COMMENTARY

Spontaneous or Deliberate: Effects of Acute Variations in Glycemia on Gastric Emptying in Type 1 Diabetes

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During the last 30 years, there has been a paradigm shift in knowledge relating to gastric emptying in diabetes, reflecting the application of novel investigative techniques. Scintigraphy, which utilizes radiolabeled solid and/or liquid meals and a γ-camera, remains the gold standard for quantifying gastric emptying (1,2). More recently, stable isotope breath tests, involving measurement of $^{13}CO_2$ in breath samples after ingestion of a ^{13}C-labeled meal, have been validated against scintigraphy with inherent advantages of simplicity, point-of-care sampling, and avoidance of radiation exposure (1). Key insights in diabetes include the recognition that solids and liquids empty from the stomach differentially and that interindividual variation—already substantial in health (1–4 kcal/min) (2)—is increased in diabetes because emptying is delayed in ∼30–40% of complicated, suboptimally controlled patients attending tertiary centers (2–4), while often modestly accelerated in well-controlled patients with type 1 or type 2 diabetes (2). Upper gastrointestinal symptoms, such as nausea and fullness, occur frequently and impact quality of life adversely, but their relationship to gastric emptying is weak (1–3). Rather than simply being a manifestation of autonomic neuropathy, the pathogenesis of gastroparesis is heterogeneous, involving loss of interstitial cells of Cajal ("pacemaker" cells), an immune infiltrate, and muscle atrophy in addition to changes in intrinsic and extrinsic (vagal) innervation (1). There is a relatively weak relationship between gastroparesis and autonomic dysfunction, as assessed by standardized cardiovascular reflexes (3). Finally, and perhaps most importantly, gastric emptying influences postprandial glycemic excursions, the dominant determinant of HbA_{1c} when the latter is less than ∼64 mmol/mol (8.0%) (5), and emptying can be modulated by dietary or pharmacological approaches (e.g., short-acting glucagon-like peptide 1 receptor agonists or pramlintide) for therapeutic gain (2). Accordingly, gastric emptying is central to the pathogenesis and personalized management of diabetes (6).

The relationship of gastric emptying with glycemia is generally considered to be bidirectional, i.e., acute changes in glycemia represent a reversible determinant of, and are also determined by, the rate of emptying (7). Dogma has it that gastric emptying is slowed by hyperglycemia and accelerated during insulin-induced hypoglycemia, although there is a lack of consensus on the magnitude of these effects and whether responses differ between health, type 1 diabetes, and type 2 diabetes. Guidelines for scintigraphic measurement of gastric emptying state that the baseline blood glucose should be <15 mmol/L (270 mg/dL) (8). Many of the studies relating to the effects of acute glycemia on gastric emptying are summarized in our review published 20 years ago (7). Stunkard and Wolff suggested, in 1956, that intravenous glucose abolished gastric "hunger contractions" (9). An effect of hyperglycemia (16–20 mmol/L [288–360 mg/dL]) to slow gastric emptying of nutrient liquids in health was reported in 1962 (10) and 1976 (11), albeit using suboptimal methodology. In a letter to this journal (12), Soler suggested in 1980 that marked hyperglycemia, in the absence of autonomic neuropathy or acidosis, could induce gastroparesis. We reported in 1990, in a study involving 10 patients with type 1 diabetes with poor glycemic control (mean HbA_{1c} 92 mmol/mol [10.6%]) that gastric emptying of solids and liquids, measured by scintigraphy, was slower at a blood glucose of 16–20 mmol/L (288–360 mg/dL) than 4–8 mmol/L (72–144 mg/dL), although the magnitude of the effect was variable (13). Elevations in blood glucose within the physiological range were also shown to delay gastric emptying, albeit modestly, in uncomplicated type 1 diabetes (14). Subsequent

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studies, predominantly in health, demonstrated that acute hyperglycemia *1*) affected proximal gastric, antral, and pyloric motility, as well as gastric electrical activity (15–17), potentially accounting for the slower emptying; *2*) increased the perception of gastric distension and small intestinal nutrient stimulation, perhaps contributing to symptoms (17); *3*) attenuated the action of drugs that accelerate (18), and potentiated the effect of drugs that slow (19), emptying; and *4*) affected esophageal, intestinal, gallbladder, and anorectal motility (7,20). In some cases, effects were related to the magnitude of elevation in blood glucose (7,16,20). Prostaglandins and nitric oxide were suggested as potential mediators (7,16). Insulin-induced hypoglycemia was shown to accelerate emptying markedly in uncomplicated type 1 diabetes, with and without gastroparesis and autonomic neuropathy (21,22). This acceleration is likely to represent an important counterregulatory response, recently shown to be greater during marked (blood glucose ~2.6 mmol/L [46.8 mg/dL]) than mild (~3.6 mmol/L [64.8 mg/dL]) hypoglycemia (23). Studies relating to the impact of acute changes in glycemia on gastric emptying have, for the main part, employed glucose/insulin clamps to elevate or reduce blood glucose concentrations abruptly and maintain them subsequently at the desired level. This approach differs from spontaneous fluctuations in blood glucose, which usually occur more slowly. Accordingly, the potential importance of the rate of change in blood glucose, likely involving different counterregulatory mechanisms, has not been evaluated. Information about the impact of chronic glycemic control (HbA_{1c}) on gastric emptying is inconsistent. In early, cross-sectional studies, HbA_{1c} was related to the (often markedly elevated) blood glucose levels recorded during gastric emptying measurements, compromising interpretation (24). More recently, in a subset of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, gastroparesis (assessed with a breath test) was related to HbA_{1c} at study entry and over the subsequent 27 years (4). The effect of improved glycemic control on gastric emptying is uncertain.

In this issue of *Diabetes Care*, the elegant and important article by Aigner et al. (25) evaluates the effects of spontaneous fluctuations in fasting glucose on gastric emptying. In a prospective study of 20 patients with type 1 diabetes and 10 healthy subjects, gastric emptying of solids was measured by breath test on three occasions and plasma glucose categorized as low, intermediate, or high. Furthermore, retrospective data from a cohort ($n = 255$) of patients with type 1 diabetes referred for measurement of gastric emptying were analyzed by tertiles of fasting plasma glucose. In neither the prospective nor cross-sectional study was there any relationship between fasting glucose, which was highly variable, and gastric emptying. In the cross-sectional analysis, slower gastric emptying was weakly associated with higher HbA_{1c}. The authors conclude that day-to-day variations in blood glucose do not affect gastric emptying in type 1 diabetes, invalidating current guidelines that gastric emptying studies be avoided during marked hyperglycemia and that delayed gastric emptying is linked to suboptimal chronic glycemic control.

In interpreting these conclusions, it should be appreciated that in both prospective and cross-sectional studies, extreme hyperglycemia (blood glucose >15.0 mmol/L [270 mg/dL]) and hypoglycemia (<3.9 mmol/L [70 mg/dL]) were uncommon, although there was no evidence to suggest an effect. Furthermore, in the cross-sectional analysis, participants had been hospitalized to improve glycemic control (although mean HbA_{1c} was ~62 mmol/mol [~7.8%]), which may account for the absence of a relationship between HbA_{1c} and fasting glucose, and gastric emptying was not usually measured because of gastrointestinal symptoms. Gastric emptying of nutrient liquids, which may be influenced by hyperglycemia more than that of solids (3,11,13), was not evaluated, and gastric emptying was not quantified with the most precise technique of scintigraphy. The outcomes of the study by Aigner et al. (25) add to the complexity of the relationships between gastric emptying and glycemia (Fig. 1) and should stimulate further studies to better characterize the impact of acute and chronic glycemic control, including blood glucose variability, on gastric emptying in diabetes, facilitated by the ready availability of ambulatory glucose monitoring. We would be circumspect about abandoning current criteria relating to the desirable blood glucose range for clinical measurement of gastric emptying in diabetes, although these authors may be correct.

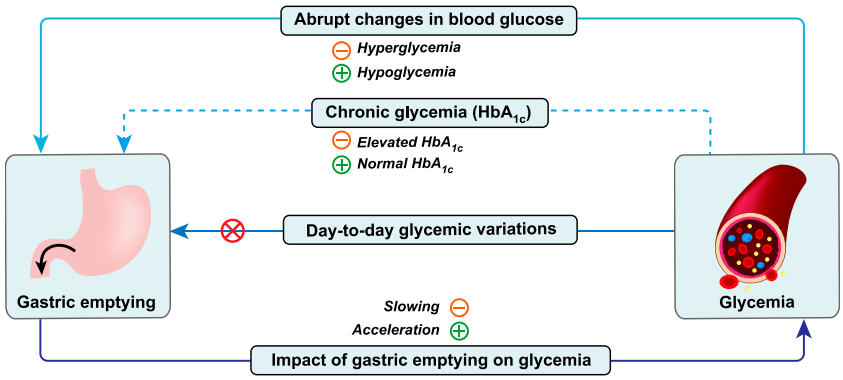

Figure 1—Interrelationships between glycemic variations and gastric emptying in type 1 diabetes. The relationship between gastric emptying and glycemia is bidirectional; while gastric emptying represents a major determinant of the blood glucose response to carbohydrate-containing meals, variations in glycemia—both hyperglycemia and hypoglycemia—may have a profound impact on gastric emptying. However, abrupt changes in glycemia (induced by glycemic clamp techniques) may slow or accelerate gastric emptying much more than gradual day-to-day variations. Chronic glycemia (as reflected by HbA_{1c}) is probably weakly associated with the rate of gastric emptying.

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