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Diabetic Gastroparesis
Diagnosis and Management

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Abstract

Gastric emptying is frequently abnormal in patients with long-standing type 1 and type 2 diabetes mellitus. Symptoms commonly associated with disordered gastric emptying include nausea, vomiting, bloating and epigastric pain, while patients are also at risk of malnutrition, weight loss, impaired

drug absorption, disordered glycaemic control and poor quality of life. Although often attributed to the presence of irreversible autonomic neuropathy, acute hyperglycaemia represents a potentially reversible cause of gastric dysfunction in diabetes. Scintigraphy represents the gold standard for measuring gastric emptying. The management of diabetic gastroparesis is less than optimal, partly because the pathogenesis has not been clearly defined. Treatment approaches include dietary modification and optimization of glycaemia, and the use of prokinetic drugs, while novel therapies such as gastric electrical stimulation are the subject of ongoing investigation.

Gastroparesis refers to the presence of delayed gastric emptying occurring in the absence of mechanical obstruction.[1] In the US, gastroparesis-related hospitalizations doubled from 1995 to 2004.[2] The most common disease complicated by gastroparesis is diabetes mellitus,[3] which accounted for about one-third of patients with gastroparesis in a large study from a tertiary referral centre.[1] Gastroparesis often occurs in patients with longstanding diabetes and concomitant microvascular complications such as retinopathy, neuropathy and nephropathy.[4] Most patients with gastroparesis present with upper gastrointestinal symptoms, such as nausea, early satiation, postprandial fullness, vomiting and bloating,[5,6] although the correlation of symptoms with delayed gastric emptying is relatively weak[7] and some patients are asymptomatic. Furthermore, the contribution of disordered gastric emptying to impaired glycaemic control in insulin-treated diabetic patients (type 1 and type 2) has been generally underestimated. The aim of this article is to review the prevalence, pathophysiology, diagnosis and management of diabetic gastroparesis.

1. Prevalence of Impaired Gastric Emptying in Diabetes Mellitus

Gastric motor dysfunction in diabetes was first reported in 1937 when, on radiographic examination, stomach contractions were observed to be "slow, lack vigour and die out quickly" compared with those in healthy subjects.[8] More recently, it has been demonstrated that gastric emptying is delayed in 30–50% of long-standing type 1 and type 2 diabetic patients (figure 1),[7,9-11] with the prevalence about equal in both types of diabetes.[12] Gastric emptying of nutrient liquid has been reported to be abnormally rapid in 'early' type 2 diabetes,[13] although this has not been observed consistently,[14] and rapid emptying is uncommon in type 1 diabetes.[15]

1.1 Physiology of Gastric Emptying

Gastric emptying depends on the integration of motor activity in the proximal stomach, antrum and pylorus with the proximal small intestine, and is under control of electrical signals ('slow waves') originating from the interstitial cells of Cajal (ICCs) in the circular and longitudinal muscle layers. The proximal stomach

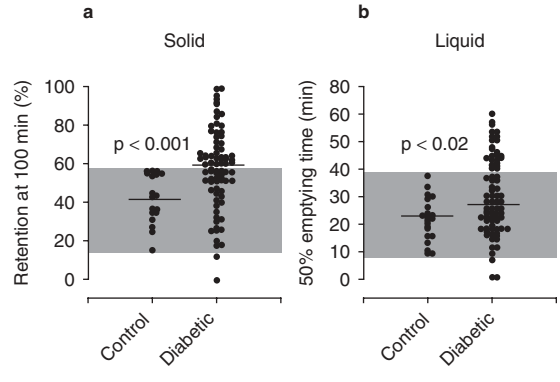

Fig. 1. Gastric emptying, expressed as retention of (**a**) a solid meal (100 g minced beef) at 100 minutes, and (**b**) 50% emptying time of a nutrient liquid (10% dextrose 150 mL), in 86 patients with diabetes mellitus (66 type 1, 20 type 2) and 20 healthy volunteers as controls. The range of gastric emptying rates in the healthy controls is represented by the shaded area (reproduced from Jones et al.,[11] by permission of the Society of Nuclear Medicine).

receives and stores ingested food, while the distal stomach grinds solids into small particles prior to emptying into the small intestine. In the fasting state, gastric motility undergoes a cyclical pattern, termed the 'migrating motor complex', consisting of phase 1 (~40 minutes; quiescence), phase II (~50 minutes; irregular contractions) and phase III (~5–10 minutes; regular contractions at 3 per minute).[16] Indigestible solids are emptied into the small intestine mainly during phase III. Fasting motility is converted by meal ingestion to a postprandial pattern, characterized by irregular activity in the antrum. During meal consumption, the proximal stomach undergoes 'receptive' relaxation and a more prolonged 'accommodative' relaxation to store ingested volume without a substantial increase in pressure.[17] Postprandial gastric motility also involves an increase in tonic and phasic pyloric pressures. The rate of gastric emptying is dependent on antral and duodenal contractions overcoming pyloric resistance, to empty food into the small intestine predominantly in a pulsatile fashion.

The rate of gastric emptying varies with the physical texture, particle size, fat, fibre and energy content of a meal.[18] Non-nutrient liquids empty rapidly in an overall monoexponential pattern.[18] With increasing caloric content, liquids empty in a linear fashion at the same rate as homogenized solid.[18] When liquid is consumed with solid, the liquid empties preferentially. Solids are stored in the proximal stomach (corresponding to an initial lag phase) before being redistributed to the antrum to be ground into small particles (<2 mm in diameter), prior to emptying.[18]

Gastric motility in healthy individuals is modulated by a complex set of neural and hormonal signals. The stomach and intestine are innervated by the enteric nervous system, distributed in the gastric wall, as well as extrinsic autonomic nerves, in parasympathetic (predominantly vagus nerve) and sympathetic divisions. Exposure of the small intestine to nutrient induces feedback to slow gastric emptying by relaxing the fundus, suppressing antral motility, and augmenting pyloric contractions.[16] This feedback inhibition is dependent on the length of intestine exposed to nutrient and is regulated by gut hormones including glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK) and peptide YY.[16]

1.2 Gastric Motor and Sensory Dysfunction in Diabetes

Delayed gastric emptying can potentially result from disordered function of the proximal stomach, antrum, pylorus and duodenum, or from incoordination of motor activity between different parts of the stomach. Impaired function of the proximal stomach has been found in patients with type 1 diabetes, with a reduced fasting fundic tone and impaired accommodation to nutrient ingestion.[19,20] In the distal stomach, infrequent or low amplitude contractions of the antrum have been observed,[21] as well as incoordination between the antrum and duodenum.[22,23] Prolonged and excessive tonic and phasic contractions of the pylorus have been documented in some patients.[24] There is also an increased prevalence of dysrhythmias of the gastric slow wave in diabetes, either abnormally fast (tachygastria) or slow (bradygastria),[25] although the association with delayed gastric emptying is imprecise.[26] In summary, the motor dysfunctions observed in diabetic gastropathy are heterogeneous, which could explain the mixed success of existing treatments, and may have implications for the need to tailor therapy to individual patients. Furthermore, most studies evaluating disordered gastric function in diabetes have not been done during euglycaemia, so the contribution of a potentially reversible component of motor dysfunction attributable to acute hyperglycaemia, as discussed in section 2.2, cannot be determined.

The presence of delayed gastric emptying does not appear to fully explain upper gastrointestinal symptoms, as discussed previously.[7] Several studies have evaluated perceptions of proximal gastric distension in diabetic patients, and have reported these to be increased when compared with healthy controls,[20,27,28] implying that visceral hypersensitivity potentially contributes to the aetiology of gastrointestinal symptoms in patients with diabetes.

2. Pathogenesis of Diabetic Gastroparesis

The pathogenesis of gastroparesis is poorly understood but appears to be multi-factorial. Many recent insights have been gained from examination of gastric tissue in animal models and humans with diabetes, while potentially reversible alterations in gastric motor function can occur with acute variations in the blood glucose concentration.

2.1 Anatomical and Functional Observations

While irreversible autonomic neuropathy has been regarded widely as the underlying cause of gastroparesis, recent evidence indicates a heterogeneous picture, with a range of fixed pathology and potentially reversible functional abnormalities. Animal models of diabetes have shown deficiencies of inhibitory neurotransmission, reduced numbers of ICCs, decreased extrinsic autonomic neuron numbers and apoptosis of enteric neurons.[29] Diabetic rodents exhibit pathologically distinctive dystrophic axons and dendrites in sympathetic ganglia without neuronal loss,[30] and these abnormalities can be reversed by exogenous insulin or pancreatic islet transplantation.[31] In the non-obese diabetic mouse model, gastric ICCs are dependent on both insulin and insulin-like growth factor-1,[32] and deficiency of these results in ICC depletion.[33] Loss of neuronal nitric oxide synthase expression within myenteric neurons is associated with dysfunction of the antrum and pylorus in diabetic animals.[34,35]

Evaluation of gastrointestinal autonomic function in humans is difficult, and tests of cardiovascular autonomic function are widely used as a surrogate marker. However, the correlation between disordered motility and abnormal cardiovascular autonomic function in diabetic patients is weak,[36] suggesting that autonomic neuropathy is unlikely to be the sole explanation for diabetic gastropathy. Recent studies of tissue from humans with gastroparesis undergoing surgical procedures have provided useful information about the pathogenesis of this condition. Documented changes include loss of neurons in the myenteric plexus of the stomach,[37] while absent or decreased ICCs have been found in about one-third of patients with diabetic or idiopathic gastroparesis, correlating with abnormalities of gastric slow waves.[38] There may be a preferential loss of inhibitory neurotransmission,[39] although changes are heterogeneous when different patients with gastroparesis are compared. Some patients also have abnormalities of gastric smooth muscle, with fibrosis of the muscle layer[39] and inclusion bodies within myocytes[40] evident in some reports.

2.2 Effects of Hyperglycaemia

Regardless of the presence of fixed pathological changes in diabetes, acute variations in blood glucose levels have a major impact on gastric motor function in both healthy subjects and diabetic patients.[41] In patients with diabetes, marked hyperglycaemia (16–20 mmol/L) leads to prolongation of the lag phase and half emptying time of solids and liquids, increasing the proportion of patients in the 'gastroparetic' range when compared with euglycaemia (5–8 mmol/L).[42] Even in the physiological postprandial glycaemic range, the rate of gastric emptying is slower at a blood glucose of 8 mmol/L than 4 mmol/L in both healthy subjects and patients with uncomplicated type 1 diabetes.[43] In contrast, insulin-induced hypoglycaemia accelerates gastric emptying, even in type 1 patients with gastroparesis.[44-46] Acute hyperglycaemia is associated with reduction of fundic tone, suppression of antral waves, increased pyloric contraction[41] and induction of abnormal gastric electrical rhythms.[47,48] Hyperglycaemia also increases the perception of gastrointestinal symptoms in patients with diabetes.[44,49] However, the long-term effects of high blood glucose concentrations on gastric motor and sensory function are not known. The effects of variations in glycaemia on gastric emptying in type 2 diabetes are less well documented than for type 1, although cross-sectional data imply similar effects in this group.[50]

3. Clinical Presentation

Disordered gastric motility in diabetes is associated with upper gastrointestinal symptoms, poor

drug absorption, impaired glycaemic control, malnutrition, poor quality of life and a high rate of hospitalization.[51,52] Gastric bezoar formation is a rare complication of delayed gastric emptying in diabetic gastroparesis,[53] probably reflecting the reduction in gastric phase III activity.[54]

The prevalence of gastrointestinal symptoms, such as fullness, postprandial nausea, vomiting, abdominal pain and bloating,[5,6] is greater in patients with diabetes compared with nondiabetic groups,[55] although the presence of symptoms correlates poorly with the rate of gastric emptying; only postprandial fullness appears to be a significant predictor of delayed gastric emptying of solids.[56] Gastrointestinal symptoms seem to be more common in those with worse chronic glycaemic control as assessed by glycated haemoglobin[55,57] and occur more frequently in patients with markers of psychological disorders.[58,59]

The rate of gastric emptying regulates the delivery of carbohydrate and other macronutrients to the small intestine, and therefore has a major impact on postprandial blood glucose. Variations in the rate of gastric emptying account for 35% of the variance in the initial rise of blood glucose after a 75-g oral glucose load, in both healthy volunteers and type 2 diabetic patients.[14,60] Even minor changes of initial rate of carbohydrate delivery to the small intestine can have a substantial impact on glycaemia.[61,62] Thus, dietary and pharmaceutical interventions that modify gastric emptying can potentially affect postprandial glycaemia in patients with diabetes. Accelerating gastric emptying with erythromycin increases postprandial blood glucose concentrations, while slowing emptying with morphine reduces the postprandial glycaemic response in patients with type 2 diabetes.[63] Similarly, the insulin dose to sustain normoglycaemia after a standard meal is substantially less during the first 2 hours of the postprandial period in patients with type 1 diabetes who have gastroparesis than those without.[64] Indeed, delayed gastric emptying has recently been documented as an important cause of otherwise unexplained hypoglycaemia in insulin-treated patients (of which an increasing proportion have type 2 diabetes) – a phenomenon that has been termed 'gastric hypoglycaemia'.[65,66] Therefore, it is important to match the rate of carbohydrate delivery into the small intestine with the action of exogenous insulin; this may potentially entail accelerating gastric emptying so that nutrient delivery occurs in a more predictable fashion. In contrast, in patients with type 2 diabetes not treated with insulin, slowing the absorption of nutrients is often beneficial for glycaemic control as long as symptoms do not arise. An increase in soluble fibre,[67] adding the non-absorbable polysaccharide, guar gum,[68] or giving fat before,[69] or with,[70] a carbohydrate-containing meal all improve blood glucose acutely by slowing the emptying of carbohydrate. Indeed, slowing gastric emptying is the predominant mechanism by which GLP-1 and its analogues, such as exenatide, reduce postprandial hyperglycaemia in patients with type 2 diabetes managed by diet and/or oral hypoglycaemic drugs.[71,72]

Delayed gastric emptying also influences the delivery and absorption of orally administered drugs in the small intestine, generally resulting in later or fluctuating maximal serum concentrations.[73] This is particularly important when a rapid onset of drug action is required and has been documented with oral hypoglycaemic drugs.[74] Drugs with longer half-lives are less likely to be affected.[54]

4. Diagnosis

Upper gastrointestinal symptoms suggestive of gastroparesis in diabetic patients should be investigated to exclude other causes, and to ascertain whether gastric emptying is indeed delayed. Acute, reversible disorders of gastrointestinal function due to:

- drugs (e.g. anticholinergics, calcium channel antagonists, opiates, levodopa, octreotide, cannabis and alcohol),
- electrolyte or metabolic disturbance (hyperglycaemia, hypokalaemia, hypomagnesaemia, hyperthyroidism, hypothyroidism, hypopituitarism, Addison's disease),
- viral infection (gastroenteritis, herpes zoster),
- postoperative ileus and
- critical illness

must be excluded.[10] Other disorders that result in similar symptoms, including peptic ulcer disease, gastroesophageal reflux disease, gastric cancer, pancreatic or biliary disease, and gastric outlet or mechanical small bowel obstruction,[1] need to be excluded with appropriate investigations, such as endoscopy and contrast radiology studies. Diabetic gastroparesis also needs to be differentiated from chronic gastric stasis as a result of previous surgery, metabolic and endocrine disease (liver or renal disease, thyroid dysfunction), CNS disease (brain tumour, stroke or trauma), malignancy and HIV infection.[54]

4.1 Methods for Measuring Gastric Emptying

Evaluation of solid emptying is more sensitive than that of low-nutrient liquid or semi-solid meals in the diagnosis of gastroparesis,[75] and there is debate as to whether liquid emptying should also be studied; some patients will only exhibit delay of the latter. Gastric emptying can be affected acutely by many factors, including medications, smoking and blood glucose concentration.[76,77] Medications that may influence gastric emptying should be withdrawn for 48–72 hours prior to the test (or for the half-life of the drug),[77] smoking should be avoided on the test day,[78] and the blood glucose concentration should be monitored and should ideally be below 10 mmol/L at the beginning of the test.[78] Failure to demonstrate delayed gastric emptying need not imply that symptoms are not attributable to 'diabetic gastropathy', of which abnormal visceral sensation may be a component, as discussed in section 1.2, but does help guide the choice of drug therapy.

4.1.1 Scintigraphy

Scintigraphy is regarded as the 'gold standard' for measurement of gastric emptying of solid and nutrient liquid meals. After meal consumption, a gamma camera is used to monitor scintigraphic counts in various 'regions of interest'. The parameters that may be derived include the half-emptying time of solids and liquids, lag phase for solids and intragastric distribution of a meal (proximal vs distal retention). The percentage of meal retention at the end of each hour may be more accurate than the half emptying time.[78] It has been suggested that extending the study time up to 4 hours increases the sensitivity for diagnosis of delayed gastric emptying compared with the retention at 2 hours,[79] although meal retention at 3 hours correlates well with the 4-hour value.[80] Intragastric distribution of the meal is frequently abnormal in diabetes,[11] but meal retention in the whole stomach is used as the diagnostic measure. The standardization of the meal between centres has been a major limitation, rectified to some extent by recent 'consensus' guidelines, which recommend a low-fat, egg-white meal labelled with ^{99m}Tc sulfur colloid, and consumed with jam and toast as a sandwich, with a glass of water.[78] Despite these guidelines, some issues are unresolved, including whether gastric emptying of nutrient liquid should also be measured. Although criteria of 'severity' based on the degree of retention at 4 hours were suggested in the 'consensus' guidelines, these do not include any measure of symptoms and therefore may not be the most appropriate guide.

4.1.2 Other Measurement Techniques

The limitations of scintigraphy are that patients are exposed to a modest dose of radiation, and the test is relatively expensive and confined to specialist centres. This has made the use of breath tests an appealing option, at least as a screening tool for delayed gastric emptying. Breath tests employ non-radioactive ^{13}C-acetate or -octanoic acid as a label and are safe, easy to administer and inexpensive.[81-83] After ingestion, the labelled meal passes through the stomach to the small intestine, where the ^{13}C-acetate or -octanoate is absorbed, metabolized into $^{13}CO_2$ in the liver and exhaled via the breath, with the rate of gastric emptying being the rate-limiting step. Breath samples are collected and analyzed for $^{13}CO_2$ by mass spectrometry.[84] Breath tests correlate well with scintigraphy in healthy volunteers and patients with diabetes,[85,86] with a sensitivity and specificity of ≥80% for detecting delayed gastric emptying.[87] This method does assume normal intestinal absorption and pulmonary excretion; therefore, further validation is required in

various patient groups. It is not valid in those patients with markedly delayed gastric emptying.

Ultrasonography is noninvasive and 2-dimensional ultrasound has been validated for measuring the emptying of liquids or semi-solids, as well as antral motility and transpyloric flow.[88] 3-Dimensional ultrasound offers more comprehensive imaging of the whole stomach.[89-92] However, obesity and abdominal gas, together with the need for an experienced operator, limit the wide use of ultrasonography.

Electrogastrography noninvasively measures gastric myoelectrical activity by placing surface electrodes on the epigastric skin.[25] The normal frequency of the gastric slow wave is about three cycles per minute. As discussed in section 1.2, gastric dysrhythmia is often associated with disordered gastric emptying and symptoms,[93] but the relationship between symptoms and dysrhythmia is variable, and electrogastrography should be viewed as a research tool at present.

A barium meal has a place in excluding mucosal lesions or obstruction, but has no role in quantifying gastric emptying.

5. Treatment

Treatment of patients with diabetic gastroparesis aims to relieve gastrointestinal symptoms, improve nutritional status, enhance quality of life and optimize glycaemic control. The latter represents a major goal in the management of diabetes, in order to reduce the risk of micro- and macrovascular complications.[94] Careful attention should be paid to improving glycaemic control, which has the capacity to affect gastric motility, as discussed in section 2.2. Patients with type 2 diabetes may need insulin therapy rather than oral medication, while patients with type 1 diabetes may benefit from an insulin pump to optimize blood glucose control.[95] Patients with unexplained hyperglycaemia or hypoglycaemia should be screened for delayed gastric emptying, in addition to those with upper gastrointestinal symptoms. Patients with severe symptoms may require hospitalization to stabilize their fluid and electrolyte status and provide nutritional support. Many aspects of treatment for gastroparesis have not been evaluated in well designed controlled trials, and this represents a major limitation.

5.1 Dietary Management

There have been no published studies evaluating the effects of dietary modification in diabetic gastroparesis.[96] Since fibre and fat in particular have the potential to slow gastric emptying, a low-fat, low-fibre diet is generally recommended. Frequent (4–6 per day), small-volume meals are also advocated,[97] with an increased percentage of nutrients in liquid form, as gastric emptying of liquids is often less affected than that of solids.[75]

5.2 Pharmacological Interventions

Most patients with gastroparesis require pharmacological therapy to relieve symptoms and/or accelerate gastric emptying. Given the weak correlation between the presence of symptoms and the degree of impairment of emptying, it is not surprising that the improvement of gastric emptying is not closely related to the relief of gastrointestinal symptoms during treatment.[98] Prokinetic agents, including erythromycin, metoclopramide and domperidone, are most commonly used in the treatment of diabetic gastroparesis (table I).[95] Prokinetic drugs tend to improve gastric emptying and/or symptoms in a dose-dependent fashion, although their mechanisms of action are diverse. The acceleration of gastric emptying is typically greater when emptying is more delayed at baseline, and can be attenuated during acute hyperglycaemia, at least for erythromycin and cisapride.[99,100] Some prokinetic drugs have additional effects such as central antiemetic properties or suppression of visceral sensation. The choice of medication is dependent on potential adverse effects, the nature of the symptoms and concomitant diseases, drug availability and the personal preference of the clinician. In a systematic analysis of clinical trials of prokinetic agents, erythromycin seemed to have the strongest effect on gastric emptying when compared with domperidone, cisapride or metoclopramide,[101] whereas erythromycin and domperidone appeared to be most effective in

Table I. Prokinetic drugs used in the treatment of diabetic gastroparesis[95]

Drug	Mechanism	Route	Dose (mg)	Adverse effects
Erythromycin	Motilin agonist	IV, PO	50–250 (tid or qid)	Nausea, vomiting, abdominal pain
Metaclopramide	D_2 receptor antagonist 5-HT_4 receptor agonist 5-HT_3 receptor antagonist	PO, SC, IM, IV	10 (tid or qid)	Dystonia, tardive dyskinesia, sedation, hyperprolactinaemia
Domperidone	D_2 receptor antagonist	PO	10–20 (bid or qid)	Hyperprolactinaemia
Cisapride	5-HT_4 receptor agonist 5-HT_3 receptor antagonist	PO	10–20 (bid or qid)	Arrhythmia, abdominal pain, diarrhoea

5-HT = serotonin; **bid** = twice daily; **D** = dopamine; **IM** = intramuscular; **IV** = intravenous; **PO** = oral; **qid** = four times daily; **SC** = subcutaneous; **tid** = three times daily.

relieving symptoms.[101] Nevertheless, there are few head-to-head comparisons of drugs, and little information about combinations of agents. Furthermore, well designed, double-blind, controlled trials generally report more modest effects than open-label or single-blind studies.[101]

5.2.1 Erythromycin

Erythromycin, a motilin receptor agonist, is one of the most potent gastrokinetic drugs when given by the intravenous route;[102,103] therefore, it has been used as first-line therapy for hospitalized patients with severe gastroparesis.[104] Administration of erythromycin is associated with increased antral contractions and accelerated emptying of solids and liquids.[102,105] Oral erythromycin suspension results in an improvement of gastric symptoms,[106] although in the long term, tolerance frequently develops as a result of the downregulation of motilin receptors.[105]

Gastrointestinal symptoms, such as abdominal cramps, nausea and vomiting are common adverse effects of erythromycin, while the drug can prolong the QT interval, with a consequent risk of sudden death,[107] especially when given concurrently with cytochrome P450 (CYP) 3A inhibitors.[107] Alteration of intestinal flora and fungal infections are further concerns with long-term use. Other macrolides, such as clarithromycin and azithromycin, have been reported to have prokinetic properties, but their potential has not been evaluated sufficiently in clinical trials.[108,109]

5.2.2 Metoclopramide

Metoclopramide acts peripherally and centrally as a dopamine D_2 receptor antagonist and stimulates smooth muscle contraction by release of acetylcholine from enteric cholinergic neurons (serotonin 5-HT_4 receptor agonist activity).[110] The former is associated with an antiemetic effect, but also entails a risk of adverse effects, including extrapyramidal reactions and hyperprolactinaemia. Metoclopramide in pill or liquid suspension forms, and as a suppository in some countries, is suitable for outpatients with gastroparesis. Subcutaneous administration provides comparable plasma concentrations to the intravenous route and is a useful alternative in patients who cannot tolerate oral medications.[111] Metoclopramide appears less effective than cisapride in improving the rate of gastric emptying, but its antiemetic effects provide significant symptom relief.[112] Tardive dyskinesia can occur in about 1% of patients with long-term use,[113] and may be irreversible.

5.2.3 Domperidone

Domperidone, acting on peripheral D_2 receptors, possesses similar antiemetic and prokinetic effects to metoclopramide. However, domperidone is not associated with CNS adverse effects because of its poor penetration of the blood-brain barrier.[104] Therefore, it is safe for use in Parkinson's disease, but like metoclopramide, its use can be complicated by hyperprolactinaemia.[110] Domperidone may be more effective than cisapride in children with diabetic gastroparesis,[114] whereas the combination of domperidone and cisapride was superior to cisapride alone in accelerating gastric emptying and improving gastrointestinal symptoms in patients with functional dyspepsia.[115] Domperidone is available in the US through the investigational new drug programme.

5.2.4 Cisapride

Cisapride used to be the first-line oral prokinetic agent in the treatment of gastroparesis, providing long-term symptomatic relief and improvement of gastrointestinal motility.[116,117] It mainly acts on the 5-HT_4 receptors of the myenteric plexus to stimulate smooth muscle contraction, and accelerates solid and liquid emptying from the stomach.[118] It also acts as a 5-HT_3 receptor antagonist, providing an antiemetic action. The effects on gastric emptying and improvement in symptoms appear to be sustained with long-term use.[119,120]

Cisapride has been withdrawn from most markets because of its potential to prolong the QT interval, which has been associated with lethal ventricular arrhythmias.[121] Predisposing factors include high dosages (80 mg/day) and combination with CYP3A inhibitors.[95] Cisapride is still available in many countries under restricted access arrangements, requiring close patient monitoring for ECG abnormalities and other risk factors. The maximum daily dose of cisapride should be limited to 40 mg, and medications that delay cisapride metabolism such as azole antifungals (e.g. ketoconazole) and macrolide antibacterials (e.g. erythromycin), or which prolong the QT interval, should be avoided.[121]

5.2.5 Antiemetics

Antiemetic medications may be beneficial in relief of symptoms, particularly when nausea and vomiting are predominant, even though most do not accelerate emptying and some can delay it. The most common antiemetic medications include 5-HT_3 receptor antagonists (e.g. ondansetron), dopamine antagonists (e.g. prochlorperazine), tricylic antidepressants (e.g. amitriptyline or nortriptyline), cannabinoids (dronabinol) and antihistamines (cyclizine, dimenhydrinate and meclozine), while there are anecdotal reports regarding the neurokinin NK_1 antagonist aprepitant.[122]

5.2.6 Other Motilin Agonists

Motilin is an endogenous hormone that accelerates gastric emptying by induction of phase III-like contractions,[123] but its therapeutic use is limited by the need for intravenous administration and a short half-life. Orally available motilin analogues have therefore been developed. These include alemcinal (ABT–229), which accelerated gastric emptying acutely,[124] but failed to relieve symptoms in diabetic patients with gastroparesis, possibly as a result of tachyphylaxis.[125,126] Unlike alemcinal, mitemcinal induces sustained acceleration of gastric emptying over 4 weeks in diabetic gastroparesis,[127] and shows modest benefit compared with placebo in terms of symptom relief.[128]

5.2.7 Itopride

Itopride acts as a D_2 receptor antagonist and an ACE inhibitor, and does not cross the blood-brain barrier.[129] One trial reported symptomatic benefit in patients with functional dyspepsia,[130] but this was not confirmed in a larger study.[131] Furthermore, itopride (200 mg three times daily for 7 days), had minimal effect on the gastric emptying of solids and liquids in patients with longstanding diabetes; only in those with delayed emptying at baseline did the improvement in liquid emptying reach statistical significance.[132] In this latter study, symptoms were not improved, but patients were not selected on the basis of being symptomatic.

5.2.8 Ghrelin

Intravenous infusion of ghrelin, an orexigenic hormone, accelerates gastric emptying in both diabetic patients and those with functional dyspepsia.[133,134] Ghrelin receptor agonists are in development and accelerate gastrointestinal transit in animal models of diabetes.[135]

5.2.9 Other Agents

Short- and long-term administration of levosulpiride, a D_2 receptor antagonist, is associated with accelerated gastric emptying and improvement in upper gastrointestinal symptoms in patients with diabetic gastroparesis;[136,137] however, the drug is not available outside Europe. Although the 5-HT_4 receptor agonist tegaserod improves gastric emptying, it has been withdrawn because of an excess of cardiac adverse events.[138,139] Sildenafil has been reported to accelerate gastric emptying in rodent models of diabetes,[34] but this has not been consistently

reported in patients with diabetic gastroparesis.[140,141] For a subset of patients, where abdominal pain is a major symptom, gabapentin and pregabalin might be useful agents,[142,143] but there are no controlled trials of these medications for this indication. The CCK-A receptor antagonist dexloxiglumide has been reported to reduce dyspeptic symptoms induced by nutrients in the small intestine.[144]

5.3 Physical Treatment

Several non-pharmaceutical treatments have been the focus of recent attention in the management of gastroparesis, including gastric electrical stimulation and intrapyloric injection of botulinum toxin.

5.3.1 Gastric Electrical Stimulation

Gastric electrical stimulation shows promise in the treatment of refractory gastroparesis. Two stimulation parameters, involving long pulses (low frequency/high energy) or short pulses (high frequency/low energy), have been investigated. Stimulation with long pulses delivers current at about three cycles per minute, and in patients with refractory gastroparesis can entrain the gastric slow wave and reverse gastric dysrhythmias, accelerate gastric emptying and improve symptoms.[145,146] However, an implantable device capable of delivering the required energy for this mode of stimulation is not currently available. Therefore, clinical research has focused on stimulation with short pulses, such as that approved by the US FDA, called Enterra™ therapy, delivering pulses at about 12 cycles per minute.[147-149] Enterra™ therapy is performed by inserting a pair of electrodes into the serosa of the greater curvature via laparoscopy or laparotomy;[150] percutaneous or oral endoscopic placement of electrodes is also feasible,[151-154] and could provide a method for identifying patients who will respond to a permanently implanted device.[151]

Enterra™ electrical stimulation has been reported to reduce the severity and frequency of symptoms such as nausea and vomiting, and to enhance quality of life,[155-158] with improvement maintained over 4 years[156] and with the potential to improve survival.[156,157] Patients with diabetic gastroparesis apparently respond better than those with idiopathic gastroparesis, whereas those with pain (as opposed to nausea and vomiting), or using narcotics at baseline, tend to respond poorly.[158]

The mechanism by which gastric electric stimulation acts is unclear. Acceleration of gastric emptying has not been consistently observed in all trials.[155] Stimulation of vagal afferents with increased thalamic activity, increased perception threshold to gastric distention,[159] and improvement in postprandial gastric accommodation have all been reported.[159]

Evaluation of the evidence for the efficacy of gastric electrical stimulation has been controversial.[160,161] While gastric electrical stimulation appears to be a promising therapy, a majority of trials have been open label, and more data from controlled trials are needed in order to recommend gastric electrical stimulation as a standard treatment for gastroparesis.

5.3.2 Intra-Pyloric Injection of Botulinum Toxin

In a manometric study from Mearin et al.,[24] a majority of patients with diabetic gastroparesis were found to have prolonged, excessive tonic contractions of the pylorus ('pylorospasm'). Botulinum toxin blocks the release of neuromuscular transmitter at cholinergic terminals[162] and is used widely for treatment of achalasia by injection into the lower oesophageal sphincter.[163] In uncontrolled series, involving patients with diabetic and idiopathic gastroparesis, injection of Botox® into the pylorus was associated with acceleration of gastric emptying and reduction in pyloric contractions, paralleled by relief of symptoms.[164-167] However, two recent sham-controlled trials, one in patients with predominantly idiopathic gastroparesis,[168] and the other with a large proportion of diabetic patients,[169] failed to show superiority of Botox® over saline in improving gastric emptying or symptoms.[168,169] Unfortunately, pyloric manometry was not carried out before or after injection in either study. Further evaluation is required before the therapy should be used widely.

5.3.3 Acupuncture

Acupuncture has been used for gastrointestinal complaints for thousands of years in China, with reported efficacy for symptom relief[170] and acceleration of solid gastric emptying in patients with diabetic gastroparesis in a sham-controlled study.[171] The underlying mechanisms are unclear and cannot be attributed to differences in hormones such as motilin, CCK or vasoactive intestinal peptide.[172] Further investigations are required to evaluate the benefits of acupuncture in patients with symptomatic diabetic gastroparesis.

5.4 Surgical Therapy

Most trials of surgical procedures for refractory gastroparesis are small, uncontrolled or retrospective, with very limited post-surgical follow-up. Therefore, these procedures should be regarded as a last resort, and should ideally be performed in centres with experience in managing such patients.[173] Gastrostomy may be performed to relieve nausea, vomiting, pain and bloating, whereas jejunostomy is indicated to maintain hydration, nutrition and glycaemic control.[173] Subtotal or complete gastrectomy and reconstruction is used as the last resort for severe refractory gastroparesis and revision of postoperative gastroparesis.[104] Pancreatic transplantation is reported to benefit diabetic patients with gastroparesis, with improvement in both gastric emptying and symptoms.[174]

6. Conclusions and Implications

The prevalence of gastroparesis associated with diabetes is likely to increase in the coming years. Patients may present with a wide spectrum of symptom severity or may be asymptomatic, but have disordered glycaemic control. Available therapeutic options are limited, and while there have been some promising developments, progress in the development of new medications is suboptimal. The pathogenesis of gastroparesis is complex and incompletely understood, and will need further investigation in order to provide more specific and effective therapy.

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