Rate of gastric emptying is a determinant of postprandial hypotension in non-insulin-dependent diabetes mellitus

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1. Postprandial hypotension is now recognized as an important clinical problem, particularly in the elderly and in patients with autonomic dysfunction. The mechanisms responsible are poorly understood; however, impaired regulation of splanchnic blood flow and the release of gastrointestinal hormones appear to be important. The effect of gastric emptying on the magnitude of the postprandial fall in blood pressure has not been evaluated.

2. The aim of this study was to determine whether there is a relationship between changes in blood pressure and the rate of gastric emptying after ingestion of 75 g of glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) and both young and older normal subjects. Sixteen patients with recently diagnosed NIDDM, median age 57 (39–79) years, 10 'young' subjects with a median age of 23 (19–26) years and nine 'older' subjects, median age 48 (40–68) years, were measured simultaneously for gastric emptying of 75 g of glucose in 350 ml of water, blood pressure and blood glucose concentrations, commencing at approximately 10.00 hours after an overnight fast. Measurements of blood pressure were made in the sitting position immediately before glucose ingestion and at 15 min intervals up to 180 min.

3. Gastric emptying of glucose was not significantly different between the three groups [50% emptying time (T50): 95 ± 7.3 min in patients with NIDDM compared with 120 ± 13.2 min in the 'young' group and 97 ± 8.1 min in the 'older' group]. There was a significant fall in mean blood pressure after the glucose load in the patients with NIDDM (P < 0.0001) and the 'older' normal subjects (P < 0.05), but not the 'young' normal subjects. Postprandial hypotension (fall in systolic blood pressure ≥ 20 mmHg) was evident in seven (44%) patients with NIDDM and three (33%) 'older' normal sub-

INTRODUCTION

Postprandial hypotension, leading to syncope and falls, is now recognized as an important clinical problem, particularly in the elderly and in patients with autonomic dysfunction [1–5]. The mechanisms responsible for postprandial hypotension are poorly understood but impaired regulation of splanchnic blood flow and the release of gastrointestinal hormones seem to be important [1–5]. The magnitude of the postprandial fall in blood pressure is dependent on meal composition. Ingestion of carbohydrates, particularly glucose, has the largest effect on blood pressure [6–8] with only minor falls occurring after ingestion of fat, protein or water [6, 9]. While oral ingestion of glucose leads to a fall in blood pressure, intravenous infusion of glucose has little, if any, effect [8], indicating that the response is mediated from the gastrointestinal tract. The onset of the fall in blood pressure after a meal is evident almost immediately, with a maximum response at 30–60 min [4, 5], suggesting a relationship to the rate of delivery of carbohydrate to the small intestine. It is therefore surprising that no studies have formally evaluated the relationship between postprandial hypotension and gastric emptying. To our knowledge the only information relating to this issue was based on a small number of patients with autonomic failure and employed sub-

Key words: diabetes mellitus, gastric emptying, postprandial hypotension

Abbreviations: BMI, body mass index; NIDDM, non-insulin-dependent diabetes mellitus.

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optimal methodology to quantify gastric emptying [5]. It is now recognized that disordered (delayed or more rapid) gastric emptying occurs frequently in patients with diabetes mellitus [10] and autonomic failure [11], as well as the elderly [12]. In patients with diabetes mellitus, abnormal gastric emptying is not predictable on the basis of gastrointestinal symptoms, such as nausea and postprandial fullness, as the relationship between gastrointestinal symptoms and gastric emptying is poor [11].

The purpose of this study was to determine whether there is a relationship between the magnitude of the fall in blood pressure and gastric emptying after ingestion of 75 g of glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM), as well as in both young and older normal subjects.

METHODS

Subjects

The study population comprised three groups: patients with NIDDM, 'young' normal subjects and 'older' normal subjects. The NIDDM group comprised 16 patients with recently diagnosed NIDDM, 11 male and five female, with a median age of 57 years (39–79) and a median body mass index (BMI) of 29 (22–36) kg/m². The patients were randomly selected from ambulant outpatients presenting to the Royal Adelaide Hospital for treatment of NIDDM. In all cases the diagnosis of NIDDM, based on World Health Organization criteria, had been established between 3 and 12 months previously. All patients were treated by diet alone and none was taking oral hypoglycaemic drugs, antihypertensive agents or any medication known to affect blood pressure or gastrointestinal motility. None of the patients had retinopathy, and in all cases the plasma creatinine concentration was within the normal range (0.05–0.12 mmol/l). At the time of the study mean glycosylated haemoglobin was 7.5 ± 0.6% (normal < 6.0%). The results of measurements of gastric emptying and blood glucose (but not blood pressure) in this group have been reported previously [13]. The 'young' normal group comprised 10 subjects (nine male, one female), median age 23 (19–26) years and median BMI 23 (20–27) kg/m². In the 'older' group there were nine subjects (six male, three female), median age 48 (40–68) years and median BMI 25 (20–35) kg/m². None of the normal subjects was taking medication, had gastrointestinal symptoms or a history of significant illness. Normal subjects responded to advertisements placed at the local University and Employment centre. There was no significant difference in either age or BMI between the NIDDM patients and the 'older' normal subjects, but both age (P < 0.0001) and BMI (P < 0.05) were greater in the NIDDM group compared with the 'young' normal subjects. All the NIDDM and control subjects were Caucasian.

Protocol

Each subject underwent concurrent measurements of gastric emptying, blood glucose and blood pressure. The gastric emptying measurement was commenced at about 10.00 h after an overnight fast (no solid food for 14 h; no liquids for 12 h). Smoking was prohibited on the study day. A cannula was placed in a right antecubital vein for blood sampling and the subjects were seated with their back against a gamma camera, with a blood pressure cuff around their left arm. Gastric emptying, blood glucose and blood pressure were monitored for 3 h after glucose ingestion. About an hour after completion of these measurements (i.e. at approximately 14.00 hours) cardiovascular autonomic nerve function was evaluated. Written, informed consent was obtained from each participant and the study protocol was performed in accordance with the Declaration of Helsinki (1989) of the World Medical Association and approved by the Human Ethics Committee of the Royal Adelaide Hospital.

Measurement of gastric emptying

Gastric emptying was measured using a technique described previously [13, 14]. Each subject drank 350 ml of water containing 75 g of glucose and 20 MBq of ⁹⁹ᵐTc-sulphur colloid within 1 min. Radiisotopic data were acquired in 30 s frames for the first 30 min and subsequently in 3 min frames for a further 150 min. Time zero was defined as the time of completion of the drink. Data were corrected for subject movement, radionuclide decay and γ-ray attenuation [14]. Gastric emptying curves (expressed as % of the maximum content of the total stomach) were derived and the content of the total stomach at 0, 15, 30, 45, 60, 90, 120, 150 and 180 min was calculated. The duration of the lag phase and the 50% emptying time (T₅₀) were also obtained. The lag phase was determined visually as the time period before any of the drink had entered the proximal small intestine [14].

Measurement of blood glucose concentrations

Venous blood samples were obtained immediately before (−2 min) ingestion of the drink and then at 10, 15, 30, 45, 60, 90, 120, 150 and 180 min. Blood glucose concentrations were immediately determined using a portable blood glucose meter (MediSense Companion 2 meter; MediSense Inc., Waltham, MA, U.S.A.) and the accuracy of these measurements was confirmed subsequently with a hexokinase technique.

Measurement of blood pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automated
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was defined as a fall in systolic blood pressure for the first 60 min and subsequently for 15 min intervals until 180 min. Postprandial hypotension was calculated using the formula MAP = DBP + \[\frac{(SBP-DBP)}{3}\]. The incremental areas under the change in mean blood pressure curve at 0-15 min, 0-30 min, 0-45 min, 0-60 min, 0-90 min, 0-120 min, 0-150 min and 0-180 min were calculated using the trapezoidal rule.

Assessment of autonomic nerve function

Autonomic nerve function was assessed using standardized cardiovascular reflex tests [15]. Parasympathetic function was calculated by the variation (R-R interval) of the heart rate during deep breathing and the immediate heart rate response to standing (30:15' ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the test results was scored according to the defined criteria as 0 = normal, 1 = borderline or 2 = abnormal. A total score of >3 was considered to indicate definite autonomic nerve damage [13].

Statistical analysis

Data were evaluated using repeated measures analysis of variance and are shown as means ± SEM, unless stated otherwise. The difference in mean arterial blood pressure between groups and the change in blood pressure from baseline over time were calculated using repeated measures analysis of variance for the first 60 min (as the maximum fall in blood pressure had occurred in all subjects within this time). Relationships between blood pressure, gastric emptying and autonomic nerve function were assessed using linear regression analysis. A P value <0.05 was taken to indicate significance.

RESULTS

All subjects tolerated the study well and there were no untoward events. In particular, none of the patients with NIDDM or the control subjects experienced nausea, faintness or dizziness after the glucose drink. Four of the patients with NIDDM had definite autonomic neuropathy and the median score for autonomic nerve function in the entire NIDDM group was 2 (range 0-4). The systolic blood pressure response to standing was not abnormal in any of the patients with NIDDM. None of the control subjects had evidence of autonomic neuropathy. Both before and after the drink blood glucose concentrations were greater in the patients with NIDDM compared with both the young (P<0.005) and older normal subjects (P<0.005), whereas there was no difference between the two groups of normal subjects. For example, mean blood glucose concentrations during the gastric emptying test were 13.1 ± 0.78 mmol/l in the patients with NIDDM, 6.4 ± 0.16 mmol/l in the ‘young’ and 6.4 ± 0.36 mmol/l in the ‘older’ normal subjects). Postprandial hypotension was evident in seven NIDDM patients and three ‘older’ normal subjects, but not in any of the ‘young’ normal subjects. Of the seven NIDDM patients with postprandial hypotension, two had autonomic neuropathy. Mean arterial pressure was higher (P<0.005) in the patients with NIDDM compared with the ‘young’ subjects, but not the ‘older’ subjects, both before and after the glucose load. Baseline blood pressures were 98.1 ± 3.1 mmHg in the patients with NIDDM, 78.4 ± 2.3 mmHg in the ‘young’ and 87.3 ± 6.1 mmHg in the ‘older’ normal subjects (Table 1). There was a significant fall in blood pressure after the glucose load in the patients with NIDDM (P<0.0001) and the ‘older’ subjects (P<0.05), but not the ‘young’ subjects, with the majority of the difference being evident at 15 min and a maximum decrease between 30 and 45 min (Fig. 1). The overall fall in mean arterial pressure was greater in the NIDDM group compared with both the ‘young’ and ‘older’ normal subjects (P<0.05 for both), whereas there was no significant difference between the latter two groups.

Gastric emptying

Gastric emptying approximated an overall linear pattern after a short lag phase in both the patients with NIDDM and control subjects (Fig. 2) [13]. There was no difference in the lag phase between the three groups (patients with NIDDM, 1.8 ± 0.3 min; ‘young’ normal subjects, 3.2 ± 0.9 min; ‘older’ normal subjects, 3.2 ± 1.0 min) or the T50 (NIDDM, 95 ± 7.3 min compared with young, 120 ± 13.2 min, and older, 97 ± 8.1 min).

Relationships between mean arterial pressure, gastric emptying, autonomic nerve function and blood glucose

In the patients with NIDDM, but not in either of the control groups, there was a significant relation-
ship between the area under the change in mean blood pressure curve and gastric emptying; for example, at 15 min the area under the mean arterial blood pressure curve was related to both the intra-gastric retention at 15 min \( (r = 0.56, P < 0.05) \) and the \( T_{50} \) \( (r = 0.67, P < 0.005) \) (Fig. 3). There were no significant relationships between the area under the blood pressure curve and either age, the score for autonomic nerve function or the blood glucose concentration in either of the three groups.

**DISCUSSION**

The results of this study indicate that in patients with recently diagnosed NIDDM the magnitude of the reduction in blood pressure after a 75 g oral glucose load is greater than in normal subjects and is related to the rate of gastric emptying. In contrast, in both ‘young’ and ‘older’ normal subjects, we were unable to demonstrate a significant relationship between the changes in blood pressure after oral glucose and the rate of gastric emptying of glucose.

In our study, postprandial hypotension was evident in 7 of 16 patients with NIDDM and three of the ‘older’ control subjects, all of whom were symptom-free. Sasaki et al. [16] reported that after ingestion of 75 g of glucose a significant post-prandial fall in blood pressure was evident in 7 of 35 (20%) patients with long-standing NIDDM, compatible with our observations. However, in contrast to our observations, a relationship between post-prandial hypotension and the presence of cardiovascular autonomic neuropathy was evident [16]. This discrepancy may reflect differences between the two studies in the duration of diabetes, as the mean duration of known NIDDM in the study by Sasaki et al. [16] was 11 (1–25) years and 23 of 35 patients had definite autonomic neuropathy, while in our study the duration of diabetes was less than 1 year and autonomic neuropathy was evident in only 4 of 16 patients. It is not surprising that some of our patients had autonomic dysfunction, as in many cases fasting hyperglycaemia is present for several years before diagnosis of NIDDM [17]. However, our study also demonstrates that postprandial hypotension may occur in patients with NIDDM who do not have evidence of cardiovascular autonomic dysfunction. The prevalence of postprandial hypotension in the ‘older’ normal volunteers is compatible with that reported in previous studies in the elderly [4]. Studies in the elderly have shown that postprandial hypotension is more marked in hypertensive subjects, as a result of impaired baro-reflex function [4]. In our study, baseline blood pressure was greater in patients with NIDDM compared
with both the ‘young’ and ‘older’ normal subjects, although none of the NIDDM patients was hypertensive. This higher baseline blood pressure may potentially have contributed to the greater fall in blood pressure after the glucose load.

The demonstration of a significant relationship between the magnitude of the fall in blood pressure after a 75 g oral glucose load and gastric emptying in patients with recently diagnosed NIDDM is novel and may be clinically important. In 30–50% of patients with both long-standing NIDDM and/or insulin-dependent diabetes mellitus gastric emptying of either solid or nutrient liquid meals is delayed compared with normal subjects, and have suggested that this increase in gastric emptying rate may predispose to the development of diabetes. In contrast, we have recently reported in these same ‘early’ NIDDM patients [13] no difference in gastric emptying of a 75 g glucose load from age-matched control subjects. Further studies are therefore required to address this issue. It is not surprising that there was no relationship between changes in blood pressure and gastric emptying in either the ‘young’ or ‘older’ normal subjects as the magnitude of the postprandial fall in blood pressure was substantially less than in the NIDDM patients; it should also be recognized that the number of subjects that we studied was relatively small. The demonstration of a relationship between the fall in blood pressure after an oral glucose load and the rate of gastric emptying has potential implications for the treatment of postprandial hypotension in NIDDM. For example, in such patients gastric emptying may be slowed significantly by either dietary [20] or pharmacological [21] means. In view of our observations, studies to evaluate the relationship between gastric emptying and postprandial hypotension in other groups, such as patients with autonomic failure, are appropriate. It should, however, be recognized that the rate of gastric emptying accounted for only 45% of the variance in the postprandial fall of blood pressure in NIDDM, indicating that other factors are important.

While the mechanisms responsible for postprandial hypotension are poorly understood, several factors are likely to play a role [1–5]. The observation that oral glucose, rather than other food components such as fat or protein, causes postprandial hypotension suggests a role for insulin [3, 4, 6], which is known to reduce blood pressure in patients with autonomic failure and in the elderly [3, 4] and to increase sympathetic activity in healthy euglycaemic subjects [22, 23]. We have reported that there is a direct relationship between venous blood glucose concentrations and the rate of gastric emptying of an oral glucose load in normal subjects [14, 24] as well as patients with NIDDM [13], despite the limitations of venous as opposed to arterial blood glucose measurements. While plasma insulin was not measured in our study, it can be anticipated that after the glucose load plasma glucose and insulin concentrations would have been closely related [24], and that the insulin response is likely to be dependent on the rate of gastric emptying [24]. It should, however, be recognized that the previous observation that intravenous infusion of glucose has little effect on blood pressure [8], argues against a role for insulin. Other vasoactive gastrointestinal peptides have also been implicated in the hypotensive response to a meal; in particular the hypotensive response to a meal is inhibited by somatostatin [3]. Changes in sympathetic nervous system activity may also be important in postprandial hypotension. In normal subjects plasma noradrenaline rises after intake of carbohydrate, but not after other nutrients such as protein and fat [25]. In both young and older subjects, oral glucose increases sympathetic activity, as measured directly by muscle sympathetic nerve activity [25]; both this and the plasma noradrenaline response are attenuated in the elderly, particularly those with insulin resistance [26]. In elderly patients with postprandial hypotension the rise in plasma noradrenaline after a meal is also less, indicative of a reduction in compensatory sympathetic nervous activity [25].

In conclusion, our study has demonstrated that while the rate of gastric emptying cannot be considered to be the direct mechanism responsible for postprandial hypotension, it appears to be a significant determinant of the hypotensive response to an oral glucose load in patients with recently diagnosed NIDDM, and is a factor that should be considered in the treatment of these patients.

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