to a reduction in dosage or cessation of the medication and to anticholinergic medications such as benztropine [5]. Domperidone is a type II dopamine antagonist similar to metoclopramide and is equally efficacious but does not cross the blood-brain barrier enough to cause similar neurologic side effects [2,39]. The main side effect is QT prolongation. Erythromycin, a macrolide antibiotic, is a motilin agonist that enhances gastric emptying. It is commonly used off-label in gastroparesis. However, long-term use of erythromycin is limited because of the onset of bacterial resistance, arrhythmias, and tachyphylaxis. Azithromycin is as effective as erythromycin but without cardiac risk. Camicinal, another motilin receptor agonist, has been shown to improve gastric emptying in diabetic gastroparesis without a decrease in response after 28 days of use. Tegaserod, also a 5HT4 agonist, can be potentially useful in gastroparesis without effects on QT prolongation. Another 5HT4 agonist, Velusetrag, administered to patients with chronic idiopathic constipation for 4 weeks, was well tolerated and accelerated gastric emptying after 4–9 days of treatment [35]. It is now undergoing clinical trials in patients with gastroparesis [40].

Levosulpiride is an antipsychotic agent that accelerates gastric emptying by exerting both antidopaminergic and 5-HT4 agonistic activities and can improve gastric emptying in patients with dyspepsia and diabetic or idiopathic gastroparesis [39]. Some of the side effects include galactorrhea and menstrual irregularities in women. Relamorelin is a potent synthetic ghrelin agonist. It has been shown to improve gastric emptying halftime in diabetic patients with Gastroparesis [35]. The etiology of abdominal pain in gastroparesis is not well-understood. Other than prokinetics, the symptomatic treatment of these symptoms remains empirical, and off-label use of these drugs from the indications for nonspecific nausea and vomiting or chemotherapy-induced emesis and palliative care, such as the 5-HT3 receptor antagonists [5]. Ondansetron is available in both parenteral and enteral forms, while granisetron is available only in a transdermal form [35]. Neurokinin antagonists are approved for the treatment of chemotherapy-induced emesis. Among these drugs, aprepitant increases gastric accommodation and improves some digestive symptoms in patients with gastroparesis but does not affect gastric emptying [39]. Synthetic cannabinoids, such as dronabinol and nabilone, are approved for the treatment of nausea and vomiting associated with chemotherapy, but their use in gastroparesis is controversial [35].

Glucose Control

In order to ensure the successful management of diabetic gastroparesis, it is essential to achieve adequate glucose control. However, typical symptoms of this condition, such as nausea, vomiting, bloating, and heartburn can make it more difficult to control blood glucose levels [41]. Several strategies are available

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for glucose control in diabetic gastroparesis. First, patients should eat smaller, more frequent meals and avoid large meals that can exacerbate symptoms [9,41]. They should also adjust their insulin doses based on the timing of their meals and the rate of gastric emptying. Insulin may need to be administered after meals instead of before, and the dose may need to be reduced [42]. It is important to note that insulin administration can be challenging because delayed gastric emptying can affect the absorption and action of insulin, leading to fluctuations in blood glucose levels [42,43]. Insulin should be administered after meals, as delayed gastric emptying can affect the timing of insulin action. Patients may need to use rapid-acting insulin or a combination of rapid-acting and long-acting insulin to achieve optimal glucose control [44,45]. In a recent large-scale randomized trial, the use of a continuous subcutaneous insulin infusion (CSII) was found to be associated with significant improvements in glycemic control and quality of life in patients with diabetic gastroparesis compared to multiple daily injections of insulin alone [45]. Moreover, patients with gastroparesis may be more sensitive to insulin and may require lower doses than those without gastroparesis [9,43,45]. It is recommended to start with a lower dose and gradually increase it to avoid hypoglycemia. However, the quantities of insulin need to be adjusted based on the timing and composition of meals, as well as the rate of gastric emptying [41,46]. Patients should work with their healthcare provider to determine the appropriate dose and timing of insulin based on their individual needs. Furthermore, patients with gastroparesis may have difficulty using traditional insulin delivery methods, such as insulin pens or syringes, due to nausea or vomiting [47]. Insulin pumps may be a better option for some patients, as they allow for more precise dosing and can deliver insulin continuously or in small increments. Finally, it is essential to monitor blood glucose levels closely, especially after meals, to ensure optimal glucose control [46,47]. Continuous glucose monitoring (CGM) may be helpful in some cases, as it provides real-time feedback on glucose levels and can help patients adjust their insulin doses [47].

In addition to insulin therapy modifications, several other alternatives can be added to the treatment of these patients to achieve glucose control. Medications such as metoclopramide, domperidone, and erythromycin can help improve gastric emptying [48]. It is vital to manage GI symptoms (i.e., nausea and vomiting) with antiemetics or prokinetic agents to help improve the chances of controlling glucose levels and enhance the quality of life [46,48]. Also, dietary modifications play an important role in glucose control. Patients should avoid high-fiber foods, fatty foods, and foods that are difficult to digest. Instead, they should focus on low-fat, low-fiber, and easily digestible foods such as broth, plain pasta, and boiled or baked potatoes [49].

The success of glucose control for diabetic gastroparesis can vary depending on several factors, such as the severity, the underlying cause, the effectiveness of the treatment regimen, and the patient's adherence to treatment. Studies have shown that combining dietary modifications, medication, and insulin therapy can effectively improve glucose levels in diabetic gastroparesis [45,49]. It is important to note that a personalized treatment plan tailored to the patient's unique needs and circumstances is essential for achieving optimal glucose control.

Endoscopic Therapy

Endoscopic therapies can be an effective treatment option for diabetic gastroparesis. These minimally invasive procedures may be indicated when conservative measures, such as dietary changes and medications, have failed to improve symptoms [39]. It may also be considered in patients with severe gastroparesis at risk of malnutrition or other complications. Several endoscopic therapies may be used to treat gastroparesis, including gastric electrical stimulation (GES), botulinum toxin injection, pyloric dilation, and gastrostomy tube placement [39,50]. Endoscopic therapy may not be appropriate for all patients as these procedures have some contraindications. Patients who are not good candidates include those with bleeding disorders, chronic heart/pulmonary disorders, end-stage renal disease, or those unable to undergo anesthesia [51]. Endoscopic therapy carries risks such as hemorrhage, infection, gastric perforation, adverse reactions to anesthesia, and device-related complications. The rates of success for endoscopic therapy in treating gastroparesis vary depending on the specific procedure used, the severity of the condition, and other individual factors [52].

GES involves placing a small device under the skin of the abdomen that sends electrical impulses to the stomach to help improve motility. The device is typically implanted during an endoscopic procedure [2,52]. The success rate of GES in improving symptoms of gastroparesis is generally reported to be around 60-70%, with some studies reporting success rates as high as 80% [2]. However, the effectiveness of GES may decrease over time, and some patients may require additional treatments or adjustments to the device. Another endoscopic option is the use of botulinum toxin injection. Botulinum toxin is a muscle relaxant that can be injected into the stomach muscles to help improve motility [50,53]. The injection is typically performed during an endoscopic procedure. The success rate of botulinum toxin injection in improving symptoms of gastroparesis varies widely depending on the specific injection site and other individual factors. Studies have reported success rates ranging from 20-80% [53]. Pyloric dilation, another endoscopic alternative, involves widening the opening between the stomach and the small intestine to help food pass more easily. This is typically done using a balloon or other device inserted through an endoscope. Pyloric dilation has been shown to be effective in improving symptoms of gastroparesis in some patients, but success rates vary widely. Some studies have reported success rates as high as 80%, while others have reported much lower success rates [2,51,53]. In some cases, a feeding tube may be placed into the stomach through an endoscopic procedure. This

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can help ensure that the patient is receiving adequate nutrition even if they are unable to eat normally. Gastrostomy tube placement can be very effective in providing proper nutrition for patients with severe gastroparesis who are unable to eat normally. However, this procedure does not directly address the underlying cause of gastroparesis, and success rates in improving overall symptoms vary [2,53].

All these mentioned endoscopic therapies may be used alone or in combination with other treatments, such as medications and dietary changes. The specific treatment approach will depend on the gastroparesis's severity and the condition's underlying cause [39,52]. It is important to note that endoscopic therapy is not a cure for gastroparesis, and some patients may require ongoing treatment and management of their symptoms [50]. The success of these procedures can also depend on various factors, such as the underlying cause of the gastroparesis and the patient's overall health. Therefore, each procedure's specific risks and benefits should be carefully weighed against the potential benefits, patient needs, and medical history.

Conclusion

Gastroparesis, a complication of diabetes mellitus, is characterized by delayed gastric emptying without mechanical obstruction. The most common symptoms are early satiety, nausea, bloating, abdominal pain, vomiting, anorexia, and weight loss. Some studies in tertiary academic medical centers have reported a prevalence of gastroparesis in up to 40% of patients with type 1 diabetes, whereas, in patients with type 2, the prevalence is 10-20%. However, a well-conducted study investigating the prevalence of gastroparesis in patients with diabetes mellitus in the community-based population is lacking. The diagnosis of diabetic gastroparesis is typically guided by symptom pattern and severity. The gold standard for diagnosis with 90% sensitivity is the scintigraphic assessment of solid emptying over four hours. The cornerstone of managing patients with diabetic gastroparesis is to maintain adequate glycemic control and reduce upper GI symptoms. The first treatment line includes restoring fluids and electrolytes, dietary modifications, and optimizing glycemic control. Nevertheless, typical symptoms of this condition can make it more difficult to control blood glucose levels. Patients managing their diabetes mellitus with insulin should eat smaller and more frequent meals and adjust their insulin dose based on the timing of their meals. Studies have shown a significant improvement in glycemic control in patients with diabetic gastroparesis who use a continuous subcutaneous insulin infusion compared with multiple daily injections. Subsequently, pharmacological therapy using prokinetic agents and/or anti-emetics, as well as motilin agent and neuromodulators, can be considered for the management of gastrointestinal symptoms. Endoscopic therapies can be an effective treatment option when conservative measures have failed to improve symptoms. A personalized treatment plan tailored to the patient's unique needs is essential for achieving optimal glucose control and decreasing gastrointestinal symptoms. Despite current evidence, further research is still required to understand better the practical approach to this commonly underdiagnosed condition.

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