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REVIEW ARTICLE

Stomach Dysfunction in Diabetes Mellitus: Emerging Technology and Pharmacology

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Abstract

Gastroparesis and other types of gastric dysfunction result in substantial morbidity in diabetes patients. The pathophysiology of these disorders is incompletely understood. This article reviews techniques applicable to the assessment of gastric function in diabetes patients, including the measurement of emptying, accommodation, and contractility. Available treatment options are also reviewed, including novel yet unapproved serotonin 5-HT_4 agonist pharmacological treatments, as well as the role of endoscopic, surgical, and device treatments of gastroparesis.

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Introduction to Diabetic Gastroparesis

Gastroparesis is defined as delayed gastric emptying in the absence of mechanical outlet obstruction from the stomach; the typical symptoms are early satiety, upper abdominal bloating, nausea and vomiting,[1] and abdominal pain.[2] In diabetes patients, abdominal fullness and bloating are associated with delayed emptying,[3] but in general, abnormal gastric emptying is weakly associated with symptoms. Two other pathophysiological mechanisms may result in postprandial symptoms: accelerated emptying in the first hour and reduced fasting and postprandial gastric volumes (or accommodation).[4,5] All three factors (delayed emptying at 4 h, accelerated emptying at 1 h, and impaired gastric accommodation) have each been reported in one-third to one-half of patients with diabetic gastropathy and postprandial symptoms.[6] The pathophysiology includes reduced fundic tone, suppression of antral contractions, impaired coordination of antroduodenal pressures, and stimulation of pyloric contractions.[7] The basis for these abnormal functions is impaired glycemic control, extrinsic (e.g., vagal) neuropathy, intrinsic neuropathy, disorders of the pacemaker cells called interstitial cells of Cajal, and, possibly, myopathy.

Whereas, in a community-based study, there was no difference between rates of nausea, vomiting, and dyspepsia in either type 1 or type 2 diabetes patients and controls,[8,9] studies from tertiary medical centers report that delayed gastric emptying is present in 25%–55% of the patients with diabetes.[10,11] Nevertheless, the association of impaired emptying and symptoms such as nausea, fullness, and bloating is generally modest. This reflects selection bias, as gastroparesis generally develops in patients who have had diabetes for at

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Abbreviations: (3D) three dimensional, (5-HT) serotonin, (EGG) electrogastrography, (FDA) Food and Drug Administration, (GEBT) gastric emptying breath test, (GES) gastric electrical stimulation, (GI) gastrointestinal, (GLP-1) glucagon-like peptide-1, (IV) intravenous, (MMC) migrating motor complex, (MRI) magnetic resonance imaging, (SPECT) single photon emission computed tomography

Keywords: diabetes, gastric emptying, gastroparesis, stomach, therapeutics

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least 10 years in association with other complications such as neuropathy, nephropathy, and retinopathy.[12] Natural history studies to date suggest that impaired gastric emptying in gastroparesis, from diverse etiologies, is associated with increased morbidity, hospitalizations, or emergency department visits[13,14] and, in one study, with increased mortality with gastroparesis, not restricted to diabetic gastroparesis.[14]

Evaluation of Gastric Dysmotility in Diabetes

Diagnosis of diabetic gastropathy is typically made by history and objective testing of gastric functions such as emptying, accommodation, and contractility. Physical examination is limited to assessment of signs of hydration and nutritional status, signs of autonomic neuropathy, and examination of the abdomen for distention and succussion splash, which is indicative of a delay in gastric emptying. **Table 1** summarizes the methods available to measure gastric motor functions[15] and addresses indications, function measured, practical considerations on devices and test performance, availability, and costs.

Measurement of Gastric Emptying

Numerous techniques assess gastric emptying;[15] the gold-standard and most widely used gastrointestinal (GI) motility test is gastric emptying scintigraphy.[16,17] Early studies utilized dual-isotope labeling of the solid and liquid phases of the meal. Liquid emptying does not become abnormal until gastroparesis is severe.[18] Measurement of gastric emptying is prognostically relevant, as it was associated with long-term morbidity due to diabetes.[13]

Table 1.
Summary of Methods Available to Measure Gastric Motor Functions[a]

	Scintigraphy	Stable isotope breath test	EGG	Antroduodenal manometry	Wireless pressure and pH capsule	Barostat	SPECT	MRI
Indication/ function measured	gastric emptying	gastric emptying	gastric electrical rhythm	antral, duodenal pressure profiles and amplitude	emptying and pressure amplitude	gastric tone, accommodation	gastric volume accommodation	gastric volume accommodation
Device, assembly or special requirements	external gamma camera and isotope-labeled meal	breath collection vials and stable isotope-labeled meal	recording device	perfusion- or solid-state system + sleeve for sphincters + recorder	intraluminal capsule with miniaturized strain gauge and pH measurement	external barostat and pressure/ volume recording	standard external SPECT camera and IV isotope	standard external MRI camera and oral contrast
Placement of device	—	—	surface electrodes	tube placed via endoscopy/ fluoroscopy	capsule swallowed	large volume balloon and tube	IV injection	IV injection
Performance/ versatility/ interpretation	excellent, standardized data acquisition and interpretation	becoming standardized; performance related to mathematics analysis	standard acquisition, endpoints identified measurable but unclear significance	technically challenging; partly quantitative, operator dependent	standard acquisition, delayed emptying fairly valid; pressures of unclear significance	technically challenging, mainly research	excellent standardization and validation; mainly research	excellent standardization some validation; mainly research
Duration of study	typically 4 h, could be added to small bowel and colon transit	3–4 h	usually 30 min fasting, 60 min postmeal	fasting (4 h) and postmeal (2 h), limited to proximal small bowel	6 h, could be added to small bowel and colon transit	usually 30 min fasting, 90 min postmeal	15 min fasting, 30 min postmeal	15 min fasting, 30 min postmeal
Availability/ potential use	+[b]	+++	+	specialty	+	research	specialty	specialty
Costs	++	+	++	+++	++	not clinical	++	+++++

[a] Reprinted with permission from American Journal of Physiology.[15]
[b] On a scale, + is lowest; +++++ is greatest.

Gastric Emptying Scintigraphy

A consensus statement from the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine details a standardized protocol for test meal and image acquisition intended for uniform adoption.[19] The standard low-fat meal is 255 kcal and consists of EggBeaters® mixed with ^{99m}Tc-sulfur colloid, two slices of bread, strawberry jam, and water.[20] After discontinuation of all medications affecting motility for 48 h prior to the test and ensuring blood glucose is <15 mmol/liter on the day of the test, the ^{99m}Tc-meal is ingested and gastric area imaged immediately after meal ingestion (t = 0) and at 1, 2, and 4 h. The percentage remaining in the stomach at each time point is reported. The normal values at the key time points are 1 h (37%–90%), 2 h (30%–60%), and 4 h (0%–10%).

There are pitfalls in the interpretation of gastric emptying scintigraphy results. There is significant biological intra-individual coefficient of variation in gastric emptying rates of up to 15% in healthy individuals.[21] The correlation of gastric emptying rates to symptoms remains controversial.[22] The test only measures gastric emptying with a meal that is relatively easy to digest. Thus it is possible for such a low-fat, low-fiber meal to empty normally, while a regular meal in the patient's diet might be retained and cause unpleasant symptoms. Interpretation of gastric emptying scintigraphy studies with a nonstandard meal or method (e.g., stopping imaging at 120 min) should be done with caution. Gastric emptying scintigraphy is not recommended for children or pregnant women, due to radiation risk and the absence of normal values in these groups.

Stable Isotope Gastric Emptying Tests

Stable isotope gastric emptying breath test (GEBT), utilizing a solid meal labeled with either ^{13}C-octanoic acid or ^{13}C-*Spirulina platensis* blue-green algae, is a promising newer method to evaluate emptying noninvasively and without radiation. The principle of the GEBT is that gastric emptying of the meal is the rate limiting step in breath $^{13}CO_2$ excretion.

In studies performed simultaneously with scintigraphy, the ^{13}C-*S. platensis* GEBT was able to identify accelerated or delayed gastric emptying induced pharmacologically.[23] In a large, prospective study of patients with symptoms referred for gastric emptying scintigraphy, the ^{13}C-*S. platensis* GEBT, utilizing individual breath samples at 45, 150, and 180 min, predicted gastric emptying category at 80% specificity; the 45 and 180 min combined samples were 93% sensitive to identify accelerated gastric emptying, and the 150 and 180 min combined samples were 89% sensitive for identifying delayed gastric emptying.[24] The test is not yet Food and Drug Administration (FDA) approved.

The potential advantages of GEBT include cost, absence of radiation, and that the performance of the test is not operator dependent. Disadvantages of the GEBT include potential loss of accuracy in patients with malabsorption or advanced liver disease,[25] advanced respiratory disease, and hyperdynamic circulation. Currently, ^{13}C-octanoic acid-based tests are less well validated than the ^{13}C-*S. platensis*-based test.

Wireless pH and Motility Capsules

Wireless capsules can measure pH, pressure, and temperature throughout the GI tract. The abrupt change, detected by the capsule, in pH from the acidic gastric milieu to the almost alkaline duodenum is indicative of gastric emptying. This event is usually associated with antral phasic contractions at the maximal frequency of the migrating motor complex (MMC).[26] When taken with a meal, the capsule generally empties from the stomach after liquids and triturable solids have emptied, and this occurs with the return of the phase III of the MMC. However, in about one-third of cases, capsule emptying occurs with high-amplitude, isolated antral contractions, which typically increase in frequency just before the phase III activity front.[27] Hence the gastric emptying time for the capsule does not accurately measure gastric emptying of a meal.

The wireless capsule acquires data continuously for up to 5 days, and this permits calculation of small bowel, colon, and whole gut transit. An "event button" is used to mark significant events (such as meal ingestion, sleep, or GI symptoms experienced by the patient). A gastric emptying time of 6 h is assigned if the capsule does not record pH > 6 over the first 6 h. There are still no reports demonstrating clinical utility or documenting correlation with symptoms for the wireless pH and motility capsule, which has received FDA approval to measure gastric emptying.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been used to document delayed gastric emptying[28] and effects of prokinetic medication on gastric contractility and emptying.[29–31] Subjects are typically examined in supine position over 120 min, with separate scans performed every 15 min to determine gastric volume, secretion, and motility. Magnetic resonance imaging provides sufficient contrast between the gastric wall and intraluminal content to

estimate diameters of proximal and distal stomach; the motor function of the stomach can be measured, providing quantitative assessment of gastric motility, including the frequency, amplitude, and speed and direction of propagated antral contractions.[32] However, MRI does not provide a direct assessment of the meal emptying from the stomach since the volume of gastric contents measured has to be corrected for the gastric secretions that dilute the meal. Thus MRI remains a promising technology, but it has not been validated to the same degree as scintigraphy, and it is comparatively expensive (equipment purchase, operation, and expertise).

Measurement of Gastric Accommodation

In patients with diabetes and postprandial symptoms, impairment of gastric accommodation may be the sole pathophysiology or it may be associated with impaired gastric emptying, such as accelerated emptying at 1 h. Earlier measurements of gastric accommodation by intragastric balloons have been used in a few research centers. The main methods to measure accommodation are single photon emission computed tomography (SPECT), ultrasonography, and MRI, which can measure gastric volumes (see previous subsection) in addition to emptying and contractility.[33]

Single Photon Emission Computed Tomography

Single photon emission computed tomography imaging has been extensively validated *in vitro* and *in vivo* for the measurement of gastric volumes during fasting and postprandially. After intravenous (IV) administration of 10-20mCi ^{99m}Tc-pertechnate, which is taken up by the parietal and mucin-secreting cells of the gastric mucosa, tomographic images of the stomach are acquired, with the patient supine, using a large field-of-view, dual-headed gamma camera.[34] From the transaxial images of the stomach, three-dimensional (3D) images can be reconstructed, and total gastric volume can be measured during fasting and during the first 30 min following a liquid nutrient meal consisting of 300 kcal. Single photon emission computed tomography demonstrates the effects of disease on postmeal change in gastric volume, a surrogate of gastric accommodation.[6] Single photon emission computed tomography imaging has demonstrated excellent intraobserver and interobserver variance, even when studies are performed many months apart, and therefore, it represents a highly reproducible imaging modality.[35,36]

The pitfalls are the use of radioactivity (with exposure approximately three times that of a standard nuclear medicine solid–liquid gastric emptying study: H_e [entrance skin exposure] for ^{99m}Tc-SPECT 619 mRem, ^{111}In-DTPA 142 mRem, and ^{99m}Tc-sulfur colloid 90 mRem) and the need for SPECT camera and sophisticated software to perform the 3D reconstruction and calculate volumes.

Ultrasonography

Imaging-based methods to measure gastric volume include analysis of surface geometry of human stomach using real-time, 3D ultrasonography or, most recently, 3D reconstruction of images acquired by ordinary ultrasonography assisted by magnetic scan-head tracking.[37,38] Three-dimensional ultrasonography has been applied in adolescents and compared to simultaneously measured gastric volumes by SPECT; further validation and standardization are necessary.[39] A limitation of 3D ultrasonography is that it allows assessment of only the stomach's response to a liquid meal.

Neither MRI nor 3D ultrasonography has had sufficient validation in health or disease to recommend use in routine clinical practice.

Cutaneous electrogastrography

Cutaneous electrogastrography (EGG) is commercially available with software/hardware packages. The surface EGG provides information about the gastric myoelectric frequency and the amplitude of the EGG signal in the normal or abnormal frequency ranges. However, the interpretation of findings is still the subject of considerable debate.

Intraluminal Measurements of Gastric Motor Functions

Antroduodenal Manometry

Antroduodenal manometry is available mainly at tertiary referral centers, but the test is invasive and time-consuming and requires skilled technical support. Antroduodenal manometry measures phasic (not tonic) contractions in the distal stomach and duodenum, and it is useful in highly selected cases to distinguish if dysmotility is limited to the stomach or is more diffuse and also involves the small bowel. It may also help distinguish neuropathic disease (normal-amplitude, disorganized contractions) from muscle disease (low-amplitude contractions).

The barostat is the gold standard for the measurement of tone in hollow organs[40] and estimates changes in tone by the change of the volume of air in an infinitely compliant intragastric balloon maintained at a low constant pressure. Pitfalls include the need for intubation and balloon distension, which are often stressful and

induce discomfort to patients during these tests. This test is rarely, if ever, performed in clinical practice.

Pharmacological Treatments Used in Management of Diabetic Gastroparesis

Current Treatment

In diabetic gastroparesis, the objectives are to restore hydration and nutrition, enhance gastric emptying, relieve symptoms, and improve glycemic control. Modification of diet ranges from adopting multiple, small, low-fat, low fiber-residue meals to consumption of blenderized food to use of liquid nutrient supplements, depending on the severity of the gastroparesis.[41] Patients in whom bezoars have been identified should consistently avoid high fiber-residue foods. Striving for euglycemia is a reasonable goal; prolonged euglycemia, in the setting of pancreatic transplantation for type 1 diabetes, has been shown to improve nephropathy[42] and neuropathy[43,44] and symptoms of gastroparesis.[45]

Incretin-based therapy to normalize glycemia in type 2 diabetes may result in retardation of gastric emptying. Amylin or glucagon-like peptide-1 (GLP-1) analogs reduce postprandial glycemia, in part, by delaying gastric emptying and by direct effects on glucose metabolism, such as by increasing β-cell mass and by suppression of glucagon secretion and stimulation of insulin secretion from pancreatic islet cells.[46] Nausea and vomiting are rarely severe enough to require treatment cessation. However, before commencing a prokinetic agent, cessation of pramlintide or exanetide should be considered and, if the diabetes control is suboptimal, a dipeptidyl peptidase IV inhibitor should be prescribed instead of amylin or GLP-1 analogs. Dipeptidyl peptidase IV inhibitors increase endogenous GLP-1 levels without causing alterations in gastric emptying,[47] gastric accommodation, nausea, or postprandial fullness. If the patient is still symptomatic with nausea, vomiting, postprandial fullness, or erratic glycemic control, a prokinetic medication is indicated.

Metoclopramide, a dopamine-D_2 receptor antagonist, is currently the only drug approved by the FDA to treat diabetic gastroparesis in the United States.[48] There is now a black box warning on this compound related to the risk of tardive dyskinesia; metoclopramide is considered the most common cause of drug-induced movement disorders.[49] Domperidone, another dopamine-D_2 receptor antagonist, is available through an FDA investigational new drug application. Both drugs accelerate gastric emptying and improve symptoms, but central nervous system side effects are more pronounced with metoclopramide.[50–52] Metoclopramide is also available in liquid and parenteral formulations for IV or subcutaneous administration.

Erythromycin is a motilin receptor agonist that accelerates gastric emptying,[53] but it has not been shown to reduce symptoms of gastroparesis, and it is associated with rapid tachyphylaxis and has the potential risks associated with its antibiotic activity.

Table 2 summarizes trials of currently available pharmacological therapy for gastroparesis (metoclopramide and, in some countries, domperidone).

Antiemetics are often needed to relieve acute nausea, but their efficacy for chronic nausea is unclear. Antihistamine antiemetics, including meclizine, doxylamine, and dimenhydrinate, are also anticholinergic and sedating, which limit their use. Dopamine antagonists, such as promethazine and prochlorperazine, are associated with extrapyramidal side effects, and the risk is increased when used in combination with metoclopramide. Serotonin (5-HT) antagonists 5-HT_3, such as ondansetron and granisetron, are potent antiemetics and are well tolerated (other than causing constipation), but they are expensive. Mirtazapine is a tetracyclic antidepressant that has significant 5-HT_3 antagonist activity and is probably efficacious as an antiemetic.[54,55] Mirtazapine has antidepressant and antianxiety effects, which may be useful because there is a frequent association between psychological comorbidities in diabetes patients with GI symptoms.[56] Unlike the tricyclic antidepressants, mirtazapine does not have significant anticholinergic activity. However, there are no controlled studies of mirtazapine in diabetic gastroparesis.[57]

Potential Novel Prokinetics

Three 5-HT_4 agonists in development are reported to have greater selectivity for 5-HT_4 over other receptors,[58] and they have been advanced to human trials. However, there are no available data that assess efficacy (short or long term) in patients with gastroparesis.

a. Prucalopride is efficacious in accelerating gastric emptying and colonic transit.[59] Cardiovascular safety was also reported in 100 elderly, constipated patients randomized (25/treatment group) to prucalopride in a dose-escalation study. Vital signs, electrocardiogram, and Holter data in these patients (~80% of whom had history of current cardiovascular disease) were not different from placebo, and importantly, no patients had QTcF > 500 ms.[67]

Table 2.
Summary of Trials of Pharmacological Therapy for Gastroparesis[60,a]

First author	Medication and study design	Number	Cause	Dose	Study length	Outcome results
Perkel[61]	metoclopramide, DB, PC, PG, RCT	28	diabetes 5, postsurgical 4, idiopathic 19	10 mg TID	3 weeks	improved symptoms by 29%
McCallum[62]	metoclopramide, PC, RCT	18	diabetes	10 mg TID	3 weeks	improved symptom score by 25%; improved GE by 25%
Patterson[51]	metoclopramide, RCT, DB, multicenter	45	diabetes	10 mg TID	4 weeks	symptoms improved by 39%
Champion[63]	domperidone, DB, PC, PG, RCT	19	diabetes	20 mg QID	4 weeks	improved symptoms; improved GE by 37%
Soykan[64]	domperidone, open-label	17	diabetes 3, postsurgical 2, idiopathic 12	20 mg QID	2 years	symptom score improved by 68%
Silvers[65]	domperidone, single-blind	287	diabetes	20 mg QID	4 weeks	symptoms improved in 208/269 patients by 63%
Patterson[51]	domperidone, DB, RCT	48	diabetes	20 mg QID	4 weeks	symptom score improved by 41%
Franzese[66]	domperidone versus cisapride RCT	28	diabetes in children	domperidone, 0.9 mg/kg; cisapride, 0.8 mg/kg	8 weeks	domperidone superior for symptom relief and improved GE

[a] DB, double blind; PC, placebo controlled; PG, parallel group; RCT, randomized controlled trial; GE, gastric emptying; TID, three times a day; QID, four times a day

b. ATI-7505 is a benzamide 5-HT_4 receptor agonist whose chemical structure was modified from that of cisapride to undergo hydrolytic esterase metabolism, not oxidative CYP450 metabolism. Therefore, drug interactions with agents that affect or are metabolized by CYP 3A4 are unlikely. A dose-response pharmacodynamic study showed ATI-7505 accelerated gastric emptying and colonic transit and enhanced evacuation of stool.[68]

c. Velusetrag (TD-5108) is a potent agonist at human 5-HT_4 receptors with high intrinsic activity and selectivity for 5-HT_4, > 500-fold selective over other 5-HT receptors (including h5-HT_{2B} and h5-HT_{3A}). At 3 μM, TD-5108 had no effect on human ether-à-go-go-related gene encoded K+ channels.[69,70] In pharmacodynamic studies, TD-5108 dose dependently accelerated colonic transit after single doses; with multiple doses, gastric and colonic transit were accelerated by 15 and 30 mg doses.[71]

All of these agents accelerate colonic transit and may cause diarrhea at doses that may be therapeutically beneficial in patients with gastroparesis.

Ghrelin agonists accelerate gastric emptying, though they reduce gastric accommodation.[72] There are parenteral and oral formulations of ghrelin agonists in development.

Endoscopic, Surgical, and Device Treatment of Diabetic Gastroparesis

Botulinum injection of the pylorus at endoscopy was ineffective in the two controlled trials of this treatment for gastroparesis.[73]

Surgeries such as pyloroplasty, distal gastrectomy, or total gastrectomy are not indicated for the management of diabetic gastroparesis, based on lack of supporting evidence.[74] Endoscopic gastrostomy or jejunostomy for drainage or feeding, respectively, may be of limited benefit,[75,76] but tube placement failure and complications are a concern with endoscopic jejunostomy placement.[77]

Gastric Electrical Stimulation

Gastric electrical stimulation (GES) of the stomach with high-frequency, low-energy settings has been clinically available since Enterra device (Medtronic, Inc.) received a humanitarian device exemption for intractable gastroparesis from the FDA in 1999. Uncontrolled studies report significant improvement in gastroparesis symptoms and reductions in medication use and hospitalizations but unimpressive improvement in gastric emptying.[78,79] There is a paucity of controlled data for this device.

In the only fully published controlled study, which included 17 patients with diabetic gastroparesis, the weekly vomiting frequency was reduced by about 50% in this group when the device was activated.[80] In another controlled trial published as an abstract, 32 patients with diabetic gastroparesis received GES, which was initially activated for 6 weeks, and then patients were randomized to 3 months of either on or off. The median weekly vomiting frequency was 50% compared to baseline, but there was no significant difference when device was active versus inactive.[81] Interpretation is problematic due to the potential confounding by the device being initially turned on in all patients.

New stimulation paradigms are being tested. In canine models, low-frequency, high-energy electrical stimulation through multiple electrodes is effective in entraining the slow wave (true pacing), facilitating gastric emptying, and relieving symptoms and may ultimately be a more effective form for gastroparesis.[82,83] At present, GES is used by specialized centers in patients who are unresponsive to more conservative approaches.

Stomach Dysfunction and Bariatric Surgery

While there are no reports of the role of bariatric procedures in the treatment of gastric motor dysfunction due to diabetes, it is theoretically possible (based on anecdotal reports summarized by Jones and Maganti[84]) that pyloroplasty, subtotal gastrectomy, or Roux-Y gastric bypass may relieve gastric stasis and enhance glycemic control through more predictable gastric emptying. Formal studies are required.

Conclusions

New technologies and advances in diagnosis and treatment are being applied to the stomach in diabetes. Collaboration between the gastroenterologist and the endocrinologist remains as important as ever in order to optimally manage the patient with diabetic gastropathy.

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