Intraduodenal Guar Attenuates the Fall in Blood Pressure Induced by Glucose in Healthy Older Adults

Deirdre O’Donovan,1 Christine Feinle-Bisset,1 Chilton Chong,1 Alexander Cameron,1 Anne Tonkin,2 Judith Wishart,1 Michael Horowitz,1 and Karen Louise Jones1

Departments of 1Medicine and 2Clinical Pharmacology, University of Adelaide, Royal Adelaide Hospital, South Australia.

Objectives. Postprandial hypotension occurs frequently in older people and may result in syncope and falls. It has recently been established that the magnitude of the fall in blood pressure is related to the rate at which glucose enters the small intestine. We addressed the hypothesis that the fall in blood pressure induced by an intraduodenal glucose infusion is influenced by the interaction of glucose with the small intestinal absorptive epithelium.

Methods. Eight healthy older participants (four male, four female, age 70.3 ± 3.4 years) were studied on two separate occasions, in single-blind, randomized order. Participants received an intraduodenal glucose infusion (3 kcal/min) with or without guar gum (4 g) for 60 minutes (0–60 minutes), followed by 0.9% saline intraduodenally for a further 60 minutes (60–120 minutes). Blood pressure and heart rate were measured every 3 minutes. Levels of blood glucose, plasma insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulintropic polypeptide (GIP) were also determined.

Results. Between t = 0 and t = 30 minutes, the magnitude of the fall in systolic blood pressure (p = .03) and increase in heart rate (p = .027) were lower after guar. The blood glucose (p = .009), plasma insulin (p = .027), plasma GLP-1 (p = .018), and GIP (p < .001) responses to intraduodenal glucose were attenuated by guar.

Conclusions. In healthy older participants, the magnitude of the fall in systolic blood pressure and increase in heart rate induced by intraduodenal glucose are attenuated when the exposure of glucose to the small intestinal mucosa and subsequent glucose absorption is slowed by guar.

Postprandial hypotension, defined as a fall in systolic blood pressure of ≥20 mmHg after a meal (1), is an important clinical entity, predisposing to syncope and falls (1–3). Those at greatest risk include elderly persons and patients with autonomic neuropathy, which is most frequently secondary to diabetes mellitus (4). The onset of the fall in blood pressure is usually within 30 minutes of meal ingestion, and the magnitude of the decrease is dependent on meal composition, particularly the carbohydrate content; fat and protein have little effect on blood pressure (1). It is also known that the effects of oral carbohydrate on blood pressure do not reflect the rise in blood glucose per se, as intravenous glucose has little, if any, effect on blood pressure (4). The pathophysiology of postprandial hypotension has, until recently, received little attention; current treatments are based largely on anecdotal evidence and are suboptimal (1,5).

We have established that the rate of gastric emptying is an important determinant of the postprandial fall in blood pressure (6–8); in an initial cross-sectional study in patients with type 2 diabetes (6), the fall in blood pressure after a drink containing 75 grams of glucose was greater when gastric emptying was relatively more rapid. More recently, we demonstrated that the hypotensive response to an intraduodenal glucose infusion in healthy older participants is dependent on the rate of glucose delivery into the small intestine (8); intraduodenal glucose infusion at a rate of 3 kcal/min resulted in falls in both systolic and diastolic blood pressures that were much greater than those after an infusion with a rate of 1 kcal/min. The latter study “excluded” the potential effects of gastric emptying and suggested that the hypotensive effects of enteral glucose are dependent on the glucose concentration and/or the length of small intestine exposed to glucose (8,9). Moreover, a distinction could not be made between the potential effects of the rate of glucose entry into the small intestine from effects which are specific to the small intestine, including the diffusion of glucose across the small intestinal mucosa.

Guar gum, a naturally occurring, gel-forming carbohydrate of vegetable origin, slows both gastric emptying and small intestinal glucose absorption (10); the slowing of gastric emptying by guar reflects the greater viscosity of the intragastric content, as well as an increase in small intestinal feedback secondary to the exposure of a greater length of the small intestinal lumen to glucose (9,11). Guar also slows the diffusion capacity of glucose across the small intestinal mucosa by acting as a physical barrier, and diminishes the contact between glucose molecules and small intestinal mucosal cells (12). We have reported that, in both healthy older participants (7) and patients with type 2 diabetes (13), the addition of guar gum to a 50-g glucose drink slowed both gastric emptying and glucose absorption and attenuated the fall in blood pressure (7,13). It is not known whether the observed effects of guar on blood pressure reflect the slower rate of glucose entry into the small intestine (i.e., retardation of gastric emptying) or changes in intestinal exposure to glucose. It has been established that the small intestinal mucosa “senses” specific nutrients (14); this capacity is important in the regulation of gastric emptying (15,16), small intestinal transit (17), appetite (18), and upper gastrointestinal sensations (19,20) and is associated with modulation of
neural and hormonal functions (20,21). We have now evaluated the effects of intraduodenal, as opposed to intragastric, administration of guar on the blood pressure response to intraduodenal glucose in older participants. If guar increased the hypotensive response to glucose, it would suggest that the response was length-dependent; in contrast, if intraduodenal guar decreased the hypotensive response, it would suggest a concentration-dependent mechanism.

The presence of glucose in the small intestine also stimulates the release of a number of peptides, including insulin and the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino-tropic polypeptide (GIP) (22,23). A role of gut peptides in mediating postprandial hypotension is suggested by the observation that administration of the long-acting somatostatin analogue, octreotide, which is known to inhibit the release of most gastrointestinal peptides, abolishes the fall in blood pressure induced by oral glucose in older participants (24). The addition of guar to an oral carbohydrate meal abolishes the fall in blood pressure.

In this study, we have evaluated the effects of intraduodenal guar on the cardiovascular and incretin responses to intraduodenal glucose in healthy older participants. The rationale for this approach was to discriminate between the effects of the rate of entry of glucose into the small intestine from those resulting from the interaction of glucose with the small intestinal mucosa.

**METHODS**

**Participants**

Eight healthy older participants (four men and four women), with a mean age of 70.3 ± 3.4 years and a body mass index of 23.6 ± 0.8 kg/m², were recruited by advertisement. All were nonsmokers, and none had a history of postprandial hypotension, gastrointestinal disease or surgery, diabetes mellitus, significant respiratory or cardiac disease, alcohol abuse, or epilepsy. No participant was taking medication known to influence blood pressure or gastrointestinal function.

The protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital, and each participant gave written, informed consent prior to the commencement of the study. All experiments were carried out in accordance with the Declaration of Helsinki.

**Protocol**

Each participant underwent paired studies; on one day participants received an intraduodenal infusion of glucose (“glucose only”) and on the other an intraduodenal infusion of glucose that included guar gum (Chipmonk, Queensland, Australia) (“glucose and guar”). The two studies were separated by a median interval of 7 days (range 5–9 days), and were performed in randomized, single-blind order. On each study day, the participant attended the laboratory at 0900 AM after a 12-hour fast from both solids and liquids. On arrival, a silicone rubber nasoduodenal catheter (outer diameter 6 mm) was inserted into the stomach via an anesthetized nostril. The assembly included an infusion channel with a port located ~10 cm distal to the pylorus and two other channels, positioned in the antrum (2.5 cm proximal to the pylorus) and duodenum (2.5 cm distal to the pylorus), respectively. The latter two channels were perfused with normal saline; a saline-filled, reference electrode (20-gauge intravenous cannula) was inserted subcutaneously into the participant’s forearm to enable measurement of the antroduodenal transmucosal potential difference. The use of this technique allows the catheter to be positioned accurately across the pylorus (26). The tip of the catheter was allowed to pass into the duodenum by peristalsis, which took between 20 and 120 minutes. An intravenous cannula was positioned in the right antecubital vein for blood sampling, and an automated blood pressure cuff (DINAMAP; Johnson & Johnson, Tampa, FL) was placed on the left arm. The participant was then allowed to rest comfortably in the recumbent position for approximately 15 minutes.

At time $t = 0$ minutes, an intraduodenal infusion of 50 g of glucose dissolved in 300 ml of water, with or without 4 g of guar gum, was infused at a rate of 5 ml/min (i.e., 3 kcal/min) for 60 minutes. Following the glucose infusion, 0.9% saline was infused intraduodenally for a further 60 minutes (i.e., $t = 60–120$ minutes). Blood pressure and heart rate were measured, and venous blood samples taken, at regular intervals throughout the study. At $t = 120$ minutes the catheter was removed. Cardiovascular autonomic function (27,28) was evaluated on one of the study days, after the manometric assembly had been removed. Participants were then provided with lunch and allowed to leave the department.

**Measurements**

**Blood pressure and heart rate.**—Baseline blood pressure (systolic and diastolic) and heart rate were measured by taking the mean of two readings immediately before commencement of the intraduodenal infusion and then at 3-minute intervals for the duration of the study (120 minutes).

**Blood glucose and plasma insulin, GLP-1, and GIP.**—Blood glucose and plasma insulin, GLP-1, and GIP levels were measured at baseline, then at 15, 30, 45, 60, 75, 90, 105, and 120 minutes. Blood glucose was measured using a portable blood glucose meter (Medisense Companion 2; Medisense, Waltham, MA). The accuracy of these measurements has been confirmed using the hexokinase technique (29). Plasma samples were stored at −70°C until assayed. Plasma insulin was measured by enzyme-linked immunosorbent assay (ELISA) (Diagnostics Systems Laboratories, Webster, TX). The sensitivity of the assay was 0.26 mU/L; the coefficient of variation 2.6% within assays and 6.2% between assays (30). Plasma GLP-1 was measured by using an antibody supplied by Professor S. R. Bloom (Hammer smith Hospital, London, UK). The intraassay coefficient of variation was 17%, and the interassay coefficient of variation...
was 18%. Sensitivity was 1.5 pmol/L (31). Plasma GIP was also measured by radioimmunoassay. The intra- and inter-assay coefficients of variation were both 15%. The minimum detectable limit was 2 pmol/L (32).

**Cardiovascular autonomic nerve function.—**Autonomic nerve function was evaluated using standardized cardiovascular reflex tests (27) parasympathetic function by the variation (R-R interval) of the heart rate during deep breathing and the response to standing (30:15 ratio). Sympathetic function was assessed by the systolic blood pressure response to standing. Each of the test results was scored, according to age-adjusted criteria, as 0 = normal, 1 = borderline, and 2 = abnormal for a total maximum score of 6. A score ≥3 was considered to indicate autonomic dysfunction (28).

**Statistical Analysis**

Systolic and diastolic blood pressure were analyzed as changes from baseline between t = 0 and t = 30 and t = 0 and t = 60 minutes; in our previous study in healthy older adults, a fall in systolic and diastolic blood pressure during a 3 kcal/min intraduodenal glucose infusion was evident at 15 minutes with a maximum response at about 30 minutes (8). All other parameters were analyzed as absolute values, between t = 0 and t = 60 minutes for heart rate and between t = 0 and t = 120 minutes for blood glucose and plasma insulin, GLP-1, and GIP. Data were evaluated using repeated measures analysis of variance and are presented as means ± standard error of the mean. A p value < .05 was considered significant in all analyses.

**RESULTS**

All the studies were well tolerated. Although most of the participants exhibited minor abnormalities of autonomic function, none had significant evidence of autonomic neuropathy. The mean score for autonomic nerve dysfunction was 1.5 ± 0.2.

**Blood Pressure and Heart Rate**

There was no significant difference between the two study days (glucose only vs glucose and guar) in baseline systolic (140.8 ± 5.4 mmHg versus 139 ± 5.9 mmHg) and diastolic (71.7 ± 2.7 mmHg versus 75.3 ± 3.5 mmHg) blood pressures. Between t = 0 and t = 60 minutes, systolic blood pressure was lower (p = .006) during the glucose-only infusion than during the glucose and guar infusion. Systolic blood pressure fell significantly between 0 and 30 minutes during the glucose-only (p = .02), but not during the glucose and guar (p = .87) infusion (Figure 1A); the fall in systolic blood pressure during the intraduodenal glucose-only infusion was evident from 15 minutes (p = .002). Between t = 0 and t = 30 minutes (p = .03) and t = 30 and t = 60 minutes (p = .01), systolic blood pressure was lower during the glucose-only infusion than during the glucose and guar infusion. The maximum fall in systolic blood pressure on the glucose-only study was 10 ± 4 mmHg at 27 minutes. On both days systolic blood pressure was not significantly different from baseline at 120 minutes (glucose only: 131 ± 7 mmHg; glucose and guar: 136 ± 7 mmHg).

There was no overall difference in diastolic blood pressure between t = 0 and t = 60 minutes (p = .9). However, between t = 0 and t = 30 minutes, diastolic blood pressure fell during the glucose-only infusion (p = .0002), but did not change with the glucose and guar infusion (p = .9) (Figure 1B); the fall in diastolic blood pressure was evident from 15 minutes during the glucose-only infusion. At 120 minutes, diastolic blood pressure was not significantly different from baseline on both days (glucose only: 63 ± 2 mmHg; glucose and guar: 68 ± 4 mmHg).

There was no difference in baseline heart rate between the two study days (glucose only: 66.3 ± 3.3 bpm; glucose and guar: 62.7 ± 3.8 bpm). Heart rate increased between t = 0 and t = 60 minutes during the glucose-only (p = .0001), but not the glucose and guar (p = .33) infusion (Figure 1C).
The magnitude of the increase in heart rate between \( t = 0 \) and \( t = 30 \) minutes was greater during the glucose-only infusion than during the glucose and guar infusion (\( p = .027 \)). Heart rate had returned to baseline by 120 minutes on both days (glucose only: 67 ± 6 bpm; glucose and guar: 65 ± 4 bpm).

**Blood Glucose and Plasma Insulin, GLP-1, and GIP Concentrations**

There were no differences in baseline blood glucose (glucose only: 5.9 ± 0.3 mmol/L; glucose and guar: 5.8 ± 0.2 mmol/L) and plasma insulin (glucose only: 5.0 ± 0.7 mU/L; glucose and guar: 5.4 ± 0.8 mU/L) levels between the two study days. On both study days, the intraduodenal infusions were associated with an increase in blood glucose (\( p = .009 \)); this increase was evident by 15 minutes (\( p = .017 \)) during the intraduodenal glucose-only infusion, and within 30 minutes during the glucose and guar infusion (\( p < .001 \)). The magnitude of the increase in blood glucose was greater with the glucose-only infusion compared with the glucose and guar infusion (\( p < .001 \)) (Figure 2A). Plasma insulin also increased during both infusions (\( p < .001 \)); the increase in plasma insulin concentration was evident by 30 minutes for both the glucose-only (\( p < .001 \)) and the glucose and guar (\( p = .004 \)) infusion. The magnitude of the increase in insulin was greater during the glucose-only infusion (\( p = .027 \)) compared with the glucose and guar infusion (Figure 2B).

There were no differences in baseline plasma GLP-1 concentrations between the two study days (glucose only: 13.7 ± 4.2 pmol/L; glucose and guar: 16.7 ± 4.0 pmol/L). Plasma GLP-1 increased during the glucose-only infusion (0–120 min) (\( p < .001 \)), but not during the glucose and guar (\( p = .165 \)) infusion (Figure 2C). The increase in plasma GLP-1 was evident by 30 minutes during the glucose-only infusion (\( p = .02 \)). There were no differences in baseline plasma GIP concentrations between the 2 days (glucose only: 15.6 ± 2.3 pmol/L; glucose and guar: 19.4 ± 6.3 pmol/L). Plasma GIP increased on both days (\( p < .001 \)) (Figure 2D). The increase in plasma GIP was evident by 15 minutes on both the glucose-only (\( p = .007 \)) and the glucose and guar (\( p = .05 \)) infusion. The magnitude of the increase in GIP was greater during the glucose-only (\( p = .002 \)) infusion compared with the glucose and guar infusion.

**DISCUSSION**

This study establishes in healthy older participants that a reduction in the rate of mucosal uptake of glucose (hence glucose absorption) resulting from the addition of guar to an intraduodenal glucose infusion is associated with...
attenuation of the fall in blood pressure, increase in heart rate and rises in blood glucose, plasma insulin, GLP-1, and GIP induced by intraduodenal glucose.

Our recent studies (7,13) have established that the magnitude of the fall in blood pressure after oral glucose in healthy older participants is dependent on the initial rate of gastric emptying and that the hypotensive response is attenuated by oral guar. To discriminate between “gastric” and “small intestinal” effects, we infused guar directly into the small intestine. The dose and concentration of guar (4 g/300 ml glucose solution) used were lower than those given orally in previous studies (7,13), but comparable doses have been shown to slow glucose absorption when administered directly into the small intestine (11). It should be recognized that the experiment was not totally controlled because of practical limitations in performing intraduodenal infusions in older participants, but neither guar alone, nor saline in the doses used, would be expected to elicit a cardiovascular response.

Glucose absorption across the enterocyte takes place via the sodium-dependent glucose transporter-1 at the luminal membrane and via the glucose transporter-2 at the basolateral membrane; absorption is dependent on contact with the receptor, as well as the length of small intestine exposed and the flow rate of nutrient (33). The slowing of small intestinal glucose absorption by guar may be attributable in part to the increased viscosity of the luminal content (12), but probably more importantly, by acting as a barrier, that is, by forming a layer closely associated with the mucosal surface, the resistance to diffusion is increased and the rate at which glucose has access to the small intestinal mucosa reduced (34). As a result of this effect, a greater length of small intestine is eventually exposed to glucose (11). The observed attenuation in the hypotensive effect of glucose with co-administration of guar suggests that the length of small intestine exposed to glucose is not of major importance in inducing the hypotensive response.

Although the attenuation of the fall in blood pressure induced by guar may potentially reflect the reduction in blood glucose concentrations as a result of a slowing of glucose absorption, this is unlikely, as quite marked elevations in blood glucose have little, if any, effect on blood pressure (4). A more probable explanation is that the fall in blood pressure is initiated by the exposure of glucose to specific small intestinal “receptors” in a concentration-dependent manner. Although our hypothesis requires further evaluation, it should be recognized that receptors in the small intestine may act as “taste cells” detecting the specific presence of glucose and activating signal transduction pathways (35). Kim and colleagues (35) have suggested the possible role of enterochromaffin cells as “glucose sensors” in the small intestine, which result in the release of 5-hydroxytryptamine (5-HT). A study in dogs (36) has demonstrated regional variations in intestinal blood flow in response to 5-HT infusions and suggest a role for 5-HT in postprandial hemodynamic responses.

The fall in blood pressure induced by oral glucose may potentially be mediated by a number of factors: Splanchnic blood volume increases by \( \approx 20\% \) following a meal and may lead to a reduction in cardiac output (1,4). The sympathetic response to meal-induced splanchnic vasodilation may also be impaired in older participants (37,38); the release of vasodilatory peptides, such as calcitonin gene-related peptide and substance P, may also be important (39). Although insulin has some vasodilatory properties (40), the observation that postprandial hypotension occurs in patients with type 1 diabetes [who are, by definition, insulin-deficient (41)] suggests that plasma or portal insulin concentrations do not contribute significantly to the pathogenesis of postprandial hypotension.

The presence of glucose in the small intestine also stimulates the release of the incretin hormones, GIP and GLP-1. About 50% of the increase in plasma insulin after oral glucose is mediated by the incretin hormones (42). As expected, in the absence of glucose, intraduodenal glucose infusion induced an increase in plasma GLP-1 within 30 minutes and an earlier plasma GIP response (within 15 min). During the glucose and guar infusion there was no increase in GLP-1; in contrast, while the GIP response was blunted, a significant increase was evident. The reduction in incretin hormone release by guar is likely to contribute to the reduction in the plasma insulin response to oral carbohydrate (43). The ageing process does not appear to alter incretin responses greatly (44). Schirra and colleagues (23) demonstrated that a duodenal delivery of glucose exceeding 1.4 kcal/min was required to maintain GLP-1 release, consistent with the concept that stimulation of GLP-1 secretion may be concentration-dependent. The plasma GLP-1 response to oral glucose is known to be inversely related to the rate of gastric emptying (31). In contrast, the plasma GIP response is related directly to the rate of gastric emptying (45), that is, a more rapid rate of glucose entry into the small intestine is associated with higher GIP levels. GIP has been shown to increase splanchnic blood flow in animals (46,47). Although its effect on blood pressure has not been evaluated, GLP-1 is known to increase blood pressure in animals (48,49). It should be recognized that the observed attenuation in the release of the incretin hormones by guar does not establish a causal relationship with the blood pressure response, and further studies are indicated. It is also possible that other peptides may play a more significant role (39). Our study has established a role for mucosal contact with glucose in mediating postprandial hypotension and was not designed to evaluate in detail the underlying regulatory mechanisms.

The current study was based on our recent report (8) on healthy older participants, which showed that an intraduodenal glucose infusion at a rate of 3 kcal/min resulted in falls in systolic and diastolic blood pressure that were apparent within 15 minutes, whereas an intraduodenal infusion rate of 1 kcal/min had no effect. We, accordingly, used an identical rate of glucose infusion (3 kcal/min) and observed a comparable blood pressure response. Although our participants were all healthy with no definite evidence of autonomic neuropathy or a history of orthostatic or postprandial hypotension, they still experienced a mean fall in systolic blood pressure of 10 mmHg when glucose was infused intraduodenally without guar. Accordingly, although no participant reached the criteria for postprandial hypotension, our observations have implications for the management of this condition. Current treatment options for
postprandial hypotension are suboptimal—furosemide therapy should be withdrawn where possible (5), caffeine is effective in some patients (50) but not always well tolerated by older people, and octreotide, although effective, is both expensive and impractical (24). On the basis of our observations and the potential role of 5-HT in postprandial hemodynamic responses (36), potential pharmacological treatment options may include the use of agents such as 5-hydroxytryptamine (5-HT)3 antagonists (51). The potential for the use of dietary manipulation is an attractive alternative to pharmacologic interventions: the alpha-glucosidase inhibitor, acarbose, attenuated the postprandial fall in blood pressure observed in a patient with type 2 diabetes (52). Acarbose would, however, not be expected to be of benefit following glucose ingestion. Dietary manipulation could slow nutrient absorption in a number of ways, either by slowing the rate of gastric emptying or reducing the rate of small intestinal carbohydrate absorption, such as with the use of pectin in the management of dumping syndrome, where its efficacy may relate to slowing the initial rate of nutrient entry into the small intestine (53).

**Conclusion**

This study has shown that the addition of guar to an intraduodenal glucose infusion attenuated the fall in blood pressure and increases in heart rate and incretin hormones induced by a glucose infusion. These observations support the concept that dietary modifications aimed at slowing glucose absorption may represent a therapeutic option for the treatment of patients with postprandial hypotension.

**Acknowledgments**

This study was supported by the National Health and Medical Research Council (NH&MRC) of Australia. Dr. Jones’ salary is derived from a Fellowship jointly awarded by the NH&MRC and Diabetes Australia. Dr. Feinle-Bisset’s salary is provided by a Career Development Award from the NH&MRC.

Address correspondence to Dr. Karen Jones, Department of Medicine, University of Adelaide, Royal Adelaide Hospital, North Terrace, Adelaide, SA, 5000, Australia. E-mail: karen.jones@adelaide.edu.au

**References**