Endotext

GASTROINTESTINAL DISORDERS IN DIABETES

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ABSTRACT

Gastrointestinal manifestations of type 1 and 2 diabetes are common and represent a substantial cause of morbidity and health care costs, as well as a diagnostic and therapeutic challenge. Predominant among them, and most extensively studied, is abnormally delayed gastric emptying or diabetic gastroparesis. Abnormally increased retention of gastric contents may be associated with symptoms, including nausea, vomiting, postprandial fullness, bloating, and early satiety, which may be debilitating. However, the relationship of upper gastrointestinal symptoms with the rate of gastric emptying is relatively weak. Moreover, gastrointestinal symptoms also occur frequently in people without diabetes, which may compromise the capacity to discriminate gastrointestinal dysfunction resulting from diabetes from common gastrointestinal disorders such as functional dyspepsia. A definitive diagnosis of gastroparesis thus necessitates measurement of gastric emptying by a sensitive technique, such as scintigraphy or a stable-isotope breath test. There is an inter-dependent relationship of gastric emptying with postprandial glycemia. Elevated blood glucose (hyperglycemia) slows gastric emptying while, conversely, the rate of emptying is a major determinant of the glycemic response to a meal. The latter recognition has stimulated the development of dietary and pharmacological (e.g. short-acting GLP-1 receptor agonists) approaches to improve

postprandial glycemic control in type 2 diabetes by slowing gastric emptying. The outcome of current management of symptomatic diabetic gastroparesis is often sub-optimal - optimizing glycemic control, the correction of nutritional deficiencies, and use of pharmacotherapy, are important. A number of promising and novel pharmacotherapeutic agents are in development. This chapter focusses on gastric motor function, but also provides an overview of the manifestations of esophageal, gall bladder, small and large intestinal function, in diabetes.

INTRODUCTION

The gastrointestinal tract extends from the mouth to the anus and performs functions vital to sustaining life including ingestion, breakdown and digestion of nutrients, facilitating nutrient absorption and preparation and expulsion of the waste product. Gastrointestinal symptoms occur commonly in people with diabetes, and include gastro-esophageal reflux, bloating, nausea, constipation, diarrhea, and fecal incontinence. It has been suggested that more than 50% of individuals attending outpatient diabetic clinics will at some stage experience a distressing gastrointestinal symptom. Gastrointestinal motor dysfunction is also common in diabetes and may have an impact on glycemic control. Of the motor dysfunctions, gastroparesis, or delayed gastric emptying, is the most important and will be discussed in relatively greater detail. This chapter is limited to the gastrointestinal manifestations of type 1 and 2 diabetes and does not address other causes of diabetes, such as that related to cystic fibrosis.

GASTROINTESTINAL SYMPTOMS

Gastrointestinal symptoms are exhibited frequently in type 1 and 2 diabetes and most, but not all, studies suggest that they are significantly more common in diabetes than in controls without diabetes (1); reported inconsistencies likely reflect discrepancies in the methodology used and the patient populations studied. It should be appreciated that gastrointestinal symptoms are often not volunteered, particularly those considered embarrassing (such as fecal incontinence) and it would not be surprising if current estimates are less than is really the case. Symptoms, unfortunately, continue to be evaluated in clinical trials solely using participant 'self-report' despite its appreciated unreliability, rather than simple, validated measures, which are used widely in the assessment of 'functional' gastrointestinal disorders (e.g. irritable bowel syndrome and functional depression) (2) (1) Symptoms appear to be more common in women with diabetes, as is the case with functional gastrointestinal disorders (3). While it is unclear whether symptom prevalence varies between type 1 and type 2 diabetes there is no doubt that gastrointestinal symptoms have a substantial negative impact on quality of life in people with diabetes (4). There is, however, a poor correlation between gastrointestinal symptoms and measures of function, such as the rate of gastric emptying. The natural history of gastrointestinal symptoms remains poorly defined, although it is known that onset and disappearance of symptoms is common i.e. there is considerable 'symptom turnover' - approximately 15-25 % over a 2-year period has been observed in type 2 patients (1). This symptom turnover has been reported to be associated with the onset of depression, but not with autonomic neuropathy or glycemic control (5).

GASTROINTESTINAL MANIFESTATIONS IN DIABETES

Esophagus

The esophagus, a muscular tube connecting the pharynx to the stomach, enables propulsion of swallowed food, with a sphincter at either end (the upper and lower esophageal sphincters) to prevent esophago-pharyngeal and gastro-esophageal reflux, respectively.

Two common esophageal symptoms are heartburn

(as part of gastro-esophageal reflux disease) and dysphagia (potentially indicating esophageal motor dysfunction). Techniques to evaluate esophageal motility include conventional and high-resolution manometry (HRM). Scintigraphy can measure esophageal transit but has not been standardized and is not commonly employed in clinical settings.

The relationship between esophageal transit and gastric emptying in diabetes is poor (6). Acute hyperglycemia inhibits esophageal motility (7), and reduces the basal lower esophageal sphincter pressure (8). While the esophagus has been less well studied than the stomach, it is clear that disordered esophageal function occurs frequently and that disordered motility in both the esophagus and stomach may share a similar pathogenesis. It has been postulated that the major mechanism underlying esophageal dysmotility is a reduction of cholinergic activity and vagal parasympathetic dysfunction (9). The pathological abnormalities associated with gastroparesis, such as a reduction in interstitial cells of Cajal and inhibitory intrinsic neurons, have also been postulated to be relevant to esophageal dysmotility (10). Diffuse esophageal muscular hypertrophy was reported in two-thirds of people with diabetes in one case series (11).

There are limited evidence-based options for the management of esophageal disorders in diabetes. General measures include lifestyle modifications (improved glycemic control, weight loss, dietary modifications, and physical exercise). Prokinetic agents have been used, albeit with limited evidence to support efficacy. The latter include dopaminergic agents (metoclopramide, domperidone), serotonin receptor agonists (cisapride), and motilin agonists (erythromycin). Botulinum toxin was trialed in a pilot study in patients with achalasia (including those with diabetes) and peripheral neuropathy and improvements in effective peristalsis induction and contraction amplitude were reported (12).

Gastro-esophageal reflux disease (GERD) is extremely common in the general population and also frequently seen in diabetes. In non-erosive GERD, treatment involves lifestyle measures (bed elevation of 30 degrees at head- end) and use of proton-pump inhibitors. In a community study, a reduced rate of heartburn was found in type 1 patients when compared with a control population (13), although this observation remains to be confirmed and the implications are unclear.

Disordered esophageal motility, especially the elderly, increases the risk of ‘pill-induced esophagitis’, with mucosal injury due to prolonged exposure to impacted medications (14). Diabetes is an independent risk factor (14), and the condition usually presents as chest pain with or without odynophagia. Treatment involves withdrawal of the offending agent and use of proton pump inhibitors (15).

Stomach - Diabetic Gastroparesis

INTRODUCTION

Delayed gastric emptying in diabetes was first reported almost a century ago, but it was Kassander who, in 1958, documented asymptomatic increased gastric retention of barium in diabetes and coined the descriptive term ‘gastroparesis diabeticorum’ (16). Interestingly, Kassander also suggested in their paper that gastroparesis could adversely impact glycemic control. Some sixty years on, diabetic gastroparesis, traditionally defined as abnormally delayed gastric emptying of solid food in the absence of mechanical obstruction, remains a diagnostic and management challenge (17). Gastroparesis occurs in both type 1 and 2 diabetes and may not, necessarily, be indicative of a poor prognosis (18,19).

The rate of gastric emptying is now appreciated as a major determinant of postprandial glycemia in both health and diabetes (20), and novel anti-diabetic

medications, such as short acting GLP-1 receptor agonists, diminish postprandial glycemic excursions predominantly by slowing gastric emptying, are used widely.

EPIDEMIOLOGY OF DIABETIC GASTROPARESIS

The 'true' incidence and prevalence of diabetic gastroparesis globally remain uncertain largely due to inconsistencies in the definition of gastroparesis, study populations, and methodology. It is, however, clear that diabetes is a leading cause of gastroparesis, accounting for about 30% of cases in tertiary referral studies (17). A recent analysis of data from the follow-up arm of the landmark prospective study in type 1 diabetes, called DCCT-EDIC (Diabetes Control and Complications –Epidemiology of Diabetes Interventions and Complications) found that delayed gastric emptying of a solid meal occurred in 47% of this population, consistent with the prevalence reported in other cross-sectional studies (21). Previously believed to be essentially a complication of advanced type 1 diabetes (T1D), it is now apparent that gastroparesis also occurs frequently in type 2 diabetes (T2D) (16,22). Risk factors for gastroparesis include a long duration of diabetes, the presence of other microvascular complications, female gender, obesity. and smoking (17). In a recent report from the NIH Gastroparesis Consortium, the proportion of T1D and T2D was comparable (although many more people with T2D have gastroparesis as its prevalence is much higher), although a US-based community study based on symptomatic cases, reported an incidence of approximately 5% in T1D and 1% in T2D (compared with 0.01% in controls) (23). Data from the US indicate that hospitalizations due to diabetic gastroparesis rose 158% between 1995-2004, which may reflect a true increase in incidence and / or greater clinical awareness of the condition (24). Not surprisingly, health care costs related to diabetic gastroparesis have also increased substantially in recent years. It should, however, also be noted that the awareness of the central importance of glycemic control to the development and progression of microvascular complications, and the consequent increased priority in management to improve it, may have led to a reduction in the incidence of gastroparesis. Consistent with this, it has recently been shown that in well-controlled T2D, even when longstanding, the prevalence of gastroparesis is low and, not infrequently, gastric emptying is modestly accelerated (19,25).

DIAGNOSIS OF DIABETIC GASTROPARESIS

As alluded to, the presence of gastrointestinal symptoms is poorly predictive of delayed gastric emptying. It is well established that patients with debilitating upper GI symptoms may have normal, or even rapid emptying, while others with unequivocally markedly delayed emptying may report few, or no symptoms. Measurement of gastric emptying, after exclusion of mechanical obstruction at the gastric outlet or proximal small intestine is, accordingly, mandatory for a formal diagnosis of gastroparesis, for which scintigraphy, developed in the 1970s, remains the 'gold standard' technique. An attempt has been made to standardize the methodology, with the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine defining gastroparesis by the intra-gastric retention of >60% of a standardized meal at 2 hours and/or >10% at 4 hours (26). The test meal advocated in the consensus statement comprises two egg-whites, two slices of bread and jam (30 g) with water (120 ml), providing 255 kcal with little fat (72% carbohydrate, 24% protein, 2% fat and 2% fiber) (26). While a useful exercise, the probability of universal adoption of a specific meal, especially outside Western cultures, is intuitively low. The advantages of scintigraphy are its capacity for precise, concurrent measurement of both solid and liquid meal components (the 'consensus' test meal only labels the solid component); however, it involves radiation exposure and requires sophisticated equipment and technical expertise. Acceptable alternatives include ^{13}C based breath tests and

ultrasonography, neither of which involve radiation exposure, although the latter is operator-dependent (22). Newer techniques, such as the wireless motility capsule, MRI, and SPECT imaging have emerged, but at present these should be considered less accurate than scintigraphy and / or only relevant to a research setting (17).

PATHOGENESIS OF DIABETIC GASTROPARESIS

Gastric emptying is a complex, coordinated process by which chyme is delivered to the small intestine at a tightly regulated rate and involves the gastro-intestinal musculature, nervous systems (intrinsic and extrinsic), gastric 'pacemaker' (so-called 'Interstitial cells of Cajal or ICC), immune cells, and fibroblast-like cells that stain positive for platelet derived growth factor receptor alpha. In the fasting state, a cyclical pattern of contractile activity known as the 'migrating motor complex' (MMC) sweeps from the stomach through to the small intestine, which serves a "housekeeping' role i.e. facilitating the movement of ingestible food particles and bacteria from the stomach through the intestine (27). There are distinct phases of the MMC: phase I consists of motor quiescence lasting approximately 40 min, phase II, approximately 50 min, is comprised of irregular contractions, and phase III is characterized by regular contractions (at approximately 3 per min in the stomach and about 10-12 per small intestine) for 10 min during which the bulk of indigestible solids are emptied (28). Following meal ingestion, the MMC is replaced by a 'postprandial' motor pattern. Solids are then mixed with gastric acid and ground into small particles (usually < 1-2 mm) in the distal stomach. Gastric accommodation is mediated by vagal and nitrergic mechanisms, antral contractions by vagal and intrinsic cholinergic mediation, and pyloric relaxation by nitrergic mechanisms (17). The resultant chyme is delivered through the pylorus to the proximal duodenum predominantly in a pulsatile manner (22,27). It is now appreciated that the rate of emptying is regulated primarily by nutrient-induced inhibitory feedback arising from the small intestine, rather than by 'intragastric' mechanisms (29). Digestible solids and high nutrient liquids empty from the stomach in an overall linear fashion as a result of this feedback (6); solid emptying is preceded by an initial so-called 'lag-phase' of 20-40 min during which solids are ground into small particles. In contrast to solids, low or non-nutrient liquids empty in an overall, volume-dependent, monoexponential pattern because small intestinal feedback is less (27). A number of gut peptides play a key role in providing intestinal feedback, including GLP-1, CCK, and peptide YY. In contrast, ghrelin and motilin, which accelerate gastric emptying, are suppressed following food intake (22,27). Both the length and region of small intestine exposed to nutrients modulate feedback to slow gastric emptying (30).

Disordered gastric emptying represents the outcome of impairments of variable combinations of these diverse components. Advances in understanding the underlying pathophysiology have been made over the past decade, particularly through the efforts of the NIH-funded Gastroparesis Clinical Research Consortium. Histological studies from this group and others have shown a reduction in the number of interstitial cells of Cajal in diabetic gastroparesis, which correlates with the magnitude of delay in emptying (31). Interstitial cells of Cajal loss appears to be driven by an immune infiltrate involving a shift from protective M2, to classically activated, M1 macrophages, with defective regulation of heme oxygenase-1 and resultant oxidative stress. Altered expression of the Ano-1 gene which influences conduction in the Interstitial cells of Cajal has also been reported (32). A reduction in inhibitory neurons expressing nitric oxide synthase also appears to contribute (31).

GASTRIC EMPTYING AND GLYCEMIA (FIGURE 1)

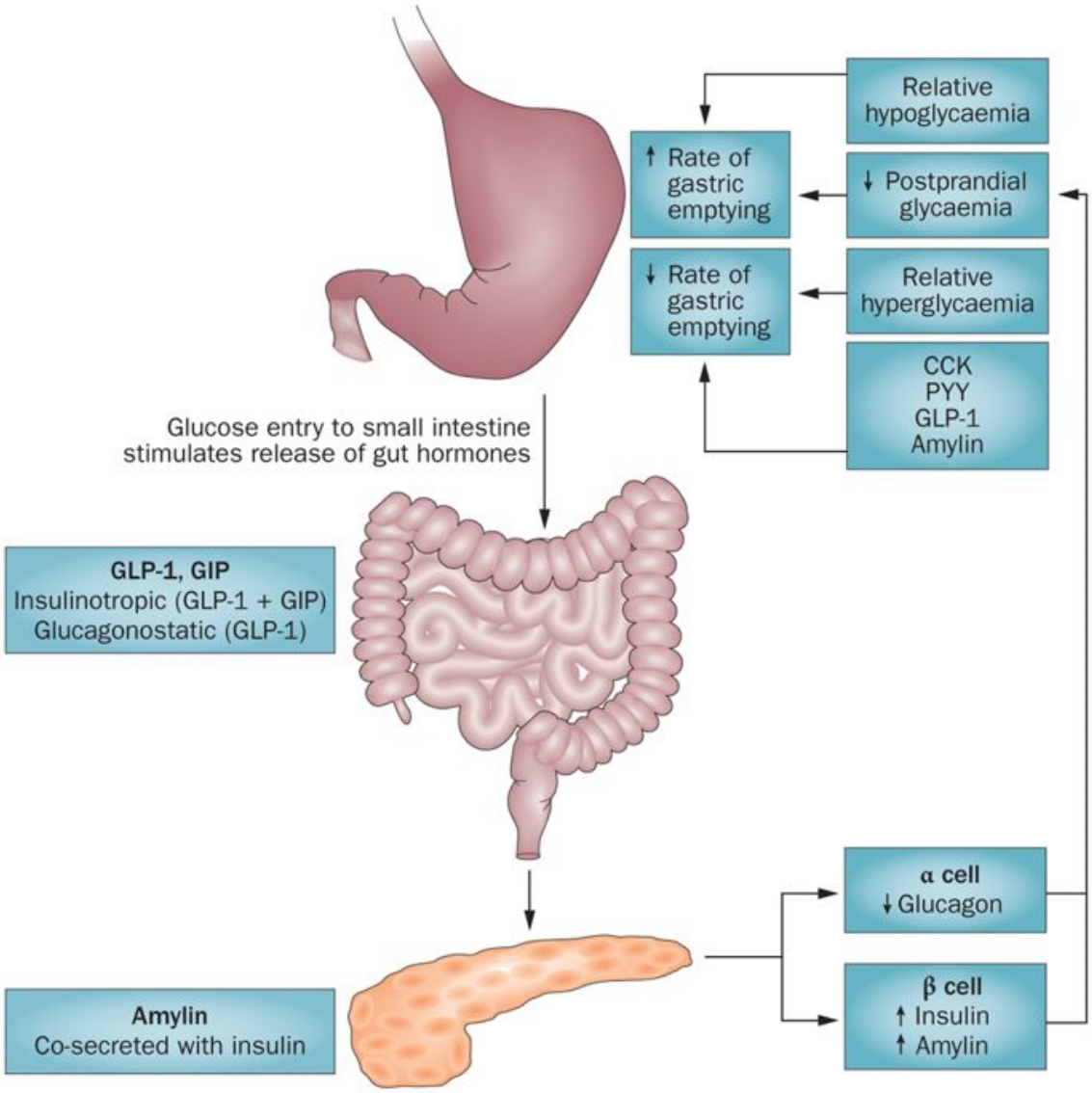

Figure 1. Bidirectional relationship between gastric emptying and glycemia. Abbreviations: CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; PYY, peptide YY. Reproduced with permission from Philips et al (22)

Gastric emptying exhibits a wide inter-individual variation (ranging between 1-4kcal /min in health and even wider in diabetes because of the high prevalence of gastroparesis and, less often, abnormally rapid emptying) (Figure 2). Gastric emptying is a major determinant of postprandial glycemia across glucose-tolerant states and these relationships are time-dependent. In individuals with normal glucose tolerance, following a 75g oral glucose drink, the early (approximately 30 min) rise in glucose is directly proportional to the rate of emptying, while the 120 min value (the standard endpoint in an OGTT) is inversely related. This relationship shifts to the right as glucose tolerance worsens, such that both 30- and 120-min glucose values are directly proportional to the gastric emptying rate in type 2 diabetes(33-

35).Epidemiological studies indicate that about 50% of people with impaired glucose tolerance or IGT will develop frank type 2 diabetes and, hence, factors affecting progression are of considerable interest. We have shown that the disposition index – a predictor of progression to type 2 diabetes – is inversely related to the gastric emptying rate (36), suggesting that the rate of emptying may influence the progression. There is evidence that the 1-hour plasma glucose level in a 75g oral glucose tolerance test is strongly associated with the risk of future type 2 diabetes (37) and this is known to be dependent on the rate of gastric emptying (34,35).

In type 2 diabetes, slowing of gastric emptying (such as by morphine) reduces the postprandial glycemic profile, while accelerating emptying by pro-kinetics (such as erythromycin) increases it (38). Bypassing the stomach and delivering glucose directly into the small intestine at specified rates (within the physiological span of gastric emptying) via naso-duodenal catheters has been used as a model to characterize the impact of gastric emptying on glycemia. These 'surrogate' studies indicate that gastric emptying is a major determinant of postprandial insulin secretion and the magnitude of the so-called 'incretin' effect (the augmented insulin secretory response to oral or enteral, compared with intravenous, glucose). Moreover, the relative contribution of the two 'incretin' hormones (GIP and GLP-1) to the incretin effect in health varies such that GIP is the predominant contributor when glucose enters the small intestine at 2kcal/ min or less, with GLP-1 contributing only at higher rates of duodenal glucose delivery (3 or 4 kcal per min) (39). It is, therefore, likely that the relative contributions of GIP and GLP-1 to the postprandial insulin response and glycemia depend on an individual's intrinsic rate of emptying. Variations in blood glucose also affect gastric emptying. Through 'glucose clamp' studies, we have shown that abrupt elevations in blood glucose slows gastric emptying in a 'dose- dependent' manner, i.e. the slowing is dependent on the magnitude of the elevation in blood glucose (7). Moreover, when blood glucose is 'clamped' at about 8 mmol/L or 144 mg/dL (i.e. physiological hyperglycemia), gastric emptying is modestly slower in both health and well-controlled type 1 diabetes (40). This may, however, not apply to spontaneous elevations in blood glucose (41) and further clarification is required. On the other hand, acute hypoglycemia (blood glucose about 2.6 mmol/L or 46.8 mg/dL) accelerates gastric emptying markedly in both groups (42), and is likely to represent an important counter-regulatory mechanism. It follows that the acute glycemic environment, by altering gastric emptying, is likely to influence intestinal absorption of nutrients, as well as oral medications, which has hitherto been poorly appreciated in clinical practice. The impact of chronic glycemic control on gastric emptying remains uncertain.

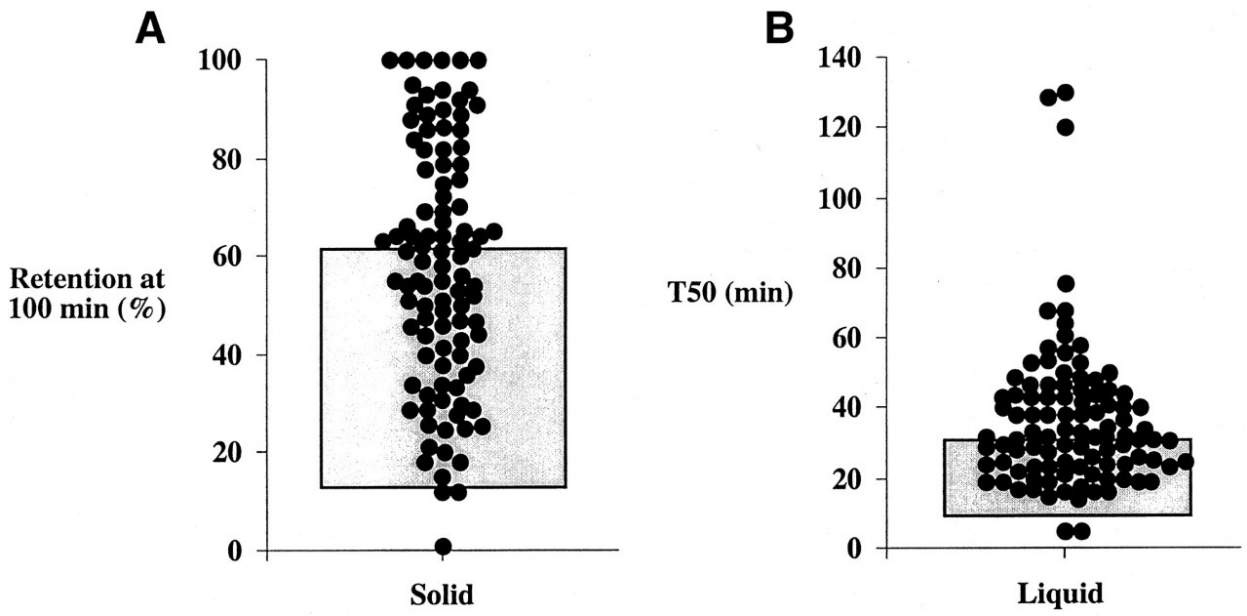

Figure 2. Gastric emptying of solids (minced beef) (A), shown as the retention at 100 min (percent); and the gastric emptying of liquids (10% dextrose) (B), shown as the 50% emptying time (minutes) in 101 outpatients with diabetes. The normal range is indicated by the shaded area. Reproduced with permission from Jones et al (43).

In people with insulin-treated diabetes (type 1 or type 2), it is important to match exogenous insulin delivery with the availability of carbohydrate to minimize the risk of postprandial hypoglycemia. It is, therefore, intuitively likely that delayed gastric emptying predisposes to lower blood glucose concentrations in the early postprandial period (so-called 'gastric hypoglycemia') (44) and subsequent hyperglycemia. A study in type 1 patients reported that insulin requirements were lower in those with gastroparesis during the first 120 min post-meal, but greater during 180-240 min, compared to patients with normal gastric emptying (45). It is increasingly appreciated that greater glycemic variability is associated with worse outcomes (46). Knowledge of the rate of emptying may potentially assist the clinician in developing strategies to reduce postprandial glycemic variability in individual patients, although this needs to be evaluated formally.

MANAGEMENT OF SYMPTOMATIC GASTROPARESIS (FIGURE 3)

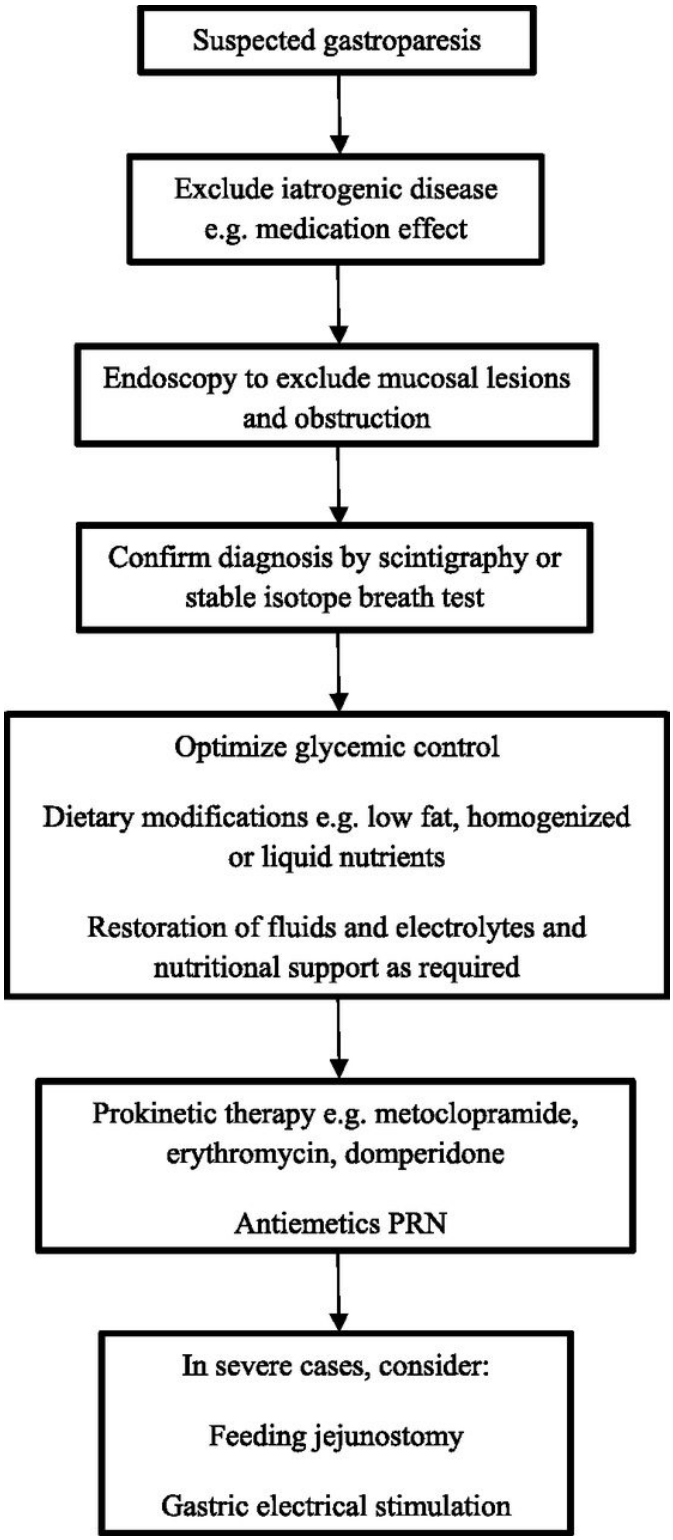

Figure 3. Treatment Algorithm for Diabetic Gastroparesis. PRN, as needed. Reproduced with permission from Du et al (1)

General Measures

Management of gastroparesis should be individualized. In clinical practice, patients are generally advised to consume small, frequent meals that are low in fat and fiber, with more calories as liquids than solids; ingested solids should be those that fragment readily into small particles (47). It should, however, be noted that this advice has not been rigorously evaluated and may be difficult to adhere to, so that the involvement of a dietitian is recommended (48). While optimizing glycemic control is intuitively important, given the inhibitory effect of acute hyperglycemia on gastric emptying, this has not been clearly established to be the case in the chronic setting, although the use of continuous subcutaneous glucose infusion and continuous glucose monitoring has recently been advocated (49).

Concurrent medications should be reviewed and, if possible, those which may slow gastric emptying (e.g. opiates, anticholinergics) ceased. In this regard, it should be appreciated that short-acting GLP-1 receptor agonists (e.g. exenatide BD and lixisenatide) and the amylin analogue, pramlintide (50), improve chronic glycemic control primarily by slowing gastric emptying.

Medications

Although studies involving pro-kinetic medications for treatment of gastroparesis have nearly all been of short duration and involved a modest number of participants, these drugs are used widely and form the mainstay of therapy. Major limitations are their adverse effect profile and tachyphylaxis i.e. diminution in pharmacological effect over time. Tachyphylaxis is thought to particularly affect motilin agonists, although this has not been well studied. Cisapride (a 5HT4 agonist) was used widely for symptomatic management, but shown subsequently to be associated with cardiac adverse effects (prolonged QT interval and 'torsades de pointes') and taken off the market. The most commonly used medications are discussed below. Some prokinetic drugs also have antiemetic properties.

Metoclopramide, a dopamine D2 receptor antagonist, improves gastric emptying (48), and can be administered via oral, intranasal, and subcutaneous routes, but is associated with central nervous system adverse events (including tardive dyskinesia), which may be irreversible. Accordingly, the US Food and Drug Administration (FDA) recommends short duration (12 weeks) use only. An intranasal formulation of metoclopramide under development was reported to be efficacious in women, but not men, implying the potential importance of gender in selecting the route of delivery (51). Metoclopramide can also be injected subcutaneously in an attempt to abort attacks of vomiting. It is the only medication that is approved currently by the FDA for the management of gastroparesis.

Domperidone is another D2 receptor antagonist, but unlike metoclopramide, does not cross the blood-brain barrier and is associated with fewer adverse events, with apparently comparable improvements in gastric emptying and upper gastrointestinal symptoms (48,52). Domperidone may prolong the QT interval and affect metabolism of other medications through the CYP2D6 pathway (48).

The antibiotic, erythromycin, is a motilin receptor agonist and is effective acutely, and inexpensive, but needs to be administered frequently and may also prolong the QT interval and interact with other medications, in this case through the CYP3A4 pathway (48). Acute, intravenous, administration of erythromycin markedly accelerates delayed gastric emptying (53) and may assist in the placement of neuroenteric tubes (54). The gastrokinetic effect of erythromycin is, however, subject to tachyphylaxis (55).

A number of novel agents are in Phase 2-3 trials, including ghrelin and 5HT4 receptor agonists. Ghrelin (sometimes referred to as the 'hunger' hormone) is secreted from the fundus of the stomach and has important roles in nutrient sensing and appetite regulation. Administration of ghrelin accelerates gastric emptying in both animals and humans (56). The outcome of phase 2 trials of the ghrelin agonist, relamorelin, have been promising, with a reduction in upper gastrointestinal symptoms in type 1- and 2 patients with gastroparesis as well as an acceleration of gastric emptying (57). An international phase 3 trial is in progress. Similarly, the oral highly selective 5 HT4 agonists, velusetrag (which was marketed for constipation) and prucalopride, accelerate gastric emptying (58,59). A recent study reported that 4 weeks' of treatment with prucalopride in 32 people with gastroparesis (including 6 with diabetes) improved both symptoms and accelerated gastric emptying, although sub-group analysis of the diabetic cohort was not performed due to small numbers (59).

Treatment-Refractory Gastroparesis

Gastroparesis refractory to dietary and pharmacological intervention is debilitating for the patient and management represents a substantial challenge. Bypassing the stomach using jejunal or parenteral feeding, may be required to sustain nutrition. Gastric electrical stimulation (GES) using the 'Enterra' device) appeared to be a promising therapeutic option when initial unblinded studies were indicative of symptom improvement (22,48) and is currently approved by the FDA for 'humanitarian exemption'; however, a subsequent blinded study failed to show a difference between periods where the stimulator was switched 'on' or 'off' (22,48,60,61). A recently reported randomized cross-over trial reported a reduction in frequency of refractory vomiting following GES for a 4-month period in gastroparesis with or without diabetes but improvement in symptom control did not accelerate gastric emptying or benefit quality of life (62). Similarly, pyloric botulinum toxin injections have fared much better in uncontrolled, than in sham-controlled trials (22). Surgical and endoscopic interventions, such as pyloroplasty and pyloromyotomy, and acupuncture have been described in literature, but lack controlled outcome data (22,48).

Gall Bladder

Gall stones are encountered more frequently in people with diabetes, which is not surprising given that risk factors for the development of stones, such as intestinal dysmotility, obesity, and hypertriglyceridemia, are more common in this group (particularly type 2 diabetes) (63). In addition, impairment of gall bladder motility and autonomic neuropathy, as well as factors such as cholesterol supersaturation and crystal nucleation promoting factors, are considered important. Common techniques used to measure gall bladder motor function include ultrasound and scintigraphy. Some studies have found increased fasting gall bladder volume, while in others, there was no difference, or even a reduction, in people with diabetes. It is possible that differences in the techniques employed (ultrasound or scintigraphy), and the presence of autonomic neuropathy may account for these discrepancies. Many studies, however, have reported impairment in postprandial gall bladder emptying in diabetes, sometimes termed 'diabetic cholecystoparesis' (63). It is also possible that delayed gastric emptying contributes to delayed emptying from the gall bladder. In health, acute hyperglycemia inhibits gall bladder motility in a dose-dependent manner (64). An increased prevalence of gall bladder-related disorders (including cholecystitis and cholelithiasis) is associated with the use of GLP-1 receptor agonists (65) and may potentially relate to a drug-induced prolongation of gall bladder refilling time (66). Similarly, an increase in gall-bladder disease has been reported post-bariatric surgery in obese individuals (including those with diabetes) with the

implication that dramatic weight loss may predispose (67).

Small Intestine

While diabetic enteropathy is common, it has been studied much less comprehensively than diabetic gastroparesis (68). Symptoms of constipation and diarrhea are discussed in the section on large intestinal disorders in diabetes, which follows.

Traditionally, vagal dysfunction has been regarded as the major impairment in diabetic enteropathy. However, as is the case with gastroparesis, recent evidence has suggested a critical role for both interstitial cells of Cajal and nNOS (31). Acute hyperglycemia also has a major effect on postprandial small intestinal motility in health (and, presumably, diabetes) by reducing the amplitude of duodenal and jejunal pressure waves, as well as retarding duodenal-cecal transit (69).

Small intestinal bacterial overgrowth (SIBO), probably secondary to altered small intestinal motility, is commonly encountered in diabetes; estimates range between 15-40% in type 1 diabetic cohorts. A major limitation of these studies is lack of a 'gold standard' method for diagnosis.

There is limited information about small intestinal glucose absorptive function in diabetes but, based on animal models, it has been suggested that carbohydrate digestion is disordered. For example, streptozotocin-induced diabetes in rats, is associated with an increase in mucosal absorption of glucose (70). We have demonstrated that small intestinal glucose absorption is comparable in uncomplicated type 1 patients and healthy controls, but probably affected by both duodenal motility and the prevailing glycemic environment (71) - when blood glucose was elevated, intestinal glucose absorption was increased, while absorption was comparable to that in healthy controls during euglycemia. A fundamental limitation in interpreting the outcome of the numerous studies which have reported the potent modulatory effect of the rate of gastric emptying on postprandial glycemia is their failure to discriminate between effects mediated by changes in gastric emptying from those potentially secondary to changes in small intestinal transit (72).

DIAGNOSIS OF ENTEROPATHY

Diabetic enteropathy is often a diagnosis of exclusion. It is essential to exclude underlying non-diabetes related etiologies where relevant – for example, testing for celiac disease in type 1 patients is recommended. It should be appreciated that gastrointestinal adverse effects occur frequently with commonly used anti-diabetic medications. Metformin, GLP-1RAs, SGLT2 inhibitors, and particularly alpha-glucosidase inhibitors (e.g. acarbose), which are used widely, are commonly associated with intestinal symptoms.

Small intestinal manometry (measurement of contractile activity) may provide mechanistic insights, but its use is limited to specialized centers. Scintigraphy can quantify small intestinal transit, but the diagnostic significance is uncertain. More recently, technologies, including ingestible wireless capsules (such as the SmartPill) and continuous tracking of capsules (3D-Transit system), have been employed; these are promising, but require further validation before clinical exploitation. Small intestinal bacterial overgrowth can be diagnosed by aspiration and culture of intestinal fluid or breath tests, but both have substantial limitations and neither technique can be regarded as a "gold standard".

MANAGEMENT OF ENTEROPATHY

Symptom management with medications is common. Prokinetic agents used for gastroparesis are

commonly employed for management of disordered intestinal motility, but much less well evaluated. Small intestinal bacterial overgrowth can be treated with antibiotics, such as rifamixin (most common but expensive), amoxicillin-clavulanic acid, or metronidazole. Not surprisingly, small intestinal bacterial overgrowth frequently relapses.

Large Intestine

The major function of the colon is to re-absorb water and electrolytes from the intraluminal contents, to concentrate and solidify the waste product, and prepare for its elimination. The most common lower gastrointestinal symptoms are constipation, diarrhea, abdominal pain, and distention. It is difficult to estimate a 'true' incidence and prevalence. Cohort studies have reported the presence of chronic constipation in up to 25% of people with type 1 and 2 diabetes, while that of chronic diarrhea is up to 5% (73). Bytzer et al reported a higher prevalence of constipation and diarrhea in people with type 2 diabetes (15.6% compared with 10% in those without diabetes) (3). A recent report analyzing data from the large-scale US public survey, NHANES, found that chronic diarrhea was more common in people with type 1 and 2 diabetes compared with non-diabetic controls (~ 11% vs 6%) (74).

CONSTIPATION

The etiology of constipation in diabetes is likely to be multifactorial. A study involving only 10 patients found prolonged colonic transit time in those with constipation (13). Autonomic neuropathy is thought to be important; constipation is more common in those with diabetes and autonomic impairment (75). Validated techniques for evaluation include colonic transit scintigraphy and the use of radio-opaque markers and wireless motility capsules (76), but their utility in routine clinical practice has not been fully established.

Management of diabetic constipation must include a medication history review and those that may cause constipation should be ceased, if feasible (figure 4). For mild constipation, the American Diabetes Association recommends lifestyle modification such as increased physical exercise and dietary fiber. Over-the-counter laxatives (bulk, osmotic or stimulatory) such as Senna, Bisacodyl and water- soluble fiber supplements are commonly prescribed. Other medications like lactulose, linaclotide, and lubiprostone (the latter two available by prescription in the United States) have been used. There are no head-to-head trials to determine which agent is superior. However, it has been suggested that lactulose may potentiate glucose- lowering (77). Lubiprostone, which acts by direct activation of CIC-2 chloride channels on enterocytes, has been reported to improve both spontaneous bowel movements and accelerate colon transit in a randomized controlled trial in a cohort with diabetes (78). In a randomized trial cholinesterase inhibition with pyridostigmine in 30 people with diabetes (12 T1D, 18 T2D) and chronic constipation, there were superior improvements in both bowel function and colonic transit compared with placebo (79).

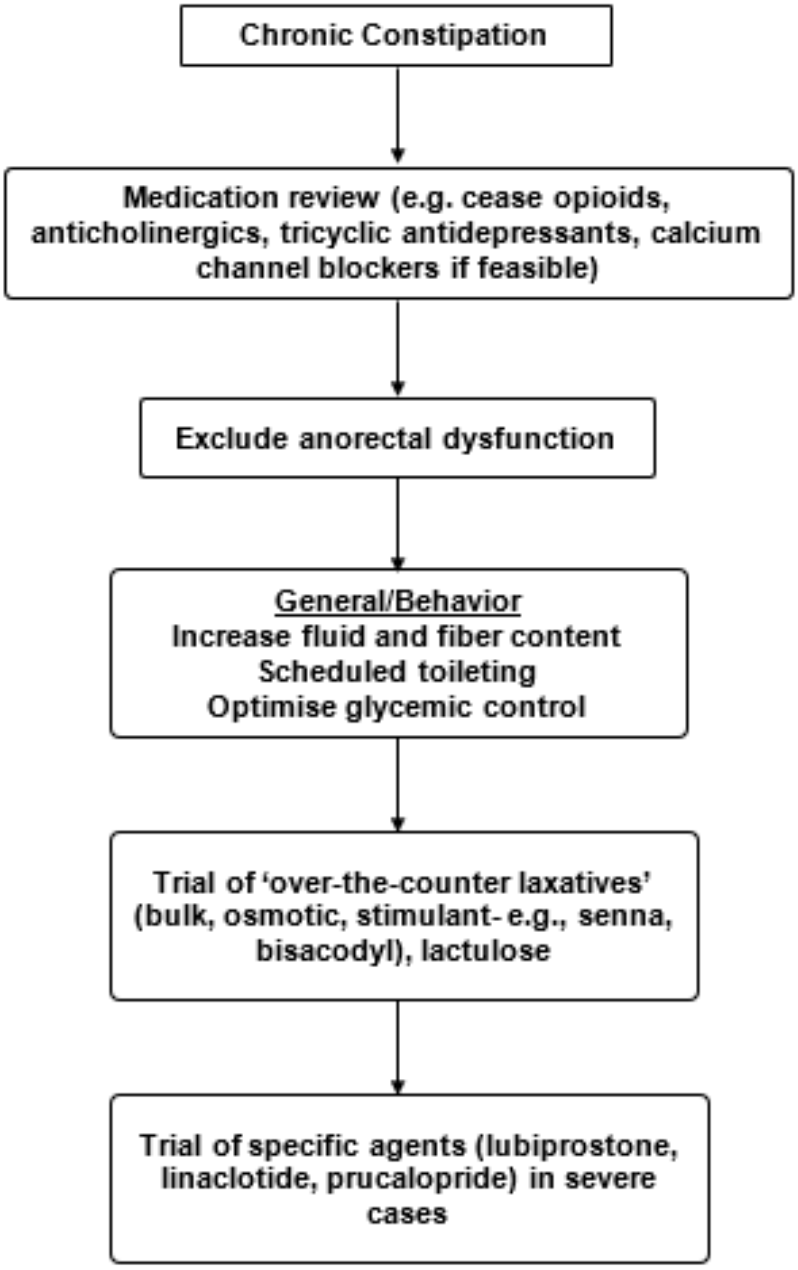

Figure 4. Algorithm for Management of Chronic Constipation in Patients with Diabetes.

CHRONIC DIARRHEA

"Diabetic diarrhea" has been traditionally considered a manifestation of autonomic neuropathy (80). The typical symptom is large volume, painless, nocturnal, diarrhea with or without fecal incontinence. Again, the diagnosis essentially represents one of exclusion and it is important to distinguish diarrhea from fecal incontinence. It should be remembered that widely used glucose-lowering therapies, including metformin (malabsorptive), acarbose (osmotic), and GLP-1 receptor agonists, not infrequently cause diarrhea. It is likely that optimizing glycemic control is important in the management of diabetic diarrhea (81), but again, this has not been rigorously evaluated. Dietary

strategies include a low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) diet under guidance of a qualified dietitian, although this has not been evaluated specifically for the diabetes population in clinical trials. Loperamide, an over-the-counter mu opioid receptor agonist, is used widely. Bile acid sequestrants, such as cholestyramine and colesevelam, are used when bile salt malabsorption is suspected, and have the added advantage of reducing LDL cholesterol and glycated hemoglobin. Other agents include clonidine, diphenoxylate, octreotide, and ondansetron (figure 5).

It has been reported that people with diabetes, especially type 1 diabetes, are more likely to have inflammatory bowel disease (IBD) such as ulcerative colitis. Diabetes also appears to be an independent risk factor for Clostridium difficile infection where metformin appears to be protective, probably via its action on the gut microbiota (82). It has also been suggested that there is a link between diabetes and colorectal malignancy (83), and diabetes is associated with worse outcomes and response to colorectal surgery. Interestingly, some observational studies suggest that metformin may have chemo-preventative properties against colorectal malignancy (84).

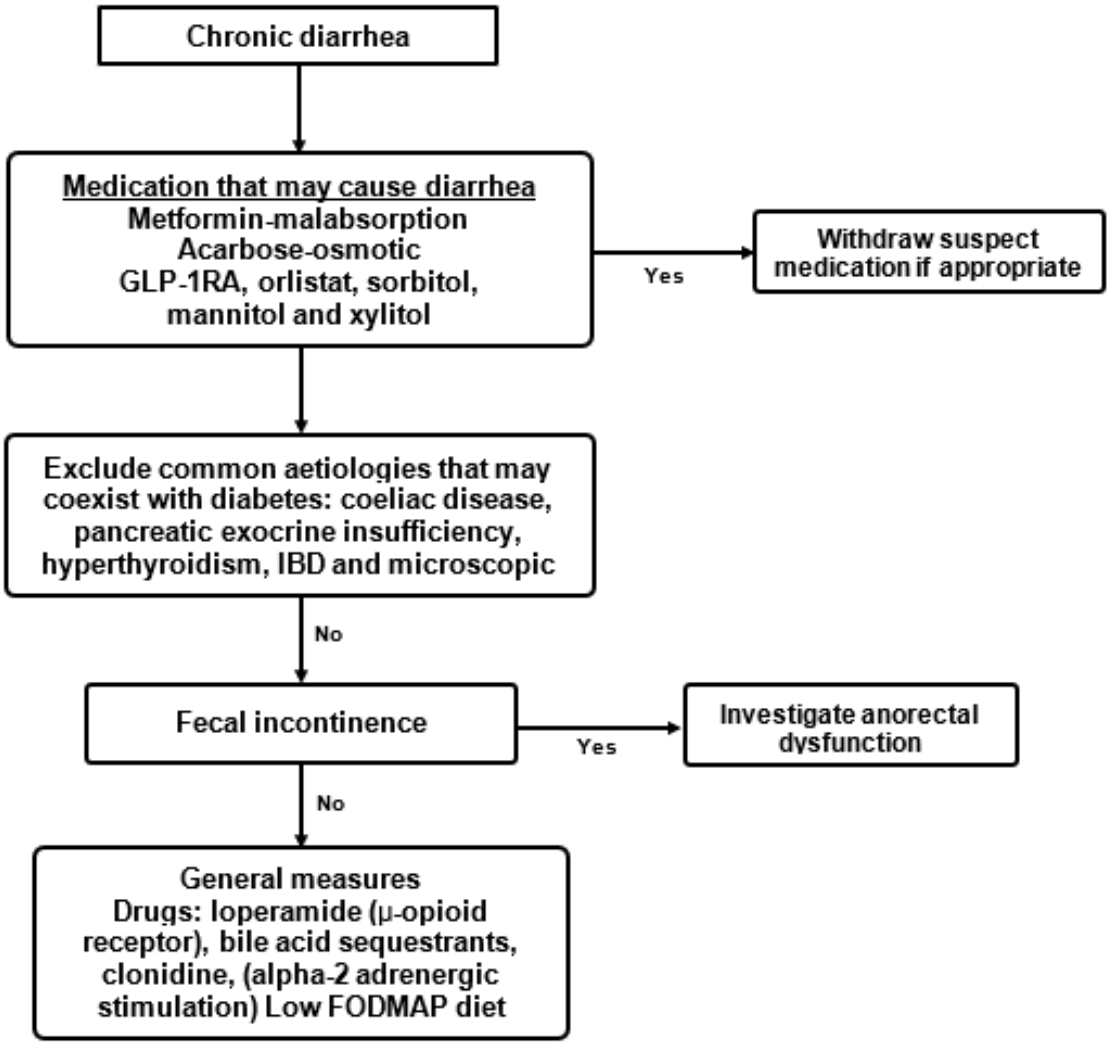

Figure 5. Algorithm for Management of Chronic Diarrhea in Patients with Diabetes.

Rectum and Anus

Fecal incontinence occurs more frequently in people with diabetes and is associated with the duration of disease, and the presence of microvascular complications, including autonomic and peripheral neuropathy (85). Both internal anal sphincter tone and anal squeeze pressures are reduced in diabetes compared with healthy controls (86,87). A key step in management is to exclude important differential diagnoses, such as colorectal malignancy and irritable bowel disease (88). No single test can be regarded as 'gold standard', but anorectal manometry (conventional, 3D or high resolution) is very useful in clinical practice to estimate ano-rectal motor abnormalities, while barium defecography is useful to detect rectal motory, sensory and structural abnormalities (89).

Treatment of fecal incontinence is rarely curative, and the focus of management is to improve symptoms and quality of life. Fecal impaction with overflow can be managed by initial manual removal of stool from the rectum and enemas (promoting evacuation) and the subsequent prescription of bulk laxatives, increasing fiber intake, and toilet training. Operant reconditioning of rectosphincteric responses, called 'biofeedback' training, was first described by Engel et al in 1974 (90) and can be useful in treating fecal, as well as urinary, incontinence. The technique involves visual demonstration of voluntary contraction of external anal sphincter (EAS) contraction to the patient and training to improve the quality of the response (both strength and duration). Biofeedback training is effective in the longer term in only about 60% of patients in clinical trials; those with a low bowel satisfaction score and having digital evacuations fare better (91).

GASTROINTESTINAL EFFECTS OF ANTI-DIABETIC MEDICATIONS AND THEIR IMPLICATIONS FOR CLINICAL PRACTICE

Gastrointestinal adverse effects are extremely common in people treated with glucose-lowering medications for type 2 diabetes. In the case of alpha glucosidase inhibitors such as acarbose and miglitol, these effects (e.g., diarrhea and abdominal distention) are predictable sequelae of the malabsorption of carbohydrate (92) . There is new information in relation to two classes of medications (biguanides and GLP-1 receptor agonists).

Metformin, a biguanide of herbal origin, remains a first line pharmacological agent of choice for type 2 diabetes. The precise mechanisms of action remain uncertain, although it clearly has multiple effects, including in the liver (block gluconeogenesis), as an insulin sensitizer, and direct actions through the gut, including slowing of gastric emptying (93) . Up to 25% of people using metformin report gastrointestinal adverse events, particularly diarrhea and nausea. Common outpatient clinic strategies to minimize these include initiating treatment at a low dose (i.e., 500mg/day) and gradually up-titrating to usually ~2000 mg/day, use of extended-release formulations and avoiding ingestion on an empty stomach, although evidence to support these approaches is not robust (94).

Similarly, GLP-1 receptor agonists (but not DPP-IV inhibitors which lead to only a modest rise in plasma GLP-1 levels), commonly cause gastrointestinal adverse effects. As mentioned, GLP-1 is a gut-based peptide with a profound, but variable, action to slow gastric emptying. This slowing is more marked when baseline gastric emptying is relatively more rapid and is predictive of the reduction in blood glucose following a meal (95) . GLP-1 plays a physiological role to slow gastric emptying - gastric emptying is accelerated by the specific GLP-1 antagonist, exendin 9-39 (96) and delayed by exogenous administration of GLP-1 in modestly supra-physiological plasma levels (97). Upper gastrointestinal events induced by GLP-1 are, likely to reflect, in part, delayed emptying. As effects

are also observed in the fasting state, a direct action on CNS GLP-1 receptors (most notably, area postrema in the brain stem) has also been postulated. A direct effect on the gut is likely to contribute to lower gastrointestinal adverse events such as diarrhea. GLP-1 secreting cells (specialized entero-endocrine 'L' cells) are found throughout the gastrointestinal tract, and GLP-1 may exert a local excitatory action in smooth muscle or through the intramural autonomic plexus to increase motility and induce diarrhea (98,99) . A fundamental limitation of the vast majority of clinical trials involving GLP-1 receptor agonists is that gastrointestinal adverse effects have been assessed using participant recall and not validated questionnaires. Nevertheless, results from large cardiovascular outcome trials relating to the use of GLP-1 agonists indicate that the proportion of participants discontinuing GLP-1 receptor agonists due to adverse gastrointestinal events ranges between 4.5 to 13% (100) . Nausea appears to be the most common symptom (up to 25%), with vomiting and diarrhea reported by about 10% (101). A retrospective analysis of 32 phase-3 trials involving 'long' and 'short' acting GLP-1 receptor agonists reported that gastrointestinal adverse effects are also dose-dependent, and that 'long' acting GLP-1 receptor agonists are associated with less nausea and vomiting, but more diarrhea when compared to short-acting GLP-1 receptor agonists (101). Symptoms are reported most frequently at the time of initiation of a GLP-1 receptor agent and may persist for several hours or days probably dependent on the T_{max} of the drug (100). Gradual titration of dose is recommended, although evidence to support this approach is uncontrolled.

We, and others, have demonstrated employing the gold standard technique of scintigraphy to quantify gastric emptying and both 'long' and 'short' acting GLP-1 receptor agonists delay gastric emptying, although the magnitude of this deceleration appears to be greater with 'short' acting GLP-1 receptor agonists (95,102-104) . Moreover, it is appreciated that GLP-1 receptor agonists may slow gastric emptying profoundly in doses much lower than those used in the management of type 2 diabetes (2). It had been suggested, incorrectly, that long acting GLP-1 receptor agonists, which are now the most widely used form, have no effect on gastric emptying with sustained use (2). A further limitation of clinical trials of GLP-1 receptor agonists is that gastric emptying has either not been measured or a sub-optimal technique used (105).

Instances of apparently GLP-1 receptor agonist-induced gastroparesis are increasingly appearing in the medical literature as case reports (106). The prevalence of marked delay in gastric emptying induced by GLP-1 receptor agonists remains uncertain but has stimulated guidelines in relation to their use prior to elective surgery or endoscopy. For example, the American Society of Anesthesiologists (ASA), has recently published consensus guidelines on pre-operative management of people using GLP-1 agonists and have advised withholding a long-acting agent for at least one week prior to the procedure/surgery (107). Such recommendations lack a strong evidence base. It is uncertain whether these recommendations from the ASA will be universally adopted but it appears intuitively unlikely. Recently a UK-based expert group comprising endocrinologists, anesthetists, and pharmacists have recommended against this generic advice (107) primarily on the lack of robust data demonstrating an increased risk of aspiration under anesthesia, while being on a GLP-1 receptor agonist, that the recommended duration of avoidance may be inadequate (for example, in people taking 1mg semaglutide, avoidance of one week is likely to reduce the plasma drug concentration by about half, which is still likely to slow gastric emptying), at least in some people and reintroduction of GLP-1 receptor agonists once normal food intake has been established has not clearly defined and there is intuitively the high potential for a deterioration in glycemic control, postoperatively including an increase in glycemic variability. They instead

recommend that preoperative assessment for risk of aspiration be individualized.

In people co-prescribed with insulin and GLP-1 receptor agonists, there is likely to be an increased risk of a mismatch between insulin delivery and availability and intestinal glucose absorption due to prolonged gastric retention to predispose to hypoglycemia. Clinicians should be circumspect in prescribing a GLP-1 agonist and insulin combination in those who have impaired awareness of hypoglycemia or suspicion of delayed gastric emptying.

PANCREATIC EXOCRINE SUFFICIENCY IN DIABETES

There is an intricate anatomical association of endocrine and exocrine components of the pancreas which appears to translate to a reciprocal relationship between endocrine and exocrine dysfunction (108). However, a wide variation in the prevalence of pancreatic exocrine insufficiency in diabetes has been reported, with evidence that it is greater in type 1 (approx. 25-75%). compared with type 2 (approx. 25-50%) diabetes (109). The majority of these studies are in hospitalized populations; it is likely that prevalence in the community is lower. Our recent study of community type 2 patients reported a lower prevalence of 9% (110). The etiology in type 1 is thought to be a combination of lack of insulin (+/- glucagon and somatostatin), autoimmunity, autonomic neuropathy, and microvascular damage while the latter two contribute to pancreatic exocrine insufficiency in type 2 diabetes – it has been suggested that this may explain why pancreatic exocrine insufficiency is more common in patients with type 1 diabetes (109). Common symptoms are variable and include diarrhea (steatorrhea), abdominal pain, and failure to thrive in children. It is important to discriminate pancreatic and non-pancreatic causes of malabsorption. The relatively deep-seated location of the pancreas hinders easy assessment of its exocrine function. Diagnostic tests can be direct or indirect (111). Direct tests involve stimulation with exogenous hormones or nutrients while simultaneously collecting pancreatic secretions via duodenal intubation. This technique has many logistical issues (high costs, requirement of expertise, invasive nature) which limits its clinical utility despite being the most sensitive and specific. Examples of indirect tests include the 3-day fecal fat, fecal elastase-1 measurement, and breath tests (^{14}C-triolein). Of these, the most common indirect and non-invasive (as well as relatively inexpensive) test in clinical practice is measurement of fecal elastase 1. It has been suggested that a fecal elastase-1 level less than 200 ug/g stool is indicative of mild pancreatic exocrine insufficiency, and a level of 100 ug/g stool of severe pancreatic exocrine insufficiency (108). It should be appreciated that sensitivity (55%) and specificity (60%) of fecal elastase-1 in diagnosing pancreatic exocrine insufficiency are modest. Measurement of fat-soluble vitamins may be indicated.

The principles of general management of pancreatic exocrine insufficiency include consumption of smaller, frequent meals, abstinence from alcohol, and involvement of an experienced dietitian. Pancreatic enzyme replacement therapy is regarded as the cornerstone of treatment (108). It is uncertain whether supplementation with pancreatic enzyme replacement therapy in those with type 2 diabetes and pancreatic exocrine insufficiency reduces postprandial glycemic excursions (110). Adjunctive therapies such as acid-suppressing agents are reserved for those with symptoms despite high-dose pancreatic enzyme replacement therapy.

CONCLUSIONS

Both gastrointestinal symptoms and dysmotility are common in diabetes and represent an important component of management. Gastric emptying is also a major determinant of postprandial glycemic control and may be modulated therapeutically to improve it. Current management of disordered gastrointestinal

function, particularly gastroparesis, is primarily empirical, although a number of novel agents are in development; results of these clinical trials are eagerly anticipated.

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