Effects of glucose supplementation on gastric emptying, blood glucose homeostasis, and appetite in the elderly

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The more rapid gastric emptying of glucose, induced by dietary glucose supplementation in young adults, is also associated with significant changes in the glycemic response to oral glucose; plasma insulin concentrations are initially higher, and plasma glucose concentrations subsequently lower, after dietary glucose supplementation (18). These observations are not surprising, as the rate of gastric emptying is known to be a major determinant of the glycemic response to an oral glucose load in both healthy subjects (19) and patients with type 2 diabetes (23). The increased insulin response to oral glucose as a result of dietary glucose supplementation in young subjects (18) may be attributable to higher levels of gastric inhibitory polypeptide (GIP), but plasma concentrations of the other important in-
cretin hormone, glucagon-like peptide-1 (GLP-1) (32), have not been evaluated. Aging is associated with an increased prevalence of glucose intolerance and diabetes mellitus and a greater GIP and GLP-1 response to carbohydrate (33).

The aims of this study were to determine, in healthy older subjects, the effects of dietary glucose supplementation on 1) gastric emptying of both glucose and fat, 2) blood glucose and plasma insulin and GIP and GLP-1 concentrations, and 3) food intake.

SUBJECTS AND METHODS

Subjects

Eight healthy, free-living, older subjects (4 male, 4 female), mean age 70.6 ± 2 yr (range 65–84 yr) with a body mass index of 26.2 ± 1.9 kg/m² (range 23.7–29.2 kg/m²), were recruited by advertisement. No subject had a history of gastrointestinal disease or surgery, significant illness (including diabetes mellitus), nor was taking medication known to affect gastrointestinal motility or appetite. All subjects were nonsmokers; all were well-nourished [score >24 on the Geriatric Mini-Nutritional Assessment (17)], unrestrained eaters [score <10 (Factor 1) on the Three-Factor Eating Questionnaire (40)]; and none were depressed [score >12 on Geriatric Depression Questionnaire (45)]. Before the commencement of the study, energy intake was assessed by a 3-day diet diary to ensure that all subjects had an average energy intake >1,000 kcal/day. The study protocol was approved by the Ethics Committee of the Royal Adelaide Hospital, and each subject gave written informed consent.

Protocol

Each subject was informed that the purpose of the study was to evaluate the effect of oral glucose supplementation on gastric emptying and gastrointestinal hormone release. Subjects completed two different diets, each for a period of 10 days in randomized order. The diets were 1) a standard diet consisting of the subject’s usual diet plus 350 ml of low-joule lemon cordial [Country Gold, Villawood, Australia; 72 ml cordial in 278 ml water (8 kcal)] consumed three times daily (immediately after each main meal) and 2) a glucose-supplement diet consisting of the subject’s usual diet supplemented with 210 g of glucose per day, given as three sachets of 70 g glucose added to 350 ml of the low-joule cordial [47 ml cordial in 303 ml water (5.3 kcal)]. Subjects were responsible for measuring the cordial and water and for adding the preweighed glucose sachets. The two dietary periods were separated by a “washout” period of at least 10 days during which each subject ate ad libitum. Compliance was assessed by weighing the unused glucose sachets returned after the glucose-supplement diet. All subjects were weighed at baseline and after each of the dietary periods. On the day immediately after each 10-day dietary period, subjects attended the Department of Nuclear Medicine after an overnight fast (14 h for solids and 12 h for liquids). A cannula was placed in a left antecubital vein for blood sampling. After a 15-min “recovery” period, subjects ingested an oil-glucose drink. Gastric emptying of the drink and appetite were then measured, and blood samples were taken for subsequent measurement of gastrointestinal hormones. Immediately after completion of the gastric emptying study (t = 210 min), each subject was offered a standard buffet-style meal and invited to eat as much as they wished over 30 min.

Subjects were not told that their food intake was to be measured (29).

Measurement of Gastric Emptying

Gastric emptying was measured for 210 min, starting immediately after the test drink, which was ingested within 2 min. The test drink comprised 15 ml olive oil (126 kcal), labeled with 20 MBq ⁹⁹ᵐTc-(V)-thiocyante (12), and 33 g glucose (124 kcal) dissolved in 185 ml water, labeled with 8 MBq ⁶⁷Gallium-EDTA (5), a total volume of 200 ml. Radioisotopic data were collected in 30-s frames for the first 30 min, followed by 3-min frames for the remaining 180 min (where t = 0 represents the time of completion of the drink). Data were corrected for subject movement, radionuclide decay, and gamma ray attenuation using established methods (10). A region of interest was drawn around the total stomach, and the percentage retention of the oil and glucose components at t = 0, 15, 30, 45, 60, 90, 120, 150, 180, and 210 min was calculated. The duration of the lag phase, calculated as the time point immediately preceding that in which activity was first seen in the proximal small intestine and the 50% emptying time (T₅₀), was also determined (10).

Blood Glucose and Gastrointestinal Hormones

Blood samples (~10 ml) were taken immediately before (~2 min) ingestion of the test drink and then at 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, and 270 min for measurement of blood glucose, plasma insulin, GIP, and GLP-1 (25, 29). Blood glucose concentrations were determined immediately, using a portable glucose meter (MediSense Companion 2 meter, MediSense, Waltham, MA). This technique has a coefficient of variation of 2.1–5.6%. The accuracy of this method in our laboratory has been confirmed using the hexokinase technique (21).

Plasma insulin was measured using the Abbott Imx Microparticle Enzyme Immunoassay (Abbott Laboratories, Diagnostic Division, Dainabot, Tokyo, Japan) (8). The sensitivity of the assay (concentration at 2 SD from the zero standard) was 1.0 mU/ml. The interassay coefficients of variation were 4.5% at 8.3 mU/ml and 3.4% at 40.4 mU/ml. The time to peak plasma insulin was also calculated.

Plasma GIP was measured by radioimmunoassay using anti-human GIP antisera according to an established method (18). The minimum detectable limit for this assay was ~5 pmol/l, and the interassay coefficient of variation was 15%.

Plasma GLP-1 was measured by radioimmunoassay after ethanol extraction using antibody (supplied by Professor S. R. Bloom, Hammersmith Hospital, London) that did not cross-react with glucagon, GIP, or other gut peptides and had been demonstrated by chromatography to measure intact GLP-1(7–36) amide (24, 43). The minimum detectable limit for this assay was ~2 pmol/l, and the interassay coefficient of variation was 18%.

Appetite and Food Intake

Energy intake during the dietary periods was assessed using a 3-day diet diary (29) maintained on the last 3 days of each diet. Each subject was instructed to weigh and measure his or her food. Diet diaries were checked by one of the investigators (C. MacIntosh or K. Beckoff).

Immediately before and after ingestion of the test drink, hunger and fullness were assessed using 10-cm visual analog scales (26, 29, 38), at –5, 0, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, and 270 min (2, 38). Subjects were familiarized with the scales at the beginning of each study and instructed
... to place a single vertical mark on the scale indicating their current feelings. The t = −5 value was used as the baseline (fasting) rating.

The buffet-style meal contained food prepared in excess of what would normally be eaten (275 ml iced coffee; 300 ml unsweetened orange juice; 4 slices whole meal bread; 4 slices white bread; 4 slices cheddar cheese; 4 slices processed chicken; 4 slices processed ham; 4 slices of tomato, cucumber, and lettuce; 2 sachets of mayonnaise; 4 sachets margarine; 1 pear; 1 apple; 1 banana; 200 g chocolate custard; 200 g strawberry yogurt; 50 g ice cream). Subjects were invited to eat as much as they wished for 30 min, and the total amount (g and kcal), as well as the macronutrient content of food consumed, was calculated using the DIET 4 Nutrient Calculation Software (Xyris Software, Queensland, Australia) (29).

**Statistical Analysis**

A two-way (diet and time) repeated-measures ANOVA (SuperANOVA Abacus concepts, version 1.11) was used to analyze differences in gastric emptying, blood glucose, plasma insulin, GIP, GLP-1, and appetite. Contrasts were performed to test hypotheses of interest, enabling paired comparisons at particular time points (18). Student’s t-tests were used to examine the effect of glucose supplementation on the lag phase, T50, number of calories emptied, time to peak insulin, food intake, and body weight. The relationships between variables were evaluated using linear regression analysis. Data are presented as mean values ± SE. A P value of <0.05 was considered significant.

**RESULTS**

The study was well tolerated by all subjects. Four of the eight subjects received the standard diet first. Compliance with the glucose supplement was excellent, with seven subjects returning 30 empty glucose sachets. One subject returned three sachets of glucose after a glucose-supplement diet. Data are presented as mean values ± SE. A P value of <0.05 was considered significant.

**Gastric Emptying**

**Oil.** Gastric emptying of oil approximated a linear pattern after an initial lag phase [glucose supplement: 58.4 ± 9.5 min vs. standard diet: 72.8 ± 15.5 min, not significant (NS); Fig 1A]. There was no difference in gastric emptying between the two diets (T50 glucose supplement: 122.1 ± 14.7 min vs. standard diet: 117.1 ± 14.2 min, NS). At t = 210 min, i.e., immediately before consumption of the buffet meal, most of the oil had emptied from the stomach (glucose supplement: 16.6 ± 1.9% remaining vs. standard diet: 20.0 ± 4.9% remaining, NS).

**Glucose.** Gastric emptying of glucose approximated a monoeponential pattern after a short lag phase (glucose supplement: 0.6 ± 0.1 min vs. standard diet: 2.1 ± 1.3 min; NS; Fig 1B). The glucose emptied faster than the oil component of the drink on both diets (glucose supplement: T50 oil vs. glucose, P < 0.01; and standard diet: T50 oil vs. glucose, P < 0.01), due to a longer lag phase for oil (glucose supplement: lag phase oil: 58.4 ± 9.5 min vs. glucose: 0.6 ± 0.1 min, P < 0.005; and standard diet: oil: 72.8 ± 15.5 min vs. glucose: 2.1 ± 1.3 min, P < 0.01). Gastric emptying of glucose was faster after the glucose supplement compared with the standard diet (T50: 48.6 ± 5.9 min vs. 62.0 ± 6.1 min, P = 0.04). At t = 210 min, most of the glucose had emptied from the stomach (glucose supplement: 12.8 ± 1.6% remaining vs. standard diet: 11.5 ± 1.8% remaining; F1,7 = 0.14, NS).

There was no difference (NS) in the total number of oil and glucose calories emptied from the stomach at t = 210 min between the two diets (data not shown).

**Blood Glucose and Gastrointestinal Hormones**

Fasting blood glucose (glucose supplement: 5.4 ± 0.2 mmol/l vs. standard diet: 5.4 ± 1.2 mmol/l, F1,7 = 0.001, NS), plasma insulin (glucose supplement: 4.7 ± 0.7 mU/l vs. standard diet: 4.1 ± 0.7 mU/l, F1,7 = 0.03, NS), GIP (glucose supplement: 27.0 ± 4.2 pmol/l vs. standard diet: 26.6 ± 4.5 pmol/l, F1,7 = 0.001, NS), and GLP-1 (glucose supplement: 7.9 ± 1.2 pmol/l vs. standard diet: 8.6 ± 1.7 pmol/l, F1,7 = 0.10, NS) were not significantly different between the two diets (Fig. 2).

**Blood glucose.** On both days, blood glucose increased after the test drink (change from baseline to 30 min: F1,7 = 39.46, P < 0.001; Fig 2A) and returned to baseline levels at ~150 min. There was no overall difference in blood glucose between the two diets (F1,7 = 2.64, NS), a significant difference over time F10,70 = 34.8, P < 0.0001), and a significant diet-by-time interaction (F10,70 = 1.94, P = 0.05). Blood glucose concentrations at 75 and 90 min were less after the
glucose-supplemented diet (at 75 min: 8.3 ± 0.5 vs. 9.4 ± 0.3 mmol/l; \( F_{1,7} = 10.26, P < 0.01 \)).

**Plasma insulin.** Plasma insulin increased after ingestion of the test drink (change from baseline to 30 min: \( F_{1,7} = 48.70, P < 0.001 \); Fig. 2B) and declined to baseline levels at ~180 min on both days. The time to peak insulin concentration was less (31.9 ± 6.0 vs. 73.1 ± 8.2 min; \( F_{1,7} = 3.27, P < 0.01 \)) after the glucose-supplemented diet compared with the standard diet. There was no overall difference in plasma insulin between the two diets (\( F_{1,7} = 1.49, \text{NS} \)), a significant change over time (\( F_{10,70} = 19.6, P < 0.0001 \)), and a significant diet-by-time interaction (\( F_{10,70} = 2.2, P = 0.03 \)). At 30 min, plasma insulin tended to be greater in the glucose-supplemented than in the standard diet condition (\( F_{1,7} = 3.66, P = 0.059 \)), with a subsequent reduction at 60 min (\( F_{1,7} = 10.31, P < 0.01 \)) and 120 min (\( F_{1,7} = 4.0, P < 0.05 \)).

**Plasma GIP and GLP-1.** Plasma GIP and GLP-1 increased after ingestion of the test drink on both days (change from baseline to 30 min: GIP: \( F_{1,7} = 48.41, P < 0.001 \) and GLP-1: \( F_{1,7} = 8.81, P < 0.01 \); Fig. 2, C and D). There was no overall difference in either plasma GIP (\( F_{1,7} = 0.47, \text{NS} \)) or GLP-1 (\( F_{1,7} = 1.69, \text{NS} \)) between the two diets. There was a significant change in plasma GIP over time (\( F_{10,70} = 10.13, P < 0.0001 \)) but no diet-by-time interaction (\( F_{10,70} = 0.55, \text{NS} \)). In contrast, there was no change in plasma GLP-1 over time (\( F_{10,70} = 1.41, \text{NS} \)) or diet-by-time interaction (\( F_{10,70} = 0.52, \text{NS} \)). There was a trend for plasma GIP concentrations to be greater immediately after ingestion of the test drink (at \( t = 15 \) min \( F_{1,7} = 3.65, P = 0.06 \)) after the glucose-supplemented diet compared with the standard diet.

**Appetite**

**Baseline energy intake and body weight.** The energy intake of the diet before entry into the study was 1,832 ± 153 kcal (43% carbohydrate, 36% fat, and 18% protein). There was no change in body weight (\( F_{2,7} = 0.85, \text{NS} \)) after either the glucose-supplemented (68.9 ± 2.7 kg) or the standard (68.6 ± 2.9 kg) diet compared with baseline body weight (68.2 ± 2.8 kg).

**Energy intake during dietary periods.** There was no difference in energy intake during the two diets when the glucose supplement was excluded (glucose supplement: 1,611 ± 139 kcal vs. standard diet: 1,653 ± 133 kcal; \( F_{1,7} = 0.08, \text{NS} \); Fig. 3). When the additional energy (840 kcal) provided by the glucose supplement was included, energy intake was greater (\( F_{1,7} = 29.96, P < 0.001 \)) during the glucose-supplemented diet compared with the standard diet. There were no differences in dietary macronutrient content (% carbohydrate, fat, or protein) during the glucose-supplement diet compared with the standard diet when the additional calories of the supplement were not included (data not shown).

**Hunger and fullness.** On the visual analog scales, subjects reported no differences after the fast in hun-
ger (glucose supplement: 7.7 ± 1.1 cm vs. standard diet: 8.1 ± 0.3 cm; F\textsubscript{1,7} = 0.11, NS; Fig. 4A) or fullness (glucose supplement: 2.7 ± 0.8 cm vs. standard diet: 3.0 ± 0.8 cm; F\textsubscript{1,7} = 0.04, NS; Fig. 4B) between the two diets. Nor did subjects report any significant difference in hunger between the diets (F\textsubscript{1,7} = 2.03, NS), but hunger did tend to decrease over time (F\textsubscript{11,77} = 1.74, P = 0.08), with no diet-by-time interaction (F\textsubscript{11,77} = 0.43, NS). Similarly, there was no effect of diet on fullness (F\textsubscript{11,77} = 0.43, NS), but fullness increased over time (F\textsubscript{11,77} = 3.04, P < 0.005), with no diet-by-time interaction (F\textsubscript{11,77} = 0.42, NS).

Food intake. Regardless of diet, the caloric (glucose supplement: 824 ± 82 kcal vs. standard diet: 851 ± 73 kcal; F\textsubscript{1,7} = 0.86, NS) and macronutrient content of the food the subjects ate at the buffet meal was the same (data not shown). There was an inverse relationship (r = −0.55, P < 0.05) between the caloric content of the food eaten at the buffet meal and the amount of the oil-glucose drink (kcal) remaining in the stomach immediately before the buffet meal (glucose supplement: r = −0.77, P < 0.05; standard diet: r = −0.51, NS) (Fig. 5).

DISCUSSION

Our study has evaluated the effects of short-term dietary glucose supplementation on gastric emptying, the glycemic response to a drink containing glucose, and subsequent food intake in healthy older subjects. The results establish that, as in young subjects, dietary glucose supplementation accelerates gastric emptying of glucose in the elderly (18) and that this is associated with significant changes in blood glucose, plasma insulin, and, almost certainly, GIP (18). Novel observations are that 1) the acceleration of gastric emptying of glucose is not associated with any change in gastric emptying of oil, 2) the stimulation of insulin secretion is not associated with any change in GLP-1, and 3) dietary glucose supplementation does not decrease food intake, so that caloric intake was substantially greater while subjects were taking the glucose supplement.

A number of studies has established that dietary modification may influence gastric emptying (11, 13, 14, 18) and gastric motor function (1) in healthy young adults. The magnitude of the acceleration of gastric emptying of glucose after dietary glucose supplementation in older subjects is similar to that observed in the young (13, 18). This is perhaps not surprising as the effects of healthy aging on gastrointestinal function, including gastric emptying, are relatively small (2). In our previous studies in younger subjects (1, 13, 18), the duration of dietary glucose supplementation was comparable, but both the glucose supplement [210 g vs. 440 g/day in the study by Horowitz et al. (18)] and
the amount of glucose in the drink used to measure gastric emptying (33 vs. 75 g) were less in the current study. Our glucose supplement was intentionally selected to be smaller, as older people eat substantially less (30–50%) than young adults (36, 44); proportionately, the increase in daily energy intake was comparable to the supplements used in younger subjects (1, 13, 18).

Gastric emptying of glucose is regulated primarily by feedback from receptors in the lumen of the small intestine (6, 27) and mediated, at least in part, by the release of gastrointestinal hormones including CCK and, possibly, GIP and GLP-1 (16, 43). Infusion of glucose and other nutrients directly into the small intestine is associated with stimulation of phasic and tonic pressure waves localized to the pylorus (1, 15), suppression of antral pressure waves (1), a reduction in proximal gastric tone (4), and slowing of gastric emptying. The stimulation of pyloric tone (basal pyloric pressure) is probably the most important of these mechanisms (41). We have recently established in young adults that dietary glucose supplementation is associated with attenuation of the tonic pyloric response to intraduodenal glucose (1). This observation provides persuasive evidence to support the concept that the acceleration of gastric emptying of glucose by dietary glucose supplementation reflects diminished small intestinal feedback on the neural and/or humoral mechanisms that regulate gastric emptying. It remains to be established whether the accelerated gastric emptying occurs as a result of a decrease in the sensitivity of small intestinal “glycereceptors” or the recruitment of fewer receptors from more rapid absorption and, hence, reduced nutrient exposure (18). It should also be recognized that elevations of the blood glucose concentration, which are within the normal postprandial range, affect gastric emptying (37) and gastric motility (3). It is accordingly possible, albeit unlikely, that the slightly higher postprandial blood glucose concentrations on the standard diet may have contributed to the slower gastric emptying of glucose.

Although gastric emptying of glucose was faster after dietary glucose supplementation, there was no difference in gastric emptying of fat (oil). Although the absence of an effect of glucose supplementation on gastric emptying of oil may represent a type 2 error, these findings are consistent with the observation that dietary glucose supplementation does not modify the pyloric motor response to intraduodenal lipid (1). Moreover, it has been established that the slowing of gastric emptying by small intestinal glucose and fat is mediated by different receptors (27, 28). These observations argue against the concept that caloric density, rather than the nature of calories, is the primary determinant of the rate of gastric emptying (7). Accordingly, it appears that adaptive changes in gastric emptying occurring as a result of dietary nutrient modification may be relatively nutrient specific.

The effects of dietary glucose supplementation on the glycemic profile are compatible with the observed acceleration of gastric emptying and more rapid delivery of glucose to the small intestine, i.e., an earlier rise in plasma insulin and subsequent reduction in blood glucose. The increased insulin response is likely to be attributable to the earlier rise in plasma GIP ($P = 0.06$), as there was no difference in plasma GLP-1. GIP is released as a result of the interaction of nutrients with the proximal small intestine, and its release is, accordingly, potentiated when gastric emptying is faster (18). In contrast, GLP-1 is released predominantly from the distal small intestine (32), and plasma concentrations are inversely related to the rate of gastric emptying (43).

Our observation that older subjects did not modify their diet to compensate for additional energy provided by the glucose supplement is consistent with the concept of an age-related impairment in the homeostatic mechanisms that regulate appetite, with a lack of compensation for dietary manipulations (35). Roberts et al. (35) demonstrated that after a 21-day period of over- and underfeeding, older subjects, in contrast to younger subjects, did not modify their food intake or body weight, at least in the short term. In our study, glucose supplementation also had no effect on perceptions of appetite after a glucose-oil “preload” or on energy intake at the buffet meal consumed at 210 min after this “preload.” Accordingly, the use of glucose or other carbohydrate supplements may prove to be effective in increasing total energy intake and preventing weight loss in the elderly. It is not surprising that there was no significant change in body weight after glucose supplementation given the number of subjects studied and the relatively short duration of glucose supplementation. Although at the time when the buffet meal had been consumed most of the glucose-oil drink had emptied from the stomach, there was an inverse relationship between the amount (kcal) eaten and the gastric content at this time. This last observation suggests that, as in the young (22), gastric distension modifies food intake in the elderly.

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REFERENCES


