Effect of solid meal on gastric emptying of, and glycemic and cardiovascular responses to, liquid glucose in older subjects

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Berry, Melanie K., Antonietta Russo, Judith M. Wishart, Anne Tonkin, Michael Horowitz, and Karen L. Jones. Effect of solid meal on gastric emptying of, and glycemic and cardiovascular responses to, liquid glucose in older subjects. Am J Physiol Gastrointest Liver Physiol 284: G655–G662, 2003. First published January 2, 2003; 10.1152/ajpgi.00163.2002.—Gastric emptying is a determinant of the postprandial glycemic and cardiovascular responses to oral carbohydrate. We evaluated the effects of a solid meal on gastric emptying and the glycemic and cardiovascular responses to oral glucose in healthy older subjects. Ten subjects aged 72.1 ± 1.9 yr were studied. Each subject had measurements of gastric emptying, blood glucose, serum insulin, blood pressure, and heart rate after ingestion of a 50-g glucose drink (300 ml) with (mixed meal) or without (liquid only) a solid meal (300 g ground beef). Gastric emptying of liquid was initially slightly more rapid (P < 0.05) after the mixed meal compared with liquid only at 5 min (92.0 ± 1.5 vs. 96.0 ± 1.3%) and much slower (P < 0.05) after 120 min. The time to peak blood glucose was less (39.0 ± 4.0 vs. 67.5 ± 10.3 min; P < 0.01) and blood glucose subsequently lower (P < 0.01) after the mixed meal. The increase in serum insulin was greater (P < 0.001) after the mixed meal. Blood pressure fell (P < 0.05) in the first 30 min, with no difference between the two meals. Increase in heart rate after both meals (P < 0.005), was greater (P < 0.05) after the mixed meal. The presence of a noncarbohydrate solid meal had discrepant effects on early and subsequent emptying of a nutrient liquid, which affects postprandial glycaemia and increased heart rate.

glycemic control; blood pressure; postprandial hypotension; blood glucose

The rate of gastric emptying is a major determinant of the glycemic and cardiovascular response to oral carbohydrate (6, 12, 14, 17, 19, 28). The former has implications for the dietary management of people with diabetes mellitus, in whom tight blood glucose control has been shown to reduce both the development and progression of microvascular complications (1b). The latter is likely to be relevant to the treatment and prevention of postprandial hypotension, which is an important clinical problem (15). Both Type 2 diabetes and postprandial hypotension occur most frequently in the elderly.

Postprandial blood glucose levels are influenced by a number of factors (1b); however, it is now recognized that gastric emptying accounts for at least 35% of the variance in peak postprandial glucose levels after oral glucose (75 g) in both healthy individuals (6, 12) and patients with Type 2 diabetes (17, 28). The modulation of gastric emptying by dietary and pharmacological means, to minimize postprandial glucose excursions, represents a new approach to the improvement of glycemic control (26). Studies in rodents have established the importance of early insulin release in the control of postprandial glucose excursions in that a small, early increase in blood/portal insulin levels is more effective than a larger, later increase in reducing blood glucose levels (7). Hence, whereas slowing of overall absorption of nutrients may be expected to be beneficial in Type 2 diabetes, because initial insulin release is both diminished and delayed (28, 29), it is possible that modest acceleration of the initial gastric emptying rate of carbohydrate would have a beneficial effect on overall glycaemia in Type 2 diabetes, as well as healthy subjects by leading to an increase in early insulin release, particularly if the subsequent emptying of carbohydrates is slower. This latter hypothesis has not been evaluated.

A number of studies has evaluated the patterns of gastric emptying of meals of varying physical and nutrient composition and volume (1c, 4, 8, 11, 13, 22). In the majority of these studies, liquids (1c), semisolids (11), and solids (8) have been ingested alone. The initial emptying rate of nutrient-containing liquids is often faster than subsequently (5). When liquids and solids are consumed together, liquids empty preferentially (5), and the presence of a solid meal results in an overall slowing of the simultaneously ingested liquid (5). The possibility that the presence of a solid meal has discrepant effects on early, as opposed to overall emptying of liquids, has not been evaluated.

Postprandial hypotension, defined as a fall in systolic blood pressure of >20 mmHg after a meal (15), occurs frequently in older persons and in patients with diabe-
tes mellitus and autonomic neuropathy and is associated with a number of clinical sequelae including syncope, falls, stroke, angina, and increased mortality (15). Ingestion of carbohydrate, particularly large amounts, induces the greatest cardiovascular response, and the latter is evident soon after a meal; fat, protein, or water has relatively little effect (16). The mechanisms mediating the fall in postprandial blood pressure are poorly defined; however, splanchnic blood flow, release of gut hormones, and sympathetic nervous system activity are thought to play a role (15). Recent studies by our group indicate that the magnitude of the fall in blood pressure in both Type 2 diabetes (19) and healthy older subjects (18) is greater when gastric emptying is relatively more rapid (18, 19). Furthermore, in healthy older subjects, the fall in blood pressure and increase in heart rate are greater during intraduodenal glucose infusion at a rate of 3 kcal/min compared with 1 kcal/min and evident at 15 min (23). These observations suggest that the postprandial fall in blood pressure and rise in heart rate may be related to the early phase of gastric emptying.

The aims of this study were to evaluate the effects of ingestion of a solid, noncarbohydrate meal on gastric emptying and intragastric distribution of, and the glycemic and cardiovascular responses to, a liquid glucose load in healthy, older subjects. The broad hypotheses to be addressed were that the presence of a solid meal would accelerate the initial emptying phase and intragastric distribution of a liquid and that this would lead to 1) an overall reduction in postprandial glycemia consequent to an increase in early insulin secretion and 2) a greater postprandial fall in blood pressure and increase in heart rate.

METHODS

Subjects

Twelve healthy older subjects (6 male, 6 female), aged 72.9 ± 2.1 yr, body mass index (BMI) 25.3 ± 0.5 kg/m², were enrolled in the study. The subjects were recruited by using advertisements placed at the Royal Adelaide Hospital, Return Service Leagues, and bowling clubs. Subjects with significant neurological, respiratory, or cardiovascular disease and those with a history of diabetes mellitus or chronic alcohol abuse were excluded. No subject was taking medication known to affect blood pressure or gastrointestinal motor function. Written, informed consent was obtained from each participant in accordance with the Declaration of Helsinki (1989) of the World Health Organization, and the study was approved by the Human Ethics Committee at the Royal Adelaide Hospital.

Protocol

Each subject underwent concurrent measurements of gastric emptying, blood glucose, serum insulin, blood pressure, and heart rate on 2 days separated by at least 3 days. Subjects attended the Department of Nuclear Medicine at the Royal Adelaide Hospital at ~9:00 AM on each study day after an overnight fast (12 h for liquids; 14 h for solids). Subjects were seated with their back against a gamma camera, and a cannula was placed in an antecubital vein for blood sampling. An automated blood pressure monitor was attached to the opposite arm, and subjects were then given a 15- to 20-min rest period before consumption of the test meal. Gastric emptying, blood glucose, serum insulin, blood pressure, and heart rate were monitored for 180 min after completion of the meal. On one of the study days, the meal comprised 300 g ground beef (54 g protein, 30 g fat; total caloric content 540 kcal) and a drink containing 50 g glucose and 30 ml lemon juice made up to a volume of 300 ml with water (200 kcal) (mixed meal). On the other day, subjects were given the drink alone (liquid only). The order of the test meals was randomized (the study could not be blinded because minced beef was included in the meal on only one of the 2 days). On day 1, immediately after the gastric emptying measurement, cardiovascular reflex tests were performed to assess autonomic nerve function (10).

Gastric Emptying

Gastric emptying was measured by using a previously described scintigraphic technique (5). The 300 g ground beef was labeled with 20 MBq technetium-99m 99mTc-sulfur colloid chicken liver. To label the liver, 99mTc-sulfur colloid was injected intravenously into the wing of a live chicken, the chicken was then sacrificed, and the liver was removed (5). The glucose drink was labeled with 6 MBq 67Ga-EDTA on the mixed-meal day and 20 MBq of 99mTc-sulfur colloid on the liquid-only day and was consumed immediately after the solid meal on the mixed-meal day. Immediately after meal ingestion, data were acquired in 1-min time frames for the first hour and, subsequently, in 3-min time frames. Time 0 was defined as the time of meal completion. Data were corrected for subject movement, Compton scatter (in the dual isotope study), and radioactive decay by using established methods (5). Correction for gamma ray attenuation was performed by using factors derived from a lateral image of the stomach acquired immediately after the gastric emptying study (30 s image) (5).

A region of interest was drawn around the total stomach, which was subsequently divided into proximal and distal areas (5). Gastric emptying curves for the total, proximal, and distal stomach, expressed as the percent retention over time were derived (5). The amount remaining in each of the regions at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, and 180 min was derived manually from the curves. The solid lag phase, defined as the time before any of the solid meal had emptied from the stomach into the small intestine, was also calculated (5).

Blood Pressure and Heart Rate

Blood pressure (systolic and diastolic) and heart rate were measured by using an automated oscillometric blood pressure monitor (DINAMAP; Johnson and Johnson, Tampa, FL) immediately before ingestion of the test meal (baseline blood pressure was derived from the mean of 3 consecutive blood pressure measurements) and then at 3-min intervals for the first hour, and at 15-min intervals, thereafter. Mean arterial pressure (MAP) was calculated from systolic (SBP) and diastolic blood pressure (DBP) measurements at each time point by using the established formula: MAP = [DBP + (SBP – DBP)/3]. Postprandial hypotension was defined as a fall in systolic blood pressure ≥20 mmHg that was sustained for at least 30 min after the meal (15).

Blood Glucose and Serum Insulin

Blood samples (~20 ml) were taken from the indwelling cannula, immediately before the test meal and then at 15, 30,
45, 60, 90, 120, 150, and 180 min for measurement of blood glucose and serum insulin. Blood glucose concentrations were determined immediately by using a portable glucometer (Medisense Companion 2 meter; Medisense, Waltham, MA). Accuracy of the method has been established by using the hexokinase technique (12). Samples were then centrifuged at 3,000 rpm at 4°C for 15 min and frozen at −70°C until analysis of insulin. Serum insulin was measured by using the DSL-10–1600 active insulin ELISA immunoassay (Diagnostic Systems Laboratories, Webster, Texas). The sensitivity of the assay was 0.26 mU/l ± 2 SD. The interassay coefficients of variation were 2.6% at 8.48 mU/l and 1.3% at 44.23 mU/l (2).

**Autonomic Nerve Function**
Parasympathetic and sympathetic nerve function were assessed by using standardized cardiovascular tests (10). Parasympathetic function was evaluated by the difference in heart rate (R-R interval) during deep breathing and the immediate heart rate response to standing (30:15). The heart rate (R-R interval) during deep breathing and the assessed by using standardized cardiovascular tests (10).

**Statistical Analysis**
Data were evaluated from 0 to 30 and 0 to 180 min to examine early and overall changes in gastric emptying and the glycemic response. Blood pressure and heart rate were also assessed during the first 30 min, because postprandial falls in blood pressure are known usually to occur within this time frame (15). Mean contrasts were used to examine point-by-point comparisons at specified time points when a test meal type by time interaction was present on the ANOVA. Relationships among gastric emptying, blood glucose, serum insulin, and blood pressure were assessed by linear regression analysis. Data are presented as means ± SE. A P value of <0.05 was considered significant in all analyses.

**RESULTS**
Of the 12 subjects studied, 10 completed the experimental protocol. Two withdrew after experiencing nausea and light headness during their first visit; one withdrew after the liquid only and the other after the mixed meal. Of the remaining 10 subjects (5 male, 5 female), age 72.1 ± 1.9 yr, BMI 25.3 ± 0.5 kg/m², none had evidence of postprandial hypotension or cardiovascular autonomic neuropathy (score 0.3 ± 0.2).

**Gastric Emptying**

Total stomach. Emptying of the solid meal closely approximated a linear pattern after an initial lag phase of 69.2 ± 12.6 min. In contrast, the overall emptying of the liquid approximated a monoeponential pattern, after a short lag phase [mixed meal, 1.6 ± 0.3 min vs. liquid only, 2.0 ± 0.4 min; not significant (NS)]. With the mixed meal, 61.1 ± 4.5% of the liquid still remained in the stomach at the end of the solid lag phase.

In the mixed meal, gastric emptying of the solid was slower than that of liquid (P < 0.0001; Fig. 1A). Emptying of liquid was initially more rapid after the mixed meal vs. liquid only e.g., at 5 min (92.0 ± 1.5% vs. 96.0 ± 1.3%; P < 0.05), with a trend at 10 min (86.9 ± 1.8% vs. 91.5 ± 2.3%; P = 0.08) but was subsequently slower (P < 0.05) between 120 and 180 min (Fig. 1A).

Intragastic distribution. In the mixed meal, more of the solid component was retained in the proximal stomach compared with the liquid (P < 0.0001; Fig. 1B). With the mixed meal, the amount of liquid in the proximal stomach was initially less than the liquid only (P < 0.05; Fig. 1B) and subsequently greater (P < 0.05) from 120 to 180 min. Distal stomach retention of the liquid was greater after the mixed meal throughout the study (P < 0.05; Fig. 1C).

**Blood Glucose and Serum Insulin Concentrations**
There was a rise in blood glucose within 30 min after both meals (P < 0.0001 for both), and blood glucose concentrations had returned to baseline by 180 min after both meals (Fig. 2A). After the mixed meal, blood glucose concentrations were initially higher (P < 0.05) (within the first 60 min) (Fig. 2A) and lower (P < 0.01) after 90 min. There was no difference in peak blood glucose (mixed meal, 12.0 ± 1.3 mM vs. liquid only, 11.9 ± 2.6 mM; NS). However, the time to peak blood glucose was shorter (P < 0.01) after the mixed meal (39.0 ± 4.0 min vs. 67.5 ± 10.3 min; Fig. 2A).

Serum insulin levels increased after both test meals (P < 0.01 for both; Fig. 2B) and were higher (P < 0.001) including peak insulin (115.2 ± 26.9 mU/l vs. 61.8 ± 16.7 mU/l; P < 0.05) after the mixed meal compared with liquid only for the duration of the study.

**Blood Pressure and Heart Rate**
There were no significant differences in baseline scores for blood pressure between the two days (systolic: mixed meal, 119.7 ± 3.6 mmHg vs. liquid only, 123.0 ± 5.4 mmHg, NS; diastolic: mixed meal, 64.3 ± 2.3 mmHg vs. liquid only, 65.4 ± 4.1 mmHg, NS; MAP: mixed meal, 82.8 ± 2.2 mmHg vs. liquid only, 84.6 ± 4.1 mmHg, NS). There were significant falls in systolic (P < 0.005), diastolic (P < 0.001), and mean arterial (P < 0.001) blood pressure after both meals, all occurring within the first 30 min (Fig. 3). There were no significant differences in the magnitude of the fall in diastolic or mean arterial blood pressure between the two days (Figs. 3, B and C). However, when investigating a meal type by time interaction by using means contrasts, the fall in systolic blood pressure was less (P < 0.05) after the mixed meal between 33 and 48 min (Fig. 3A). Blood pressure returned to baseline by 180 min, for systolic, diastolic, and MAP.

There was no significant difference in baseline heart rate between the two study days (mixed meal, 70.2 ± 4.7 vs. liquid only, 69.7 ± 3.9 beats/min). Heart rate increased within 30 min after both meals (P < 0.005; Fig. 3D) and the magnitude of the increase was greater after the mixed meal compared with liquid only (P < 0.05) for the duration of the study. The rise in heart rate returned to baseline by 180 min after the liquid only but not after the mixed meal.
Fig. 1. Gastric emptying of 50 g glucose in 300 ml water with (mixed meal-liquid) and without (liquid only) 300 g ground beef (mixed meal-solid) for total (A), proximal (B), and distal (C) stomach regions of interest. Data are shown for the early phase (0–30 min) of gastric emptying as well as from 0–180 min. Data are means ± SE. *P values represent whole curve ANOVA (†mixed meal-solid vs. mixed meal-liquid; §mixed meal-liquid vs. liquid only) unless indicated by means contrasts (*P < 0.05, **P < 0.01, ***P < 0.001) for point-by-point comparisons due to meal type by time interaction.

Fig. 2. Blood glucose (A) and serum insulin (B) concentrations after 50 g glucose in 300 ml water with (mixed meal) and without (liquid only) 300 g ground beef. Data are mean values ± SE. *P values represent whole curve ANOVA (†mixed meal vs. liquid only) unless indicated by mean contrasts (*P < 0.05, **P < 0.01, ***P < 0.001) for point-by-point comparisons due to meal type by time interaction.
greater. There were no significant relationships between the rise in serum insulin and gastric emptying.

The magnitude of the falls in systolic (r = 0.83, P < 0.005) Fig. 5A and mean arterial blood pressure (r = 0.75, P < 0.01) Fig. 5B were significantly related to the rate of gastric emptying of liquid after liquid only but not after the mixed meal. There was no significant relationship between the change in diastolic blood pressure and heart rate with gastric emptying on either day. There were also no significant relationships between blood pressure and heart rate with the change in blood glucose or serum insulin concentrations on either day.

DISCUSSION

Results of this study establish that 1) the presence of a 300-g noncarbohydrate solid meal has discrepant effects on early and subsequent emptying of a nutrient liquid meal, so that gastric emptying of a 50-g glucose drink is initially slightly faster and then much slower compared with when the liquid is consumed alone; 2) the acceleration of the early liquid emptying induced by the solid meal is associated with a change in intragastric distribution, so that relatively more liquid is retained in the distal stomach; 3) the more rapid, early emptying of glucose is associated with an earlier peak in blood glucose, a greater serum insulin response, and an overall reduction in postprandial glycemia; and 4) whereas the initial (0–30 min) postprandial fall in blood pressure was not affected by the presence of a solid meal, the increase in heart rate was greater. These observations are consistent with the concept that the early phase of gastric emptying is a major determinant of postprandial glycemia as well as the cardiovascular response to a meal and have implications for the dietary management of Type 2 diabetes and postprandial hypotension.

Gastric emptying is a complex process and dependent on a number of factors, including meal composition and volume (1c, 4, 8, 13, 22). Whereas the differential overall emptying rates of solids and nutrient and nonnutrient liquids when ingested alone is well established (1c, 8, 11), there is much less information about the interaction between different meal components. The observation that the addition of a solid meal to a high nutrient liquid slows the overall emptying of liquid is not novel (4, 13). This slowing is potentially attributable to both the presence of solid in the distal stomach acting as a barrier and, perhaps most importantly, small intestinal feedback generated by the emptying of triturated solids (22). Previous studies have, however, not evaluated the potential effects of a solid meal on the early phase of liquid emptying. Measurements of the amount of liquid emptied were only made at 15 and 30 min (4, 13) rather than at 5-min intervals, as in the present study. The magnitude of the observed change in early emptying of liquid was modest, only evident for the first ~10 min and may result from an increase in intragastric volume (8), with subsequent compensation by small intestinal feedback (22). Ac-
cordingly, with higher-volume solid meals, the initial acceleration of emptying of liquid may be greater, although this remains to be determined. It intuitively appears somewhat surprising that a slight acceleration of the initial rate of gastric emptying of a nutrient liquid would be of relevance. However, this appears to be associated with substantial changes in the glycemic and cardiovascular responses to the meal.

In both normal subjects and diabetic patients, gastric emptying is an important determinant of blood glucose concentrations by controlling the delivery of carbohydrate to the small intestine (6, 12, 17, 28). Observations in this study support this concept i.e., the rise in blood glucose was related to gastric emptying of glucose and also suggest that the early phase of gastric emptying is a major determinant of insulin release and overall glycemia. Studies by de Souza (7) in rat models of Type 2 diabetes mellitus have established that the pattern of insulin release is pivotal to postprandial blood glucose concentrations. In our present study, the consumption of a noncarbohydrate solid meal before a liquid glucose load induced an earlier peak in blood glucose, compared with when the liquid was consumed alone, and a much more marked serum insulin response. The latter probably reflects both the greater initial rise in blood glucose and, the release of incretin hormones, glucagon-like peptide-1 (29), and gastric inhibitory polypeptide (27). It should be recognized that differences in serum insulin levels between the two meals were evident well before any of the solid meal had started to empty from the stomach. Protein content of the ground beef may have contributed to higher plasma insulin levels after ~70 min. Hence, increased early insulin release was associated with an overall reduction in postprandial glycemia. The latter may be attributable to both more efficient glucose disposal and changes in hepatic glucose metabolism (3).

Whereas our subjects were healthy volunteers, the observations are consistent with evidence that modulation of gastric emptying by dietary or pharmacological means could be used to optimize blood glucose control in Type 2 diabetes (26). The novel concept is that dietary strategies should be directed at the stimulation of a greater initial insulin response by accelerating the early emptying of carbohydrate and, subsequently, slowing it to delay glucose absorption. Studies in patients with Type 2 diabetes are required to evaluate this further. It should also be recognized that,
whereas none of our subjects had a history of diabetes mellitus, in healthy older populations, there is a high prevalence (~30%) of impaired fasting glycaemia and glucose tolerance (9) on the basis of fasting whole blood glucose (30). Our glucose load was 50 g, rather than the 75 g traditionally used to evaluate oral glucose tolerance (30). Moreover, subjects were studied under atypical conditions and glycaemia was assessed by glucometer measurements that are not recommended for diagnostic purposes (1a). Whereas we cannot comment specifically about the postprandial glucose levels, in a number of individuals, the postprandial blood glucose concentrations were suggestive of impaired glucose tolerance, and this should be considered in interpreting our observations. None of the subjects, however, had impaired autonomic nerve function, as is recognized in diabetes mellitus.

As discussed, the fall in blood pressure occurs soon after a meal and is usually related to ingestion of glucose. Fat and protein have little to no effect on blood pressure or heart rate (16). Moreover, other simple sugars, including fructose and xylose are substantially less potent than glucose in affecting blood pressure (15). We have established, in healthy older subjects, that the rate of delivery of glucose to the small intestine is a determinant of the postprandial fall in blood pressure and increase in heart rate (23). The latter study also indicated that the initial rate of caloric delivery is the major determinant of the cardiovascular response i.e., these differences were apparent within 5 min.

In the present study, the initial fall in blood pressure after an oral glucose load was not affected by a solid meal, whereas it may have been expected that more rapid, early liquid emptying would induce a greater fall in blood pressure. It should, also, be recognized that none of our subjects had postprandial hypotension. Surprisingly, the magnitude of the fall in systolic blood pressure from baseline was greater between 33 and 48 min when liquid was consumed alone. The significance of this observation is uncertain, particularly in view of the short duration and the absence of any effect on diastolic or MAP, and further confirmation would be indicated. However, it is possible that glucose absorption (which was not measured) may have been greater during this time. In contrast, the postprandial increase in heart rate was substantially greater and more sustained after the solid meal, consistent with recent observations (23). Hence, it appears that the initial absorption rate of glucose is a fundamental determinant of the cardiovascular response to carbohydrate, although the mechanisms mediating these effects remain uncertain. Accordingly, dietary strategies for the prevention of postprandial hypotension should perhaps focus on delaying the initial gastric emptying and/or small intestinal absorption of carbohydrate. Studies are now required to address these hypotheses.

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REFERENCES


