Relationships Between Gastric Emptying, Postprandial Glycemia, and Incretin Hormones

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The importance of achieving tight glycemic control, usually assessed by glycated hemoglobin (HbA_{1c}), for both the prevention and delay in the progression of diabetes-related microvascular complications, is established, and the American Diabetes Association/European Association for the Study of Diabetes joint committee has recommended an HbA_{1c} <7% as the goal in patients with type 2 diabetes (1). The relative contributions of pre- and postprandial glycemia to HbA_{1c} have been clarified during the last decade following the seminal report by Monnier et al. (2) indicating that in type 2 diabetes, postprandial glycemic excursions account for about 70% of variability when HbA_{1c} is <7.3%, while the contribution of "fasting" glycemia is greater in less well-controlled patients. Subsequent studies have confirmed the predominance of postprandial glycemia in determining overall glycemic control in "well-controlled" type 2 diabetic patients managed by oral hypoglycemic agents or basal insulin (3). The importance of postprandial glycemia to overall glycemic control is not surprising considering that *1*) humans in modern societies spend only about 3 or 4 h before breakfast in a truly fasting state because in health, gastric emptying of meals occurs at an overall rate of 1–4 kcal/min (4), and *2*) postprandial hyperglycemia occurs frequently in diabetes (1). The relevance of postprandial glycemia is further increased by the recognition that it may represent an independent risk factor for adverse cardiovascular outcomes in both diabetic and nondiabetic populations (5).

The determinants of postprandial glycemia include preprandial glycemic levels, meal composition, gastric emptying, insulin secretion, small intestinal glucose absorption, and hepatic and peripheral glucose metabolism. Furthermore, the relative contribution of each of these factors may vary over time during the postprandial state. Nevertheless, both the rate of gastric emptying and the secretion and action of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), exert a major influence (6). The latter limit postprandial glycemia through their insulinotropic and, in the case of GLP-1, glucagonostatic actions. They account for the "incretin effect"—an augmentation of insulin secretion following oral or enteral glucose exposure when compared with an isoglycemic intravenous glucose infusion—which is diminished in type 2 diabetes (7). GIP and GLP-1 are released from entero-endocrine cells located most densely in the proximal small intestine and distal small intestine/colon, respectively, following nutrient exposure. Each macronutrient has the capacity to stimulate GLP-1 and GIP release, although the mechanisms underlying secretion differ, and fat and carbohydrate may be more potent stimuli than protein (8). Carbohydrates, for example, stimulate incretin secretion through a number of interrelated mechanisms that are likely to include the sodium-glucose cotransporter-1 (SGLT-1) and intestinal "sweet taste" receptors (8). Following their release, the incretin hormones are rapidly degraded to inactive metabolites by the ubiquitous enzyme, dipeptidyl peptidase-4 (DPP-IV). While GIP may be the most important incretin hormone in health, its capacity to stimulate insulin is markedly diminished in type 2 diabetes (8).

Even relatively minor variations in gastric emptying can have a major impact on the postprandial glycemic profile in health and type 2 diabetes (9–12). It is now recognized that complex, interdependent relationships exist between gastric emptying, the incretin axis, and postprandial glycemia, with the rate of gastric emptying having a major impact on the magnitude of both the glycemic excursion and incretin hormone secretion and, conversely, acute hyperglycemia and GLP-1 exerting negative feedback on gastric emptying (6). This review focuses on these interrelationships, summarized in Fig. 1, and the consequent implications for dietary and pharmacological strategies to manage postprandial glycemia in type 2 diabetes.

Gastric emptying in health and diabetes

—It is not well recognized that in both health and diabetes, the rate of gastric emptying shows wide interindividual—with much less intraindividual—variation (4). Gastric emptying is determined by the integration of motor activity of the stomach and upper small intestine, controlled by electrical slow waves generated by the interstitial cells of Cajal (4,13). The proximal stomach initially relaxes to accommodate a meal and the antrum then grinds solids to a small particle size (1–2 mm), before the chyme is pumped across the pylorus, predominantly in a pulsatile manner (4). These processes are regulated primarily by inhibitory feedback arising from the interaction of nutrients with the small intestine rather than by "intragastric" mechanisms, and modulated by both stimulation of the vagus nerve and the secretion of gut hormones, including GLP-1, cholecystokinin (CCK), and peptide YY (PYY). The magnitude of small intestinal inhibitory feedback is dependent

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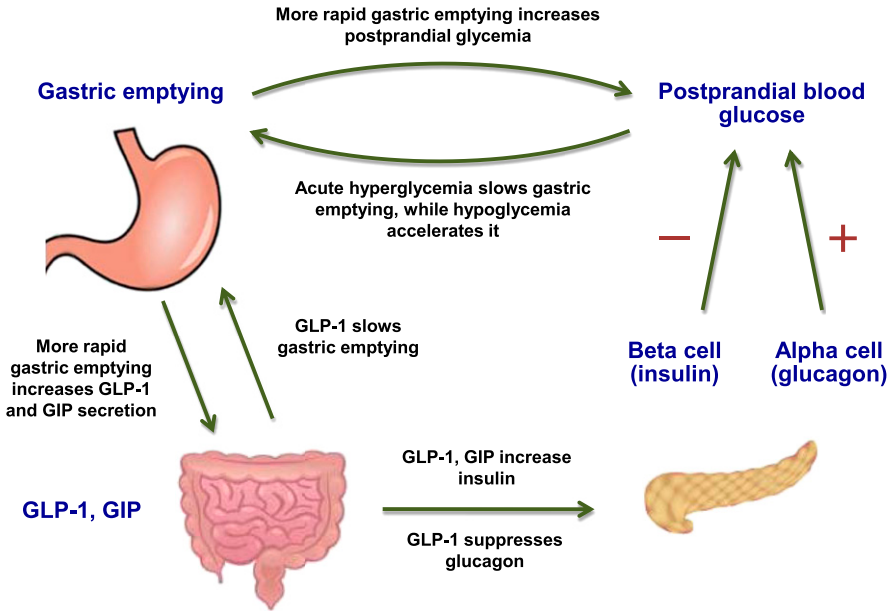

Figure 1—*Summary of the interdependent relationships of gastric emptying, incretin hormones, and postprandial glycemia. (A high-quality color representation of this figure is available in the online issue.)*

on the nutrient load and the length of intestine exposed and is associated with fundic relaxation, suppression of antral contractions, and stimulation of tonic and phasic contractions localized to the pylorus to retard the subsequent rate of nutrient delivery to the intestine (4).

While it has been suggested for many years that gastric motor function is frequently disordered in diabetes—the term gastroparesis diabeticorum was introduced by Kassander (14) more than 50 years ago—it has only much more recently been confirmed that abnormally delayed gastric emptying occurs frequently with both type 1 and type 2 diabetes (6). The true prevalence, however, remains uncertain because of a lack of population-based studies and inconsistent criteria to define gastroparesis, including variations in the technique used to quantify gastric emptying (where scintigraphy remains the gold standard method and stable isotope breath tests and ultrasonography represent acceptable alternatives), the desirable blood glucose levels during the emptying measurement, the magnitude of the delay in gastric emptying regarded as abnormal, and whether the presence of gastrointestinal symptoms represents a prerequisite for the diagnosis. In relation to the latter, it has been suggested that gastroparesis should not be diagnosed in the absence of upper gastrointestinal symptoms (15), but we believe this is inappropriate given that delayed gastric emptying can have other manifestations, particularly in relation to glycemic control. Nevertheless, there is no doubt that the prevalence of delayed gastric emptying with symptoms is less than that of delayed emptying per se. While recognizing these limitations, it appears that gastric emptying of solids and/or nutrient liquids is delayed in 30–50% of patients with longstanding type 1 or type 2 diabetes, and is sometimes abnormally rapid (6,13,16). As would be predicted, motor dysfunction of different regions of the stomach is also frequently observed, but is heterogeneous (13). This high prevalence of disordered emptying is not surprising given that it is consistent with the prevalence of other diabetic complications, including peripheral neuropathy. Because the relationship of gastrointestinal symptoms—such as fullness, nausea or vomiting—with disordered emptying is relatively weak (16–18), and the magnitude of delay in gastric emptying is in many cases modest (17), it is likely that many, if not the majority, of such patients do not come to clinical attention. Nevertheless, hospital admissions in symptomatic patients given a diagnosis of diabetic gastroparesis are reported to be increasing (19).

Diabetic gastroparesis has long been attributed to the presence of irreversible autonomic (vagal) neuropathy, but the pathogenesis is now recognized to be heterogeneous. Important insights have resulted from the work of the Gastroparesis Clinical Research Consortium in the U.S. Loss or dysfunction of the interstitial cells of Cajal and defects in inhibitory transmission, particularly involving neuronal nitric oxide synthase, appear to be of central importance, as well as abnormalities in immune cells (CD45, CD206) and an upregulation of heme oxygenase-1 in macrophages, which impacts on the enteric neurotransmitter carbon monoxide (13,20). The prognosis in patients with delayed gastric emptying is not necessarily poor (21)—preliminary data indicate that there is little, if any, change in gastric emptying over periods of up to 25 years (22) and that mortality is not increased (21), although the latter may not apply to patients with severe gastroparesis.

Impact of gastric emptying on glycemia and incretin hormones—The recognition that gastric emptying is a major determinant of postprandial glycemia in health, as well as in type 1 and type 2 diabetes, is relatively recent (10,11,23–25). In retrospect, such a relationship is not surprising given the substantial interindividual variation in gastric emptying in health, which is even greater in patients with diabetes because of the frequent occurrence of delayed, and occasionally accelerated, gastric emptying. Gastric emptying accounts for about 35% of the variance in the glycemic response (both peak and total area under the curve) to oral glucose and/or carbohydrate-containing meals in health (23) and type 2 diabetes (24). Insulin-treated patients with gastroparesis initially require less insulin to maintain euglycemia postprandially when compared with patients with normal emptying (25). In patients with type 2 diabetes not managed with insulin, slowing gastric emptying decreases postprandial glycemic excursions, while acceleration of emptying has the opposite effect (12). In patients with cystic fibrosis and concomitant pancreatic exocrine insufficiency, gastric emptying of high-fat/carbohydrate meals is accelerated and incretin secretion is impaired due to maldigestion of nutrients, leading to elevated postprandial glucose levels, even in those without overt diabetes. In this situation, pancreatic enzyme supplementation given with a meal slows gastric emptying and restores the GLP-1 response, thereby diminishing postprandial glycemia substantially (26).

The relationship of glycemia with small intestinal glucose delivery has recently been shown to be nonlinear based on the outcome of studies in which glucose was infused directly into the duodenum at rates spanning the normal range of gastric emptying (i.e., 1–4 kcal/min) in healthy young (10) and older (27) subjects and patients with type 2 diabetes managed by diet alone (11). In these groups, intraduodenal infusion of glucose at 1 kcal/min was associated with only a modest rise in blood glucose, and while the glycemic responses to loads of 2 kcal/min, 3 kcal/min, and 4 kcal/min were substantially greater, there was little difference between them (Fig. 2). The latter probably reflects the much greater plasma insulin response to the higher (i.e., 3 and 4 kcal/min) intraduodenal glucose loads, which is, in turn, attributable to a much greater GLP-1 response. Plasma GIP, unlike GLP-1, rises in an approximately linear fashion with increasing glucose loads (10,11,27). In other studies of healthy subjects and patients with type 2 diabetes, the effects of initially more rapid intraduodenal glucose delivery, when compared with delivery of the same amount of glucose at a constant rate, were explored (9,28). While the initial plasma insulin, GLP-1, and GIP responses were predictably greater with the former approach, there was no difference in the overall glycemic response, implying that the initial increase in insulin was inadequate to compensate for the greater load of glucose absorbed. A fundamental implication of these studies is that the magnitude of the incretin effect in a given individual will be dependent on their rate of gastric emptying, i.e., the incretin effect should be greater in an individual, healthy or with type 2 diabetes, whose stomach empties at 4 kcal/min when compared with another in whom emptying occurs at 2 kcal/min, although the former situation would also favor an initially greater postprandial glycemic excursion. This concept is supported by recent evidence from our laboratory (29). Hence, studies relating to incretin hormone secretion should take into account the rate of gastric emptying (which has hitherto frequently not been the case). The incretin hormone responses to a meal, particularly that of GLP-1, appear to represent a dynamic compensatory mechanism to minimize postprandial glycemia when emptying is relatively more rapid. In a healthy individual, the relative importance of GIP and GLP-1 in determining the incretin effect is likely to be dependent on the rate of gastric emptying. In an individual

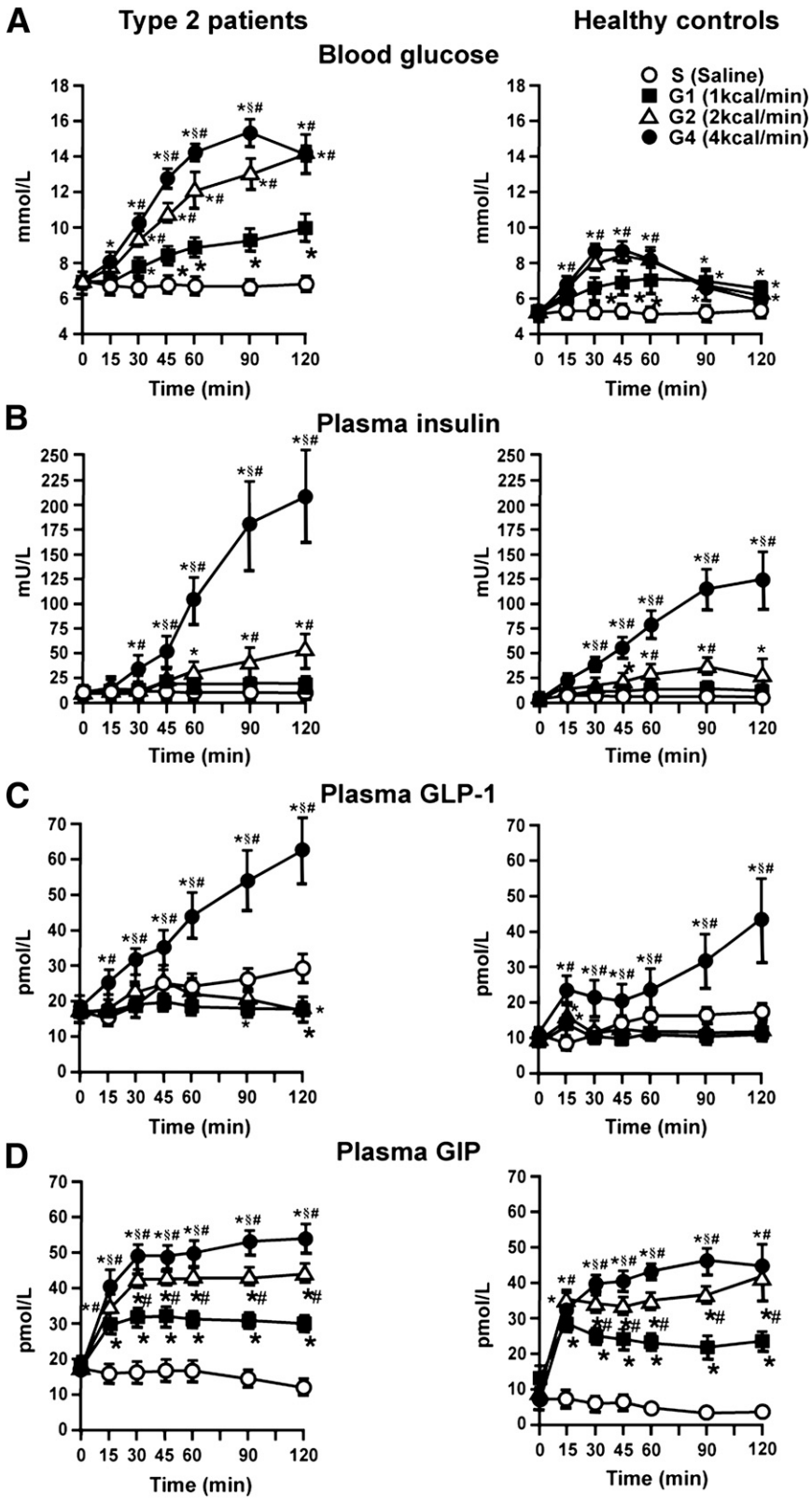

Figure 2—*Data are mean ± SEM. Blood glucose* (A)*, plasma insulin* (B)*, plasma GLP-1* (C)*, and plasma GIP* (D) *concentrations in response to a 120-min intraduodenal glucose infusion at 1 kcal/min (G1), 2 kcal/min (G2), 4 kcal/min (G4), or (intraduodenal) saline control (S) in 10 healthy subjects and eight type 2 diabetic patients.* *P < *0.05 vs. control,* #P < *0.05 vs. G1,* §P < *0.05 vs. G2. Reprinted with permission from Ma et al. (11).*

with type 2 diabetes, the magnitude of GLP-1 response is likely to be crucial given the reduced insulinotropic effect of GIP (7). We would speculate that to minimize postprandial glycemic excursions in individuals with type 2 diabetes, gastric emptying of carbohydrates should be slowed to about 1 kcal/min in those whose emptying is more rapid than this. As has been suggested, the prompt amelioration of type 2 diabetes after Roux-en-Y gastric bypass surgery is likely to reflect, at least in part, an exaggerated incretin (particularly GLP-1) response (30) consequent to dramatically accelerated gastric emptying of nutrient-containing liquids and "semisolids" (31).

As well as being a determinant of glycemia, gastric emptying is itself modulated by acute changes in the blood glucose concentration (6,32). While there is a lack of consensus in relation to the magnitude of the effect of acute hyperglycemia and the potential influence of chronic elevation of blood glucose, it is clear that marked acute hyperglycemia (i.e., blood glucose level ~15 mmol/L) delays gastric emptying substantially in both health and type 1 diabetes when compared with euglycemia (~5 mmol/L). Emptying is slowed even at physiological degrees of hyperglycemia (~8 mmol/L) (32) and is accelerated during insulin-induced hypoglycemia (33); the latter response is evident even in patients with autonomic neuropathy and gastroparesis and likely represents an important counterregulatory mechanism to facilitate carbohydrate absorption (33). Acute hyperglycemia attenuates the gastrokinetic effect of erythromycin (34), and this effect is likely also to apply to other prokinetic drugs. It remains to be determined whether the effects of drugs that slow gastric emptying are also modulated by acute changes in the blood glucose concentration, but this appears intuitively likely. The mechanisms by which acute hyperglycemia modulates gastric emptying are poorly defined, but nitrergic pathways appear important (35).

Effects of endogenous and exogenous incretin hormones on gastric emptying

—GIP and GLP-1 differ in their effects on gastric emptying. Studies using the GLP-1 receptor antagonist, exendin 9–39, indicate that endogenous GLP-1 slows gastric emptying modestly (36) and affects intragastric meal distribution (37) as a result of suppression of antro-duodenal motility and stimulation of pyloric contractions (38). That not all investigators have demonstrated effects on emptying probably reflects methodological issues, including the composition of the test meal and the use of suboptimal techniques to measure gastric emptying (37,39). The indirect assessment of gastric emptying using the absorption kinetics of oral paracetamol is imprecise, but has been widely used.

Acute, intravenous infusion of GLP-1 (in pharmacological doses) slows gastric emptying markedly in both healthy subjects and patients with type 2 diabetes in a dose-dependent manner (40–42) by mechanisms that include relaxation of the proximal stomach, reduction of antral and duodenal motility, and an increase in pyloric tone (43), and which involve vagal pathways (44). With pharmacological doses of GLP-1, nausea appears to occur rarely, unlike the situation with GLP-1 agonists (as discussed below). By contrast, in healthy subjects, exogenous GIP in pharmacological doses does not slow gastric emptying (45) and may accelerate it modestly (46).

The magnitude of the retardation of gastric emptying induced by exogenous GLP-1 is influenced by the baseline rate of emptying, i.e., slowing is more marked in those with more rapid gastric emptying. For example, in the critically ill, GLP-1 slows gastric emptying when the latter is normal but not when it is delayed (47) (Fig. 3). Importantly, the reduction in postprandial glycemia induced by exogenous GLP-1 is also closely related to the magnitude of the slowing of gastric emptying being greater when baseline emptying is relatively more rapid (42,47). Indeed, the effect of acute administration of GLP-1 to slow gastric emptying outweighs its insulinotropic effect, so that while GLP-1 stimulates insulin during hyperglycemia in the fasted state, postprandial insulin concentrations are suppressed, rather than stimulated, in both health and type 2 diabetes (40,42), and when the GLP-1-induced slowing of gastric emptying is reversed by administering erythromycin, the insulinotropic action of GLP-1 is unmasked (48). Accordingly, it is arguable whether GLP-1 should be regarded as a true incretin hormone according to Creutzfeldt's definition (49). No studies have evaluated the effect of exogenous GLP-1 on gastric emptying in patients with gastroparesis, although it is known that the relaxation of the proximal stomach induced by exogenous administration of GLP-1 is attenuated in diabetic patients with autonomic neuropathy (50). Hence the magnitude of the slowing of gastric emptying induced by GLP-1 will almost certainly be reduced in

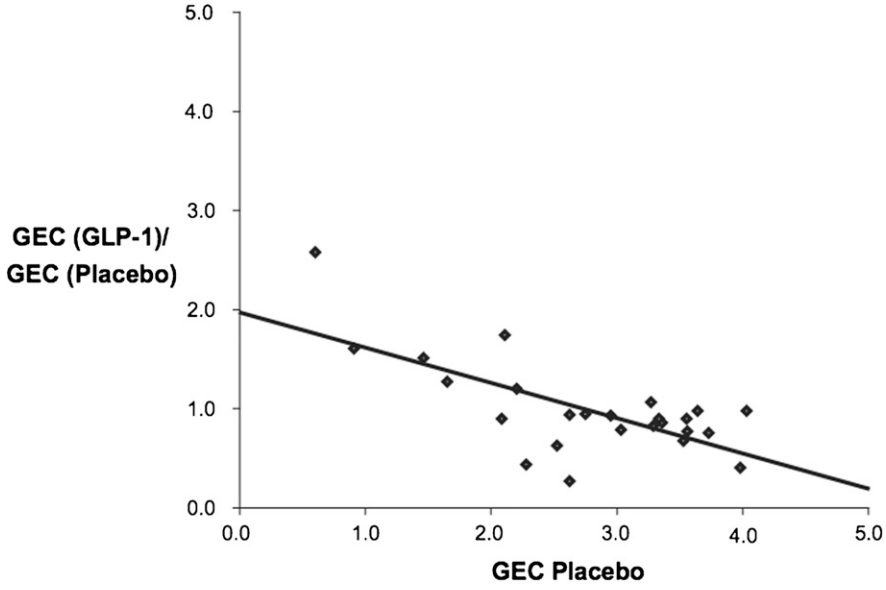

Figure 3—*Relationship between the effect of GLP-1 (1.2 pmol/kg/min intravenous) on gastric emptying and the rate of gastric emptying on placebo in critically ill patients* (n = 25). *Gastric emptying of a 100-mL nutrient liquid (Ensure) labeled with ^{13}C octanoic acid was measured with a breath test and the gastric emptying coefficient (GEC) determined. A lower GEC is indicative of more rapid gastric emptying.* $R = -0.48$, $P < 0.001$. *Reprinted with permission from Deane et al. (47).*

gastroparesis. It is also not known whether the GLP-1–induced slowing of gastric emptying can be "overridden" by hypoglycemia, which, as discussed, is associated with prompt acceleration of emptying (33). This issue should be addressed, particularly where GLP-1 agonists are used in combination with sulfonylureas or insulin when the propensity to hypoglycemia will be increased.

A recent report suggests that there may be rapid tachyphylaxis to the slowing of gastric emptying induced by exogenous GLP-1 (51). In that study, two liquid meals, separated by 4 h, were given to healthy volunteers during intravenous infusion of GLP-1 or placebo. GLP-1 was shown to slow emptying of both meals markedly, but the magnitude of the slowing of the second meal was less. It was suggested that this tachyphylaxis occurs at the level of the vagus nerve (51). While the study had methodological limitations, the observations are of considerable interest and likely to be relevant to the observed effects of GLP-1 agonists on gastric emptying (as discussed below).

Modulation of gastric emptying to minimize postprandial glycemic excursions in type 2 diabetes

—A number of strategies have been proposed to optimize postprandial glycemic control based on modulation of gastric emptying, stimulated by insights relating to the impact of emptying on glycemia and incretin hormone secretion. The focus of these strategies has been type 2 diabetes, underpinned by the rationale that a slower rate of nutrient delivery to the small intestine would be desirable to compensate for the delay in insulin release and the resistance to its actions, which are characteristic of this disease. The approaches include modifying the macronutrient content of meals, the use of fat and protein preloads, and pharmacological agents, particularly GLP-1–based therapies and the amylin analog, pramlintide (6).

In type 1 diabetes, gastric emptying needs to be predictable rather than specifically normal, delayed, or more rapid, to allow for accurate dosing of exogenous, short-acting insulin, although gastroparesis probably increases the propensity for hypoglycemia in the postprandial period (52), providing a rationale for measurement of emptying in patients with otherwise unexplained hypoglycemia. Studies using gastrokinetic drugs to improve glycemic control in type 1 diabetic patients have substantial methodological limitations and have yielded inconsistent observations.

A number of studies have evaluated the effects of modifying the macronutrient and fiber content of meals based on their putative effects on gastric emptying and/or incretin secretion. For example, increasing dietary fiber (53) or adding guar gum (54) slows emptying and reduces postprandial glucose in type 2 diabetes probably as a result of retardation of both gastric emptying and intestinal glucose absorption. Incorporating fat into a carbohydrate-rich meal also slows gastric emptying and improves the postprandial glycemic profile, albeit at the cost of increasing the energy load (55). An increase in the protein content of the diet from 15 to 30% for 5 weeks reduces postprandial glycemia, as well as HbA_{1c}, in patients with type 2 diabetes (56). In the latter study, the higher protein content was at the cost of carbohydrates, and the total energy intake remained stable. Longer-term studies are indicated to determine whether these benefits are sustained.

Macronutrient preloads

As discussed, fat, protein, and carbohydrates stimulate incretin secretion by various mechanisms and retard gastric emptying. These effects underlie the novel strategy of administering a small amount of macronutrient (a preload) 30–60 min before a meal with the rationale of triggering neurohormonal feedback via stimulation of GLP-1 and GIP, as well as PYY and CCK from the small intestine, to slow gastric emptying, stimulate insulin, and suppress glucagon in advance of the main meal and potentially to reduce subsequent energy intake (57). Fat is a potent inhibitor of gastric emptying because of its high-caloric density, but while acute administration of a fat preload predictably slows gastric emptying markedly, it results in only a modest reduction in peak postprandial glucose in type 2 diabetic patients (58). On the other hand, a 55-g whey protein preload, when given acutely to type 2 diabetic patients, slows gastric emptying, stimulates GIP and GLP-1, and markedly reduces postprandial glycemic excursions (59) (Fig. 4). The latter effect is likely to be attributable in part to the stimulation of insulin secretion by absorbed amino acids. In view of these promising observations, studies to evaluate the optimum dose and composition of protein preloads and to determine whether the beneficial effects on glycemia are sustained with chronic use are indicated.

A potential disadvantage of all macronutrient preloads is that they involve additional energy consumption. Two recent studies evaluating the effects of preloads entailing minimal additional energy are, accordingly, of interest (60,61). Sucralose, a noncalorific artificial sweetener, stimulates GLP-1 in vitro, but apparently has no effect on incretin secretion in healthy humans when administered as a preload (61,62). A nonmetabolized SGLT-1 substrate, 3-*O*-methylglucose, does stimulate GLP-1, slow gastric emptying, and diminish the glycemic response to a subsequent oral glucose load (60). Further evaluation of the effects of preloads that entail minimal added energy intake is warranted. A recent study indicates that bile acids can stimulate endogenous GLP-1 in type 2 diabetic patients when administered directly to the distal large intestine (63).

Pharmacological agents: GLP-1 agonists, DPP-IV inhibitors, and pramlintide

While the beneficial effect of GLP-1 agonists and DPP-IV inhibitors on glycemia in type 2 diabetes has been attributed to glucose-dependent insulinotropic and glucagonostatic properties, GLP-1 agonists also slow gastric emptying and that is, at least in some cases, an important mechanism by which they lower postprandial glucose excursions. The GLP-1 receptor agonists—exenatide, liraglutide, and exenatide LAR (long-acting release)—are now widely available, while a number of other drugs including lixisenatide, albiglutide, dulaglutide, and semaglutide are in late-phase development. Because of variable half-lives, there are major differences between these drugs in the frequency of dosing and the resulting plasma drug levels. It is also recognized that they vary in the magnitude of their effects on pre- versus postprandial glycemia (7), although differences in effects on HbA_{1c} hitherto appear subtle (1). All of these drugs cause gastrointestinal adverse effects such as anorexia, nausea, and diarrhea and are associated with modest weight loss. Most patients respond to GLP-1 agonists, but there is substantial interindividual variation in the response, and certainly not all achieve the target HbA_{1c} of $<7\%$. With some rare exceptions, no clear factors have hitherto been established to indicate which patients will respond best to these drugs, except that the reduction in HbA_{1c} is predictably

greater when baseline HbA_{1c} is higher. The relative effect of these drugs on gastric emptying as a determinant of their effect on glycemia has inappropriately received little attention.

It is now clear that all GLP-1 agonists have the capacity to slow gastric emptying in a variable but often marked manner when administered acutely, although emptying has often been quantified by the suboptimal paracetamol absorption test. The effects on gastric emptying have been most comprehensively examined for exenatide given twice daily, which slows emptying in a dose-dependent manner in type 2 diabetic patients apparently irrespective of the presence of cardiovascular autonomic neuropathy (64,65). Indeed, the slowing of emptying appears to be the predominant mechanism by which exenatide reduces postprandial glycemia (64) (Fig. 5), and the magnitude of this effect is dependent on the baseline rate of emptying (64) as is the case with exogenous GLP-1 (47). Hence, like GLP-1, GLP-1 agonists would be anticipated to have minimal, if any, effect on gastric emptying in gastroparesis. Moreover, the reduction in postprandial glycemia and the impact on postprandial insulin induced by GLP-1 agonists are also related to the degree to which emptying is slowed, at least in the case of exenatide twice daily and lixisenatide, i.e., when the slowing of gastric emptying is substantial, improvement in postprandial glycemia is most marked, while postprandial insulin secretion is diminished rather than stimulated (64,66).

The different durations of action of GLP-1 agonists appear to determine their impact on gastric emptying with repeated dosing. Evidence from animal and human studies indicates that the slowing of gastric emptying induced by a long-acting formulation of exenatide (exenatide LAR) (67) and liraglutide (68) and presumably other long-acting GLP-1 agonists—but not exenatide twice daily or lixisenatide (which are short-acting)—diminishes with time, presumably reflecting the tachyphylaxis phenomenon reported with GLP-1 by Nauck et al. (51). For example, in mice, the initial marked slowing of paracetamol absorption induced by acute administration of liraglutide diminishes within 2 weeks of continuous dosing, whereas the initially comparable marked slowing of paracetamol absorption induced by exenatide is sustained (68). In a human study comparing exenatide twice daily with exenatide LAR (administered once a week), the latter did not slow paracetamol absorption significantly at 14 weeks, while exenatide twice daily did (67). This is not to suggest that long-acting GLP-1 agonists such as liraglutide do not have any sustained effect to slow gastric emptying, but rather that the magnitude of this effect diminishes with time. In type 2 diabetic patients, liraglutide slowed paracetamol absorption slightly after administration for 3 weeks (69) despite significant glucose lowering, which would favor more rapid gastric emptying (32). Moreover, the reduction in paracetamol absorption was related to the magnitude of the decrease in postprandial glycemia, which is consistent with the concept that even modest slowing of gastric emptying can affect postprandial glycemic excursions. As a short-acting GLP-1 agonist, lixisenatide appears likely to have a sustained, major effect to slow gastric emptying (66), so that after 4 weeks' administration it lowers postprandial

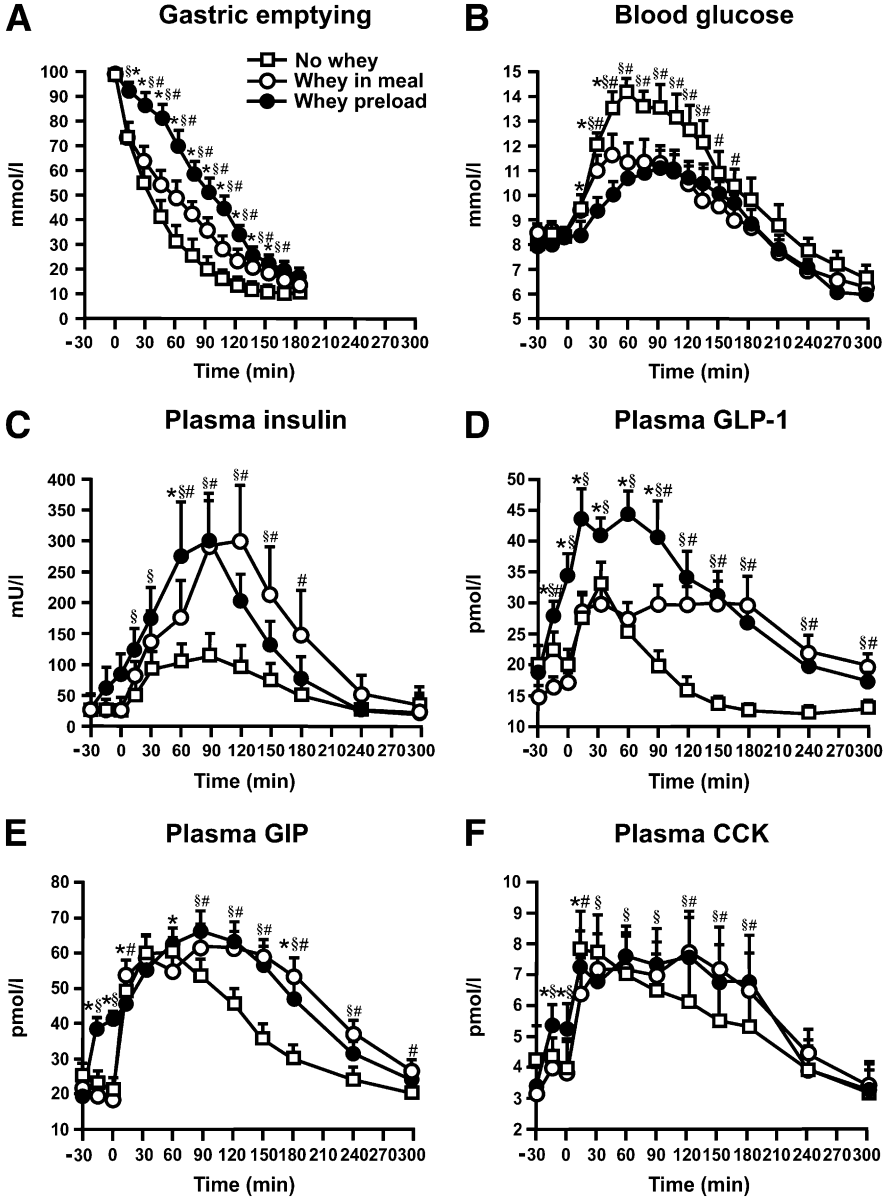

Figure 4—*Data are mean ± SEM. Gastric emptying* (A) *and blood glucose* (B)*, plasma insulin* (C)*, plasma GLP-1* (D)*, plasma GIP* (E)*, and plasma CCK* (F) *concentrations in response to a mashed potato meal in eight type 2 diabetic patients. On each study day, subjects ingested 350 mL beef-flavored soup 30 min before a radiolabeled mashed potato meal; 55 g whey protein was added either to the soup (whey preload), to the potato (whey in meal), or no whey was given (no whey).* *P $<$ *0.05, whey preload vs. whey in meal;* #P $<$ *0.05, whey in meal vs. no whey;* §P $<$ *0.05, whey preload vs. no whey. Reprinted with permission from Ma et al. (59).*

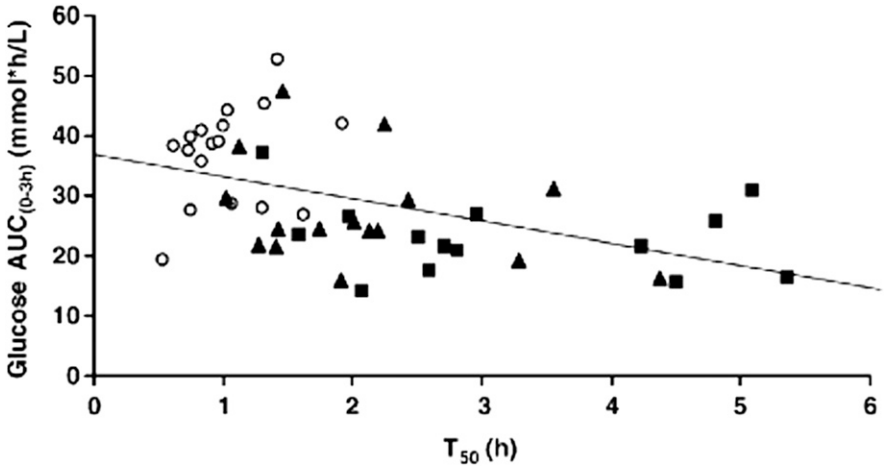

Figure 5—*Relationship between the effect of exenatide subcutaneously twice a day for 5 days on postprandial glycemia (plasma glucose area under the curve (AUC) [0–3 h]) and gastric emptying (50% emptying [t_{50}]) of a radiolabeled solid meal in type 2 diabetic patients* (n = *17). Placebo, white circles; 5 μg exenatide, black triangles; and 10 μg exenatide, black squares. R = −0.49,* P < *0.0001. A longer t_{50} is indicative of slower gastric emptying. Reprinted with permission from Linnebjerg et al. (64).*

glucose much more than liraglutide and suppresses rather than stimulates postprandial insulin (70). Hence, it appears that in the longer term, the short-acting GLP-1 agonists may act predominantly by lowering postprandial glycemia (through a sustained, substantial inhibition of gastric emptying), while the long-acting GLP-1 agonists predominantly lower preprandial hyperglycemia through insulinotropic and glucagonostatic effects. Accordingly, in the future the choice of GLP-1 agonists may be dictated by whether the dominant target is pre- or postprandial glycemic control and by the baseline rate of gastric emptying. A short-acting drug would intuitively be most effective at lowering postprandial glycemia in those with normal or rapid emptying and relatively lower HbA_{1c}, while those with already delayed emptying are less likely to require a focus on postprandial glucose given that when duodenal carbohydrate delivery is ≤1 kcal/min, there appears to be little rise in blood glucose (10,11). These hypotheses now warrant formal evaluation.

There is increasing interest in combining a GLP-1 agonist with exogenous basal insulin in type 2 diabetes (71) based on the rationale that the latter primarily targets preprandial glucose but is associated with weight gain and an increased risk of hypoglycemia (1) and the addition of a GLP-1 agonist that targets postprandial blood glucose by slowing gastric emptying while inducing weight loss and without increasing the risk of hypoglycemia would, therefore, provide a complementary strategy to optimize glycemic control. There is now clear evidence to support this strategy. For example, in a recent study by Buse et al. (71), exenatide twice daily improved glycemic control (reduction in HbA_{1c} of 0.7%) in type 2 diabetic patients managed with insulin glargine, associated with modest weight loss, and without an increased hypoglycemia. While there is hitherto no evidence of an increased risk of hypoglycemia with the addition of a GLP-1 agonist to basal insulin, this issue should be viewed circumspectly. While the majority of these patients will have an intact glucagon response to hypoglycemia, it would also be relevant to know whether hypoglycemia overrides the deceleration of gastric emptying induced by a GLP-1 agonist.

The DPP-IV enzyme acts on both GLP-1 and GIP, and DPP-IV inhibitors can be given orally, unlike GLP-1 agonists. An important distinction from GLP-1 agonists is that DPP-IV inhibitors have minimal, if any, effect on gastric emptying. For example, 2 days' dosing with 100 mg sitagliptin failed to affect gastric emptying (72). Vella et al. (73) similarly found no change in gastric emptying following 10 days' administration of vildagliptin (50 mg) in type 2 diabetic patients. In contrast, Woerle et al. (74) reported a modest slowing of gastric emptying following a single dose of vildagliptin (100 mg) in patients with type 2 diabetes, raising the possibility that tachyphylaxis may have been responsible for the negative outcome of repeated dosing. In healthy subjects, the magnitude of the initial rise in glucose after a carbohydrate meal is related to the rate of gastric emptying on sitagliptin, although sitagliptin itself had no effect on emptying (72). This indicates that gastric emptying is, as would be predicted, also an important determinant of postprandial glycemia in the presence of DPP-IV inhibition. The lack of effect of DPP-IV inhibitors on gastric emptying is likely to contribute to their apparently lesser effect on postprandial glycemia than GLP-1 agonists in clinical trials.

Amylin, a pancreatic hormone cosecreted with insulin by the β-cell, slows gastric emptying in addition to suppressing glucagon. The synthetic amylin analog, pramlintide, which is available in the U.S. for the management of diabetes, also slows gastric emptying, which no doubt contributes to its beneficial effect on postprandial glycemia (75).

Conclusions—Gastric emptying exhibits a substantial interindividual variation in health, is frequently abnormally delayed in patients with long-standing diabetes, and is a major determinant of postprandial glycemia and the secretion of the incretin hormones GIP and GLP-1. The relation of glycemia and GLP-1 secretion with small intestinal glucose delivery is nonlinear in health and type 2 diabetes. Macronutrients, particularly protein preloads, show promise in the management of type 2 diabetes by stimulating incretin and insulin secretion and slowing gastric emptying. Acute, exogenous GLP-1 slows gastric emptying and thereby carbohydrate absorption, but there may be tachyphylaxis to this effect. GLP-1 agonists also slow gastric emptying and, when administered acutely, this may represent their dominant mechanism of glucose lowering. With both exogenous GLP-1 and GLP-1 agonists, the magnitude of slowing of gastric emptying and the consequent reduction in postprandial glucose are greater when baseline gastric emptying is relatively more rapid. The slowing of gastric emptying induced by long-acting GLP-1 agonists, such as exenatide LAR and liraglutide, appears to diminish with time in contrast to short-acting agonists, such as exenatide twice daily and lixisenatide. Hence, in an individual type 2 diabetic patient, the impact of a GLP-1 agonist on postprandial glycemia is likely to be dependent on both the baseline rate of emptying and the choice of

GLP-1 agonist. If postprandial glycemia is to be targeted preferentially, short-acting analogs are likely to be optimally combined with basal insulin.

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