Glycemic, Hormone, and Appetite Responses to Monosaccharide Ingestion in Patients With Type 2 Diabetes

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To investigate the relative effects of fructose and glucose on blood glucose, plasma insulin and incretin (glucagon-like peptide-1 [GLP-1] and gastric inhibitory peptide [GIP]) concentrations, and acute food intake, 10 (6 men, 4 women) patients with diet-controlled type 2 diabetes (diabetic) (44 to 71 years) and 10 age and body mass index (BMI)-matched (6 men, 4 women) nondiabetic, control subjects with varying degrees of glucose tolerance (nondiabetic), were studied on 3 days. In random order, they drank equienergetic preloads of glucose (75 g) (GLUC), fructose (75 g) (FRUCT) or vehicle (300 mL water with noncaloric flavoring [VEH]) 3 hours before an ad libitum buffet lunch. Mean glucose concentrations were lower after FRUCT than GLUC in both type 2 diabetics (FRUCT *v* GLUC: 7.5 ± 0.3 *v* 10.8 ± 0.4 mmol/L, *P* < .001) and nondiabetics (FRUCT *v* GLUC: 5.9 ± 0.2 *v* 7.2 ± 0.3 mmol/L, *P* < .05). Mean insulin concentrations were approximately 50% higher after FRUCT in type 2 diabetics than in nondiabetics (diabetics *v* nondiabetics: 23.1 ± 0.7 *v* 15.1 ± 1.3 μU/mL; *P* < .0001). Plasma GLP-1 concentrations after fructose were not different between type 2 diabetics and nondiabetics (*P* > .05). Glucose, but not FRUC, increased GIP concentrations, which were not different between type 2 diabetics and nondiabetics (*P* > .05). Food intake was suppressed 14% by GLUC (*P* < .05 *v* CONT) and 14% by FRUC (*P* < .05 *v* CONT), with no difference between the amount of food consumed after GLUC and FRUC treatment in either type 2 diabetics or nondiabetics (*P* > .05). We have confirmed that oral fructose ingestion produces a lower postprandial blood glucose response than equienergetic glucose and demonstrated that (1) fructose produces greater increases in plasma insulin concentration in type 2 diabetics than nondiabetics, not apparently due to greater plasma incretin concentrations and (2) fructose and glucose have equivalent short-term satiating efficiency in both type 2 diabetics and nondiabetics. We conclude that on the basis of improved glycemic control, but not satiating efficiency, fructose may be useful as a replacement for glucose in the diet of obese patients with type 2 diabetes.

GLUCOSE INGESTION PROMOTES insulin secretion by a direct action on the pancreatic β cells and by stimulating incretin hormone release (glucagon-like peptide-1 [GLP-1] and gastric inhibitory peptide [GIP]). Incretin release accounts for over 50% of the increase in plasma insulin concentrations after ingestion of a glucose load in healthy individuals.[1] Fructose ingestion also induces insulin secretion, but less than that of glucose. While no study has directly compared the effect of fructose ingestion on plasma insulin in adults with and without non–insulin-dependent diabetes mellitus (type 2 diabetes), the results of separate studies[2,3] suggest that oral fructose is a more potent insulin secretagogue in type 2 diabetes. Greater fructose-induced incretin release in people with type 2 diabetes may explain this. Fructose stimulates GLP-1 secretion in nondiabetics, but less than glucose[2] and has no effect on GIP concentrations.[4] In type 2 diabetics, GIP is secreted in response to glucose, but has almost no insulinotropic activity, whereas the extent of GLP-1 release in people with type 2 diabetes after glucose ingestion is unclear; some studies reporting enhanced and some reporting decreased secretion compared with nondiabetics.[5,6] The relative effects of fructose on insulin, GLP-1 amide and GIP release in people with and without type 2 diabetes have not been reported.

The comparative effects of glucose and fructose on appetite remain controversial. Results of several,[7-9] but not all[2,10] studies in healthy people indicate a greater suppression of short-term food intake by oral fructose than equienergetic glucose. The relative satiating effects of these monosaccharides have not been examined in people with diabetes. Intravenous GLP-1 reduces food intake in healthy humans without type 2 diabetes.[11] It is not yet clear if this is a physiologic or pharmacologic effect, but GLP-1 may be an endogenous satiety factor,[12] in which case, its secretion may account for some of the reduction in food intake after glucose and fructose ingestion.

This study was conducted to determine the relative acute effects of oral glucose and fructose on appetite and food intake and plasma insulin and incretin concentrations in people with and without type 2 diabetes.

MATERIALS AND METHODS

Subjects

Ten patients with early (<4 years since diagnosis), well controlled, type 2 diabetes and 10 nondiabetic subjects with varying degrees of impaired glucose tolerance (nondiabetics) were recruited from the Royal Adelaide Hospital diabetes clinic and by advertisement (subject characteristics are detailed in Table 1). The diabetic patients were all treated with diet alone, ie, none was taking oral hypoglycemic agents or insulin. All diabetics met World Health Organization and American Diabetic Association criteria for the diagnosis of diabetes at the time of the study (fasting venous whole blood glucose concentration ≥6.1 mmol/L (n = 10) and/or blood glucose concentration ≥10.1 mmol/L 2 hours after 75 g glucose (9 of 10)[13] (diagnostic values for venous whole blood are lower than those for venous plasma or capillary whole blood). All subjects were nonsmokers and unrestrained eaters as determined by a score of less than 10 on the eating restraint questionnaire of Stunkard

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Table 1. Characteristics of Subjects and Comparisons Between Nondiabetic and Diabetic Groups

	Nondiabetic	Type 2 Diabetic	*P* Value
Gender (M/F)	6 M, 4 F	6 M, 4 F	-
Age (yr)	54.7 (44-69)	56.5 (44-71)	.77
Weight (kg)	84.8 (71-120.9)	86.9 (62-112.3)	.64
Body mass index (kg/m^2)	30.9 (27-37.7)	30.2 (25.3-36.2)	.67
Duration of known diabetes (mo)	-	18 (0.5-43)	-
Body fat (%)	37.7 (27.4-45.8)	35.4 (20-48.7)	.39
Fasting blood glucose (mmol/L)*	5.6 (5.2-6.0)	7.0 (6.2-8.8)	.001†
HbA_{IC} (%)‡	5.2 (4.9-5.4)	5.9 (5.2-7.1)	.06

NOTE. Body fat was quantified using bioelectrical impedance.[44] Values are mean (range) (except for gender). Comparisons were performed using a Student's unpaired *t* test.

*Mean of the 3 study days, venous whole blood.

†$P = .001$.

‡HbA_{IC} (glycated hemoglobin) measurements were performed using the HPLC with cation exchange column method of Philcox et al.[45] Reference range for nondiabetics, 4% to 6%.

and Messick.[14] Potential subjects with significant gastrointestinal symptoms, disease or surgery, intake of more than 20 g alcohol/day on a daily basis, and current use of medications that might affect glycemic control, gastrointestinal motor function, or appetite were excluded. The Royal Adelaide Hospital Human Ethics Committee approved the study protocol and written, informed consent was obtained from each subject prior to enrolment.

Protocol

Each subject was studied on 3 occasions, separated by at least 5 days. Subjects maintained their normal diet between study days and refrained from vigorous exercise and alcohol intake for 24 hours before each study. Subjects attended the study center at 8:30 AM following an overnight fast, except for water. On arrival, a blood sampling cannula was inserted into a forearm vein. Subjects remained either seated or lying on a bed during all 3 studies and could, except during the meal, read (but not about food-related topics) or listen to the radio.

Fifteen minutes after intravenous cannulation ($t = 0$ minutes), subjects received, in a random order and single-blind fashion, a noncaloric lemon flavoring (Green's Foods, Glendenning, NSW, Australia) (60 mL) in water (240 mL) (1) alone (vehicle [VEH]), (2) plus glucose (75 g) (GLUC), or (3) plus fructose (75 g) (FRUCT), which was consumed in 2 minutes. Three hours later subjects were offered a buffet meal and asked to eat until comfortably full or 30 minutes had elapsed. Subjects were monitored for 0.5 hours postprandially. Venous blood samples (10 mL) were taken at $t = -15$, 0, 5, 10, 15, 30, 45, 60, 75, 90, 120, 150, and 180 minutes for measurement of glucose, GLP-1, GIP, and insulin and also at $t = 210$ and 240 minutes for measurement of glucose and insulin. Visual analogue scale questionnaires (VAS)[15] were administered at 15-minute intervals, starting at $t = -15$ minutes except during the meal.

Biochemical Measurements

Blood samples were collected on ice into EDTA tubes containing a protease inhibitor (Trasylol; Bayer, Leverkeusen, Germany). Plasma was obtained by centrifugation at 4°C at 3,200 rpm for 12 minutes, and stored at −20°C until assayed.

Blood glucose. Blood glucose concentration (mmol/L) was measured at the bedside on venous whole blood using a Medisense II glucometer (Medisense, Bedford, MA).[2] The accuracy of this method has been confirmed previously with an *R* of .961 and slope of 1.005 for the correlation between Medisense II and laboratory measurements on whole venous blood.

Plasma insulin. Plasma insulin concentration was measured using the Abbott IMx Microparticle Enzyme Immunoassay (Abbott Laboratories, Diagnostic Division, Dainabot, Tokyo, Japan). The sensitivity of the assay (concentration at 2 SD from the zero standard) was 1.0 μU/mL. The intra-assay coefficients of variation were 4% at 8.3 μU/mL, 2.9% at 40.4 μU/mL, and 2.5% at 121.7 μU/mL. The inter-assay coefficients of variation were 4.5% at 8.3 μU/mL, 3.4% at 40.4 μU/mL, and 3.6% at 121.7 μU/mL.

Plasma GLP-1. Plasma GLP-1 (7-36) concentration was measured after ethanol extraction of plasma samples by a radioimmunoassay method.[2,17] The antibody, provided by Professor S.R. Bloom (Hammersmith Hospital, London, UK), had been raised in a rabbit immunized with GLP-1 (7-36) conjugated to bovine serum albumin (BSA) by carbodiimide. The antibody had 100% cross-reactivity with synthetic entire GLP-1 (7-36), but does not cross-react with GLP-1 (7-37), glucagon, GIP, or other gut or pancreatic peptides and has been demonstrated by chromatography to measure intact GLP-1 (7-36) amide.[16] It is likely that this antibody also reacts with the degraded GLP-1 (9-36) amide. The minimum detectable limit for the assay was approximately 2 pmol/L, and 11 determinations were used to establish an interassay coefficient of variation of 18%.

Plasma GIP. Plasma GIP concentration was measured, after ethanol extraction of plasma samples by a radioimmunoassay method.[18] Commercially available antiserum was used (Peninsula Laboratories, Belmont, CA). Bound from free fragments were separated using the double-antibody technique. The minimum detectable limit for the assay was approximately 15 pmol/L, and the interassay coefficient of variation was 15%.

Assessment of Symptoms

Hunger, fullness, and nausea were assessed using linear VAS[15] in the form of a questionnaire with the opposites of a particular sensation written at either end of a 10-cm horizontal line; for example hungry versus not hungry and full versus empty.[19] Subjects placed a vertical mark at the appropriate place on each line to indicate the strength of that symptom. Sensations associated with appetite were quantified (cm) as a change from baseline, which was the mean of −15, −10, and 0 minute values.

The test meal was a cold buffet lunch of sliced bread (white and whole meal), margarine, mayonnaise, sliced ham, chicken, cheese, tomato, cucumber and lettuce, plain milk, orange juice, tinned fruit-salad, low-fat strawberry yoghurt, chocolate custard, vanilla ice cream, an apple, pear, and banana, all of which were prepared in excess of what the subject would normally be expected to eat.[20] The total energy content of the food offered was approximately 2,400 kcal (10 MJ). All food items were weighed (to the nearest 0.1 g) before and after the meal and the duration of eating recorded (to the nearest minute). Energy

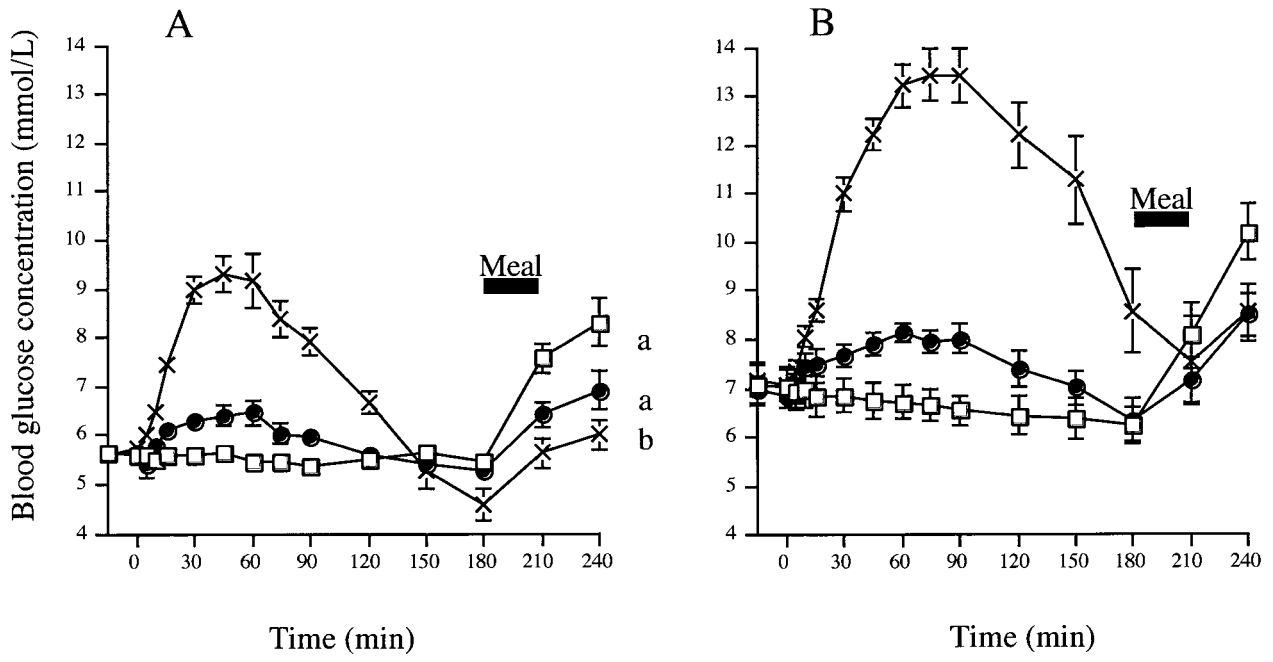

Fig 1. (A) Blood glucose concentrations (mmol/L) after ingestion of glucose (75 g) (GLUC) (✖), fructose (75 g) (FRUCT) (●), or vehicle (VEH) (□) by nondiabetics (n = 10) and (B) by patients with type 2 diabetes (n = 10). Data are mean ± SEM. *P* < .001 for treatment (all treatments were different from each other), *P* < .001 for patient group, *P* < .001 for treatment × patient group ([a,b]different letters indicate that curves are statistically different), *P* < .001 for time by 3-way ANOVA (*t* = 5 to 180 minutes) with repeated measures followed by contrasts.

consumption (kcal) and macronutrient intake (% of total) were calculated from the amount of food consumed during the buffet meal, using DIET/4 food composition software (Xyris Software, Highgate Hill, Qld, Australia).[20,21]

Statistical Analysis

Baseline data were analysed using 2-way analysis of variance (ANOVA) with repeated measures (treatment × patient group). Hunger, fullness, and nausea, blood glucose and plasma insulin, GLP-1, and GIP concentrations were initially analyzed using a 3-way ANOVA with repeated measures (patient group × treatment × time). When a significant interaction was observed, contrasts were used to test hypotheses of interest, enabling paired comparisons between the studies. Fructose-induced changes in plasma insulin GLP-1 and GIP concentrations were assessed using 2-way ANOVA with repeated measures (patient group × time). Relationships between baseline and fructose-induced increases in blood glucose and plasma insulin concentrations were assessed using Pearson's correlations. Food intake was compared using a 2-way ANOVA (treatment × patient group) with repeated measures. Subject characteristics were compared with Student's unpaired *t* tests. SuperANOVA Version 1.11 (Abacus Concepts, Berkley, CA) software was used to perform these analyses. A *P* value of less than .05 was considered statistically significant. All data are expressed as means ± SEM.

RESULTS

One subject experienced a severe headache prior to commencing the buffet meal on the fructose treatment day; all food intake data for this subject were omitted from the food intake analysis. All other subjects tolerated studies well; with no untoward side effects reported.

Biochemical Measurements

Blood glucose. On the basis of their responses to the 75-g oral glucose load, 7 of the nondiabetic subjects had impaired glucose tolerance, 2 had impaired fasting, and 1 normal glucose tolerance (Fig 1).

Fasting (baseline) blood glucose concentrations (mean of −15 and 0 minutes) were greater in type 2 diabetics than in nondiabetics (7.0 ± 0.2 *v* 5.6 ± 0.1 mmol/L, $P < .001$) with no difference between the 3 treatment days for either subject group ($P > .05$).

Blood glucose concentrations were higher in type 2 diabetics than in nondiabetics after both GLUC (mean, 5 to 180 minutes) (10.8 ± 0.4 *v* 7.2 ± 0.3 mmol/L; $P < .001$) and FRUCT (mean, 7.5 ± 0.3 *v* 5.9 ± 0.2 mmol/L; $P < .001$). The mean blood glucose concentration after GLUC, but not FRUCT, was greater than after VEH in all subjects ($P < .001$). At the start of the meal ingestion, blood glucose concentrations were higher in type 2 diabetics than in nondiabetics (7.1 ± 0.7 *v* 5.1 ± 0.2 mmol/L, $P < .01$) and were higher after GLUC than FRUCT in type 2 diabetics (8.6 ± 0.9 *v* 6.4 ± 0.4 mmol/L; $P < .05$). Blood glucose concentrations after lunch (mean of $t = 210$ and 240 minutes) were lower after GLUC ($P < .001$) and FRUCT ($P < .001$) than VEH, with no difference between the monosaccharides (type 2 diabetics, GLUC *v* FRUCT: 8.1 ± 0.8 *v* 7.8 ± 0.5 mmol/L, $P > .05$, nondiabetics; GLUC *v* FRUCT: 5.8 ± 0.2 *v* 6.6 ± 0.2 mmol/L, $P > .05$) in all subjects.

Plasma insulin. Baseline plasma insulin concentrations were similar in type 2 diabetics and nondiabetics (12.2 ± 0.9 *v*

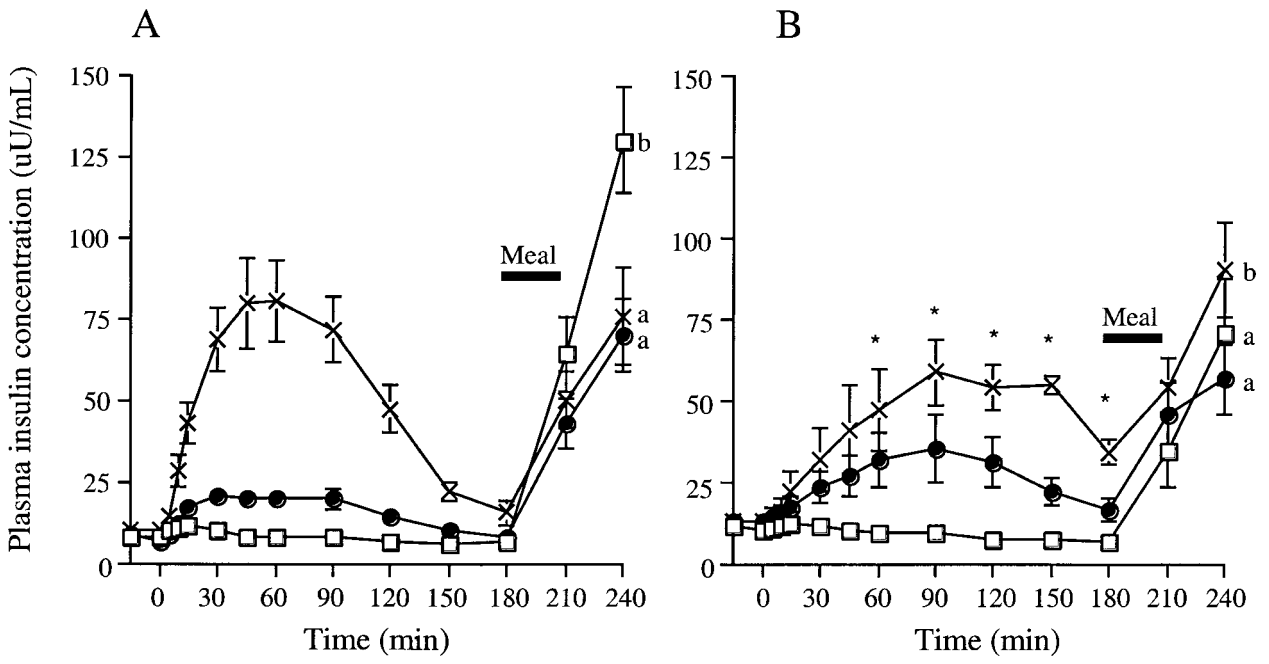

Fig 2. (A) Plasma insulin concentrations (μU/mL) after ingestion of glucose (75 g) (GLUC) (✖), fructose (75 g) (FRUCT) (●), or vehicle (VEH) (□) by nondiabetics (n = 10) and (B) by patients with type 2 diabetes (n = 10). Data are mean ± SEM. $P < .001$ for treatment (all treatments were different from each other), $P < .05$ for treatment × patient group ([a,b]indicates that curves are not statistically different), $P < .001$ for time by 3 way ANOVA (t = 5 to 180 minutes) with repeated measures followed by contrasts. $P < .001$ for time × patient group (* indicates time points at which fructose-induced plasma insulin concentrations in type 2 diabetics differ from nondiabetics), $P < .001$ for time by 2-way ANOVA (t = 5 to 180 minutes) with repeated measures.

8.6 ± 0.6 μU/mL; $P = .2$) with no differences between the treatment days in either subject group (Fig 2). Mean plasma insulin concentrations were significantly ($P < .01$) higher (t = 5 to 180 minutes) after GLUC than after both FRUCT and VEH in type 2 diabetics and nondiabetics. Overall, insulin concentrations were higher after FRUCT than VEH ($P < .001$), but were significantly higher only in type 2 diabetics ($P < .01$). From 60 to 180 minutes after fructose ingestion, plasma insulin concentrations were significantly higher in subjects with type 2 diabetes than in nondiabetics (time × group, $P < .001$) and mean insulin concentrations after fructose (t = 60 to 180 minutes) were approximately 50% higher in type 2 diabetics (23.1 ± 0.7 *v* 15.1 ± 1.3 μU/mL; $P < .05$). Fructose-induced increases in plasma insulin concentrations from baseline were also greater in type 2 diabetics than in nondiabetics ($P < .05$ time × patient group). The time to peak plasma insulin concentrations was delayed in type 2 diabetics compared with in nondiabetics, regardless of the monosaccharide ingested (74.2 ± 8.7 *v* 51.5 ± 8.0 minutes; $P < .01$). After fructose ingestion, plasma insulin concentrations remained higher in type 2 diabetics than in nondiabetics at the start of the buffet meal (16.4 ± 3.3 *v* 8.0 ± 0.8 μU/mL, $P < .05$). Postbuffet meal (mean t = 210 and 240 minutes) plasma insulin concentrations on the fructose day did not differ between type 2 diabetics and nondiabetics (50.1 ± 10.4 *v* 56.3 ± 9.4 μU/mL, $P > .05$).

Plasma insulin concentrations (5 to 180 minutes) after FRUCT ingestion were not significantly correlated with baseline blood glucose concentrations in the whole subject group ($r = -.1$, $P > .05$) or in either nondiabetics ($r = -.48$, $P > .05$) or type 2 diabetics ($r = -.38$, $P > .05$) when they were assessed separately. Similarly, increases in plasma insulin concentration (mean (5 to 180 minutes) concentration - baseline concentration) after fructose ingestion were not significantly correlated with increases in blood glucose after fructose ingestion in the whole group ($r = -.19$, $P > .05$), type 2 diabetics ($r = .3$, $P > .05$) or in nondiabetics ($r = .6$, $P = .07$).

Plasma GLP-1. Baseline plasma GLP-1 concentrations were slightly, but not significantly, higher in type 2 diabetics than nondiabetics (10.6 ± 1.9 *v* 8.0 ± 1.3 pmol/L, $P = .12$), with no difference between 3 treatment days in either subject group ($P > .05$) (Fig 3). Overall, GLP-1 concentrations (mean 5 to 180 minutes) were higher after both GLUC and FRUCT than VEH ($P < .001$), but not different after GLUC compared with FRUCT ($P > .05$). Plasma GLP-1 concentrations after fructose were not different between type 2 diabetics and nondiabetics (14.0 ± 0.1 *v* 10.2 ± 0.1 pmol/L; $P > .05$). GLP-1 concentrations were not different after GLUC than FRUCT in nondiabetics (12.2 ± 0.5 *v* 10.2 ± 0.5 pmol/L; $P > .05$) or in type 2 diabetics (13.9 ± 0.1 *v* 14.1 ± 0.6 pmol/L; $P > .05$). At the start of the meal, plasma GLP-1 concentrations were similar in type 2 diabetics and nondiabetics (10.8 ± 1.7 *v* 11.4 ± 1.4 pmol/L, $P > .05$) and not different after different treatments in either subject group ($P > .05$).

Plasma GIP. Baseline GIP concentrations were similar in type 2 diabetics and nondiabetics (40.9 ± 3.1 *v* 32.6 ± 6.8 pmol/L, $P = .4$), with no difference between the treatments in

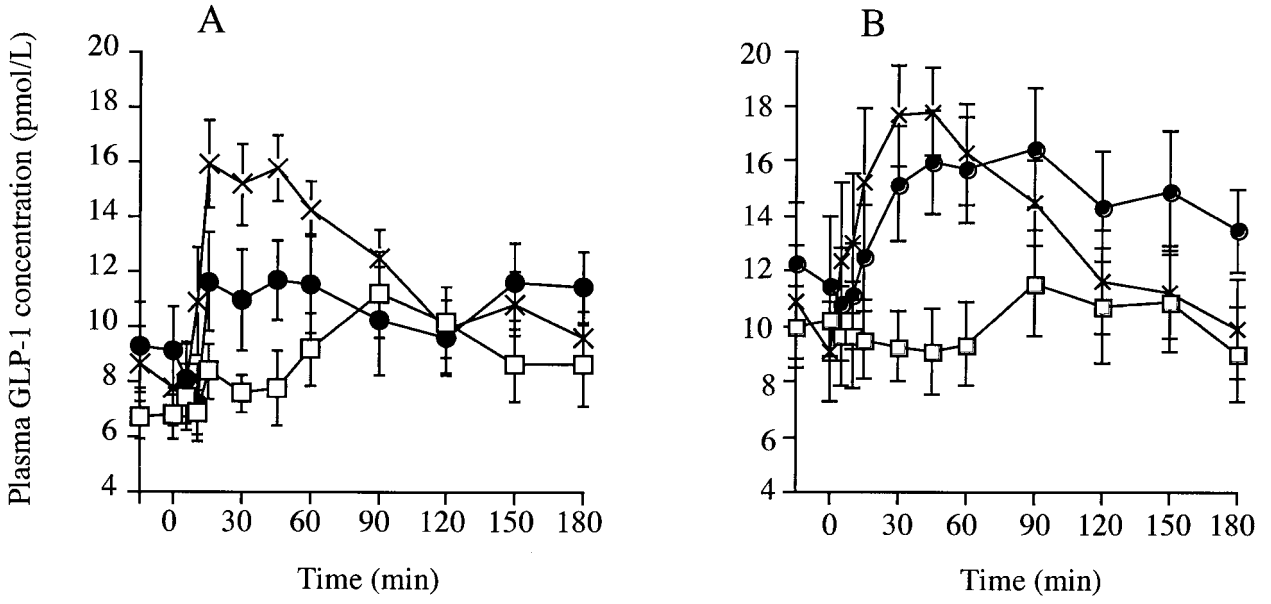

Fig 3. (A) GLP-1 concentration (pmol/L) after ingestion of glucose (75 g) (GLUC) (✖), fructose (75 g) (FRUCT) (●), or vehicle (VEH) (□) by nondiabetics (n = 10) and (B) by patients with type 2 diabetes (n = 10). Data are mean ± SEM. *P* < .001 for treatment (VEH *v* GLUC, VEH *v* FRUCT), *P* < .001 for time by 3-way ANOVA (*t* = 5 to 180 minutes) with repeated measures followed by contrasts.

either subject group ($P > .05$) (Fig 4). Plasma GIP concentrations increased following GLUC, but not after FRUC or VEH in the type 2 diabetics or nondiabetics, so GIP concentrations were significantly higher after GLUC than both FRUC and VEH, with no difference between FRUC and VEH ($P > .05$). Plasma GIP concentrations after FRUCT were similar in type 2 diabetics and nondiabetics ($P > .05$).

Appetite and Food Intake

Sensations of appetite. Baseline hunger, fullness, and nausea ($P > .05$) did not differ between the 3 treatment days for either type 2 diabetics or nondiabetics (Fig 5).

Both monosaccharides increased fullness (GLUC *v* VEH, $P < .01$; FRUCT *v* VEH, $P < .05$) and decreased hunger

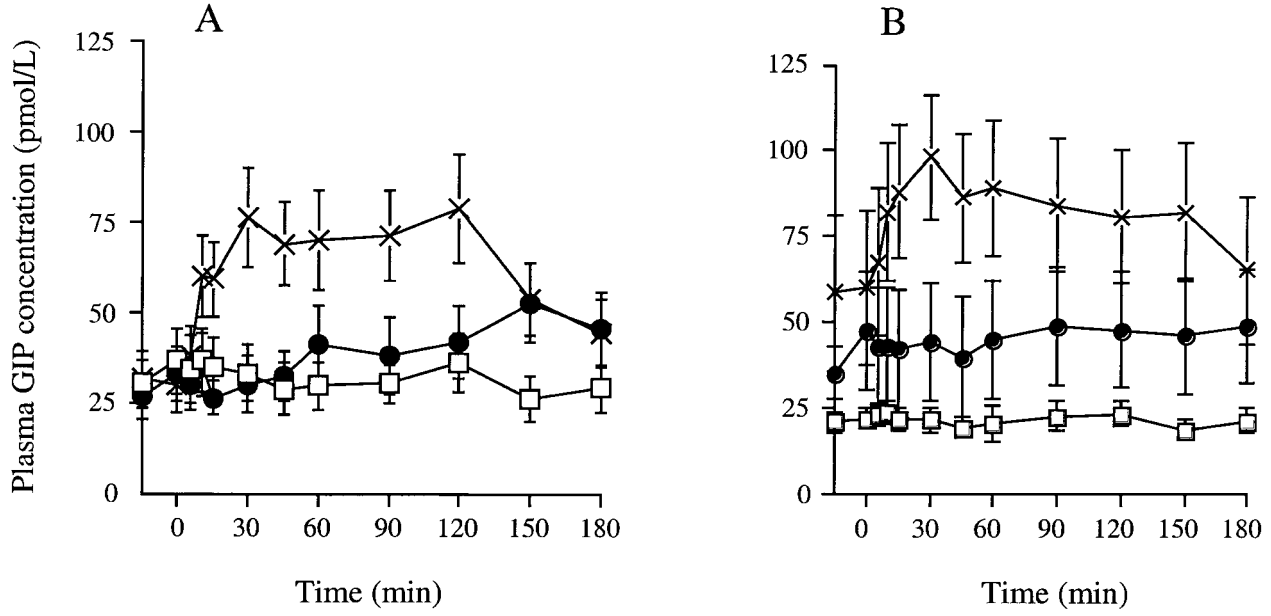

Fig 4. (A) Plasma GIP concentrations (pmol/L) after ingestion of glucose (75 g) (GLUC) (✖), fructose (75 g) (FRUCT) (●), or vehicle (VEH) (□) by nondiabetics (n = 10) and (B) by patients with type 2 diabetes (n = 10). Data are mean ± SEM. *P* < .001 for treatment (VEH *v* GLUC, FRUCT *v* GLUC) and *P* < .001 for time by 3-way ANOVA (*t* = 5 to 180 minutes) with repeated measures followed by contrasts.

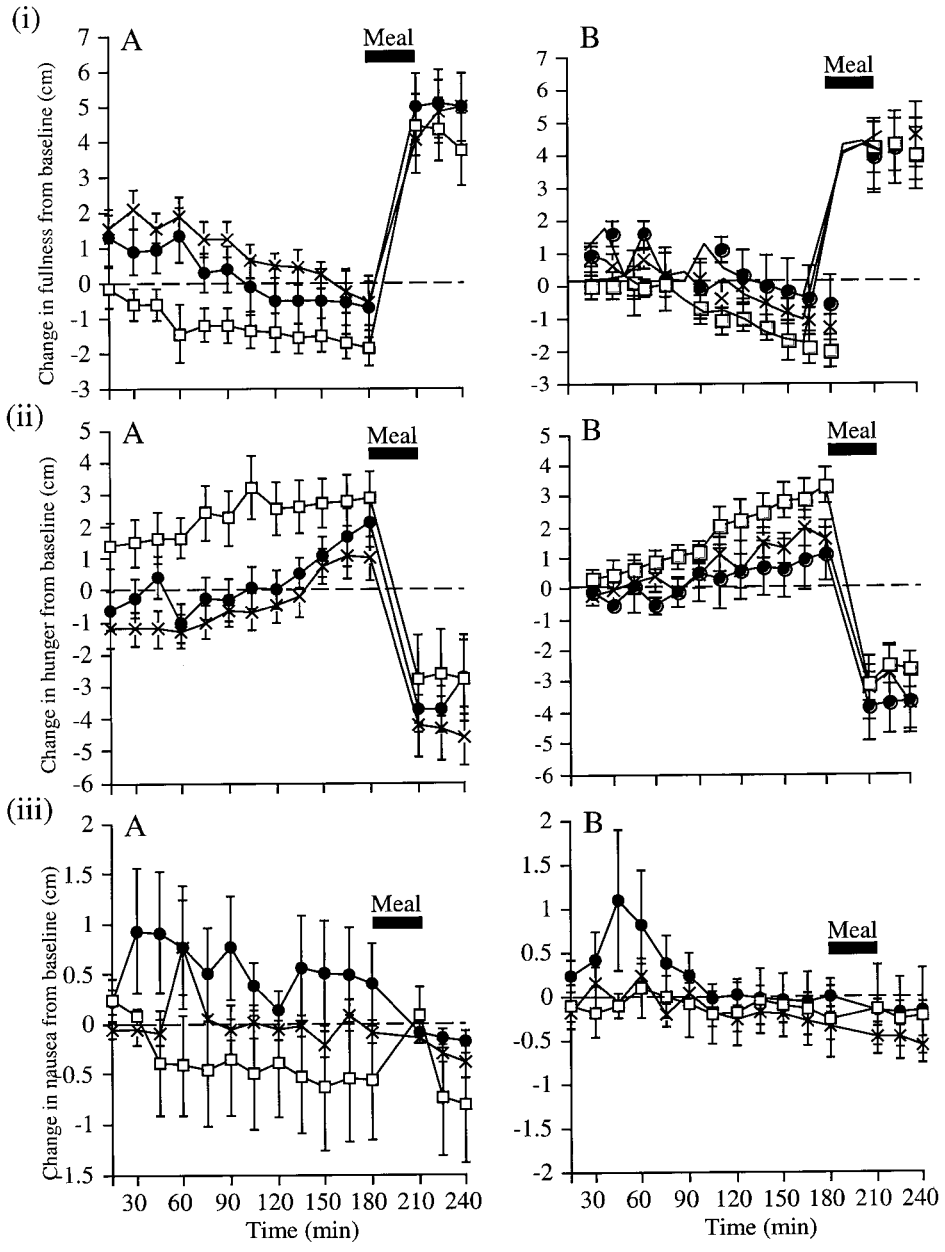

Fig 5. The effect of oral glucose (75 g) (GLUC) (✖), fructose (75 g) (FRUCT) (●), or vehicle (VEH) (□) on sensations of (i) fullness, (ii) hunger, and (iii) nausea in (A) nondiabetics (n = 10) and (B) in patients with type 2 diabetes (n = 10). Data are mean ± SEM. For sensations of hunger and fullness, $P < .001$ for treatment (VEH *v* GLUC, VEH *v* FRUCT) and $P < .001$ for time, and for the sensation of nausea, $P < .001$ for time, by 3-way ANOVA (t = 5 to 180 minutes) with repeated measures followed by contrasts.

(GLUC *v* VEH and FRUCT *v* VEH, $P < .05$), and neither had an effect on nausea ($P > .05$). Nausea was higher after FRUCT than GLUC and VEH, more so in nondiabetics than type 2 diabetic subjects, although this difference was not statistically significant ($P = .07$). There were no differences in hunger or fullness perceptions between GLUC and FRUCT in either subject group ($P > .05$ for type 2 diabetics and nondiabetics).

Food intake. No subject consumed all the food offered, but 1 subject ate for the full 30 minutes on all of the 3 treatment days. Energy intake was suppressed approximately 14% (~147 kcal) compared with VEH, by 75 g monosaccharide ingestion ($P < .05$), with no difference between the suppressive effect of GLUC and FRUCT (908 ± 97 kcal, ~14% suppression *v* 901 ± 71 kcal, ~14% suppression, $P > .05$). The suppression of food intake after monosaccharide ingestion represents approximately 40% of the energy content of the preloads. Diabetics ate less than nondiabetics on every study day (Fig 6) and about 23% less overall (type 2 diabetics *v* nondiabetics: 824 ± 69 *v* 1,070 ± 71 kcal; $P > .05$). There was no patient group × treatment interaction ($P > .05$) and no differences in the macronutrient composition of the foods eaten on different days ($P > .05$) or eaten by type 2 diabetics compared with nondiabetics ($P > .05$).

DISCUSSION

We have confirmed that fructose ingestion produces smaller increases in blood glucose concentrations than glucose inges-

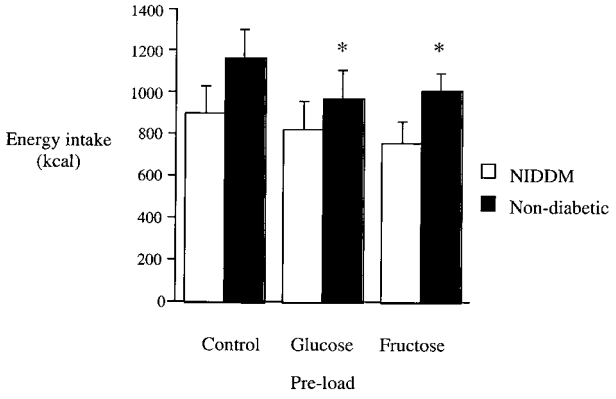

Fig 6. Food intake at a buffet meal 3 hours after ingestion of glucose (75 g) (GLUC), fructose (75 g) (FRUCT), or vehicle (VEH) by nondiabetics (solid bars) (n = 10) and by patients with type 2 diabetes (open bars) (n = 9). Data are mean ± SEM. *Indicates a significant effect of preload $P < .05$ (VEH *v* GLUC, VEH *v* FRUCT) by 2-way ANOVA with repeated measures.

tion in subjects with and without type 2 diabetes. In addition, we provide evidence that fructose ingestion is associated with higher plasma insulin concentrations in diabetics than in nondiabetics and without greater increases in diabetics of plasma GLP-1 or GIP concentrations. Consistent with our previous finding that oral fructose and glucose were equally satiating in lean, young adults without diabetes,[2] we have now found them to be equally satiating in older, overweight people with and without type 2 diabetes.

Our finding of lower blood glucose concentrations after fructose than glucose ingestion is consistent with the results of previous studies in people with diabetes[3,22] and obese[23] and nonobese[2] people without diabetes, showing smaller increases in blood glucose concentration after ingestion of fructose than glucose or the glucose-containing disaccharides, sucrose and lactose.[24] The small increase in circulating glucose concentrations after fructose ingestion is probably the result of hepatic conversion of fructose to glucose.[25,26] Lowering blood glucose concentrations in people with diabetes reduces the microvascular and probably macrovascular complications of this disease.[27,28] Therefore, substitution of fructose for glucose in the diet of diabetics may represent a way of lowering average blood glucose concentrations and possibly reducing hyperglycemia-induced diabetic complication responses. The present study evaluates responses to a supraphysiologic dose (75 g) of fructose. Several studies that have examined the chronic effect of including smaller doses of fructose in the diet of diabetics, either as a supplement,[29-32] or instead of other sugars,[33] demonstrate either no change or improved glycemic control after 3 to 6 months. There are, however, suggestions that chronic fructose ingestion may increase circulating triglyceride and/or cholesterol concentrations.[34] While addition of fructose to the diabetic diet for its glucose-lowering effects is a practical treatment option, it cannot be assumed that this will reduce metabolic complications. Studies to determine if this is so have not been performed.

We have demonstrated for the first time in this study that plasma insulin concentrations are higher after fructose ingestion in subjects with type 2 diabetes than in nondiabetic subjects. Although insulin secretion was not directly assessed, this finding suggests that fructose is a more potent insulin secretagogue in type 2 diabetics than in nondiabetics. We compared overweight people with type 2 diabetes who had good glycemic control on diet alone to age- and weight-matched nondiabetic controls. It is not surprising to find a significant degree of impaired glucose tolerance in an older and overweight nondiabetic healthy population. This highlights the contribution of increasing body weight to the development of insulin resistance, impaired glucose tolerance, and eventually diabetes mellitus. It is likely that the differences between diabetics and nondiabetics would have been even more marked if we compared a lean, nondiabetic population with a group of diabetics with worse glycemic control than those in this study.

We hypothesized that a greater increase in plasma insulin concentrations in response to fructose in diabetics than nondiabetics would be due to a greater release of 1 or more of the incretin hormones, GLP-1 and GIP. We found no evidence for this. Although absolute plasma GLP-1 concentrations were (nonsignificantly) higher after fructose in diabetics than in nondiabetics, this was probably due to higher basal GLP-1 concentrations in diabetics. As previously reported,[35] the increase in plasma GLP-1 concentrations after fructose was similar in the 2 subject groups (from ~8 to 12 pmol/L in the nondiabetics and from ~11 to 16 pmol/L in diabetics). As our assay measures both active and inactive GLP-1, we do not know the exact proportions of each and cannot exclude the possibility that the ratio of active:inactive GLP-1 is different in diabetics to nondiabetics. Similarly, we cannot be sure that the degradation of GLP-1 after monosaccharide ingestion will be similar after glucose and fructose. There was a greater variability in plasma GLP-1 concentrations in the diabetics than nondiabetics, and our sample size was relatively small, so a type 2 statistical error cannot be excluded. Nonetheless, the finding of similar plasma GLP-1 concentrations after fructose ingestion in people with and without type 2 diabetes is consistent with a recent report by Toft et al[35] that plasma GLP-1 concentrations after a mixed meal are similar in type 2 diabetics and nondiabetics. While increased GLP-1 release seems unlikely to be a cause of the greater plasma insulin concentrations in diabetics, increased sensitivity to the insulinotropic actions of GLP-1 remains a possibility. Baseline GIP concentrations were higher (although not significantly) in diabetics, possibly as a consequence of the glucose-dependent nature of GIP release.[36] As previously reported,[37] there was no increase in plasma GIP concentration after fructose ingestion in either type 2 diabetics or nondiabetics.

Fructose-induced insulin release is known to be glucose-dependent and may be enhanced in type 2 diabetics by the hyperglycemia characterizing this condition. In vitro pancreas and isolated islet preparation studies show that fructose is incapable of stimulating insulin in the complete absence of glucose,[38-40] and insulin release after intravenous fructose is greater during hyper- than during euglycemia in nondiabetics.[41] Fructose has only a weak insulinogenic action during euglycemia in people without diabetes, but elevation of the blood glucose concentration even slightly (eg, from 5.5 to 6.4

mmol/L) substantially increases the stimulatory effect of fructose on insulin release.[23] Mean baseline blood glucose levels were similarly elevated in the diabetic compared with the nondiabetic subjects in this study (7.0 *v* 5.6 mmol/L). In addition to enhancing the stimulatory effects of fructose on the β cell, hyperglycemia may indirectly enhance the insulinotropic effects of fructose by increasing the insulinotropic actions of GLP-1. GLP-1 acts on the pancreatic β cell to stimulate insulin secretion, and this insulinotropic effect is enhanced by hyperglycemia.[42] Although hyperglycemia may provide an explanation for the greater fructose-induced increases in plasma insulin concentrations in diabetics, in the present study, the lack of a significant correlation between the increase in plasma insulin concentration after fructose ingestion and either fasting blood glucose concentration or the increase in glucose concentrations after ingestion of the preload does not support this. Nevertheless, the substantial variances in insulin concentrations in the diabetic subjects and the relatively small subject numbers mean that this possibility cannot be excluded, and further studies will be needed to explore this possibility.

The relative effects of monosaccharides on food intake are controversial. Three previous studies, all by Rodin et al,[7,9,43] have found oral fructose ingestion to be more satiating than isoenergetic glucose in subjects without diabetes, whereas 3 other studies, including this one, show no difference.[2,10] The discrepancy may be related to differences in study design. Studies in which fructose has been more satiating than glucose have tended to use higher volume preloads (500 mL *v* 300 mL in our study[7]) and have shorter time periods between preload and test meal ingestion. We have also used higher concentrations of sugar in the preload than did Rodin et al (75 g in 300 mL *v* 50 g in 500 mL). This may result in small intestinal satiety receptors becoming saturated with the monosaccharide, thus producing similar satiating effects of the 2 sugars.

The dose of fructose used in this study was supraphysiologic. It is conceivable that fructose may have suppressed appetite and food intake, in part, by producing a side effect such as nausea. This seems unlikely. The fructose solution in this study was sweeter than the glucose solution, and nausea ratings were somewhat higher in the first 60 minutes after fructose ingestion than glucose ingestion in both diabetics and nondiabetics. Nevertheless, this difference was not significant, and any nauseating effect of fructose, as indicated by these ratings, had resolved by the time of meal ingestion. No subject spontaneously complained of any side effects from fructose ingestion.

This was an acute study that involved the ingestion of each monosaccharide in isolation. It did not investigate the possibility that fructose and glucose have different effects on satiety or blood glucose when ingested chronically from naturally occurring sources (eg, fructose in fruit). Nevertheless, our findings do not support a use for fructose in the diet of people with type 2 diabetes as a means of suppressing food intake and reducing body weight. Furthermore, we studied diabetic patients soon after diagnosis (all $<$4 years) on diet treatment alone. We cannot be sure that fructose will have the same effect in patients who have had diabetes for longer and/or those who are taking hypoglycemic medication. Further studies will be needed to examine the reduced glycemic response to dietary fructose, particularly its effects on long-term diabetic complications.

In summary, we have found that in people with and without type 2 diabetes, oral fructose ingestion produces a smaller increase in blood glucose concentration than equienergetic oral glucose ingestion, a greater increase in plasma insulin concentration in diabetics than in nondiabetics, and is as satiating as glucose.

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