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Current Concepts in Diabetic Gastroparesis

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Abstract

Diabetic gastroparesis is a common and debilitating condition affecting millions of patients with diabetes mellitus worldwide. Although gastroparesis in diabetes has been known clinically for more than 50 years, treatment options remain very limited. Until recently, the scientific literature has offered few clues regarding the precise aetiology of gastric dysfunction in diabetes.

Up to 50% of patients with diabetes may experience postprandial abdominal pain, nausea, vomiting and bloating secondary to gastric dysfunction. There is no clear association between length of disease and the onset of delayed gastric emptying. Gastroparesis affects both type 1 (insulin dependent) and type 2 (non-insulin dependent) forms of diabetes. Diagnosis requires identifying the proper symptom complex, while excluding other entities (peptic ulcer disease, rheumatological diseases, medication effects). The diagnosis of gastroparesis may be confirmed by demonstrating gastric emptying delay during a 4-hour scintigraphic study. Treatment options are limited and rely on dietary modifications, judicious use of available pharmacological agents, and occasionally surgical or endoscopic placement of gastrostomies or jejunostomies. Gastric pacing offers promise for patients with medically refractory gastroparesis but awaits further investigation.

Current pharmacological agents for treating gastroparesis include metoclopramide, erythromycin, cisapride (only available via a company-sponsored programme) and domperidone (not US FDA approved). All of these drugs act as promotility agents that increase the number or the intensity of gastric contractions. These medications are not uniformly effective and all have adverse effects that limit their use. Cisapride has been removed from the open market as a result of over 200 reported cases of cardiac toxicity attributed to its use. Unfortunately, there is a paucity of clinical studies that clearly define the efficacy of these agents in diabetic gastroparesis and there are no studies that compare these drugs to each other.

The molecular pathophysiology of diabetic gastroparesis is unknown, limiting the development of rational therapies. New studies, primarily in animals, point to a defect in the enteric nervous system as a major molecular cause of abnormal gastric motility in diabetes. This defect is characterised by a loss of nitric oxide signals from nerves to muscles in the gut resulting in delayed gastric emptying. Novel therapies designed to augment nitric oxide signalling are being studied.

This brief review focuses on the pathophysiology, clinical diagnosis, treatment and novel therapies for diabetic gastroparesis.

1. Normal Gastric Function

1.1 Digestive Function

The essential physiological functions of the stomach are to receive, mix and empty nutrients in an appropriate size and form into the small bowel to facilitate proper absorption. The anatomical parts of the stomach, the cardia, fundus, body and antrum, execute these tasks. These functions of the stomach are coordinated through the central, autonomic and enteric nervous systems (ENS). At the beginning of a meal, the fundus relaxes to receive the ingested food (figure 1). This process, involving an initial receptive relaxation followed by further fundic accommodation, occurs through neural reflex pathways involving the intrinsic nerve cells of the stomach and vagal efferent fibres. Nitric oxide (NO) is released by the intrinsic neurons of the fundal wall

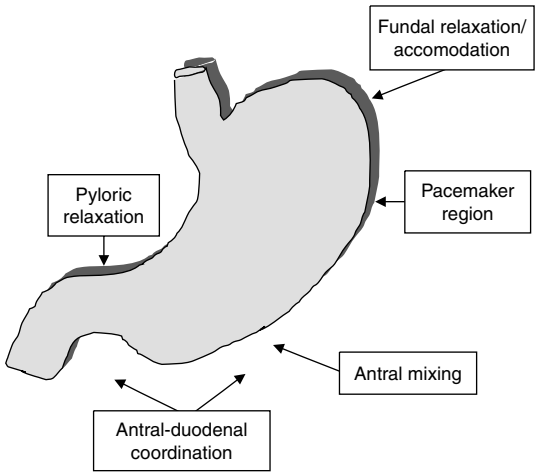

Fig. 1. Normal gastric function. The stomach, when functioning properly, serves to accomplish the following neuromuscular activities: (i) fundic relaxation and accommodation of the volume ingested; (ii) fundic emptying; (iii) peristaltic contractions of the antrum for mixing and trituration; and (iv) pyloric relaxation coordinated with receptive duodenal relaxation and antral contraction to effect the final emptying of the chyme.[2] Failure of any one of these activities may contribute to upper gastrointestinal symptoms and result in delayed gastric emptying or gastroparesis.

and diffuses to the smooth muscle cells to stimulate receptive relaxation. Next, regular contractions of the antrum mix and triturate the food (lag phase, about 30 minutes) before emptying into the duodenum begins. Solids are retained until the particles are less than 2mm in diameter and properly mixed with acid and pepsin into a suspension known as chyme. The rate at which the stomach empties is determined by the physiochemical characteristics of the stomach contents (e.g. solid or liquid state, size of solids, osmolality and caloric content of the nutrients). Liquids empty faster than solids. Isotonic fluids travel faster than hypertonic fluids. Individual nutrients empty from the stomach in the following order according to their caloric content per gram: carbohydrates, then proteins, followed by fats.[1] Depending on the amount and nutrient content of the food ingested, the usual gastric transit time is between 1 and 4 hours.

1.2 Interdigestive Function

The interdigestive (or fasting) motor activity of the stomach is characterised by the major migrating motor complex (MMC) and is divided into four phases based on the frequency and amplitude of spontaneous gastric contractions. Phase I is a period of quiescence characterised by the lack of spontaneous contractile activity. Phase II is notable for the occurrence of irregular motor activity. Phase III contractions are rhythmic contractions occurring every 2 hours, lasting for 10–15 minutes. Phase III contractions are marked by an increase in the frequency of contractions to three per minute. During phase III, contractions of the stomach musculature are determined by the intrinsic electrical activity of the interstitial cells of Cajal (ICC), often referred to as the 'pacemaker' cells of the stomach and gut. Within the stomach, these cells are situated along the greater curvature of the gastric body and function to initiate slow waves of depolarisation at a frequency of three cycles per minute (cpm) establishing the contraction rate of the gastric circular muscles. Undigestible solids remaining in the stomach are emptied by the MMC of phase III. These large amplitude contractions are believed to serve a 'housekeeping' function by clearing the stomach and preventing bezoar formation. Phase IV is a brief period of irregular contractions sometimes noted before the return of a period of quiescence (phase I).

2. Aetiology of Gastroparesis

Nearly any disease that causes neuromuscular dysfunction of the stomach can lead to gastroparesis. However, the most common cause of gastroparesis is diabetes mellitus. Some other causes of delayed gastric emptying are listed in table I.

Drug-induced delayed gastric emptying, diabetes, post-surgical gastroparesis, and idiopathic gastroparesis are important because they can lead to chronic, often severe gastroparesis. Up to 9% of patients who undergo gastric surgery may develop chronic gastroparesis,[4] especially if the surgery involves a vagotomy and partial gastrectomy in the setting of preoperative gastric outlet obstruction or peptic ulcer disease. Idiopathic gastroparesis may present like non-ulcer dyspepsia. However, a substantial number of patients with idiopathic gastroparesis have a history of a viral syndrome preceding

Table I. Common aetiologies of gastroparesis (reproduced from Hornbuckle and Barnett,[3] with permission)

Medications
Opiates, anticholinergics, glucagons, β-adrenergic agonists, calcium channel antagonists
Surgery
Vagotomy and gastric resection, fundoplication, esophagectomy, gastric bypass, Whipple procedure, heart/lung transplantation
Infections
Epstein-Barr virus, varicella, parvo-like viruses, Chagas disease, *Clostridium botulinum*
Central nervous system disorders
Cerebrovascular accidents/trauma, malignancy, seizures
Peripheral nervous system disorders
Parkinson's disease, Guillain-Barre disease, multiple sclerosis, dysautonomias
Neuropsychiatric disorders
Anorexia nervosa/bulimia, rumination syndrome
Rheumatological diseases
Scleroderma, systemic lupus erythematosus, polymyositis/ dermatomyositis
Endocrine and metabolic disorders
Diabetes mellitus, hypothyroidism, parathyroid disease, electrolyte disorders, renal failure, pregnancy
Paraneoplastic disorders
Associated with breast cancer, small cell lung cancer, pancreatic cancer, others
Neuromuscular disorders
Idiopathic gastroparesis, amyloidosis, chronic intestinal pseudo-obstruction, myotonic dystrophy

symptoms and delayed gastric emptying. Indeed, one author suggests that up to a third of patients with idiopathic gastroparesis may actually have a post-viral syndrome.[5] Rotavirus, Norwalk virus, Epstein-Barr virus, cytomegalovirus and herpes simplex viruses have been implicated in post-viral gastroparesis. Unlike patients with other causes of gastroparesis, patients with post-viral gastroparesis often demonstrate slow but substantial improvement in symptoms and quality of life over time.

3. Gastric Dysfunction in Diabetes

3.1 Pathophysiological Considerations

Gastroparesis literally means paralysed stomach.[3] The occurrence of gastric dysfunction in patients with diabetes has been known for more than 50 years. In 1945, Rundles noted an increased frequency of postprandial epigastric discomfort and early satiety in 125 patients with diabetic neuropathy.[6] Later, in 1958, Kassander described the condition of gastroparesis diabeticorum. In this paper, Kassander wrote of asymptomatic gastric retention in diabetes.[7] Historically, gastroparesis was thought to be an infrequent complication of long-standing diabetes, similar to autonomic neuropathy. While the detailed natural history of diabetic gastroparesis remains poorly understood, diabetic gastroparesis may be a more common disorder than once thought. Most studies on the prevalence of diabetic gastroparesis and upper gastrointestinal symptoms are from tertiary referral centres, and may overestimate the occurrence of gastroparesis in the community. The prevalence of diabetic gastroparesis in several of these studies is high with delayed gastric emptying present in 50–60% of diabetic patients.[8] Community-based studies have demonstrated the prevalence of upper gastrointestinal symptoms in diabetic patients ranging between 10–15% and is similar to community controls.[9-11]

Diabetic gastroparesis does occur in patients with long-standing type 1 diabetes with or without evidence of peripheral and autonomic neuropathy. However, it is also seen in patients with type 2 diabetes with a relatively short duration of disease. Systemic complications of diabetes, including autonomic and peripheral neuropathy, are not reliable predictors of diabetic gastroparesis.[12] Delayed gastric emptying of solids is more frequent than delayed emptying of liquids.[13] Gastric symptoms (early satiety, nausea, vomiting, bloating, fullness, abdominal pain or discomfort) occur in between 30–60% of patients with type 1 diabetes.[2] Interestingly, the presence of symptoms does not necessarily predict the presence of delayed gastric emptying by a scintigraphic gastric emptying study.[14-16] Other studies have shown that up to 50% of patients with delayed gastric emptying may have no symptoms referable to their stomach.[17-19] In such patients, a clinical clue to poor gastric emptying may be difficulty in controlling blood glucose levels reflecting mismatching of insulin administration and emptying of nutrients into the small bowel.[1]

The term diabetic gastroparesis does not encompass all patients with gastric symptoms occurring in association with diabetes (figure 2). For example, impaired fundic relaxation, poor coordination between antral and duodenal contractions, gastric dysrhythmias and visceral hypersensitivity may coexist in diabetic patients with or without a documented delay in gastric emptying. Similarly, a diabetic patient with a normal gastric emptying rate by scintigraphy may have gastric dysrhythmia and/or altered fundic relaxation leading to symptoms such as nausea or abdominal bloating. The molecular cause(s) of delayed gastric emptying or other forms of gastric dysfunction in diabetes and the relationship between these dysfunctions and symptoms remains obscure.

Since delayed gastric emptying is not present in all patients with diabetes-associated upper gastrointestinal symptoms, a broader term, diabetic gastropathy, has been developed. Diabetic gastropathy refers to disorders in motility, sensation or other neuromuscular function that can occur in association with diabetes without other identifiable aetiologies, and with or without scintigraphic evidence of delayed gastric emptying (figure 3). Thus the term 'diabetic gastropathy' includes all diabetic patients with signs or symptoms of gastric dysfunction and recognises that these signs and symptoms may share underlying molecular cause(s) whether or not delayed gastric emptying is observed. Furthermore, diabetic patients may develop motility disorders throughout the gastrointestinal tract. Bacterial overgrowth in the small intestine can cause diarrhoea, while colonic dysmotility can lead to chronic consti-

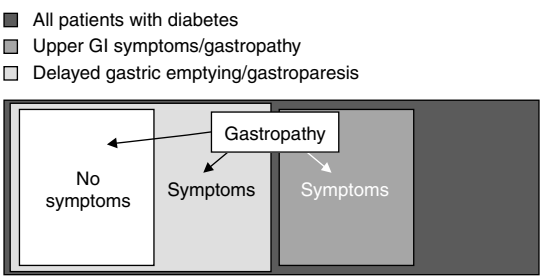

Fig. 2. Clinically important effects of diabetes on the upper gastrointestinal (GI) tract. This figure illustrates the relationships between symptoms, gastroparesis and gastropathy. Many authors suggest that between 50–70% of patients with diabetes have upper gastrointestinal symptoms that may relate to gastric dysfunction (see section 3.1). Gastroparesis represents a subset of patients with gastropathy. Patients with gastropathy may or may not have evidence of delayed gastric emptying. Patients with gastroparesis may present with symptoms or may remain asymptomatic for years with the exception of difficult to control blood glucose, so called 'brittle diabetes'. These 'asymptomatic' patients may benefit from treatment that normalises their gastric emptying and, thus, improves glycaemic control. We speculate that improved glycaemia may help prevent the long-term complications of diabetes including renal failure, heart disease, peripheral neuropathy, blindness and autonomic dysfunction.

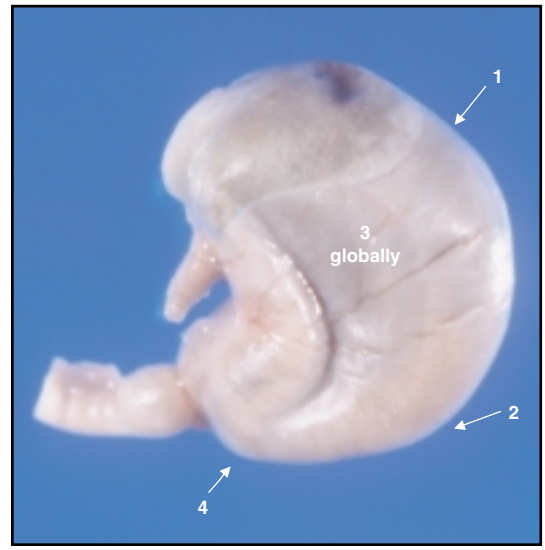

Fig. 3. Abnormalities in neuromuscular function in diabetic gastropathy. This figure of a genetically modified mouse stomach from the author's laboratory is intended to emphasise that any of the normal neuromuscular functions of the stomach may be disturbed resulting in diabetic gastropathy. (**1**) Failure of fundic relaxation. Fundal relaxation and subsequent accommodation in response to food ingestion is significantly less in diabetic patients than in controls.[20] Conceivably, impaired accommodation may cause early satiety. (**2**) Impaired antral motility. Manometric studies have demonstrated that the postprandial antral contractions in diabetic patients are of lower amplitude than those found in healthy individuals.[21] (**3**) Diminished MMC phase III activity. Less frequent or even absent phase III activity has been observed in diabetic patients with recurrent nausea and vomiting, and may result in bezoar formation.[22-24] (**4**) Failure of pyloric relaxation. Decreased spontaneous pyloric relaxations accompanied by episodes of intense and prolonged tonic contractions of the pylorus are more frequent in diabetic patients.[25] Any or all of these neuromuscular dysfunctions contribute to signs and symptoms of gastropathy in patients with diabetes. The mouse stomach provided is derived from a mouse with genomic deletion of nitric oxide synthase. These mice demonstrate delayed gastric emptying early in life and form bezoars.[26] **MMC** = migrating motor complex.

pation. Accordingly, intestinal dysfunction in diabetes is increasingly referred to as diabetic enteropathy.

3.2 Specific Pathophysiological Factors Contributing to Gastric Dysfunction in Diabetes

3.2.1 Hyperglycaemia

In healthy individuals, the rate of gastric emptying is slower in states of induced hyperglycaemia.[27] Increasing blood glucose levels from normal ranges to 230 mg/dL (12.765 mmol/L) is associated with a significant decrease in antral motility.[28] In both patients with type 1 and those with type 2 diabetes, the rate of gastric emptying is slowed by induced hyperglycaemia.[17,29] High glucose impairs intracellular metabolic pathways and membrane function contributing to decreased antral contractions and increased pyloric contractions leading to gastric stasis.[30] Because of these effects, there exists an inverse relationship between gastric emptying and glucose control. Higher blood glucose levels lead to a slowing of gastric emptying. There is increasing evidence that the delay in gastric emptying seen in patients with diabetes may have a major impact on upper gastrointestinal symptoms (in particular abdominal bloating) and glycaemic control.[31,32] This may explain why some patients with diabetes have more difficulty controlling their blood glucose levels on a daily basis. Furthermore, administration of drugs that improve gastric emptying times have been shown to improve glycaemic control as evidenced by reduced glycosylated haemoglobin values.[33]

3.2.2 Autonomic Neuropathy

Within a few years of the onset of clinical diabetes, many patients develop signs of autonomic neuronal damage ranging from subclinical alterations in nerve conduction velocities to life threatening autonomic dysfunction.[34] Perhaps autonomic neuropathies contribute to neuromuscular disorders in diabetic gastropathy. However, investigators have failed to consistently find an association between autonomic neuropathy and gastroparesis.[14,35] In fact, one study suggested the presence of autonomic neuropathy was a poor predictor of delayed gastric emptying.[12] Other studies have found an increased presence of impaired gastric emptying in patients with cardiac autonomic neuropathy compared with those without neuropathy.[36,37] Pathophysiologically, loss of vagal tone and increases in sympathetic activity may result in gastric dysrhythmias leading to gastroparesis.[38,39] Autonomic neuropathy might alter gastric secretory function, antroduodenal motility and gastroesophageal reflux activity, all of which may contribute to symptoms experienced by patients with gastropathy.

3.2.3 Enteric Neuropathies

In addition to hyperglycaemia and autonomic neuropathy, dysfunction of the enteric nervous system may also contribute to the pathophysiology of diabetic gastropathy. In humans, enteric neuropathies can be difficult to differentiate from autonomic ones. Studies in diabetic rats describe a modest depletion of neuronal NO synthase (nNOS) protein and mRNA in association with the development of diabetes.[40,41] This loss of nNOS does not reflect neuronal cell death.[42] Moreover, the loss of nNOS expression has physiological consequences. Another study involving spontaneously diabetic mice showed nearly absent pyloric relaxation and greatly delayed gastric emptying that could be reversed with insulin administration.[42] The loss of pyloric relaxation is similar to the pyloric dysfunction described in diabetic patients and may cause a functional gastric outlet obstruction. The dramatic clinical presentation of infants with infantile hypertrophic pyloric stenosis (IHPS) attests to the importance of NO-mediated pyloric relaxation in gastric emptying.[43] Since nNOS-derived NO is required for fundic accommodation and antral peristalsis, NO depletion represents a possible unifying hypothesis for the molecular aetiology of diabetic gastropathy. Indeed, a recent case report of a type 1 diabetic patient with gastroparesis describes a significant reduction in nNOS neurons in addition to a depletion of several other neurotransmitters.[44]

In addition to smooth muscle cells and neurons, neuromuscular transmission in the intestine requires

a third cell type, the ICC. ICC are required for generation of the intestinal slow waves in the stomach and may modulate neuromuscular transmission events. Non-obese diabetic mice demonstrated marked impairment of electrical pacemaking and reduced motor neurotransmission in the stomach[45] in association with a decreased number of ICC. Similarly, greatly reduced numbers of ICC were found in the jejunum of a patient with type 1 diabetes with gastroparesis.[44]

4. Diagnosis

Although the pathophysiology of diabetic gastroparesis is still being discovered, a careful history and physical exam are the keys to diagnosis. Consideration of disease processes other than diabetes that may lead to delayed gastric emptying and upper gastrointestinal symptoms should be entertained in every diabetic patient presenting with upper gastrointestinal complaints. The timing, chronicity, nature and severity of symptoms may be important clues as to the underlying disorder.

Diabetic patients with gastroparesis may present with symptoms related to gastric stasis, that is, postprandial fullness, bloating, nausea, vomiting, early satiety, excessive belching after meals, epigastric discomfort and epigastric pain; whereas, in other patients symptoms of dyspepsia or gastroesophageal reflux may predominate. Symptoms of gastroparesis usually relate to eating, but some patients with diabetes may have nausea and vomiting during periods of prolonged fasting. One study involving 28 patients with gastroparesis followed over 4 years at a tertiary referral centre reported nausea (92.9%) and abdominal pain (89.3%) as the most common complaints. Furthermore, 60% of these patients reported post-prandial abdominal pain, while 80% experienced nocturnal pain.[46]

Delayed gastric emptying may result in gastric distension and an increased propensity for transient relaxation of the lower oesophageal sphincter,[47] which in turn may increase gastroesophageal reflux.[48] Thus, the mechanism for reflux disease in diabetic patients with gastroparesis may be different than in the general population. Symptoms of chest pain, dysphagia and odynophagia should alert to the possibility of underlying reflux disease. Back pain or an increase in severity of typical symptoms may herald the formation of a bezoar further complicating gastric emptying.

During the history taking and physical examination, clinicians should be aware of concomitant disorders of diabetic enteropathy that can occur throughout the gastrointestinal tract in patients with diabetes. Bacterial overgrowth in patients with diabetes results in increased bloating, abdominal discomfort and diarrhoea. Diabetes may affect innervation to the colon leading to chronic constipation.

The physical exam may be particularly helpful to rule out signs of an underlying systemic disease, e.g. systemic sclerosis, lupus, malignancy or thyroid disease. In any patient with diabetes, consideration should be given to other causes of similar gastrointestinal complaints including chronic cholecystitis, chronic pancreatitis, or metabolic disorders such as hypercalcemia, hypokalemia, adrenal insufficiency and uraemia.

Patients with diabetes may be placed into one of four groups based on their presentations (refer to figure 2). One group will have evidence of delayed gastric emptying on nuclear scintigraphy as well as symptoms compatible with the diagnosis. Another group will have delayed gastric emptying but no symptoms attributable to gastric stasis except difficult to control blood glucose levels as a result of a mismatch of insulin administration and emptying of nutrients from the stomach.[1] Speculation as to why these patients have no symptoms centres around altered visceral sensation and vagal nerve damage often seen in diabetic patients. This asymptomatic presentation may be similar to diabetic patients with myocardial infarction, who often lack typical chest pain at presentation.[49] Furthermore, this presentation may reflect variations in either cerebral appreciation of visceral sensory information or personality as seen in irritable bowel syndrome (IBS). A third group may have 'normal' gastric emptying by nuclear scintigraphy but present with symptoms (gastropathy) compatible with gastric stasis. While a fourth group of patients with diabetes may be

asymptomatic and have no evidence of delayed gastric emptying.

4.1 Diagnostic Studies

Several diagnostic studies exist to aid in the diagnosis of gastropathy. These include nuclear scintigraphy, radioisotope breath testing, oesophagogastroduodenoscopy (OGD/EGD), upper gastrointestinal barium swallow study, electrogastrography (EGG), magnetic resonance imaging (MRI), real-time ultrasonography, among others. The choice of test or the decision to acquire a test depends on the presenting symptoms, available modalities, cost and physician preference.

4.1.1 Scintigraphy

Gastric scintigraphy is the gold standard for diagnosing delayed gastric emptying. Gastric scintigraphy has been shown to be reproducible in healthy individuals and diabetic patients with or without gastroparesis despite the somewhat high intra- and interindividual variability of gastric emptying.[50] Although the test can be performed to evaluate emptying of either solids or liquids depending on the test meal used, solid-phase emptying is more sensitive for documenting gastroparesis.[51] Until recently, no uniform test existed for comparisons among medical centres. Now it is accepted that a 4-hour test using a standardised meal consisting of 99-m technetium-sulfur colloid in low-fat eggs allows for valid comparisons of gastric emptying of solids between individuals at different centres.[52] After ingesting the meal, a γ-camera images the abdomen at regular intervals (in the past every 15 minutes, now it may done every 30–60 minutes) for up to 4 hours. Results are stated in terms of the percentage of the meal emptied at certain times throughout the study. Emptying of greater than 50% ($t_{1/2}$) of the meal by 2 hours is considered normal, whereas a gastric retention of greater than 10% at 4 hours is considered delayed. The blood glucose level should be measured in patients with diabetes during the test as it might influence the rate of emptying.[53] Scintigraphy involves minimal radiation exposure; in fact, the radiation burden is less than half of the burden resulting from a plain radiograph of the abdomen.[53]

4.1.2 Radioisotope Breath Testing

An indirect measurement of gastric emptying by detection of exhaled radiolabeled CO_2 provides a safely used, relatively inexpensive method of detecting gastroparesis. Detection of gastroparesis by breath testing is increasing in popularity and may provide an acceptable alternative to radioscintigraphy in certain situations. Participants ingest a meal containing octanoic acid labelled with ^{13}C. In the duodenum, the octanoic acid is digested, quickly absorbed and metabolised by the liver to labelled CO_2 that is exhaled and measured in the breath. Assumptions are made that octanoic acid is absorbed rapidly in the duodenum and not appreciably in the stomach, that its disappearance from the blood is constant, and that there is little or no tracer recirculation from other body pools.[53] In addition, normal small bowel, pancreas, liver and lung function are required for the test to measure gastric emptying accurately. Studies have shown a strong correlation between carbon labelled breath tests and nuclear scintigraphy;[54-57] however, it is generally agreed that carbon breath testing, as currently performed, is not as accurate as scintigraphy.[58] The advantages of labelled breath testing include: (i) the lack of radiation exposure, which will allow studies in pregnant patients and children; (ii) the ability to perform the test at the bedside or in the community; and (iii) low cost, particularly if used in multicentre trials comparing new pharmaceutical agents where multiple samples could be sent to a single remote centre for analysis.[59] The lack of validity for inter-individual comparisons and inaccuracies of the test due to estimates in the nonlinear model used to calculate CO_2 recovery are two of the major disadvantages of labelled breath testing.[57,59] A recent study employing a simple formula using breath $^{13}CO_2$ in an office-based setting demonstrated results comparable with scintigraphy.[57]

4.1.3 Electrogastrography

EGG is a noninvasive method of measuring gastric myoelectrical activity via electrodes placed on the skin of the epigastrium. EGG can reflect the

normal 3 cpm electrical rhythm of the stomach and abnormal gastric dysrhythmias termed tachygastrias (3.6–9.9 cpm) and bradygastrias (1.0–2.4 cpm).[2,60] Some authors suggest that dyspeptic symptoms may correlate better with EGG than scintigraphic studies.[61] Although EGG is a promising technique for detecting altered myoelectrical activity in symptomatic patients, it cannot monitor gastric contractile activity accurately.[62,63]

4.1.4 Antroduodenal Manometry

Antroduodenal manometry involves positioning a catheter extending from the antrum to the duodenum under fluoroscopic guidance in order to record intraluminal pressure differences in the fasting and postprandial states. Manometry may help diagnose and distinguish a variety of motor disturbances in patients with unexplained upper gastrointestinal symptoms. This test is time consuming, difficult to interpret, stressful for the patients and requires radiation exposure;[2] therefore, it is best reserved for patients with refractory symptoms referred to tertiary care centres.[3]

4.1.5 Oesophagogastroduodenoscopy

EGD or an upper gastrointestinal barium swallow study can be employed to look for structural causes that may relate to upper gastrointestinal symptoms or gastric outlet obstruction, such as esophagitis, peptic ulcer disease or the presence of a bezoar. If an EGD demonstrates retained food products after an 8-hour fast, then a diagnosis of gastroparesis can be made with confidence.

4.1.6 Other Tests

MRI, computerised tomography (CT), impedance epigastrography,[64] impedance tomography,[65] real-time ultrasonography and positron emission topography (PET) are additional modalities used to document delayed gastric emptying. These tests are more complicated and for the most part are limited to the research setting at this time. MRI provides three-dimensional images that can measure meal and total gastric volumes in addition to providing information about wall motion during emptying. Unfortunately, MRI is expensive and not universally available. Real-time ultrasonography is a less expensive method to evaluate changes in total stomach volumes; however, sonography is operator-dependent, may be complicated by gas in the stomach or obesity, and requires significant expertise to interpret. More advanced techniques employing sonography are currently being developed but have yet to be validated versus scintigraphy.[66] PET scans have been used to demonstrate that patients with diabetes may have decreased gastric metabolic activity in the post-prandial period when compared with healthy controls.[67]

5. Treatments

Treatment of diabetic gastroparesis must focus on relieving upper gastrointestinal symptoms of nausea, early satiety, bloating and postprandial fullness in addition to improvement in glycaemic control. These goals are often difficult to obtain resulting in frustration for both the patient and clinician. Therapy should include attention to dietary and lifestyle modification, glycaemic control and judicious use of available pharmacological agents. Patients who fail to respond to these approaches may require surgical or endoscopic intervention for placement of either a venting gastrostomy to relieve chronic vomiting or a jejunostomy to maintain enteral nutrition.

5.1 Dietary and Lifestyle Modifications

Although never proven in a randomised, controlled trial, it is generally accepted that patients with gastroparesis should have a diet that is low in fibre and dietary roughage as these products may be difficult for the stomach to empty and lead to bezoar formation. Additionally, the diet should have a low lipid content (less than 40g of fat per day) as lipids slow gastric emptying.[1] It is suggested that patients with gastroparesis eat six small meals per day in order to lessen the neuromuscular work of the stomach at any given time.[68] Some foods leading to bezoar formation include oranges, figs, berries, green beans, apples, coconuts and brussel sprouts.[1] Since hyperglycaemia itself disrupts normal gastric myoelectrical activity, careful attention to blood glucose control is essential.[27,69,70]

Moderate exercise, such as brisk walking, has been shown to accelerate gastric emptying in healthy volunteers and may have a role in the management of diabetic gastroparesis.[71,72] However, other studies have shown that strenuous activity, such as running, has either no effect or a negative effect on gastric function.[73,74]

5.2 Pharmacological Agents

Available drugs to treat gastroparesis can be classified by their major mechanism of action as either prokinetic agents, antiemetic agents or a combination of both. Most of the drugs available today are prokinetics that aim to increase the frequency and amplitude of contractions within the stomach in an attempt to accelerate expulsion from the stomach. The most commonly used drugs to treat gastroparesis include metoclopramide, erythromycin, cisapride and domperidone. The heterogeneous nature of both the pathogenesis and motor dysfunctions involved in gastroparesis implies that it may be extremely difficult to control symptoms or improve gastric emptying with any one drug.[63] Unfortunately, there are few trials comparing the efficacy of these drugs; therefore, the decision to use a particular drug is based on the clinical scenario, drug toxicity, and physician and patient preference.[75]

5.2.1 Metoclopramide

Metoclopramide is a benzamide that possesses central antiemetic as well as prokinetic effects. It is the only agent approved by the US FDA for treatment of diabetic gastroparesis. Metoclopramide is a central and peripheral dopamine (D_2) receptor antagonist, a serotonin (5-HT_4) agonist, a 5-HT_3 antagonist (at high doses) and a cholinesterase inhibitor.[1,2,76] The central nervous system antiemetic properties of metoclopramide are provided via D_2 and 5-HT_3 receptor antagonism in the area postrema.[77] Prokinetic effects are thought to relate to augmented release of acetylcholine from enteric cholinergic neurons, D_2 receptor antagonism in the myenteric plexus and direct smooth muscle contraction via muscarinic receptor sensitisation.[75,78,79] The prokinetic effects may lessen over time; however, prolonged symptom improvement has been reported.[80] The efficacy of metoclopramide in treating symptoms of gastric stasis may have more to do with its central antiemetic properties than to its prokinetic effects.

Metoclopramide can be given orally, intravenously and subcutaneously. Onset of action is approximately 5 minutes by intravenous administration, 30–40 minutes when given subcutaneously and 60 minutes if taken orally.[81] The serum half-life is four hours and the primary route of excretion is via the kidney. Usual oral doses range from 5–20mg four times daily (30–40 minutes before meals). Intravenous dose administration is typically 5–10mg every 4–6 hours. A subcutaneous dose of 5mg given three or four times daily may be useful for patients with intractable nausea and vomiting making oral administration unreliable.

Unfortunately, metoclopramide use is associated with numerous adverse effects. These are primarily due to its central nervous system actions and limit its clinical utility. With long-term use of metoclopramide, up to 10% of patients develop serious neurological adverse effects.[82] Acute dystonic reactions, extrapyramidal side effects (EPS), tardive dyskinesia, akathisia, drowsiness, depression, impotence and hyperprolactinemia are some of the effects attributed to metoclopramide. Acute dystonic reactions such as facial spasms, trismus, torticollis and opisthotonos, occasionally occur and usually respond to discontinuation of the drug and administration of anticholinergic agents or antihistamines that possess anticholinergic properties. Tardive dyskinesia is a syndrome of involuntary movements (usually of the mouth or head) that can persist despite stopping the drug and often remain indefinitely.[75,83] Even more worrisome is the 3–4 times greater risk of parkinsonism found in patients treated long-term with metoclopramide versus a control population. This risk was found to be even higher in the elderly and patients taking more than 20 mg/day of metoclopramide.[84,85]

Efficacy data on metoclopramide in treating gastroparesis are conflicting. Studies from the early 1980s reported symptom improvement and accelerated gastric emptying, whereas more recent studies

fail to show a benefit for either symptoms or gastric emptying.[86,87] With a lack of strong evidence documenting its efficacy coupled with its poor tolerability profile, the use of metoclopramide as a long-term treatment for diabetic gastroparesis is debatable.[88]

5.2.2 Erythromycin

Erythromycin is a macrolide antibiotic that binds to motilin receptors, which are G protein-coupled receptors located throughout the enteric nervous system, with greatest density in the stomach and proximal gastrointestinal tract.[88] As a motilin agonist, erythromycin serves to increase the frequency and amplitude of antral contractions, and to initiate gastric phase III contractions responsible for sweeping the stomach of any residual debris and chyme.[89]

Erythromycin is available in oral and intravenous forms. The half-life of erythromycin ranges between 60–150 minutes. Primarily the liver metabolises erythromycin with only 5% of metabolites excreted in the urine. Typical oral doses of between 50–250mg are given three to four times per day, while intravenous regimens range from 1–2 mg/kg up to 6 mg/kg given every 8 hours. The minimal intravenous dose needed to induce an increase in antral contractility is 40mg.[81] Current studies are underway to determine the optimal dosage and delivery route for erythromycin. Some have suggested that there may exist a dose-dependent effect of erythromycin depending on different subtypes of the motilin receptor. Low doses tend to generate premature antral contractions via cholinergic pathways, whereas higher doses produce a more sustained contraction via noncholinergic pathways including direct stimulation of smooth muscle motilin receptors.[88] Compared to intravenous dose administration, oral erythromycin is less potent and there are questions related to its efficacy when given long-term.[63,90] There has been no advantage shown to higher oral doses as adverse effects become more apparent.

The major adverse effects of erythromycin and other macrolide antibiotics relate to abdominal pain and cramping (51%), nausea (up to 37%), diarrhoea (24%) and vomiting (7%).[91] These adverse effects limit the long-term use of erythromycin especially in patients with gastroparesis who may already experience similar gastrointestinal complaints. In some patients, erythromycin may accelerate gastric emptying too well resulting in impairment of the normal sieving function of the distal stomach. This could lead to delivery of large untriturated particles into the small bowel and, subsequent, malabsorption or a dumping syndrome.[92] In addition, erythromycin has similar activity to class IA antiarrhythmic drugs and may cause QT prolongation, cardiac depression and possibly torsades de pointes. These toxicities, which are usually seen at higher intravenous dosages than provided here, lead some to suggest cardiac monitoring during intravenous administration of erythromycin.[93] These adverse effects plus the development of allergic complications such as a rash limit the utility of erythromycin for long-term treatment of diabetic gastroparesis.

Of all the available prokinetic agents, many feel erythromycin exhibits the most powerful gastrokinetic effect leading to acceleration of both liquid and solid gastric emptying in patients with gastroparesis. However, a meta-analysis concluded that erythromycin was the least likely prokinetic agent to relieve symptoms of gastroparesis.[92,94] Furthermore, erythromycin is known to accelerate gastric emptying in healthy volunteers as well as in patients with diabetic gastroparesis or those post vagotomy.[95,96] One study reported greatly accelerated solid phase gastric emptying in patients with type 1 diabetes receiving intravenous erythromycin.[97] Another study showed improved glycaemic control in patients with type 2 diabetes receiving oral erythromycin.[98] Whether the long-term use of erythromycin is beneficial is unclear as debate exists about the development of tachyphylaxis or the down regulation of motilin receptors.[99] From a practical standpoint, intravenous erythromycin can be used short-term for an acute flare of diabetic gastroparesis. Effects have been sustained for up to 4 weeks using intravenous erythromycin in an outpatient setting.[75]

Ongoing research seeks to develop macrolide derivatives termed motilides and motilactides that possess the chemical backbone to promote gut motility but lack the antibiotic properties of erythro-

mycin. Importantly, a recent randomised, controlled trial of the motilin receptor agonist alemcinal (ABT-229) failed to show a benefit in relieving post-prandial symptoms in patients with diabetes in the presence or absence of delayed gastric emptying.[58] Another motilin agonist, KW-5139, has shown favourable effects on gastric emptying in patients who have undergone pylorus-sparing pancreatoduodenectomy.[100] It remains unclear whether these potential drugs will possess similar tolerability profiles to erythromycin leading to a decrement in their usefulness.

5.2.3 Cisapride

Cisapride promotes gastric emptying by acting as a partial 5-HT_4 agonist causing release of acetylcholine from the myenteric plexus. Antiemetic effects of cisapride are thought to result from its weak antagonism of 5-HT_3 receptors.[101] Cisapride has little to no direct dopamine activity and, therefore, no central nervous system adverse effects. Cisapride was indicated for the treatment of symptoms of gastro-oesophageal reflux disease (GORD) due primarily to its effect on the lower oesophageal sphincter (LES). Specific actions of cisapride include increasing the pressure of the LES and increasing antral, jejunal and colonic motility. Cisapride increases the number of antral, pyloric and duodenal pressure waves in a temporal manner, and suppresses those pressure waves localised to the pylorus.[102] This changes the organisation of gastric contractions to an expulsive pattern. Perhaps the usefulness of cisapride in treating GORD relates as much to accelerating gastric emptying as to tightening the LES.

The usual dose of cisapride is 10–20mg orally four times daily (typically 30 minutes before each meal and at bedtime). Peak serum concentrations are obtained at 2 hours[75] and the elimination half-life of cisapride in healthy volunteers is between 7–10 hours.[103] Cisapride is extensively metabolised in the liver by oxidative N-dealkylation and aromatic hydroxylation with the resultant metabolites excreted equally between bile and urine.[104]

Adverse effects of cisapride include abdominal cramping, diarrhoea, headaches and arrhythmias. The occurrence of more than 250 reported cases of cardiac arrhythmias associated with the use of cisapride between 1993–1999 led the US FDA to withdraw cisapride from the open market. It is currently only available in the US via a special programme from the manufacturer. Cisapride is metabolised by cytochrome P450 (CYP)3A4; therefore, medicines that interact with this system may lead to an increase in the serum cisapride concentration. High cisapride concentrations have been shown to prolong the cardiac QT interval, which increases the risk of torsade de pointes, a potentially lethal ventricular arrhythmia. Some of the medications to be avoided with use of cisapride because of their effects via CYP3A4 include macrolide antibiotics (erythromycin and clarithromycin), azole antifungals (ketoconazole and fluconazole), and protease inhibitors. In addition, cisapride should be avoided in any patient with a personal or family history of a prolonged QT interval or patients currently receiving medications that prolong the QT interval: antiarrhythmics such as procainamide, sotalol and amiodarone.[75] The unavailability, toxicity and unclear long-term efficacy of cisapride warrants a limited role for the drug in the management of patients with chronic gastroparesis.

Cisapride has been shown to relieve gastric outlet obstruction in patients with diabetic autonomic dysfunction, possibly through modulating inhibitory nitrergic transmission.[105] Multiple studies show cisapride accelerates gastric emptying and may improve symptoms in diabetic and idiopathic gastroparesis.[106-109] Early studies comparing intravenous metoclopramide versus cisapride in the acute treatment of gastroparesis found cisapride to be superior in both accelerating gastric emptying and improving symptoms;[87] while other more long-term studies demonstrate consistent improvement in gastric emptying but inconsistent improvement in symptoms.[108] The few studies evaluating the long-term efficacy of cisapride in treating gastroparesis give conflicting results and contain too few participants.[108,110-112] The toxicity and equivocal data regarding improvement in symptoms with cisapride

prevent its acceptance as a long-term treatment for diabetic gastroparesis.

5.2.4 Domperidone

Domperidone is a benzimidazole derivative that acts as a peripheral antagonist at D_2 receptors used in many countries for the chronic management of gastroparesis; however, the US FDA has never approved it for treatment of gastroparesis. Domperidone is thought to improve antral and duodenal contraction via dopaminergic antagonism of the myenteric plexus in a similar manner to metoclopramide. Domperidone does not possess the serotonin effects of metoclopramide and cisapride; furthermore, unlike metoclopramide, domperidone does not cross the blood-brain barrier but rather elicits its antiemetic effects via action on the chemoreceptor trigger zone outside the blood-brain barrier.[75]

Domperidone is available in oral and suppository forms. Little data are available regarding the pharmacokinetics of domperidone in patients with delayed gastric emptying. In healthy volunteers, the serum half-life of domperidone is 7 hours, with peak serum concentrations obtained within 120 minutes after oral administration. A typical oral dose is between 10–40mg four times daily. The drug is metabolised primarily by the liver through oxidative N-dealkylation and hydroxylation to two major metabolites without significant activity. Renal dysfunction is known to increase the half life of the drug, but does not appear to lead to dangerous accumulation of domperidone owing to the much higher rate of plasma clearance versus renal clearance.[113]

Since it does not cross the blood-brain barrier, adverse effects such as acute dystonic reactions are extremely rare. The major adverse effects of domperidone relate to hyperprolactinaemia leading to gynecomastia, impotence, galactorrhoea and amenorrhoea.[75] In a retrospective study of 57 diabetic patients with gastropathy treated with domperidone for up to 3 years, 16% reported symptoms compatible with hyperprolactinaemia (galactorrhoea, breast tenderness and amenorrhoea).[114]

The effect of domperidone on gastric emptying is controversial with some studies demonstrating accelerated emptying, while other studies show no benefit or a failure to sustain benefits in gastric emptying over time.[61,115,116] Use of domperidone long-term has been shown to correct gastric dysrhythmias leading to improvement in nausea and other upper gastrointestinal symptoms.[61] In a large multicentre, randomised, controlled trial, domperidone was shown to significantly relieve upper gastrointestinal symptoms and improve quality of life in patients with diabetes.[117] This improvement in symptoms may result from the antiemetic effects of domperidone on the chemoreceptor trigger zone or from resolution of primary gastric dysrhythmias.[118]

5.2.5 Bethanechol

Bethanechol is a short acting muscarinic cholinergic agent known to increase the amplitude of antral contractions.[119,120] However, this effect may occur in a disorganised manner and, therefore, not lead to aboral transit.[63] In addition, the nonspecific actions of bethanechol induce a number of adverse effects, most noticeably nausea, vomiting, diaphoresis, flushing, salivation and abdominal cramping. Dose administration of bethanechol is 25mg taken orally four times per day. Peak levels are obtained within 90 minutes and the duration of action is between 1–2 hours.[81] Several studies show bethanechol does not improve gastric emptying.[121,122] It is generally concluded that bethanechol is not an effective drug for the treatment of gastroparesis despite increasing antral contractions.

5.2.6 Antiemetics

Patients may require antiemetic therapy if symptoms of nausea and vomiting persist despite treatment with prokinetic medications. Promethazine and prochlorperazine are phenothiazine antiemetics that exert effects via dopamine antagonism in the area postrema. Promethazine may be given orally, intramuscularly, rectally or intravenously (although not approved intravenously) at doses of 12.5–50mg every 4–6 hours. Prochlorperazine is given orally, intramuscularly and intravenously at a dose of 5–10mg every 6 hours. A longer acting suppository form of prochlorperazine is available at a dose of 25mg given every 12 hours. Both of these antiemetics can cause sedation and EPS especially when used in conjunction with metoclopramide.[75] Selec-

tive 5-HT_3 receptor antagonists such as ondansetron, granisetron and dolasetron may be used to treat nausea in patients with gastroparesis who fail to respond to more traditional treatment. Expense and unproven efficacy limit their role in treating gastroparesis.

5.3 Endoscopic and Surgical Interventions

Some patients will continue to remain symptomatic with chronic nausea and vomiting despite dietary and pharmacological interventions. These patients may benefit from endoscopic or surgical interventions aimed at maintaining nutrition, decreasing hospitalisations and improving quality of life. A venting gastrostomy may be placed either endoscopically or surgically, and opened intermittently in an attempt to alleviate postprandial nausea, bloating and abdominal discomfort. One study evaluating the efficacy of gastrostomy in patients with idiopathic gastroparesis found a dramatic improvement in symptoms, weight and functional status over a 3-year period in patients with venting gastrostomy.[123]

Placement of percutaneous tubes is not without risk. Localised cellulitis (especially in patients with diabetes), fasciitis, peritonitis, bowel perforation, gastrocolocutaneous fistula formation, aspiration and misplacement are some of the more common complications encountered. Nearly 25% of patients experience infectious problems within 1 month of placement of a percutaneous tube.[124]

Total parenteral nutrition (TPN) may be required in patients unable to tolerate adequate oral or gastrotomy feeding. TPN can be used briefly during hospitalisations for an acute flare of symptoms; however, long-term TPN use should be discouraged because of its cost and the risks of sepsis, thrombosis and liver disease. Fortunately, most patients can tolerate enteral feedings via a jejunostomy tube making TPN less necessary.

Patients not responding to or unable to tolerate venting gastrostomy and medical therapy should be considered for endoscopic or surgical jejunostomy placement to maintain nutrition and hydration. A disadvantage of an endoscopically placed combination gastrostomy/jejunostomy tube is the frequent migration of the jejunostomy tube back into the stomach resulting in a return of symptoms. However, if two separate tubes are placed, patients may take adjunct nutrition distally through the jejunostomy tube while continuing to eat and vent as needed through the gastrostomy tube. Surgical jejunostomy alone appears to improve quality of life and limit hospitalisations; however, it may not alleviate symptoms, especially if the patient continues to attempt to eat.[125]

In patients with refractory post surgical or post vagotomy gastroparesis, surgical intervention with a near-total or subtotal gastrectomy with Roux-en-Y reconstruction has been shown to alleviate symptoms.[124,126] Roux-en-Y gastrectomy has also been used diabetic patients with gastroparesis with some success.[127,128] The radical nature and inherent risks of this surgical intervention limits its use to patients with the most refractory symptoms.

5.4 Gastric Pacing

Gastric pacing involves the surgical placement of cardiac pacing wires into the serosa of the gastric corpus. This approach to treat patients with medically refractory gastroparesis has received renewed interest within the last 3 years. Since its first use in the early 1960s, attempts have been made to perfect gastrointestinal electrical stimulation to treat disorders including postoperative ileus and gastroparesis.

Earlier trials involving gastric electrical stimulation resulted in unimpressive results;[129,130] however, several recent trials of this technology in medically refractory gastroparesis show new promise. The major differences in these trials relate to varying frequency stimulation protocols. One trial involved producing an electrical stimulus at a frequency close to the intrinsic gastric slow wave (3 cpm) with the goal of entraining and coordinating an artificial gastric slow which would serve to increase gastric emptying.[131] Another as of yet unpublished trial uses a series of brief electrical stimuli at a frequency four times greater than the intrinsic rate. Both of these trials demonstrated improvements in symptoms related to gastroparesis; however, the

higher frequency study failed to show any improvement in the rate of solid-phase gastric emptying.[92] Gastric pacing has been shown to normalise gastric postprandial dysrhythmias in canine studies. Additional effects attributed to gastric pacing include improvement of nausea and vomiting through an unknown centrally acting mechanism, enhancement of gastric compliance and decrease in sensitivity to gastric distension.[132]

Unfortunately, all published trials to date involving gastric pacing have been uncontrolled. Until controlled/sham trials can be performed to confirm the efficacy of gastric pacing, one must remain sceptical of its use in patients unresponsive to medical therapy. Gastric pacing should only be considered in patients with the most medically refractory symptoms. One institution's inclusion criteria involve: symptoms for over 1 year refractory to medical therapy, greater than seven episodes of vomiting per week and evidence of abnormal gastric retention as measured by scintigraphy (>60% retention at 2 hours or >10% at 4 hours). Typical exclusion criteria include history of gastric surgery, pregnancy, any patient with an organ transplant, chemical dependency, eating disorder or intestinal pseudo-obstruction.

6. Future Directions

As no single pharmacological agent has proven uniformly safely usable and efficacious in treating diabetic gastroparesis, much work remains to find effective treatments for this chronic disorder. Other novel agents under investigation but not yet available include phosphodiesterase (PDE) inhibitors, 5-HT_4 agonists, antidopaminergic agents (levosulpiride), cholecystokinin (CCK) antagonists (loxiglumide), opiate agonists and antagonists, and various macrolide derivatives. Other modalities used with some success include injection of botulism toxin into the pylorus and acupuncture.[133]

Recently, we have discovered a possible role for PDE inhibitors in diabetic gastropathy.[42] Specifically, we found that NO production is deficient in diabetic mice leading to delayed gastric emptying and loss of inhibitory neurotransmission in the pylorus. This pathophysiology results from a downregulation of nNOS that is reversed by insulin therapy. These data suggest that the relapsing nature of clinical diabetic gastropathy may result from recurrent down regulation of nNOS. In addition, we found that treatment with a single dose of a selective PDE type V (PDE5) inhibitor, sildenafil, reversed the delayed gastric emptying. Presumably, this results from augmentation of NO signalling through increases in cGMP levels. NO signals smooth muscle relaxation by activation of soluble guanylate cyclase and subsequent increases in cGMP; moreover, NO signalling is terminated by phosphodiesterase catabolism of cGMP. Phosphodiesterase V is a cGMP specific phosphodiesterase that is abundant in vascular and smooth muscle, particularly the pylorus. The use of selective PDE inhibitors in humans with diabetic gastroparesis shows great promise but is yet to be evaluated in a randomised, controlled trial.

Several serotonin agonists are currently being studied for their effect on gastric emptying. Tegaserod, a 5-HT_4 partial agonist, has been used as a promotility agent to treat constipation-predominant IBS.[134] It may prove useful in some patients with gastroparesis. In a recent trial, tegaserod demonstrated increased gastric emptying when given orally or intravenously to 12 healthy individuals.[135] Other 5-HT_4 agonists involved in ongoing studies include mosapride and prucalopride.

Levosulpiride, the levorotatory enantiomer of sulpiride, is a D_2 receptor antagonist and weak 5-HT_4 receptor agonist. It has been shown to improve both gastric emptying times and symptoms of gastroparesis in diabetics; however, there was no significant correlation between improved gastric emptying and symptom improvement.[136] Another study in non diabetic patients with delayed gastric emptying and dyspeptic symptoms demonstrated that levosulpiride and cisapride were equally affective in accelerating gastric emptying, but levosulpiride was better than cisapride at improving symptoms of dyspepsia.[137] Furthermore, levosulpiride was shown to improve glycaemic control and gastric emptying when given to insulin-dependent diabetic patients over a 6-month period.[33]

CCK, a gastrointestinal protein released from intestinal-I cells in response to nutrient components including amino acids and fatty acids, is thought to play a role in gastric motility. CCK slows gastric emptying by a negative feedback mechanism and stimulates the perception of early satiety.[88] Loxiglumide is a 5-oxo-pentanoic acid derivative that displays specific, competitive antagonism of the CCK-1 receptor. It has been shown to accelerate gastric emptying in humans by increasing both the frequency and amplitude of contractions in the distal stomach.[138] The role of CCK-1 receptor antagonists in the treatment of gastroparesis is still under investigation.

Opiate receptor agonists and antagonists have been studied as possible treatments for gastroparesis. Unfortunately, the data on such drugs is limited and somewhat conflicting. A recent study of fedotozine, a peripheral κ-opioid receptor agonist known to accelerate gastric emptying in animals, failed to demonstrate any effect of the drug on gastric emptying in patients with diabetes.[139] Fedotozine has been shown to decrease the perception of gastric distension leading to postprandial fullness and pain; therefore, it may prove useful for treating disorders of visceral hypersensitivity like IBS or non-ulcer dyspepsia.[140-142] In one study, trimebutine, an agonist of μ-, κ- and δ-opioid receptors, accelerated gastric emptying in patients with non-ulcer dyspepsia but failed to have a positive effect on symptoms.[143]

7. Conclusion

Symptoms of delayed gastric emptying may affect up to 50% of patients with diabetes. Despite increased awareness and advances in diagnosing diabetic gastroparesis, our understanding of the pathophysiology and currently available treatments of the disorder are limited. Research is underway to explore the mechanisms that cause disordered gastroduodenal motility. Emphasis is being placed not only on designing prokinetic agents but also on developing drugs that help coordinate gastric motility or alter visceral hypersensitivity. Perhaps as the pathophysiology of diabetic gastropathy is better understood, more effective treatment modalities can be developed to treat this chronic, often debilitating disorder.

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