Relationships of Upper Gastrointestinal Motor and Sensory Function With Glycemic Control

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Acute changes in the blood glucose concentration have a major reversible effect on esophageal, gastric, intestinal, gallbladder, and anorectal motility in both healthy subjects and diabetic patients. For example, gastric emptying is slower during hyperglycemia than euglycemia and accelerated during hypoglycemia. Acute hyperglycemia also affects perceptions arising from the gastrointestinal tract and may, accordingly, be important in the etiology of gastrointestinal symptoms in diabetes. Elevations in blood glucose that are within the normal postprandial range also affect gastrointestinal motor and sensory function. Upper gastrointestinal motor function is a critical determinant of postprandial blood glucose concentrations by influencing the absorption of ingested nutrients. Interventions that reduce postprandial hyperglycemia, by modulating the rate of gastric emptying, have the potential to become mainstream therapies in the treatment of diabetes.

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Recent studies have provided important insights into the complex relationships between upper gastrointestinal function and glycemic control in diabetes; it is now recognized that postprandial blood glucose concentrations are both a determinant of, as well as determined by, the delivery of nutrients from the stomach into the small intestine. Furthermore, the prevalence of upper gastrointestinal symptoms, which occur frequently in diabetic patients (1,2), is related to glycemic control (3,4).

Disordered gastrointestinal function in diabetes has been attributed to irreversible autonomic neuropathy (5), but it is now clear that acute changes in the blood glucose concentration have a major reversible influence on upper-gut motor and sensory function (6–31). Marked hyperglycemia (blood glucose concentration ~15 mmol/l) appears to affect every region of the gastrointestinal tract. Smaller elevations of blood glucose that are within the normal postprandial range (8–10 mmol/l) also influence gut function and may be important in the regulation of gut motility and sensation in healthy individuals.

Although it is now accepted that glycemic control, as assessed by HbA_{1c} concentrations, is a major determinant of both the development and progression of diabetic microvascular complications (32,33), the contribution of transient postprandial hyperglycemia has only recently been demonstrated (34). Upper gastrointestinal motor function, particularly the rate of gastric emptying, is a major determinant of postprandial blood glucose concentrations, and there is increasing support for the concept that the modulation of gastric emptying could be used to optimize glycemic control in diabetes (35).

The purpose of this review is to summarize current knowledge relating to the effects of the blood glucose concentration on gastrointestinal motor and sensory function and the impact of upper gastrointestinal function on glycemic control.

EFFECTS OF BLOOD GLUCOSE CONCENTRATION ON UPPER GASTROINTESTINAL MOTOR AND SENSORY FUNCTION

The majority of studies that have evaluated the effects of acute changes in blood glucose concentration on gastrointestinal motor and sensory function have involved healthy subjects; furthermore, studies in diabetic patients have usually not taken any account of the blood glucose concentration. Nevertheless, observations in both animal models and diabetic patients have, in general, been consistent with those obtained in healthy humans. Most studies have focused on gastric motility and emptying, and there is less information about small-intestinal motility or sensory function of the upper gut. Information about the impact of chronic, as opposed to acute, glycemic control on gut function is also limited, although it appears that acute changes in the blood glucose concentration play the dominant role.

Motor function

Esophagus. Delayed esophageal transit and abnormal esophageal motility occur frequently in patients with long-standing diabetes (36), and the prevalence of gastroesophageal reflux disease also appears to be increased (37). In healthy volunteers, marked hyperglycemia (blood glucose ~15 mmol/l) decreases lower esophageal sphincter pressure and the velocity of esophageal peristalsis, but increases the duration of peristaltic waves, when compared with euglycemia (6). In contrast, "physiological" hyperglycemia (blood glucose ~8 mmol/l) increases the peristaltic velocity compared with euglycemia (~4 mmol/l) (7). In both healthy subjects and patients with gastroesophageal reflux disease, the majority of

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Abbreviations: 3-OMG, 3-*O*-methylglucose; GLP-1, glucagon-like peptide 1; NO, nitric oxide.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

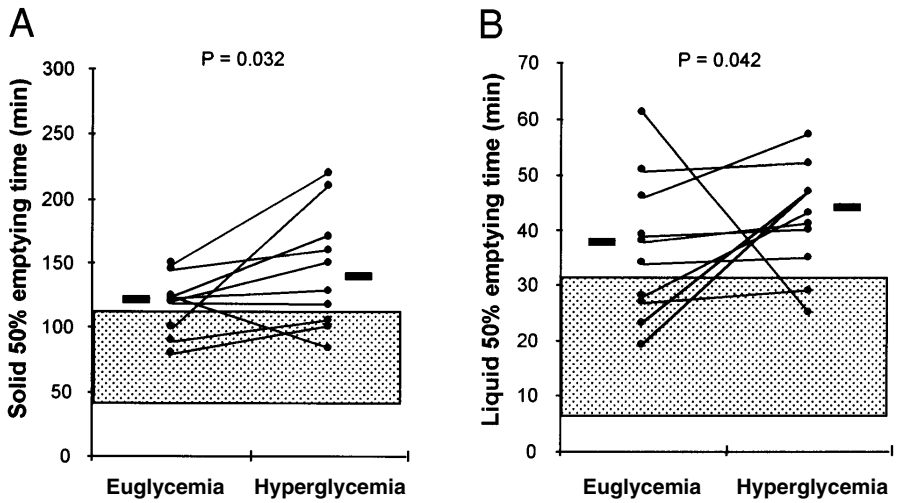

Figure 1—*Solid gastric emptying (A) and liquid gastric emptying (B) in 10 type 1 diabetic patients during euglycemia and hyperglycemia. Mean values are indicated by the solid bars. The ranges in healthy subjects are shown by the shaded areas. From Fraser et al. (13).*

reflux episodes are associated with spontaneous relaxation of the lower esophageal sphincter (38,39); in healthy subjects, the number of transient sphincter relaxations is increased during hyperglycemia (8). The effects of acute hyperglycemia on esophageal motility have not been formally evaluated in diabetic patients.

Stomach. Initial studies of the effects of acute changes in the blood glucose concentration on gastric emptying were performed in healthy subjects. Stunkard (40) reported in 1957 that intravenous glucose abolished gastric "hunger contractions," whereas Aylett (41) established in 1962 that there is an inverse relationship between the rate of gastric emptying of water and the blood glucose concentration. Acute hyperglycemia, induced by intravenous glucose infusion, was subsequently shown to slow the emptying of nutrient-containing liquid and solid meals (9,10). Conversely, gastric emptying of both solids and liquids is accelerated during insulin-induced hypoglycemia (11).

As early as 1937, Ferroir reported that, in diabetic patients, stomach contractions were "slow, lack vigor, and die out quickly," and that treatment with insulin "alleviates secretory and motor abnormalities even without resulting in hypoglycemia" (42). In type 1 diabetic patients, as in healthy subjects, acute hyperglycemia (blood glucose 16–20 mmol/l) slows emptying of both solids (13,14) and nutrient liquids (13) when compared with euglycemia (5–8 mmol/l) (Fig. 1). It is not known whether the response to hyperglycemia depends on the rate of gastric emptying during euglycemia or previous (long-term) glycemic control, although it is clear that hyperglycemia slows gastric emptying even in patients with established autonomic neuropathy (14). The effect of acute hyperglycemia on gastric emptying in patients with type 2 diabetes has not been specifically studied, although in a cross-sectional study of type 2 diabetic patients, both the emptying of liquids and the duration of the lag phase for solids were related to the blood glucose concentration (15). In type 1 diabetic patients without complications, gastric emptying is accelerated markedly during hypoglycemia when compared with euglycemia (16), as in healthy subjects (11); it is not known whether hypoglycemia has the capacity to accelerate gastric emptying in patients with autonomic neuropathy and established gastroparesis, nor have patients with type 2 diabetes been studied. Hyperglycemia has recently been shown to attenuate the prokinetic effect of intravenous erythromycin on gastric emptying in both healthy subjects (17) and diabetic patients (43); it is not known whether the action of other prokinetic drugs is impaired by hyperglycemia, although this would appear likely. The effects of extreme hyperglycemia (blood glucose concentrations >20 mmol/l) have not been formally evaluated, although it is well recognized that diabetic ketoacidosis may be associated with nausea, vomiting, and acute gastric dilatation.

Changes in the blood glucose concentration that are within the normal range also influence gastric emptying; emptying of solids and liquids is slower at a blood glucose level of 8 mmol/l than it is at a level of 4 mmol/l in both healthy subjects and patients with type 1 diabetes (18) (Fig. 2). The acceleration of gastric emptying by erythromycin is also impaired by physiological hyperglycemia (44). There is, accordingly, a dose-dependent relationship between the rate of gastric emptying and the blood glucose concentration, as reflected in progressively slower absorption of glipizide, as the blood glucose increases above 7 mmol/l (45).

The rate of gastric emptying is determined by the integrated activity of the proximal stomach, antrum, pylorus, and duodenum (5). The proximal stomach has the capacity to slow emptying by retaining ingesta in the fundus, while the antropyloroduodenal region appears to drive the pulsatile flow of contents across the pylorus. Pyloric contractile activity, particularly sustained tonic pressure, is associated with cessation of transpyloric flow (46). The interaction of nutrients with the small intestine plays a major role in the regulation of gastric emptying; small-intestinal nutrient slows gastric emptying, and this is associated with relaxation of the proximal stomach, suppression of antral contractions, and the stimulation of pyloric motility (47). The gastric electrical slow wave, which normally has a frequency of three cycles per minute, underlies the spatiotemporal arrangement of gastric contractions (48); disturbances of this rhythm, particularly an increased frequency (tachygastria), occur commonly in diabetic patients with delayed gastric emptying and gastrointestinal symptoms and may be of pathogenetic significance (49).

A number of studies have evaluated the motor mechanisms by which hyperglycemia influences gastric emptying; various stomach regions appear to have differing thresholds to the effects of hyperglycemia (for example, a lower threshold in the antrum than in the fundus). In healthy volunteers (19,20) and patients with type 1 diabetes (21), marked hyperglycemia (~15 mmol/l) relaxes the proximal stomach. Physiological hyperglycemia does not affect proximal gastric motility, at least in the fasted state (50). Acute hyperglycemia suppresses the frequency and propagation of antral pressure waves under fasting and postprandial conditions (22–24). Although most evident during marked hyperglycemia (blood glucose ~14 mmol/l), suppression of antral motility is apparent from

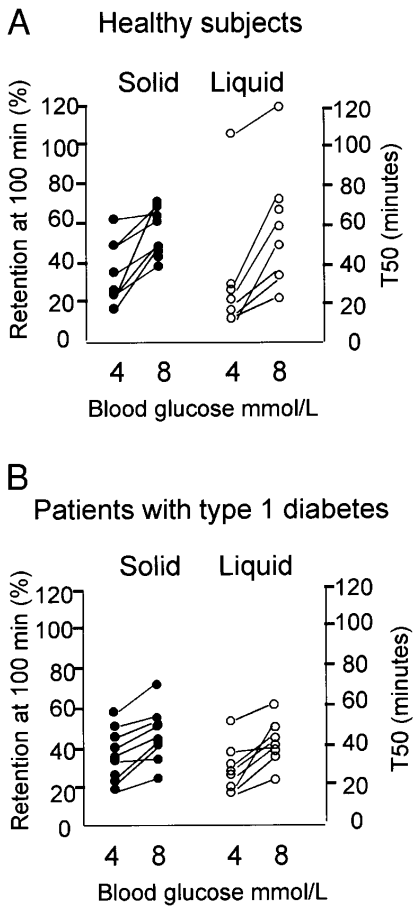

Figure 2—*Solid and liquid gastric emptying in healthy subjects (A) and patients with type 1 diabetes (B) during euglycemia (blood glucose 4 mmol/l) and physiological hyperglycemia (blood glucose 8 mmol/l). (From Schvarcz et al. [18].)*

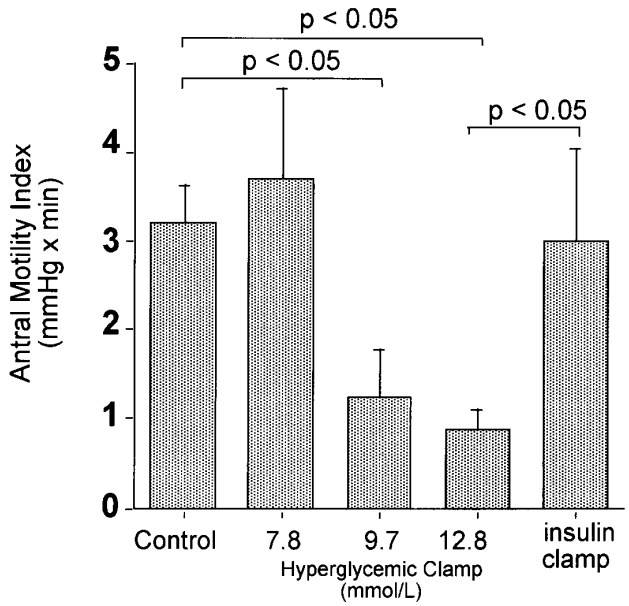

Figure 3—*Dose-dependent effect of hyperglycemia on postprandial antral motility in healthy subjects. The antral motility index is less than the control value during hyperglycemic clamping at both 9.7 and 12.8 mmol/l and at 12.8 mmol/l is less than during euglycemic hyperinsulinemia. (From Hasler et al. [24].)*

a threshold blood glucose concentration as low as 8 mmol/l (22,24,31) (Fig. 3); this dose-response relationship is concordant with that observed between the rate of gastric emptying and the blood glucose concentration. In patients with type 1 diabetes, both the antral motility index (derived from frequency and amplitude) and the number of propagated postprandial antral waves are less during hyperglycemia (blood glucose concentration 16–19 mmol/l) when compared with euglycemia (5–8 mmol/l) (14). In healthy subjects, hyperglycemia attenuates the stimulation of antral pressure waves and propagated antral wave sequences by erythromycin (51). Marked hyperglycemia (~15 mmol/l) stimulates phasic pressure waves localized to the pylorus in healthy subjects during fasting (25); the effects of hyperglycemia on pyloric motility in diabetes have not been evaluated. Acute hyperglycemia is associated with an increased prevalence of tachygastria in both healthy subjects (24) and patients with type 1 diabetes (52).

There is evidence that physiological changes in blood glucose concentration act synergistically with stimuli arising from the small intestine to slow gastric emptying. For example, at a blood glucose concentration of 10 mmol/l, the phasic and tonic pyloric responses to duodenal distension are greater than during euglycemia (26), whereas the stimulation of pyloric tone by exogenous cholecystokinin, a peptide normally released by the interaction of nutrients with the small intestine, is greater at a blood glucose concentration of 8 mmol/l than 4 mmol/l (53).

The motor correlates of the acceleration in gastric emptying during hypoglycemia are poorly defined, and no studies have been performed in diabetic patients. In healthy subjects, insulin-induced hypoglycemia does not appear to affect antral or pyloric motility in the fasted state (54); postprandial motility has not been evaluated.

Small intestine. In healthy volunteers, marked hyperglycemia (blood glucose 12–15 mmol/l) decreases the motility index and propagation of duodenal and jejunal waves (23), reduces the cycle length of interdigestive motor activity in the fasted state (27), and slows small-intestinal transit (28,29). Elevation of the blood glucose to the upper end of the physiological range (10 mmol/l) decreases duodenal compliance while increasing the stimulation of duodenal waves by duodenal balloon distension (26); a less compliant (more "stiff") duodenum may contribute to the slowing of gastric emptying during hyperglycemia. The effects of physiological hyperglycemia on the remainder of the small intestine have not been evaluated. In type 1 diabetic patients, acute hyperglycemia is associated with suppression of proximal duodenal pressure waves (14).

Other gut regions. Effects of acute hyperglycemia on motor function have been observed at every level of the gastrointestinal tract that has been studied. In healthy subjects, hyperglycemia inhibits gallbladder contraction in response to intraduodenal fat or intravenous cholecystokinin (28,55) and, as with gastric emptying and antral motility, the effect is dose dependent, at least in the 8–16 mmol/l range of blood glucose concentrations (56,57) (Fig. 4). Both the gastrocolic and ascending components of the colonic peristaltic reflex are inhibited at a blood glucose concentration of 15 mmol/l (58), although no effects on colonic tone or motor patterns were evident in another study (59). Rectal compliance has been reported to be increased (60) or unchanged (61) during marked hyperglycemia (12–15 mmol/l), whereas resting and maximal squeeze pressures in the anus are either decreased (60) or

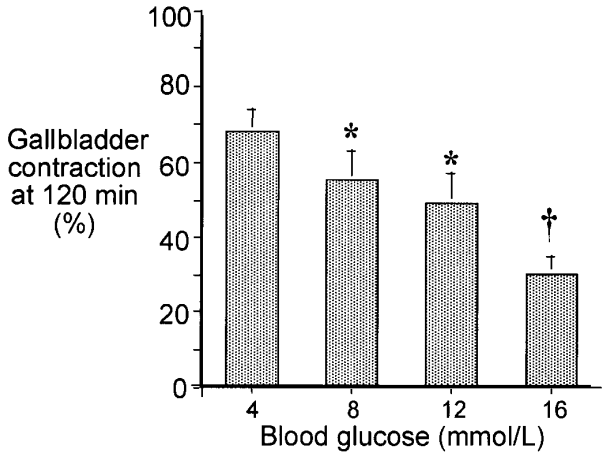

Figure 4—*Dose-dependent effect of hyperglycemia on postprandial gallbladder motility in healthy subjects. *P < 0.05 compared with 4 mmol/l; †P < 0.05 compared with 4, 8, and 12 mmol/l. (From Gielkens et al. [57].)*

unchanged (61,62). Methodological differences, particularly relating to the mode of rectal distension (slow ramp or rapid phasic), may account for some of the apparent discrepancies between studies (61,63).

In patients with type 1 diabetes, gallbladder contraction stimulated by intravenous cholecystokinin is also blunted at a blood glucose of 15 mmol/l when compared with euglycemia (55). Reductions in rectal compliance and maximum anal squeeze pressures during hyperglycemia have recently been confirmed in a group of patients with type 1 and type 2 diabetes (64). There is no information about the effects of hyperglycemia on colonic motility in diabetes; this issue is potentially important, since constipation occurs frequently in these patients (65).

In addition to its effects on motor function, acute hyperglycemia also affects upper gastrointestinal exocrine secretory function, with suppression of gastrin, gastric acid, and pancreatic exocrine secretion in healthy subjects (66–68).

Sensory function

The prevalence of symptoms referable to the upper gastrointestinal tract, such as early satiation or nausea, is greater in diabetic patients with poor glycemic control, as assessed by HbA_{1c} concentration (3) and self-report (4), supporting the concept that the effects of blood glucose concentration on the perception of upper gastrointestinal stimuli are clinically important. To date, most studies addressing this issue relate to the stomach and have involved healthy subjects.

In the esophagus, the threshold for perception of balloon distension is reduced by elevations of the blood glucose concentration within the physiological range in healthy subjects (7). The amplitude of cortical evoked potentials, recorded in response to rapid esophageal balloon distension, is increased during marked hyperglycemia (~13 mmol/l), and this is likely to represent an objective correlate of heightened visceral sensation (69).

In healthy subjects, marked hyperglycemia (blood glucose ~15 mmol/l) increases perceptions, such as nausea and fullness, during proximal gastric distension, both in the fasted state and during intraduodenal lipid infusion (19,20,30), when compared with euglycemia. Although physiological hyperglycemia (blood glucose 8–9 mmol/l) does not affect upper-gut sensations in the fasted state (50), including those elicited by proximal gastric distension (70), perceptions arising from duodenal balloon distension (26) or intraduodenal lipid infusion (31) are greater at a blood glucose concentration of 8–10 mmol/l than 4 mmol/l, suggesting a synergistic relationship between small-intestinal stimuli and the glycemic state. Although a recent study in patients with type 1 diabetes failed to demonstrate an effect of acute hyperglycemia on the perception of gastric distension in the fasted state, the sensitivity to gastric distension was substantially greater than that in healthy control subjects during euglycemia (21), which may have made a further increase in sensitivity difficult to detect. Furthermore, in a cross-sectional study of type 1 diabetic patients, the perception of postprandial fullness was related to the blood glucose concentration (71).

Marked hyperglycemia (~15 mmol/l) does not appear to influence the perception of colonic distension in healthy subjects (59). In both healthy and type 1 diabetic subjects, perception of rectal distension has been reported to be either blunted (61–63) or enhanced (60) by hyperglycemia; as with studies of motor function, the method of rectal distension may well have influenced the observations.

Significance of the effects of blood glucose concentration on upper-gut motor and sensory function

The observed effects of variations in the blood glucose concentration on upper gastrointestinal function have major implications for diabetic patients. Clinical studies of gut function, such as the measurement of gastric emptying, as well as trials evaluating prokinetic agents, should take into account the blood glucose concentration at the time of the study; ideally, patients should be studied during euglycemia. Furthermore, poor glycemic control could potentially exacerbate upper gastrointestinal symptoms as well as delay the absorption of oral medications. Conversely, the acceleration of gastric emptying during hypoglycemia represents a counterregulatory mechanism promoting more rapid systemic availability of ingested glucose.

In healthy volunteers, the slowing of gastric emptying associated with elevation of the blood glucose concentration to postprandial levels is likely to constitute a physiological mechanism that regulates the release of nutrients into the small intestine. Furthermore, the apparent synergy between physiological hyperglycemia and the presence of nutrients in the small intestine, in their effects on appetite-related gut perceptions, such as hunger and desire to eat (31), potentially constitutes a mechanism of satiation.

Mechanisms mediating the effects of hyperglycemia on gastrointestinal motor and sensory function

Although numerous studies have demonstrated that the blood glucose concentration has major effects on upper gastrointestinal motor and sensory function in humans, much of the data have been observational, and there is relatively little information relating to potential mechanisms by which these effects are mediated. Further studies are called for to address this issue. The major-

ity of the available information relates to motor rather than sensory function, as the latter is more difficult to study objectively.

In considering the effects of systemic changes in blood glucose concentration, rather than those directly related to glucose absorption from the gut, animal studies have established the presence of glucose-responsive neurons in the central nervous system, which may modify vagal efferent activity (72). Diminished central responsiveness to opioids may account for the reduced threshold to somatic pain observed in healthy humans during hyperglycemia (73); whether a similar process applies to visceral sensation remains to be established. Elevated blood glucose concentrations may have other central effects, including enhancement of memory (74–76), shortening of reaction time (77), and modulation of mood (78).

In healthy subjects, the secretion of pancreatic polypeptide, which is under vagal cholinergic control, is diminished during acute hyperglycemia in healthy control subjects, suggesting a reversible impairment of vagal efferent function (67). The reduced heart rate response to standing (30:15 ratio) in healthy volunteers during hyperglycemia when compared with euglycemia is also indicative of impairment of vagal parasympathetic function (79).

Nitric oxide (NO) is a key neurotransmitter in the regulation of gastrointestinal motor function (80,81). In rodents with streptozotocin-induced diabetes, NO synthase expression in gastric myenteric neurons is diminished (82,83) and associated with delayed gastric emptying, which is reversed by insulin treatment or the NO donor sildenafil (83). The effect of hyperglycemia per se on NO expression in the enteric nervous system has not been investigated. Similarly, the effects of hyperglycemia on mediators of visceral perception, such as serotonergic pathways (84), remain to be evaluated. Neurons responsive to glucose have recently been identified in the rat small intestine (85), but their response to systemic rather than luminal glucose is unclear. Insulin, released in response to glucose in healthy subjects and patients with type 2 diabetes, has the potential to modify upper-gut motor and sensory function, but probably does not play a major role. Although euglycemic hyperinsulinemia has been reported to suppress fasting antroduodenal motility (23) and to slow gastric emptying in healthy volunteers (86), insulin concentrations of a magnitude similar to those observed during glucose clamping at 13 mmol/l do not suppress antral pressure waves during euglycemia (24), nor does euglycemic hyperinsulinemia affect gastric emptying in patients with type 1 or type 2 diabetes (87). Moreover, as discussed, hyperglycemia slows gastric emptying (13,14) and suppresses antral motility (14) in type 1 diabetic patients, who do not have endogenous insulin secretion. In healthy volunteers, plasma concentrations of motilin are less during hyperglycemia when compared with euglycemia (22); however, antral motility is suppressed even at blood glucose concentrations below the threshold for suppression of motilin (22). A direct effect of hyperglycemia on gastric smooth muscle appears unlikely given that smooth muscle is stimulated in some regions, such as the pylorus (25), but suppressed in others, such as the antrum (22).

Prostaglandins are potentially involved in the mediation of abnormal gastric electrical rhythms during hyperglycemia. As in healthy subjects, tachygastria is prevented by prior administration of indomethacin; however, this mechanism does not extend to the suppression of antral pressure waves (24).

Much work is required to elucidate the neural, humoral, and cellular mechanisms by which systemic glucose affects gastrointestinal motility and sensation. It should be recognized that even though animal studies have yielded insights (74,75,82,83), caution is indicated in extrapolating this information to humans, in whom the effect of mediators such as NO (88) may differ.

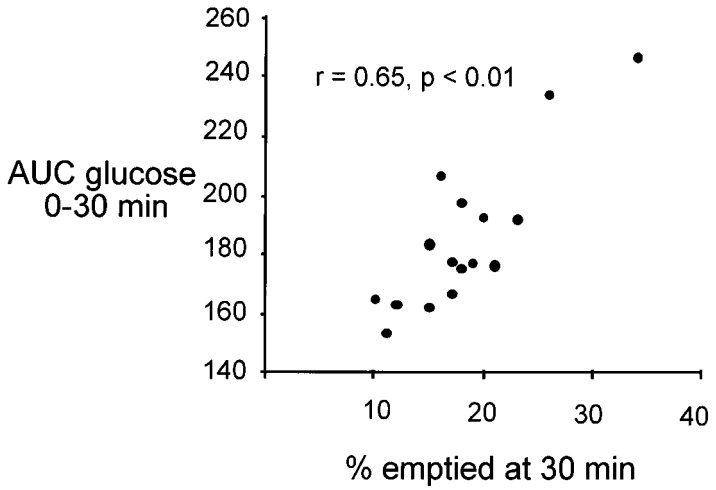

Figure 5—*Relationship between glycemic response (area under blood glucose concentration curve [AUC] between 0 and 30 min after ingestion) and gastric emptying of 75 g glucose in healthy subjects. (From Horowitz et al. [89].)*

THE CONTRIBUTION OF UPPER GASTROINTESTINAL MOTOR FUNCTION TO POSTPRANDIAL BLOOD GLUCOSE LEVELS

— Potential determinants of postprandial blood glucose concentrations include the following: *1*) the rate of delivery of nutrients to the small intestine, *2*) absorption of glucose from the small intestine, and *3*) hepatic glucose metabolism. The relative contribution of each of these factors is controversial, and varies over time after a meal. Different methods of measurement may also emphasize particular elements; for example, isotope techniques that are well suited to quantifying hepatic glucose release later in the postprandial period, but may be less able to define the origin of systemic glucose immediately after a meal. Nevertheless, it is clear that interventions directed at modulating upper gastrointestinal motor and absorptive function have a major effect on the postprandial blood glucose excursion.

Gastric emptying

Since transit of nutrients through the esophagus in most cases is rapid, gastric emptying is the major determinant of nutrient delivery to the small intestine. Indeed, variation in the rate of gastric emptying accounts for ~35% of the variance in peak blood glucose concentrations after ingestion of oral glucose (75 g) in both healthy volunteers (89) and patients with type 2 diabetes (90) (Fig. 5); since these are cross-sectional studies, the contribution of gastric emptying is likely, if anything, to have been underestimated. In type 1 diabetic patients

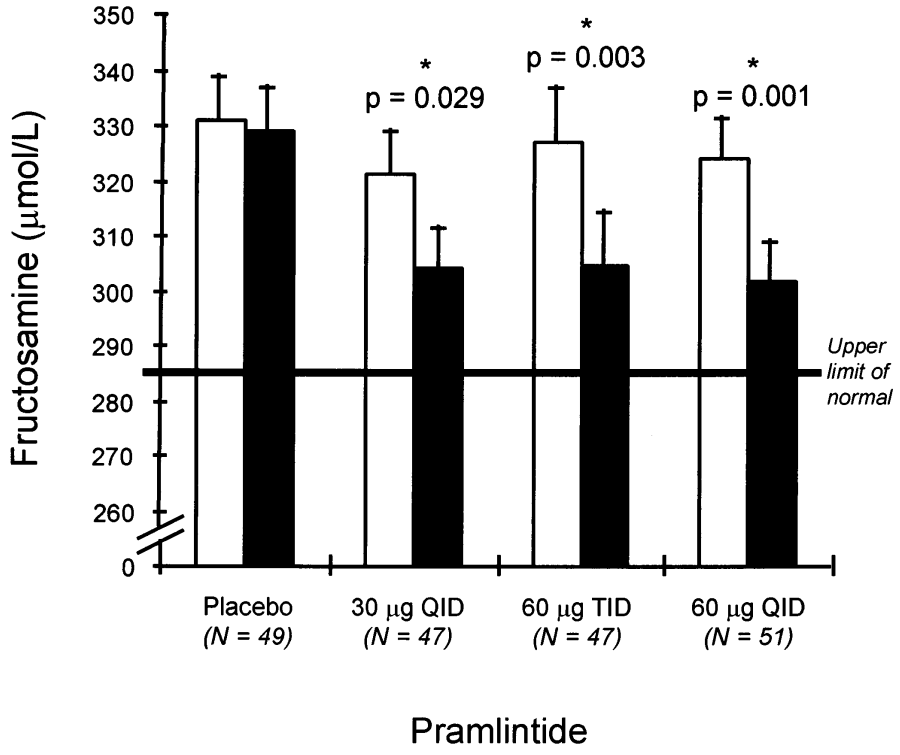

Figure 6—*Change in serum fructosamine concentration from baseline to week 4 for type 2 diabetic patients receiving placebo or pramlintide. Differences compared with placebo are indicated.* □*, Baseline;* ■*, week 4. (From Thompson et al. [134].)*

with gastroparesis, less insulin is required to maintain euglycemia than in those with normal gastric emptying (91).

It is well recognized that the physical properties of food, such as various forms of dietary starch, affect postprandial blood glucose profiles; this understanding is the basis of the glycemic index (92). Much of the variation in postprandial glycemic response, such as differences in postprandial blood glucose concentrations between rice, bread, and potato, can be accounted for by different rates of gastric emptying (93,94). For some foods, such as white beans, slower small-intestinal absorption of glucose may be the more important determinant of a low glycemic index (95). In patients with type 2 diabetes, a high dietary fiber intake improves glycemic control (96); slowing of gastric emptying is likely to be important in mediating this effect (97). Feedback from the small intestine can also reduce the postprandial blood glucose peak by slowing gastric emptying; this is evident when oil is infused into the duodenum or ileum before a carbohydrate-containing meal (98). After short-term starvation, the peak plasma glucose concentration after oral glucose is less, consistent with slower emptying of glucose from the stomach (99). Gastrointestinal hormones, including cholecystokinin, glucagon-like peptide 1 (GLP-1), and gastric inhibitory polypeptide, may be important in mediating small-intestinal feedback (100–102).

Small-intestinal glucose absorption

After the entry of nutrients into the small intestine, factors that determine the appearance of glucose in the portal circulation potentially include the breakdown of complex carbohydrates to glucose, mucosal absorption of glucose, small-intestinal motor patterns, and splanchnic blood flow. There is relatively little information about the impact of small-intestinal motility and absorptive function on glycemic control.

Polysaccharides are broken down into oligosaccharides and monosaccharides by luminal and brush-border enzymes before absorption. Inhibition of intestinal α-glucosidases delays the digestion of starch and sucrose and flattens postprandial blood glucose excursions in type 2 diabetes (103); the α-glucosidase inhibitor, acarbose, is used widely in the management of type 2 diabetic patients. An additional action of α-glucosidase inhibitors may be to inhibit the entry of glucose into enterocytes (104). Hyperglycemia increases the activities of intestinal disaccharidases in the rat (105); this result has potential implications for glucose absorption in patients with diabetes.

Glucose absorption across enterocytes takes place predominantly in the proximal small intestine, via the sodium-glucose cotransporter (SGLT 1) at the luminal membrane and the GLUT2 at the basolateral membrane (106). Upregulation at the luminal membrane appears to be responsible for enhanced glucose transport in streptozotocin-induced diabetes and for changes in glucose uptake in response to dietary modifications (107). In streptozotocin-induced diabetes, a larger segment of the intestinal villus takes part in glucose transport (108). An increase in the number or activity of carriers at the basolateral membrane appears responsible for the increased glucose uptake observed during hyperglycemia in the rat (107). Knowledge of glucose absorption in humans with diabetes is limited; glucose absorption has been reported to be normal in type 1 diabetic patients when studied with a jejunal perfusion technique (109), whereas glucose absorption may be slightly reduced in type 2 diabetes (110). In a recent study, type 1 diabetic patients received an intraduodenal infusion of the glucose analog, 3-*O*-methylglucose (3-OMG); absorption of 3-OMG was greater in these subjects than in healthy control subjects (111). The quantitative contribution of enhanced intestinal glucose absorption to postprandial hyperglycemia in both type 1 and type 2 diabetes requires further evaluation.

The impact of small-intestinal motor patterns on glucose absorption is likely to be important, though little is known about this issue. Changes in duodenal and jejunal motility—specifically, less-stationary contractile activity and increased propagated activity—have been implicated in the blunting of the postprandial glycemic peak associated with ingestion of sugar beet and ispaghula fiber (112). Pharmacologically induced inhibition of small-intestinal motility decreases absorption of glucose from the small-intestinal lumen (113). Small-intestinal motility is frequently abnormal in diabetic patients (114–117) and may potentially affect glucose absorption.

The appearance of glucose in the systemic circulation is also likely to be influenced by superior mesenteric blood flow. The latter, assessed with Doppler ultra-

sonography, is influenced by meal composition; for example, a high-fat meal produces more sustained mesenteric hyperemia than a high-carbohydrate meal (118). The relationship between superior mesenteric flow and postprandial blood glucose concentrations in diabetic patients has not been assessed.

Hepatic glucose production

After reaching the liver through the portal circulation, glucose may be taken up and converted to glycogen or stored via the glucose-6-phosphate pathway, though the majority is available to the systemic circulation. Glucose uptake by the liver is dependent on its concentration gradient between portal venous and hepatic arterial blood (119); accordingly, high systemic blood glucose levels may themselves favor an increased availability of absorbed glucose to the systemic circulation. Furthermore, the neural sensing of the portal venous-hepatic arterial gradient is impaired in a rat model of chronic diabetes, suggesting that diabetic neuropathy involving intrahepatic nerves could contribute to postprandial hyperglycemia (120).

During hepatic glucose uptake, glycogenolysis and gluconeogenesis are concurrently suppressed, limiting the increase in systemic glucose concentrations (121,122); impairment of this suppression could also potentially contribute to postprandial hyperglycemia in patients with both type 1 (123) and type 2 (124) diabetes. Although studies using radiolabeled glucose isotopes in type 2 diabetes have suggested that excessive hepatic glucose release is the major mechanism in postprandial hyperglycemia (124), this is difficult to reconcile with the unequivocal evidence that interventions that slow gastric emptying have a profound effect on postprandial glycemia. However, the relative contribution of the upper gut to postprandial blood glucose concentrations, compared with that of the liver, is likely to vary over time after a meal; hepatic glucose metabolism may be the predominant factor after the first hour, whereas gastroduodenal function may be dominant earlier in the postprandial period.

Therapeutic modulation of gastric emptying

The potential for modulation of the rate of gastric emptying to be therapeutically useful in the control of postprandial hyperglycemia in diabetic patients is now being explored vigorously by the pharmaceutical industry. In type 1 diabetes, interventions that improve the coordination between nutrient absorption and the action of exogenous insulin would be expected to be beneficial; in patients with type 1 diabetes and delayed gastric emptying, both the rate of emptying and the HbA_{1c} improved after 6 months of treatment with the prokinetic drug levosulpiride, a D_2 dopamine receptor antagonist (125). Conversely, when gastric emptying was increased with cisapride, postprandial blood glucose levels increased (126); HbA_{1c} concentration was unchanged after 8 weeks of treatment, possibly because the acceleration of gastric emptying was modest. In type 2 diabetes, slowing the absorption of nutrients should prove to be effective, in line with the delayed release of insulin characteristic of this disorder; for example, inhibition of trypsin/chymotrypsin by Pot II (127), an increase in meal viscosity using guar gum (128), and parenteral administration of the human amylin analog, pramlintide (AC137) (129), reduce postprandial blood glucose concentrations in type 2 diabetes, predominantly by slowing gastric emptying. Pramlintide has no effect on intestinal transit, and its inhibition of gastric emptying is likely to be vagally mediated (130). Pramlintide also suppresses postprandial glucagon secretion (131,132), which may contribute to a reduction in postprandial blood glucose. In theory, pramlintide may have particular application to patients with type 1 diabetes, who are amylin- as well as insulin-deficient (132), and indeed both fructosamine and 24-h blood glucose concentrations are reduced in this group by therapy for 4 weeks (133). It should be recognized, however, that unlike in some animal models, rapid gastric emptying occurs only occasionally in type 1 diabetes. Clarification of the physiological role of amylin in humans awaits the development of a specific antagonist. Moreover, pramlintide appears to have similar benefits in patients with type 2 diabetes (134) (Fig. 6). The outcomes of long-term studies in both groups are awaited (135).

Another potential therapeutic strategy for type 2 diabetic patients is the administration of GLP-1 (136). As an "incretin" hormone, it augments the postprandial insulin response, as well as suppressing both glucagon secretion and food intake (137). However, the effect of GLP-1 on postprandial blood glucose concentrations is mediated predominantly by slowing gastric emptying (102,138). The usefulness of GLP-1 in clinical practice awaits the development of an analog of sufficiently long half-life to be effective by subcutaneous injection or by an alternative route.

CONCLUSIONS — Acute changes in the blood glucose concentration have major effects on the motor and sensory function of the upper gastrointestinal tract; at the same time, the upper gut plays a major role in regulating postprandial blood glucose concentrations. This complementary relationship has implications for both physiological regulation of gut function and the management of patients with diabetes. Approaches to lower postprandial blood glucose concentrations by modulating the absorption of nutrients from the upper gut are likely soon to enter the mainstream of therapy for diabetes.

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