Changes in meal composition and duration affect postprandial endothelial function in healthy humans

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IN ARTERIES WITH INTACT ENDOTHELIAL function, increased blood flow following an ischemic stimulus results in dilatation (22, 32) via the release of the endothelium-derived relaxing factor (29) nitric oxide. Impaired endothelial function is now well-recognized as a forerunner of atherosclerosis (20) and is predictive of long-term adverse cardiovascular outcomes (45). Factors known to affect endothelial function acutely include diet (7), exercise (11), ambient temperature (49), and time of the day (31). Because gastric emptying of a meal usually approximates a rate of 1–4 kcal/min, people who generally consume three meals daily spend most of the day in the postprandial state, with only a few hours of true fasting before breakfast (26). Therefore, endothelial function in the postprandial state is arguably more likely to contribute to overall cardiovascular risk than fasting endothelial function. In the case of a majority of patients with type 2 diabetes, who have reasonably good glycemic control (HbA1C <7.5%, or less), it is now well-recognized that postprandial glycemia predominates over fasting blood glucose in contributing to HbA1C and may be an independent risk factor for cardiovascular events (26).

The mechanisms of postprandial endothelial dysfunction (21, 36) are poorly understood, although several variables appear to be of relevance, including the glycemic index (23) and salt content (14) of the meal, as well as the postprandial elevation of triglycerides (7). After an oral glucose load, endothelial dysfunction is related to the degree of rise in blood glucose in both health and type 2 diabetes (21, 42), with the duration of dysfunction being greater in the latter (1).

The rate of gastric emptying is a major determinant of postprandial glycemic increments (8, 25). Modulating gastric emptying and/or nutrient absorption from the upper gut can be achieved nonpharmacologically by modifying the composition of a meal, for example, by adding soluble fiber such as guar gum (18, 43) or by decreasing the rate of meal ingestion (50). The glycemic reduction achieved by incorporating guar into a meal is most pronounced at around 30 min postprandially, when gastric emptying plays a major role in determining the glycemic profile (43). Although the effects of dietary manipulations on glycemia have been described previously, their influence on postprandial endothelial function has not yet been investigated.

We therefore evaluated the effects of dietary modifications designed to slow gastric emptying and/or small intestinal nutrient absorption on postprandial endothelial function in healthy humans, with the hypothesis that, in addition to lowering postprandial blood glucose, they would attenuate postprandial endothelial dysfunction, resulting in improved vasodilation in response to increased blood flow induced by an ischemic stimulus.

METHODS

Subjects

Twelve healthy subjects [6 male and 6 female; mean age 33 ± 5.6 (SE) yr; mean body mass index (BMI) 23.3 ± 0.8 kg/m²] were studied after providing written informed consent. None was a smoker or was taking medication known to affect gastrointestinal and/or endothelial function. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and was conducted in accordance with the principles of the Declaration of Helsinki as revised in 2000.

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Protocol

Each subject was studied on three separate occasions, at least 5 days apart, in a randomized crossover design. On each study day, the subject arrived in the laboratory at 0800 h after a 12-h overnight fast and rested in a temperature-controlled room for 20 min. Baseline endothelial function was evaluated by measuring the flow-mediated dilatation (FMD) of the right brachial artery (37), as described subsequently. An intravenous cannula was then inserted in an antecubital vein of the left arm for blood sampling. Thereafter, each subject ate a semisolid mashed potato meal consisting of 65 g powdered potato (Deb Instant Mashed Potato; Continental, Epping, NSW, Australia) and 20 g glucose reconstituted with 250 ml boiling water and an egg yolk containing 100 μl [13C]octanoic acid [total volume 300 ml; energy 368.5 kcal; carbohydrate 61.4 g; protein 7.4 g; fat 8.9 g (with “meal 2,” there was an additional 36 kcal from guar gum)]. On each of the three study days, the meal was given in a different way, in randomized order: 1) “meal 1”: consumption of the meal within 10 min, 2) meal 2: addition of 9 g guar gum (34) (Lotus Guns & Chemicals, Jodhpur, India) to the meal and ingestion within 10 min, and 3) “meal 3”: division of meal 1 into 12 equal portions, each of 25 ml ingested over 5 min ([13C]octanoic acid in the first portion only), with a total meal duration of 60 min [time (T) = 0–60 min].

With meal 1 and meal 2, T = 0 min was defined as the time of finishing the meal, whereas with meal 3, T = 0 min was defined as the beginning of the meal. Venous blood was sampled at baseline (i.e., immediately before meal ingestion) and then at T = 15, 30, 60, 90, 120, 180, and 240 min. Blood samples were collected into ice-chilled serum tubes and stored on ice before centrifugation at 3,200 rpm for 15 min at 4°C within 15 min of collection. Serum was separated and stored at −80°C for subsequent analysis. Breath samples were collected into airtight tubes at baseline and every 5 min for the first hour and every 15 min for a further 3 h for measurement of gastric emptying.

FMD was measured at baseline and then at T = 30, 60, 90, and 120 min. At the time of each FMD measurement, heart rate (HR) was also recorded. At T = 140 min, 400 mg glyceryl trinitrate (GTN) spray were administered sublingually, and the vascular response was recorded to demonstrate the capacity for vasodilation independent of endothelial function (15).

Measurements

FMD and HR. Measuring the FMD of the brachial artery as an index of endothelial function is a well-established noninvasive technique (9), using high-resolution vascular ultrasound with FMD expressed as the percentage change in arterial diameter relative to baseline (4). In our study, the assessment of FMD involved inflation of the sphygmomanometer cuff on the forearm to 200 mmHg for 5 min to induce ischemia, followed by deflation. The diameter of the brachial artery was measured 5 cm above the olecranon process using ultrasound (Logiq e; GE Medical Systems), with a 12-MHz transducer placed in a longitudinal plane over the artery. Three-second scans were recorded at baseline (before inflation of the cuff) and every 15 s for 2 min, after cuff release. A concomitant electrocardiogram (ECG) recording was superimposed on the ultrasonographic images. The transducer position was marked on the skin, and the arm was held immobile with the aid of a foam support and stereotactic clamp until T = 120 min. A single trained operator blinded between meal 1 and meal 2, but not with meal 3, made all of the observations. Images corresponding to end diastole, coincident with the beginning of the R wave on the ECG, were compared to determine differences in arterial diameter. FMD responses were expressed as percentage change in diameter of the artery from baseline at each time point (37). HR was calculated from the R-R interval of the ECG.

Blood glucose and serum insulin concentrations. Blood glucose was measured by glucometer, using the glucose oxidase technique (Medisense Precision QID; Abbott Laboratories, Bedford, MA). Serum insulin was measured by ELISA (10–11; Mercodia, Uppsala, Sweden), with sensitivity of 1.0 μIU/l and coefficient of variation of 2.1% within assays and 6.6% between assays.

Gastric emptying. Assessment of gastric emptying by the measurement of 13CO2 concentrations in breath samples has previously been validated against scintigraphy (10). 13CO2 concentrations in the breath samples from our study were measured by an isotope ratio mass spectrometer (ABCA 2020; Europa Scientific, Crewe, UK) with an on-line gas chromatographic purification system. The cumulative 13CO2-to-12CO2 ratio was reported as a measure of meal delivery in the small intestine. The half-emptying time of meal 1 and meal 2 was calculated, using the formula described by Ghoos et al. (16). Breath test data from meal 3 were not included in the analysis, since they would not have provided a comparable measure of gastric emptying to meal 1 and meal 2.

Statistical Analysis

Based on a previous study (14), we determined that, in a crossover design, 12 subjects were required to detect a mean difference in FMD of 2.0% (α = 0.05; β = 0.2). The incremental area under the curves (IAUC) from T = 0 to 240 min for HR, blood glucose, and serum insulin and the decremental area above the curve (dAAC) for FMD were calculated using the trapezoidal rule. The fasting values, peaks, and IAUC0–240 min of postprandial blood glucose, serum insulin and HR, as well as the nadirs and dAACs of FMD on the three study days were compared using one-factor repeated-measures ANOVA. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni’s correction, were performed if ANOVAs revealed significant effects. Repeated-measures ANOVA, with treatment and time as factors, was used to compare blood glucose, serum insulin, FMD, and HR responses only between meal 1 and meal 2 because of the different definition of T = 0 min for meal 3. Pearson’s correlation analysis was used to assess the relationships of basal FMD with age and BMI. Within-subject correlation analysis was used to assess the relationships of dAAC for FMD with the IAUC for blood glucose and serum insulin (3). All analyses were performed using SPSS 21 (IBM, Armonk, NY). Results are expressed as means ± SE; P < 0.05 was considered statistically significant.

RESULTS

Of the 14 subjects recruited, 12 completed the study. The others were unable to ingest the test meal within 10 min and subsequently withdrew from the study. All subjects reported that meal 2 was less palatable than meal 1.

Gastric emptying

Addition of guar to the meal (meal 2 vs. meal 1) was associated with prolongation of gastric half-emptying time and a reduction of cumulative 13CO2-to-12CO2 ratio (treatment effect: P = 0.002; treatment × time interaction: P < 0.001; AUC: P < 0.001). The latter was manifest in the first half hour postprandially (AUC: P < 0.001) (Table 1 and Fig. 1A).

Blood Glucose Concentrations

Fasting blood glucose did not differ between the three study days. After all three meals, blood glucose concentrations increased and subsequently returned to baseline (P < 0.001 for each), with the peak occurring ~30 min after meal 1 and ~60 min after meal 2. Although the peak blood glucose concentrations did not differ between the three study days (P = 0.49), there was a treatment effect on IAUC (P = 0.03) such that the rise in blood glucose was less after meal 3 than meal 2 (P =
Table 1. Results

<table>
<thead>
<tr>
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<th>Meal 1</th>
<th>Meal 2</th>
<th>Meal 3</th>
<th>P</th>
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<tbody>
<tr>
<td>Gastric half-emptying</td>
<td>208 ± 15</td>
<td>285 ± 27</td>
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<td>0.02</td>
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<tr>
<td>time, min</td>
<td></td>
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<tr>
<td>Fasting blood glucose,</td>
<td>5.3 ± 0.1</td>
<td>5.4 ± 0.1</td>
<td>5.3 ± 0.1</td>
<td>0.95</td>
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<td>mmol/l</td>
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<tr>
<td>Peak blood glucose,</td>
<td>7.9 ± 0.4</td>
<td>7.5 ± 0.3</td>
<td>7.6 ± 0.4</td>
<td>0.49</td>
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<td>mmol/l</td>
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<tr>
<td>Blood glucose iAUC,</td>
<td>182.9 ± 44.3</td>
<td>221.6 ± 43.3</td>
<td>131.3 ± 56.8</td>
<td>0.03</td>
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<td>mmol · l⁻¹ · min</td>
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<tr>
<td>Fasting serum insulin,</td>
<td>2.9 ± 0.4</td>
<td>3.6 ± 0.5</td>
<td>3.1 ± 0.3</td>
<td>0.19</td>
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<td>mU/l</td>
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<tr>
<td>Peak serum insulin,</td>
<td>45.3 ± 9.9</td>
<td>21.4 ± 2.7</td>
<td>51.2 ± 16.2</td>
<td>0.02</td>
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<tr>
<td>mU/l</td>
<td></td>
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<tr>
<td>Insulin-to-glucose ratio</td>
<td>714.3 ± 174.0</td>
<td>469.4 ± 70.5</td>
<td>699.2 ± 184.9</td>
<td>0.05</td>
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<td>AUC, U/mol</td>
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<td>Serum insulin iAUC,</td>
<td>4.8 ± 1.3</td>
<td>3.0 ± 4.7</td>
<td>4.5 ± 1.2</td>
<td>0.05</td>
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<td>U · l⁻¹ · min</td>
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<tr>
<td>Basal HR, beats/min</td>
<td>61 ± 2</td>
<td>62 ± 2</td>
<td>60 ± 2</td>
<td>0.64</td>
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<tr>
<td>Peak HR, beats/min</td>
<td>72 ± 2</td>
<td>66 ± 2</td>
<td>72 ± 3</td>
<td>0.02</td>
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<tr>
<td>HR iAUC, beats</td>
<td>351.3 ± 210.3</td>
<td>-102.9 ± 163.3</td>
<td>626.3 ± 238.1</td>
<td>0.00</td>
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<td>Basal FMD, %</td>
<td>5.4 ± 0.58</td>
<td>6.1 ± 0.93</td>
<td>4.8 ± 0.56</td>
<td>0.22</td>
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<tr>
<td>Max. reduction of FMD, %</td>
<td>-3.2 ± 0.6</td>
<td>-4.2 ± 0.7</td>
<td>-2.6 ± 0.60</td>
<td>0.20</td>
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<tr>
<td>FMD dAAC, %/min</td>
<td>-216.3 ± 42.3</td>
<td>-310.1 ± 48.1</td>
<td>-157.9 ± 50.1</td>
<td>0.08</td>
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</table>

Data are means ± SE; n = 12 subjects. iAUC, incremental area under the curve (AUC); HR, heart rate; FMD, flow-mediated dilatation; dAAC, decremental area above the curve. Shown are basal and peak values and the iAUCs for blood glucose, serum insulin, HR, AUC for the insulin-to-glucose ratio and basal and nadir values, and the dAAC for FMD after a high-carbohydrate meal consumed within 10 min (“meal 1”), a high-carbohydrate meal mixed with 9 g guar consumed within 10 min (“meal 2”), and the same high-carbohydrate meal consumed as 12 equal portions over 60 min (“meal 3”). *P < 0.05 for meal 2 vs. meal 3.

0.03), without a significant difference between meal 1 and meal 3, or between meal 1 and meal 2. However, compared with meal 1, the addition of guar to the meal (meal 2) was associated with an initially delayed, but more sustained, rise in blood glucose (treatment × time interaction: P < 0.001) so that blood glucose was lower at T = 30 min and higher at T = 240 min (P < 0.05 for each) (Table 1 and Fig. 1B).

Serum Insulin Concentrations

Fasting serum insulin did not differ between the three study days. After all three meals, serum insulin increased before gradually returning to baseline (P < 0.001 for each), with the peak insulin occurring ~30 min after meal 1 and meal 2 and ~60 min with meal 3. There was a treatment effect on both the peak AUC and iAUC for serum insulin between the three study days (P = 0.02 for each) such that peak insulin was lower after meal 2 than meal 1 (P = 0.02) and tended to be lower after meal 2 than meal 3 (P = 0.15) with no significant difference between meal 1 and meal 3. The iAUC for serum insulin tended to be less after meal 2 than meal 1 (P = 0.09) without a significant difference between meal 1 and meal 3 or between meal 2 and meal 3. The addition of guar to the meal (meal 2 vs.

Fig. 1. Cumulative ¹³CO₂-to-¹²CO₂ ratios (meal 1 vs. meal 2) (A), blood glucose concentrations (B), serum insulin concentrations (C), and insulin-to-glucose (I/G) ratio (D) in response to meal 1, meal 2, and meal 3. Data are means ± SE. *P < 0.05 for meal 1 vs. meal 2.
meal 1) was associated with changes in serum insulin concentrations (treatment effect: \( P = 0.04 \); treatment \( \times \) time interaction: \( P < 0.001 \)), with serum insulin being lower at \( T = 30 \) and 60 min and higher at \( T = 240 \) min (\( P < 0.05 \) for each) (Table 1 and Fig. 1C).

Serum Insulin-to-Blood Glucose Ratio

The addition of guar to the meal (meal 2 vs. meal 1) influenced the insulin response to the prevailing blood glucose concentration [insulin-to-blood glucose ratio (I/G ratio)] (treatment effect: \( P = 0.03 \); treatment \( \times \) time interaction: \( P < 0.001 \); AUC: \( P = 0.04 \)), with the I/G ratio being lower at \( T = 30 \), 60, and 90 min and higher at \( T = 240 \) min (\( P < 0.05 \) for each). The I/G ratio (iAUC) with meal 2 tended to be lower than with meal 3 (\( P = 0.06 \)) (Table 1 and Fig. 1D).

FMD

Fasting FMD did not differ between the three study days. The basal arterial diameter did not change during the postprandial period (\( P = 0.22 \)), but FMD decreased postprandially on all three days (\( P < 0.001 \) for each) with distinct patterns: after meal 1, there was a rapid reduction in FMD reaching a nadir at 30 min followed by partial recovery by 60 min; after meal 2 there was a delayed, but more sustained, FMD reduction and with meal 3, and the reduction in FMD was minimal. The overall reduction in FMD (dAAC) did not quite show a significant treatment effect (\( P = 0.08 \)). However, addition of guar to the meal (meal 2 vs. meal 1) was associated with a relatively delayed, but more sustained, suppression of postprandial FMD (treatment \( \times \) time interaction: \( P = 0.002 \)), with greater reductions at \( T = 60 \) and 90 min (\( P < 0.05 \) for each). Furthermore, compared with meal 2, prolonging the duration of meal consumption (meal 3) was associated with attenuation of the postprandial reduction of FMD (dAAC: \( P < 0.05 \)) (Table 1 and Fig. 2A).

Endothelium-independent vasodilation of the brachial artery, assessed by sublingual GTN, did not differ between the three study days (13.5 ± 1.4, 12.8 ± 1.1, and 12.0 ± 0.8%; \( P = 0.59 \)).

Heart Rate

Basal HR did not differ between the three study days but increased after meal 1 and meal 3, peaking at ~30 min before gradually returning to baseline (\( P = 0.002 \) and 0.003, respectively). HR was unchanged after meal 2. Accordingly, both the peak AUC and iAUC for HR were greater after meal 1 and meal 3 than meal 2 (\( P < 0.05 \) for both), without significant difference between meal 1 and meal 3. When compared with meal 1, the addition of guar to the meal (meal 2) was associated with attenuation of the postprandial increase in HR (treatment \( \times \) time interaction: \( P = 0.05 \)), with HR being lower at \( T = 30 \) min (\( P = 0.02 \)) (Table 1 and Fig. 2B).

Relationships Between Variables

Basal FMD was related inversely to age (\( r = -0.62; \ P = 0.03 \)) but was not related to BMI. The magnitude of the increment in blood glucose (iAUC) in the early postprandial period after meal 1 and meal 2 (\( T = 0–30 \) min) was related directly to gastric emptying, indicated by the cumulative \(^{13}\text{CO}_2\)-to-\(^{12}\text{CO}_2\) ratio (\( r = 0.86; \ P < 0.001 \)). The magnitude of reduction in FMD within each subject at \( T = 30 \) min in response to the three meals was related directly to the iAUC(0–30) for blood glucose (\( r = 0.43, \ P = 0.03 \)). In addition, the dAAC for FMD within each subject in response to the three meals was related directly to the iAUC for blood glucose (\( r = 0.46, \ P = 0.02 \)) and inversely to the iAUC for HR (\( r = -0.55, \ P = 0.005 \)).

DISCUSSION

Our study shows that, in healthy humans, 1) the inclusion of guar gum in a meal, leading to slowing of gastric emptying, results in a relatively delayed but more sustained suppression of postprandial FMD that is associated with attenuation of the early rise in postprandial blood glucose concentration as well as the overall rise in serum insulin and HR; and 2) compared with adding guar gum, consuming a meal more slowly attenuates the overall increase in postprandial glycemia as well as the postprandial decline in FMD. It is unlikely that the changes in FMD demonstrated in this study were an artifact related to postprandial variations in the basal arterial diameter (33), since the latter did not change during our study. We also noted an inverse relation between FMD and age, in keeping with existing reports (39).

Previous studies on postprandial endothelial function have focused primarily on the effects of nutritional content (7) and glycemic index (23) of the test meal. Here, we gave the same meal on 3 days, modifying only its composition (by the addition of guar) or duration of consumption (by dividing it into small portions) with the aim of altering gastric emptying and/or small intestinal nutrient absorption. The addition of 9 g

![Fig. 2. Flow-mediated dilatation (FMD) (A) and heart rate (B) in response to meal 1, meal 2, and meal 3. Data are means ± SE. *\( P < 0.05 \) for meal 1 vs. meal 2.](http://ajpgi.physiology.org/Downloadedfrom)
guar in our study, a dose previously known to slow gastric emptying (24), resulted in a reduction in the rate of small intestinal nutrient absorption, reflected by the reduced \(^{13}\text{CO}_2\)-to-\(^{12}\text{CO}_2\) ratio. However, the degree of glycemic variation was modest, as would be anticipated in subjects with normal glucose tolerance (48). Regardless, postprandial FMD was substantially altered, suggesting that manipulation of gastrointestinal function by dietary means can modulate postprandial endothelial function.

The “glycemic index” is a measure of the ability of dietary carbohydrates to increase blood glucose concentrations postprandially (47); whether it predicts which foods are “healthy” has recently been a subject of debate (46). In the present study, addition of guar gum (meal 2) reduced the effective glycemic index of the high-carbohydrate meal but was associated with a sustained suppression of endothelial function, suggesting that an index based on a measurement made only at 2 h postprandially may not be an ideal predictor of cardiovascular risk.

We demonstrated a direct relationship between the reduction in FMD and the increase in blood glucose, consistent with existing literature (38). However, in our study, after meal 2, FMD remained persistently low even after the first 30 min despite improvements in glycemia, and, with meal 3, the glycemic spike at 60 min was not accompanied by a marked reduction in FMD. These discrepancies may be accounted for, at least in part, by the differences in postprandial insulin secretion, since insulin is known to have vasodilatory and anti-inflammatory properties (12) and would be expected to counteract the postprandial reduction in FMD. Therefore, we cannot rule out the possibility that the markedly elevated insulin levels at \(T = 60\) min after meal 3 might have counterbalanced any tendency for postprandial suppression of FMD due to hyperglycemia, whereas the attenuated insulin response associated with meal 2 could potentially have contributed to the sustained suppression of postprandial FMD.

Even though a higher serum insulin concentration appears to have a favorable effect on FMD, we could not demonstrate a relationship between these outcome measures in this study, probably because of interfering factors, as described subsequently. Furthermore, the rise in serum insulin did not correlate with the magnitude of the postprandial increment in glycemia. Although this is difficult to explain, it seems plausible that the high variability of insulin concentrations could have contributed.

Other dynamic factors, such as gastric distension associated with meal ingestion, might be of importance in the regulation of postprandial FMD, especially in the early postprandial phase. Gastric distension is known to induce sympathetic stimulation in proportion to the distending pressure in healthy young adults (44), and sympathetic activation has been reported to suppress FMD (17). In the present study, it is likely that slowing of gastric emptying by guar was associated with prolonged gastric distension, whereas consumption of the meal in portions over 1 h (meal 3) resulted in the least gastric distension; this could explain the sustained suppression of postprandial FMD after meal 2 and a lesser reduction in FMD after meal 3. That we observed a slight delay in the maximal suppression of FMD with meal 2 compared with meal 1, despite similar gastric volumes in the early postprandial phase, suggests that the difference in glycemia at this point (\(T = 30\) min) may potentially have suppressed FMD in the early part of the study more for meal 1 than meal 2.

Addition of guar to the meal was also associated with attenuation of the rise in HR, an effect probably attributable to slowing of gastric emptying (34) and/or inhibition of nutrient absorption in the small intestine (28). We observed an inverse relationship between the dAAC for FMD and iAUC for HR and accordingly cannot exclude potential enhancement of the local shear stimulus on the endothelium as a result of the rise in postprandial HR, which would tend to enhance FMD.

Consumption of dietary fiber, especially soluble fiber such as guar gum, is generally recommended (30) and is reported to reduce the risk of cardiovascular disease (41) via metabolic effects, including production of short-chain fatty acids through colonic bacterial fermentation, slowing of gastric emptying, promotion of satiety, improvement in glycemic and lipid profiles, and loss of body weight (19). Although the long-term benefits of fiber-rich food remain undisputed, our study points to the possibility of an acute detrimental effect on postprandial endothelial function by adding guar gum (a soluble fiber) to a high-carbohydrate meal, which could potentially be of clinical significance in high-risk patients with preexisting cardiovascular disease. In hyperinsulinemic patients with obesity and type 2 diabetes, the cardiovascular effect of suppression of postprandial insulin release by guar gum or by other dietary fiber needs further evaluation.

By reducing the rate of carbohydrate digestion and absorption in the proximal small intestine, the addition of guar to a high-carbohydrate meal could also potentially allow greater exposure of nutrient to the L cells, located more densely in the distal gut, which might enhance secretion of endogenous glucagon-like peptide-1 (GLP-1) (40), although we did not measure this hormone. It is uncertain whether the addition of guar to a meal, in conjunction with the use of a GLP-1 receptor agonist in patients with type 2 diabetes, would have an additive effect on the deceleration of gastric emptying leading to further improvements in postprandial glycemia and endothelial function.

There is now persuasive evidence that, with long-term use, GLP-1 agonists improve vascular function directly by stimulating endothelial GLP-1 receptors, indirectly by triggering insulin release, and also by reducing weight gain (6), but there have been few attempts to assess their acute postprandial effects, and those showed either a direct protective effect on the endothelium (5) or an indirect effect via improvements in the lipid profile (35). If our current observations in healthy lean adults are applicable to type 2 patients, slowing of gastric emptying induced by GLP-1 agonists (2, 27) may result in more prolonged gastric distension (13). Therefore, their potential for an acute detrimental impact on postprandial endothelial function should now be evaluated, since it could be relevant in patients with significant cardiovascular disease.

This study was conducted as “proof of principle” and has several limitations. The sample size was relatively small, and some comparisons had the potential to be affected by type 2 error; however, our observations appeared clear cut. The regulation of postprandial FMD is clearly multifactorial, and our study was not designed to address potential mechanisms in isolation. Further studies incorporating nonnutrient gastric distension, such as with an intragastric balloon, and measurement of splanchnic blood flow, may enable us to dissect out the individual roles of gastric distension, sympathetic activation,
REFERENCES


AUTHOR CONTRIBUTIONS

S.S.T., K.L.J., M.H., and C.K.R. conception and design of research; S.S.T., K.L.J., M.H., and C.K.R. performed experiments; S.S.T., T.W., and C.K.R. analyzed and interpreted data; S.S.T., M.J.B., and H.L.C. wrote the manuscript; S.S.T., T.W., and C.K.R. approved the final version of the manuscript.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.S.T., K.L.J., M.H., and C.K.R. conceived and designed the research; S.S.T., T.W., and C.K.R. performed experiments; S.S.T., M.J.B., and H.L.C. acquired data; S.S.T., T.W., S.W., M.H., and C.K.R. analyzed and interpreted data; S.S.T., T.W., K.L.J., M.H., S.W., M.H., and C.K.R. drafted the manuscript; S.S.T., M.J.B., and H.L.C. revised the manuscript; S.S.T., T.W., S.W., M.H., and C.K.R. approved the final version of the manuscript.

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DISCLOSURES

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