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Pathophysiology and Management of Diabetic Gastropathy

A Guide for Endocrinologists

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Abstract

Delayed gastric emptying is frequently observed in patients with long-standing type 1 and type 2 diabetes mellitus, and potentially impacts on upper gastrointestinal symptoms, glycaemic control, nutrition and oral drug absorption. The pathogenesis remains unclear and management strategies are currently suboptimal. Therapeutic strategies focus on accelerating gastric emptying, controlling symptoms and improving glycaemic control. The potential adverse effects of hyperglycaemia on gastric emptying and upper gut symptoms indicate the importance of normalising blood glucose if possible. Nutritional and psychological supports are also important, but often neglected. A number of recent pharmacological and non-

pharmacological therapies show promise, including gastric electrical stimulation. As with all chronic illnesses, a multidisciplinary approach to management is recommended, but there are few data regarding long-term outcomes.

Gastric emptying is delayed in ≈30–50% of outpatients with long-standing type 1 and type 2 diabetes mellitus,[1,2] and its importance in diabetes management is now being recognised.[3,4]

'Gastroparesis' refers to severely delayed gastric emptying, outside two standard deviations from the healthy mean, in the absence of mechanical obstruction.[1,3,5] In recent years, the term 'diabetic gastropathy' has emerged, to encompass not only delayed gastric emptying, but also the presence of upper gastrointestinal symptoms such as bloating, nausea and discomfort. However, it is recommended that the term not to be used in isolation, but rather be accompanied by a more detailed description of the symptoms and the magnitude of delay in gastric emptying, as the focus of management may differ accordingly.

Glycaemic control has often received less than adequate attention in the management of diabetic gastropathy. Acute hyperglycaemia not only contributes to delayed gastric emptying, but can exacerbate upper gastrointestinal symptoms.[1] Furthermore, hyperglycaemia potentially attenuates the effect of prokinetic drugs such as erythromycin.[6] Optimisation of glycaemic control is therefore important in the management of diabetes-related upper gastrointestinal motor and sensory dysfunction.

This article aims to provide clinicians with an overview of normal upper gastrointestinal motor and sensory function, together with the pathophysiology, clinical manifestations, investigations and treatments of diabetic gastropathy.

1. Regulation of Gastric Emptying

In health, gastric emptying results from the coordinated activity of the proximal and distal regions of the stomach, together with the upper small intestine.[3] An impairment of function of one region is usually compensated for by the others, so disordered emptying usually implies dysfunction of multiple gastroduodenal components.[3]

The timing of contractions of the distal stomach (antrum and pylorus) is controlled by an electrical slow wave generated by specialised pacemaker cells, the interstitial cells of Cajal, in the greater curvature of the stomach, which discharge at a rate of about three per minute.[1] This slow wave can be recorded from electrodes applied to the skin overlying the stomach, a procedure termed 'electrogastrography'. During fasting, the stomach and small intestine display cyclical activity termed the 'migrating motor complex' (MMC).[7,8] The MMC is divided into three phases, with a total duration of ≈100 minutes.[9] Phase I (≈40 minutes) is characterised by motor quiescence, phase II (≈50 minutes) by irregular contractions, and phase III (≈5–10 minutes) by regular, high amplitude contractions occurring at the maximum rate of three per minute in the stomach and 10–12 per minute in the small intestine.[9] The MMC functions as the 'intestinal housekeeper', which sweeps indigestible solids and bacteria aborally from the gastric antrum to the distal small intestine.[10] Ingestion of a meal interrupts the MMC, and produces a 'postprandial' pattern that aids the trituration and propulsion of chyme.[11]

The stomach empties at a relatively constant rate of 2–3 kcal/min, regulated by neural and hormonal feedback generated by exposure of the small intestine to nutrients.[1] Direct infusion of nutrients into the small intestine leads to relaxation of the gastric fundus, suppression of antral contraction, and stimulation of tonic and phasic pyloric motor activity (figure 1).[3] A number of hormones have been implicated in small intestinal feedback on gastric motility, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY 3-36 (PYY), amylin and ghrelin.[11,12] The neural feedback mechanisms are less well understood, but for fundic relaxation at least, there is strong evidence for the

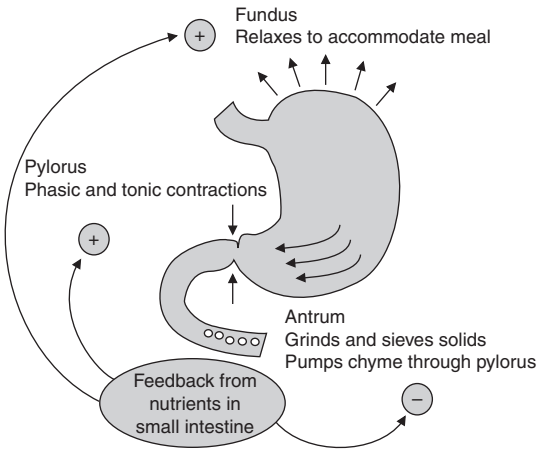

Fig. 1. Motor control of normal gastric emptying. Nutrient-gut interaction in the small intestine sets off neurohormonal feedback mechanisms that slow the rate of gastric emptying to ≈2–3 kcal/min (reproduced from Rayner and Horowitz,[3] with permission). + indicates positive feedback; − indicates negative feedback.

involvement of nitric oxide, the major inhibitory neurotransmitter in the gut.[13-15]

The overall pattern of gastric emptying is dependent on the physical and chemical composition of a meal.[11] Solids empty relatively slowly in a linear pattern, after an initial lag phase; non-nutrient liquids empty rapidly in monoexponential fashion, but as the caloric content of liquids increases, emptying slows and approximates a linear pattern.[11,16] When liquids and solids are consumed together, liquids empty preferentially.[11] These different patterns of emptying reflect the requirement of solids to be ground into small particles before they empty,[9] and that there may be a varying degree of inhibitory feedback from the small intestine,[2] determined by the caloric load and the length of small intestine exposed to nutrient.[3]

Various abnormal patterns of upper gut motility are observed in patients with diabetes, including impairment of meal-induced relaxation of the gastric fundus,[17] excessive pyloric contractile activity,[18] reduced antral contraction, and impaired coordination between the antrum and the duodenum.[4] Diabetes is also associated with gastric dysrhythmias on electrogastrography (EGG): either slow (bradygastria), fast (tachygastria) or mixed.[19] However, the presence of gastric dysrhythmia, although common in patients with diabetes, is not necessarily associated with the rate of gastric emptying.[20] More sophisticated methods have recently been developed for measuring gastric dysrhythmia that may make the technique a more useful clinical tool.[21]

2. Pathogenesis of Diabetic Gastropathy

Studies of the pathogenesis of diabetic gastroparesis to date have been limited by small numbers and heterogeneous patient profiles. In animal models, diabetes has been associated with a wide range of reversible and irreversible pathology, including axonopathy of extrinsic autonomic nerves, loss of interstitial cells of Cajal, apoptosis of enteric neurons and loss of inhibitory neurotransmission.[4] A reduction in pyloric neuronal nitric oxide synthase (nNOS) levels has been reported in diabetic mice and is reversed by insulin.[22] More recently, gastric myopathy has been implicated in murine models of diabetes.[23] Not all of these have been observed in humans, but loss of interstitial cells of Cajal has been identified in patients with medically refractory gastroparesis,[24] while gastric myopathy was reported in a small group of patients with type 1 diabetes and intractable vomiting.[25] Among a group of gastric cancer patients, reduced densities of interstitial cells of Cajal, nNOS and substance P, were associated with the presence of diabetes.[26]

The degree of vagal axonopathy remains controversial in humans.[27-29] Diabetic gastroparesis is often attributed to irreversible autonomic neuropathy, based on the observation of similar symptoms in vagotomised patients.[30] This concept was reinforced by studies that demonstrated an association between delayed gastric emptying and abnormal cardiovascular autonomic function.[20,31-33] However, this association is weak and inconsistent.[1,34,35] In part, this may reflect the lack of specific tests for the assessment of gastrointestinal autonomic function, but also suggests that other mechanisms may be involved.[36,37]

Changes in blood glucose levels have reversible effects on motility in every region of the gastrointestinal tract.[2] Elevation of blood glucose from fasting (≈4 mmol/L) to normal (≈8 mmol/L) postprandial

levels slows gastric emptying in both healthy volunteers and patients with type 1 diabetes,[38,39] while marked hyperglycaemia (blood glucose 16–20 mmol/L) can substantially retard gastric emptying of solids and liquids in patients with type 1 diabetes, including those with established autonomic neuropathy.[40,41] On the other hand, insulin-induced hypoglycaemia (blood glucose 2.6 mmol/L) accelerates gastric emptying in patients with type 1 diabetes.[42] The slowing of gastric emptying induced by acute hyperglycaemia is associated with reduced tone of the proximal stomach,[43,44] inhibition of antral pressure waves,[45,46] stimulation of pyloric contractions[47] and induction of abnormal gastric electrical rhythms.[46,48] It remains to be established whether the response to hyperglycaemia is dependent on the rate of gastric emptying during euglycaemia, the degree of long-term glycaemic control, or intact autonomic nerve function.[1] Acute hyperglycaemia (blood glucose ≈15 mmol/L) also increases perception of upper gastrointestinal symptoms such as nausea and fullness, in both healthy volunteers[43,49-51] and patients with type 1 diabetes.[44,52]

Currently, there is an inadequate understanding of the mechanism(s) mediating the effect of hyperglycaemia on gastric emptying. Autonomic nerve dysfunction has been suggested as one potential mechanism. In animal models, glucose-responsive neurons have been demonstrated in the CNS[53] and the small intestine,[54] and acute hyperglycaemia causes reversible inhibition of vagal efferent activity.[55] Furthermore, autonomic nerve function is impaired by acute hyperglycaemia in healthy humans.[56] Insulin does not seem to be involved, as euglycaemic hyperinsulinaemia does not affect gastric emptying,[57] and the effects of hyperglycaemia are also observed in type 1 (insulin-deficient) patients.

3. Clinical Manifestations

Abnormal gastric emptying is clinically important because it is associated with poor glycaemic control, altered drug absorption, malnutrition, decreased quality of life and, in severe cases, recurrent hospitalisations with significant associated costs.[1,9,58,59] Gastroparesis is also now recognised as a risk factor for hypoglycaemia in insulin-treated patients.[60] Information regarding the natural history of diabetic gastroparesis is scarce, but available data suggest a relatively stable long-term course and no association with increased mortality.[11,61] Gastric bezoar is a well recognised but rare complication, which may occur as a result of a reduction in gastric phase III activity,[1,62] since the latter is responsible for the emptying of indigestible solids.

The prevalence of upper gastrointestinal symptoms among patients with both type 1 and type 2 diabetes has been reported to be higher than in the general community (up to 15%),[63,64] particularly affecting women,[65,66] and is associated with decreased quality of life [67,68] and psychological dysfunction,[68,69] independent of other diabetic complications.[1] Common symptoms include early satiation, postprandial fullness, epigastric pain, nausea, vomiting and weight loss.[6] However, only postprandial fullness and bloating have been shown to correlate with delayed gastric emptying,[35] suggesting that the aetiology of symptoms is multifactorial. Symptoms are usually most severe postprandially, but may persist long after food ingestion.[6] Conversely, some patients with delayed gastric emptying experience no upper gut symptoms.[3]

Other than disordered motility, gastrointestinal symptoms in diabetes could potentially be influenced by glycaemic control, psychological and demographic variables, autonomic neuropathy, visceral hypersensitivity, disordered gastric myoelectrical activity, and the use of medications.[1]

Little attention has been paid to the potential for orally administered drugs, which are largely absorbed from the small intestine, to be affected by disordered gastric motility. Therefore, delayed gastric emptying is of clinical significance where a rapid onset of drug effect is desired, including oral hypoglycaemic drugs.[70] Reduced or absent phase III activity could contribute to the problem, particularly for drugs not easily degraded in the stomach.[1] Nevertheless, steady-state concentrations for a majority of drugs are usually not substantially affected.[1]

3.1 Postprandial Glycaemia

The association between overall glycaemic control and diabetic microvascular and probably macrovascular complications, is now well established in both type 1[71,72] and type 2 [73] diabetes. The contribution of postprandial, as opposed to fasting, glycaemia to overall glycaemic control (indicated by glycated haemoglobin [HbA_{1c}]) is now being increasingly recognised.[4] Recent evidence in patients with type 2 diabetes indicates that postprandial hyperglycaemia is more closely associated with diabetic retinopathy and neuropathy than either fasting blood glucose or HbA_{1c}.[74] Postprandial glycaemia appears to be an independent risk factor for cardiovascular disease and associated mortality in both healthy and diabetic populations.[75,76] The 2-hour blood glucose level after oral glucose predicts cardiovascular and all-cause mortality better than fasting glucose or HbA_{1c},[77-79] and its predictive value persists even when the latter two indices are normal.[76,80,81] Lowering postprandial blood glucose concentrations, even at the expense of higher fasting glucose levels, can improve overall glycaemic control.[82]

The effect of acute hyperglycaemia on the motor and sensory function of the gastrointestinal tract, as well as its potential to inhibit the effects of prokinetic drugs such as erythromycin,[83] suggests that achieving good glycaemic control is an important goal in the management of diabetic gastroparesis. This can be achieved in several ways, with the main objective being to improve the coordination between nutrient absorption and insulin availability.[1,6] Many factors contribute to postprandial glycaemia, including gastric emptying, preprandial glucose levels, meal composition, small intestinal glucose absorption, gastrointestinal hormones, insulin secretion, hepatic glucose metabolism and peripheral glucose uptake.[1] Potential strategies to improve postprandial glycaemic control therefore include dietary modification, improving glucose utilisation (e.g. weight loss), optimisation of insulin or oral hypoglycaemic therapy and modulation of the rate of gastric emptying (figure 2). Specific discussion regarding exogenous insulin or oral hypoglycaemic therapy is beyond the scope of this article.

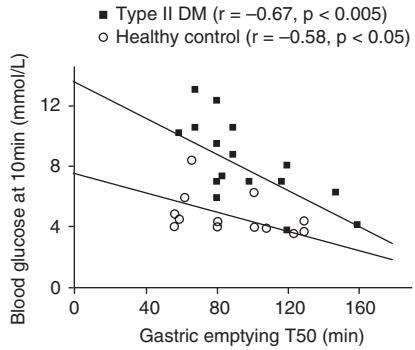

Fig. 2. Relationship between postprandial glycaemia and gastric emptying after oral glucose 75g in healthy volunteers and patients with type 2 diabetes mellitus (DM) [reproduced from Jones et al.,[84] with permission from the Society of Nuclear Medicine]. **r** = correlation co-efficient; **T50** = median time taken for 50% of liquid marker to empty from the stomach.

The rate of gastric emptying is now recognised as a major determinant of the postprandial glycaemic response and contributes about one-third of the variation in blood glucose after a meal.[85,86] Manipulation of gastric emptying, through either pharmacological or non-pharmacological means, has therefore been the subject of intense investigation over recent years. Dietary modifications that slow gastric emptying are beneficial in improving glycaemic control in patients with non-insulin-requiring type 2 diabetes. A high intake of dietary fibre, particularly the soluble type, has been shown to improve glycaemic control and decrease hyperinsulinaemia in patients with type 2 diabetes.[87] Similarly, when guar gum is added to a glucose drink, the postprandial glycaemic excursion is reduced in type 2 diabetes,[86] attributable to both slower gastric emptying and inhibition of small intestinal glucose absorption.

Slowing of gastric emptying by consuming oil before a meal,[88] or with morphine,[89] the amylin analogue pramlintide,[90-92] CCK-8,[93] the oral proteinase inhibitor POT-II,[94] and GLP-1 and its analogues (e.g. exenatide),[95,96] have all been shown to attenuate the postprandial rise in blood glucose. In fact, the predominant mechanism of GLP-1 analogues in lowering postprandial glucose is most likely to be by inhibiting gastric emptying, rather

than stimulating insulin secretion.[97] However, long term evidence that this approach will lead to a reduction in diabetes-related complications is not yet available.

The goal of modulating gastric emptying may differ substantially depending on whether a patient is treated with insulin. In patients with type 1 or insulin-requiring type 2 diabetes, gastric emptying may need to be either slowed or accelerated in order to improve the coordination between nutrient absorption and insulin action. Conversely, in patients with type 2 diabetes not requiring exogenous insulin, it is often advantageous to delay gastric emptying (provided this does not provoke gastrointestinal symptoms), as a result of the deficiency of the early phase of insulin secretion that is characteristic of this disorder.

Gastric emptying is occasionally abnormally rapid in diabetes; this occurs infrequently in patients with long-standing type 1 and type 2 diabetes,[98-100] but has been reported more often in patients with 'early' type 2 diabetes.[101,102]

4. Diagnosis and Evaluation

Diabetic gastroparesis is usually chronic and, indeed, has been defined arbitrarily as persisting for >3 months.[9] A slow onset of typical symptoms (early satiation, bloating, fullness, nausea, vomiting and weight loss) in a patient with long-standing diabetes, without features on history or physical examination to indicate another cause, is suggestive of diabetic gastroparesis. However, in all patients, it is mandatory that mechanical obstruction be excluded by way of upper gastrointestinal endoscopy, with or without other imaging such as a small bowel series, prior to embarking on empirical treatment.

Acute onset of upper abdominal symptoms in patients with diabetes should not automatically be attributed to gastroparesis, and efforts should be made to exclude other possible causes such as drugs, viral infection, electrolyte abnormalities and endocrine disorders.[3] Gastroparesis can also be a complication of malignancy, particularly with carcinomas of the pancreas, lung and breast (table I).[9]

4.1 Measurements of Gastric Emptying

Scintigraphy is regarded as the gold-standard test for evaluating gastric emptying.[1,3,6,103,104] Breath tests and gastric ultrasound are two promising non-invasive techniques to measure gastric emptying. They are simple (in the case of breath tests) and cheap to perform, and do not require exposure to ionising radiation.

4.1.1 Scintigraphy

Recent efforts have been made to improve a lack of standardisation between centres.[105,106] It has been suggested that a solid test meal alone is adequate, since solid emptying is more often delayed than that of liquids;[3,107] however, liquid emptying is often impaired, and ideally, emptying of both solids and liquids should be evaluated concurrently using a dual isotope technique.[1,3,108] Measurements should be carried out with blood glucose monitoring,[1] and should be continued for at least 2 hours

Table I. Causes of gastroparesis[3]

Acute
Drugs (anticholinergics, opiates, calcium channel antagonists, levodopa, alcohol, octreotide, nicotine, cannabis)
Electrolyte or metabolic disturbances (hyperglycaemia, hypokalaemia, hypomagnesaemia)
Viral infection (gastroenteritis, herpes zoster)
Critical illness
Postoperative state
Chronic
Diabetes mellitus
Idiopathic (including functional dyspepsia)
Surgery (vagotomy, heart or lung transplantation)
Gastro-oesophageal reflux disease
Achalasia
Connective tissue diseases (systemic sclerosis, polymyositis/dermatomyositis, amyloidosis, systemic lupus erythematosus)
Metabolic and endocrine causes (chronic liver or renal failure, hyper- or hypothyroidism, Addison's disease, porphyria)
Chronic idiopathic intestinal pseudo-obstruction
Neuromuscular diseases (head trauma, stroke, brain tumour, brainstem or spinal cord lesions, Parkinson's disease, myotonic and muscular dystrophies, autonomic degeneration)
Malignancy
Infection (HIV, Chagas' disease)
Anorexia nervosa
Irradiation

and possibly up to 4 hours in order to optimise specificity and accuracy.[109] Some have also advocated a simplified approach involving hourly scans for 4 hours, with gastric retention of >10% at 4 hours indicating gastroparesis.[105,110,111]

4.1.2 Breath Tests

Stable isotope breath tests usually employ ^{13}C-octanoic acid for labelling of solids[20,112-114] and ^{13}C-acetate for liquids.[115] Solid and liquid emptying can also be measured concurrently using a ^{14}C/^{13}C dual label technique.[115] Breath tests are based on the principle that gastric emptying is the rate-limiting step in the absorption of the ^{13}C-labelled meal, its metabolism in the liver and appearance in exhaled air as $^{13}CO_2$. Breath samples are usually collected for 4–6 hours.[112-116] Validation studies have generally indicated a high sensitivity and specificity in detecting delayed gastric emptying in both adults and children,[112,114-117] but further evaluation is needed in certain patient groups, such as those with previous gastrointestinal surgery, pancreatic insufficiency and liver or lung diseases, in whom gastric emptying may not be the only rate-limiting step in conversion of the substrate to $^{13}CO_2$. Furthermore, the test is not well validated in patients with markedly delayed gastric emptying. Nevertheless, it shows promise as a screening tool.

4.1.3 Ultrasonography

Conventional 2-dimensional ultrasound measures the cross-sectional antral area as an indicator of gastric emptying and correlates well with scintigraphy.[118-123] It is limited by being operator dependent and is not suited to evaluating solid meals or obese individuals. More recently, 3-dimensional ultrasound, with the aid of a magnetometer-based position and orientation measurement (POM) device, offers more comprehensive imaging of the whole stomach[124] and has been shown to correlate closely with scintigraphy in measuring gastric emptying.[125]

4.1.4 Summary

Despite the development of alternative modalities, scintigraphy remains the most accurate diagnostic tool. However, it is not recommended for screening all long-standing diabetes patients because of significant radiation exposure and uncertain impact on subsequent treatment (e.g. whether to treat someone who has markedly delayed gastric emptying but is otherwise well). Nevertheless, it is reasonable to perform such a test if either the diagnosis is suspected on clinical grounds or the test is performed to exclude abnormal gastric emptying as a cause of poor glycaemic control.

5. Management

The goals of treatment are to relieve symptoms, improve oral intake and nutritional status, and optimise glycaemic control.[1,3] In symptomatic patients, dietary modifications are usually inadequate and most will require medical therapy.[6]

Once a mechanical obstruction and other reversible causes are excluded, it is reasonable to commence an empirical trial of prokinetic therapy for 4 weeks, realising there is a substantial placebo response.[1,3,6,9] Those who do not improve, or relapse after cessation of therapy, should have a scintigraphic study to confirm the presence of delayed gastric emptying prior to embarking on further therapy.[1]

5.1 Dietary Modification

Products of fat digestion are well known to slow gastric emptying, while non-digestible solids may predispose to gastric bezoar formation. Therefore, small-volume, frequent meals, low in insoluble fibre and fat, are generally recommended, despite a lack of evidence to support this approach.[3,126] Thorough chewing, remaining upright for 1–2 hours postprandially and supplementation with multivitamins have also been advocated.[126] Increasing the proportion of energy provided as liquids rather than solids may be beneficial, as liquid emptying is delayed less often.[126] An elemental diet is limited by unpalatability,[11] but may be a short-term option, despite no evidence to support its superiority over polymeric feeding. Total parenteral nutrition is expensive and impractical, and is associated with potentially serious complications, including sepsis.

Indications for nutritional supplementation include weight loss of ≥10% during a period of 3–6 months, inability to maintain recommended bodyweight, and severe symptoms requiring hospitalisation or non-pharmacological interventions, e.g. nasogastric tube to relieve nausea and vomiting.[110,126]

5.2 Medical Therapy

The mainstay of pharmacological therapy involves the use of prokinetic agents. Efficacy appears to be greater when gastric emptying is more delayed.[1] The most commonly used prokinetic agents include metoclopramide, domperidone, erythromycin and cisapride.[1,3,6,9,104] The aim of therapy is to improve symptoms by accelerating gastric emptying, despite a poor correlation between the two.[6,104] Some prokinetic drugs have additional properties, including centrally mediated antiemesis,[127] proximal gastric relaxation,[128] suppression of visceral sensation[128] and improvement in gastric dysrhythmias.[3] Agents that provide the greatest symptom relief are therefore not necessarily the most potent in accelerating gastric emptying.[3] The main targets of pharmacotherapy include dopamine (D_2), serotonin (5-HT_4 and 5-HT_3) and motilin receptors.[3,6] D_2 and 5-HT_4 receptor activation has been shown to accelerate gastric emptying by stimulating acetylcholine release in the gastrointestinal tract.[129]

Most drugs are well tolerated, although adverse effects can occur, especially at high doses. Tachyphylaxis is a potential problem in the long-term use of erythromycin,[130,131] metoclopramide[6] and domperidone,[6] and is probably secondary to downregulation of receptors.

Studies of prokinetic medications in gastroparesis are limited by small sample sizes, relatively few 'prolonged' studies and heterogeneity among patient groups. In addition, there are few data directly comparing different prokinetic agents, but there is limited evidence that combination therapy may be more effective than a single agent.[132] It has been suggested that serotonergic drugs may be more potent than antidopaminergic agents for accelerating gastric emptying.[129] All of the four most commonly used prokinetic agents have been shown to improve symptoms and quality of life.[6,9,110] In general, it has been said that, compared with placebo, these agents increase gastric emptying by 25–72% and reduce symptom severity by 25–68%.[110]

5.2.1 Erythromycin

Erythromycin is a motilin receptor agonist and the most potent drug for accelerating gastric emptying when given acutely by the intravenous route (at doses <3 mg/kg).[133] Therefore, it is often used as the initial treatment for patients hospitalised with severe gastroparesis.[3] Of the oral formulations, a suspension appears to have greater efficacy than tablets.[134] Benefit is reported with long-term use, albeit with some limitations due to probable downregulation of motilin receptors.[130,131] Hyperglycaemia should be corrected, as it attenuates the effect of erythromycin on gastric emptying[83] and may have contributed to a loss of efficacy in some studies.[135] Long term exposure to an antibiotic represents an additional concern with prolonged therapy.[136] Other adverse effects include abdominal pain, vomiting, diarrhoea, headache, rash and prolongation of the cardiac QT interval with subsequent cardiac arrhythmias. Motilin agonists devoid of antibacterial properties appeared promising initially, but have been disappointing in clinical trials. For example, the motilin agonist alemcinal (ABT-229) failed to demonstrate any symptomatic improvement in patients with either type 1 diabetes[137] or functional dyspepsia,[138] with or without delayed gastric emptying. Another motilin agonist (KC 11458) showed no benefit on either gastric emptying or symptoms.[139] However, glycaemic control was not evaluated in these studies. Newer motilin agonists include atilmotin, which accelerates solid and liquid emptying in healthy subjects,[140] and limited data suggest mitemcinal (GM-611) improves gastric emptying in those with diabetic and idiopathic gastroparesis.[109]

5.2.2 Cisapride

Cisapride is the most intensively studied prokinetic drug,[1,9,141-145] and stimulates oesophageal[144] and small and large intestinal motility,[145] in addi-

tion to its effects on gastric emptying. Its use in gastroparesis from a variety of causes has been associated with prolonged symptomatic relief of >1 year.[141]

Before concerns about its cardiac arrhythmogenic effect, cisapride was the oral prokinetic of first choice. Its arrhythmogenic potential stems from its class III antiarrhythmic property, rather than its action on the 5-HT_4 receptors, leading to prolongation of the cardiac QT interval and concomitant risk of potentially lethal ventricular arrhythmias such as torsade de pointes.[129] Most reports of arrhythmia were associated with high doses (80 mg/day).[6,9] Cisapride has since been withdrawn from widespread use, but remains available in some countries through special access schemes. At greatest risk of arrhythmia are those with pre-existing QT prolongation, the young, and those receiving another drug that either prolongs the QT interval or slows the metabolism of cisapride via cytochrome P450 (CYP) 3A4 inhibition (e.g. class III antiarrhythmic agents, certain antihistamines, -azole antifungals and macrolide antibiotics);[129] combination with erythromycin is therefore contraindicated. A careful medical history, measurement of serum electrolytes and an ECG to exclude a prolonged QT interval (>450ms) are essential before commencing treatment. A significant abnormality on any of these tests is a contraindication to the use of cisapride; however, borderline abnormality in the presence of debilitating symptoms refractory to other therapies may warrant a trial of low dose therapy (up to 40 mg/day in divided doses) with close monitoring for adverse effects, provided the patient is fully informed of the risks.

5.2.3 Metoclopramide

Metoclopramide is less effective than cisapride in accelerating gastric emptying,[146] but has additional antiemetic properties. Its D_2-receptor antagonist and 5-HT_4-receptor agonist effects result in prokinesis, while central D_2- and 5-HT_3-receptor antagonist effects result in antiemesis. Its low cost, wide availability and ability to be given parenterally are further advantages. Subcutaneous administration achieves 80% of the plasma concentration achieved by the intravenous route and three times the level after oral administration,[147] and provides an option for outpatient therapy. CNS reactions affect up to 20% of patients, particularly women, children and the elderly.[129] Tardive dyskinesia is an uncommon but potentially irreversible adverse effect, occurring in ≈1% of patients. Endocrine effects, including hyperprolactinaemia, are not uncommon.

5.2.4 Domperidone

Domperidone crosses the blood-brain barrier poorly, so has fewer CNS adverse effects than metoclopramide, and is emerging as the oral drug of choice, especially in the elderly. Non-CNS adverse effects are similar to those of metoclopramide. It acts on gastrointestinal D_2 receptors to accelerate gastric emptying, but also influences the vomiting centre, which lies outside the blood-brain barrier. Its prokinetic effect appears to be comparable to that of metoclopramide.[3] Use of domperidone over a period of 4 weeks in the treatment of diabetic gastroparesis has been shown to provide significant symptomatic and quality of life improvements, and is well tolerated.[67,148] Combination with cisapride has been shown to be more effective than cisapride alone in patients with functional dyspepsia, in terms of accelerating gastric emptying and relieving symptoms.[132] This medication has recently become available in the US through the Investigative New Drug Program (table II).

5.2.5 Antiemetics

Antiemetic agents, including the phenothiazines (promethazine and prochlorperazine), can be useful adjuncts to prokinetic therapy.[3] Anti-serotonergic antiemetics (ondansetron, tropisetron, dolasetron, granisetron) and butyrophenones (haloperidol, droperidol) are alternatives, but their role in gastroparesis has not been established[3] and the cost is substantial. The option of parenteral administration is an advantage of all of these medications.

Aprepitant, a new class of potent antiemetic agent targeting the neurokinin NK_1 receptor, is available for chemotherapy-related nausea and vomiting, but efficacy in diabetic gastropathy is yet to be reported.[149]

Table II. Commonly used prokinetic drugs[6]

Drug	Mechanism of action	Administration route	Dose (mg)	Adverse reactions
Erythromycin	Motilin agonist	IV, oral	50–250 (3–4 times per day)	Nausea, vomiting, abdominal pain, arrhythmia
Cisapride	5-HT_4-receptor agonist; 5-HT_3-receptor antagonist	Oral	10–20 (2–4 times per day)	Arrhythmia, abdominal pain, diarrhoea, headache
Metoclopramide	D_2-receptor antagonist; 5-HT_3-receptor antagonist; 5-HT_4-receptor agonist	IV, SC, IM, oral	10	Dystonia, tardive dyskinesia, sedation, hyperprolactinaemia
Domperidone	D_2-receptor antagonist	Oral	10–20 (2–4 times per day)	Hyperprolactinaemia, dry mouth, headache

5-HT = serotonin; **D** = dopamine; **IM** = intramuscular; **IV** = intravenous; **SC** = subcutaneous.

5.2.6 Other Therapies

Ghrelin is a peptide produced in the gastric mucosa, which stimulates appetite and growth hormone release. Early trials using parenteral ghrelin have demonstrated improvements in gastric emptying and symptoms in patients with diabetic and idiopathic gastroparesis,[150-152] but only small numbers of individuals have been studied and there are no long-term data.

Other 5-HT_4-receptor agonists, in particular tegaserod and mosapride, have been reported to accelerate gastric emptying, without significant potential for cardiac arrhythmias.[126,153] Renzapride is a combined 5-HT_4-receptor agonist and 5-HT_3-receptor antagonist, with an effect on gastroparesis that is currently under investigation.[126] Levosulpiride, a selective D_2-receptor antagonist, is effective in the short- and long-term (up to 6 months) treatment of diabetic gastroparesis, leading to improvements in gastric emptying and upper gut symptoms,[154,155] as well as overall glycaemic control (HbA_{1c}),[155] but is not available outside Europe. Itopride, a prokinetic that possesses antagonistic effects on both D_2 receptors and acetylcholinesterase, has recently been reported to reduce upper gastrointestinal symptoms in patients with functional dyspepsia,[156,157] with efficacy comparable to that of domperidone.[157] A recent study of itopride in diabetic gastroparesis found modest acceleration of gastric emptying of liquids but not solids.[158]

The phosphodiesterase-5 inhibitor sildenafil reverses delayed gastric emptying in rodent models of diabetes;[22] however, evidence is limited and inconsistent in humans with diabetic gastroparesis.[159,160] The CCK-1 receptor antagonist dexloxiglumide attenuates the inhibition of gastric emptying by small intestinal feedback in patients with functional dyspepsia;[161] its use in gastroparesis is yet to be reported. Activation of the endocannabinoid (CB_1) receptor slows gastric emptying[162] and its antagonist is therefore a potential prokinetic agent. The aldose reductase inhibitor epalrestat has been reported to improve diabetic autonomic neuropathy (heart rate variation at rest and during deep breathing)[163] and normalise the gastric slow wave[164] in patients with type 2 diabetes. Antioxidants have been found to reverse the retardation of gastric emptying caused by the generation of free radicals in rats[165] and celecoxib has been shown to reverse the delay in gastric emptying caused by glucagon in dogs,[166] but data are lacking in humans. The κ-opioid receptor agonist fedotozine failed to improve either symptoms or gastric emptying in patients with diabetic gastroparesis.[167] There is evidence that C-peptide can improve autonomic function, but its administration has failed to accelerate gastric emptying in patients with long-standing type 1 diabetes.[168] The acetylcholinesterase inhibitors neostigmine and physostigmine stimulate motor activity in the gut,[126] but are not associated with significant clinical benefit, probably because the stimulation of motility is uncoordinated.[169] Herbal medicines, such as rikkunshi-to and Zhishi-Xiaopiwan, have been reported to accelerate gastric emptying and improve upper abdominal symptoms in small studies.[170,171] The effect of acupuncture on gastrointestinal motility appears inconsistent.[172-174]

Injection of botulinum toxin into the pyloric sphincter improved gastric emptying and gastrointestinal symptoms in small uncontrolled studies in patients with diabetic and idiopathic gastroparesis.[126,175-180] No significant complications were reported. In the largest study, involving 63 patients with refractory gastroparesis (26 diabetic, 35 idiopathic, 2 postoperative), 43% experienced symptomatic improvements that lasted for a mean of 5 months; vomiting was associated with poor response.[176] A separate study involving 20 gastroparesis patients (3 diabetic, 17 idiopathic) also demonstrated an improvement in solid, but not liquid, gastric emptying, after intrapyloric botulinum toxin injection, accompanied by significant reductions in meal-related symptoms.[180] Further evidence is required from sham-controlled trials before this therapy can be widely recommended, especially as there are no good data on the prevalence of excessive pyloric contraction in patients with diabetic gastroparesis.

Many patients will have experienced prolonged symptoms and are subject to the same psychological stresses as those associated with other chronic illnesses. In functional dyspepsia, psychological stress is well known to exacerbate gastrointestinal symptoms.[181,182] Therefore, it is important to recognise the impact of psychological influences on symptoms, although there is no evidence to support the use of any particular psychotherapeutic intervention.

5.3 Gastric Electrical Stimulation

Gastric electrical stimulation has been the subject of recent attention in the treatment of refractory gastroparesis. Two types of stimulation have been described: one uses low frequency, long duration pulses at, or just above, the frequency of gastric slow waves (three per minute), and the other uses high frequency, short duration pulses at four times the slow wave frequency (12 per minute).[3] The latter protocol, delivered by the Enterra® [1] gastric electrical stimulator, was approved in 2000 by the FDA in the US for patients with refractory diabetic or idiopathic gastroparesis.[3,126] The device consists of a pair of electrodes sutured to the anterior gastric wall, connected to a subcutaneous generator implanted in the anterior abdominal wall.[126] Temporary, endoscopically placed electrodes can be used initially, to assess efficacy.[183]

In diabetic and idiopathic gastroparesis, gastric electrical stimulation using the high frequency protocol is associated with improvements in symptoms and quality of life, despite minimal acceleration of gastric emptying.[184,185] In diabetic patients, glycaemic control also improves, as indicated by a reduction in HbA_{1c} of ≈1–2%.[186-188] Benefits were sustained at both 6 and 12 months,[184,186,187] and may extend beyond 3 years.[188] One study has also suggested that stimulation parameters need to be individualised for different patient groups in order to achieve greatest efficacy,[189] and that an algorithm can be used to identify optimal stimulation parameters for each patient.[189] The mechanism of clinical benefit is unclear, given the lack of entrainment of slow waves or substantial acceleration of gastric emptying.[126] Possible effects include modulation of sensory function or proximal gastric accommodation.[126] Infection is the major risk, requiring removal of the device in up to 10% of patients.[185,186] The absence of interstitial cells of Cajal on gastric biopsy predicts more severe symptoms and a poor response to treatment.[24] Anecdotal evidence suggests that patients with diabetic gastroparesis respond better to gastric electrical stimulation than those with idiopathic gastroparesis. Overall, the available evidence argues favourably for the benefit of electrical stimulation, but the device is expensive and invasive and should, at present, be used for patients with refractory gastropathy in referral centres, preferably in the context of a clinical trial. A new device utilising sequential neural electrical stimulation with multiple electrodes implanted in the distal two-thirds of the stomach is currently being evaluated.[190]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

5.4 Gastrostomy/Jejunostomy

Insertion of a venting gastrostomy has been advocated to improve symptoms and nutritional status in gastroparesis, although supporting data are limited.[5] Feeding jejunostomy helps to improve symptoms, nutritional status and overall health, and leads to fewer hospitalisations, but is associated with a high incidence of complications, often requiring further hospitalisation or surgery.[5,191]

5.5 Surgical Therapy

Surgical treatments are usually reserved a as last resort, since the benefit of these procedures is uncertain.[3,5] There is a paucity of data regarding gastrectomy in diabetic gastroparesis. Most studies are small and uncontrolled, and involve patients who have undergone previous surgical procedures. Most authors favour either a complete or extensive subtotal gastrectomy.[5] One study reported favourable outcomes in seven women with type 1 diabetes and refractory gastroparesis after extensive subtotal gastrectomy with Roux-en-Y gastrojejunostomy,[192] but in general, such procedures should be restricted to those with severe vomiting and a short life expectancy.

Limited studies have reported an improvement in glycaemic control, gastric emptying and gastrointestinal symptoms following kidney-pancreas transplantation,[193,194] while isolated pancreatic transplant may improve autonomic function.[195,196] In a rodent model of gastroparesis, deficiency of NOS was overcome by intrapyloric injection of neural stem cells, with subsequent improvement in gastric emptying;[197] it is unclear whether this approach could be translated to humans.

6. Conclusion

Diabetic gastropathy is a well recognised complication of long-term diabetes and the number of patients affected is likely to increase with the rising prevalence of type 2 diabetes in affluent societies. The pathogenesis is incompletely understood, and the limited relationship between symptoms and impaired gastric emptying represents a challenge to its management, and indicates that both motor and sensory function are disturbed. Current treatment strategies aim to relieve symptoms, improve nutrition, accelerate gastric emptying, optimise glycaemic control and support the patient psychologically. A multidisciplinary approach is recommended. Gastric electrical stimulation appears promising in medically refractory cases, but more information is needed to determine who is likely to benefit.

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