Acute Fructose Administration Improves Oral Glucose Tolerance in Adults With Type 2 Diabetes

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OBJECTIVE — In normal adults, a small (catalytic) dose of fructose administered with glucose decreases the glycemic response to a glucose load, especially in those with the poorest glucose tolerance. We hypothesized that an acute catalytic dose of fructose would also improve glucose tolerance in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Five adults with type 2 diabetes underwent an oral glucose tolerance test (OGTT) on two separate occasions, at least 1 week apart. Each OGTT consisted of 75 g glucose with or without the addition of 7.5 g fructose (OGTT + F or OGTT – F), in random order. Arterialized blood samples were collected from a heated dorsal hand vein twice before ingestion of the carbohydrate and every 15 min for 3 h afterward.

RESULTS — The area under the curve (AUC) of the plasma glucose response was reduced by fructose administration in all subjects; the mean AUC during the OGTT + F was 14% less than that during the OGTT – F ($P < 0.05$). The insulin AUC was decreased 21% with fructose administration ($P = 0.2$). Plasma glucagon concentrations declined similarly during OGTT – F and OGTT + F. The incremental AUC of the blood lactate response during the OGTT – F was ~50% of that observed during the OGTT + F ($P < 0.05$). Neither nonesterified fatty acid nor triglyceride concentrations differed between the two OGTTs.

CONCLUSIONS — Low-dose fructose improves the glycemic response to an oral glucose load in adults with type 2 diabetes, and this effect is not a result of stimulation of insulin secretion.

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Numerous investigations have examined the effect of oral fructose, either given alone or as part of a meal, on carbohydrate metabolism in normal and diabetic individuals. Acute substitution of 54 g fructose for a similar amount of starch in a meal resulted in a significantly smaller postprandial glucose (Δ96%) and insulin (Δ50%) response in six individuals with type 2 diabetes and a significantly smaller insulin response (Δ50%) in six nondiabetic adults (1). In another acute study, 9 normal adults, 10 subjects with impaired glucose tolerance (IGT), and 17 subjects with type 2 diabetes received 50 g glucose, sucrose, or fructose, either alone or as part of a meal (2). In the normal subjects and those with IGT, the serum glucose and insulin responses were significantly reduced during the fructose test (both when fructose was given alone and when given as part of a meal) compared with the glucose and sucrose tests. The serum glucose response was also significantly smaller during the fructose tests in the diabetic subjects, but the serum insulin responses, which were severely blunted during all tests, did not differ among the tests with different carbohydrates (2). Subjects with type 2 diabetes exhibited ~20% reduction in the blood glucose response and ~80% reduction in the plasma insulin response after consumption of 25 g fructose compared with consumption of 25 g glucose (3).

Most studies of chronic fructose ingestion have also shown some benefits of the substitution of fructose for other carbohydrates. In a double-blind crossover study, 10 individuals with type 2 diabetes were studied for 3 weeks on a control diet devoid of fructose and for 3 weeks while fructose was substituted for 20% of other carbohydrates in the diet (4). Fasting plasma insulin concentrations did not change from basal with either diet, but fasting blood glucose declined significantly with both diets (2.7 and 2.1 mmol/l with the fructose and control diets, respectively), as did basal endogenous glucose production. Insulin sensitivity evaluated with a euglycemic-hyperglycemic clamp increased by 34% on the fructose diet but did not improve on the control diet. Subjects with type 1 or type 2 diabetes who consumed two isocaloric diets for 28 days each, with one diet providing 20% of total calories as fructose and one diet providing <3% of calories as fructose, achieved significantly lower mean plasma glucose values while consuming the 20% fructose diet (5). However, glycosylated albumin levels were not significantly reduced by the 20% fructose diet (5). Seven individuals with type 2 diabetes who consumed fructose 80–115 g/day for 2 weeks were found to have a reduced serum glucose response to a 50-g OGTT, without a decrease in the insulin response, compared with baseline values (6). However, this study had no control

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Abbreviations: AUC, area under the curve; GKRP, glucokinase regulatory protein; IGT, impaired glucose tolerance; NEFA, nonesterified fatty acid; OGTT, oral glucose tolerance test; OGTT + F, oral glucose tolerance test with addition of fructose; OGTT – F, oral glucose tolerance test without addition of fructose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

group to allow examination of change over time in the absence of the high fructose diet. Because glucose tolerance has been shown to improve with repeated OGTTs (7), the findings are confounded as a consequence of the subjects' undergoing three OGTTs within 14 days.

Fructose has not always been found to be beneficial in improving carbohydrate metabolism. High-fructose diets induce insulin resistance in animal models, including dogs and rats (8,9). Humans consuming 250 g fructose per day for 1 week also became insulin resistant (10). However, smaller intakes of fructose have also been associated with either deterioration or lack of improvement in glucose metabolism in some investigations. In a study of insulin-resistant and healthy control men maintained for 5 weeks on diets containing 0, 7.5, or 15% of calories as fructose, Hallfrisch et al. (11) found that basal glucose concentrations were significantly higher in both groups of men on the 7.5 and 15% fructose diets than in those on the 0% fructose diet. In addition, the insulin and glucose responses to a sucrose load were significantly greater during the consumption of the 15% fructose diet than during the 0% fructose diet (11). In a study of six subjects with type 2 diabetes consuming a 13% fructose diet for 3 months, there was no improvement in insulin sensitivity (12). Obese adults who consumed a hypocaloric diet containing no carbohydrate or 36 g glucose or galactose daily exhibited a significant increase in numbers of erythrocyte insulin receptors; subjects consuming the same hypocaloric diet with 36 g fructose daily experienced no increase in insulin receptors (13).

Virtually all of the studies cited above had the purpose of determining whether fructose could be safely substituted for other carbohydrates in the diets of diabetic individuals. For this reason, in most of the studies, fructose supplied a relatively large percentage of the total energy intake. However, fructose not only has a role as a source of energy, replacing other carbohydrates in the diet, it also has a "catalytic" role, i.e., it can stimulate the translocation of glucokinase out of the hepatocyte nucleus (14). The translocated glucokinase is responsible for phosphorylation of glucose, a rate-determining step in hepatic glucose metabolism. Normal adults displayed significant improvement in glucose tolerance when a low (catalytic) dose of fructose was added to the glucose load during an OGTT (15). The improvement occurred despite the lack of an increase in the insulin response, and it was greatest in those normal individuals with the poorest (albeit normal) glucose tolerance (15). Therefore, we hypothesized that a catalytic dose of fructose, given simultaneously with the glucose load, would improve glucose tolerance in individuals with IGT or type 2 diabetes. Because glucose tolerance has never been examined in such individuals during acute administration of a catalytic dose of fructose, we examined our hypothesis in volunteers with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Studies were conducted on five obese individuals with type 2 diabetes (one man and four women; one African-American and four Caucasians; aged 42 ± 5 years [range 34–57]; BMI 42 ± 4 kg/m^2 [range 28–51]). HbA_{1c} concentration in these subjects was 8.5 ± 0.5% (range 6.9–10.1%). Two subjects were not on diabetic pharmacotherapy. One subject was taking glyburide, one was taking repaglinide, and one was taking both repaglinide and metformin. These medications were discontinued 5 days before the study. The subjects had normal blood counts, serum electrolyte levels, and liver and renal function. All subjects consumed a diet containing at least 200 g carbohydrate daily for 1 week before study. The studies were approved by the Institutional Review Board of Vanderbilt University Medical Center, and all subjects gave written informed consent before study.

Experimental design

All subjects were studied twice in a single-blind randomized fashion; the two studies were performed in the same subject at least 1 week apart. The subjects were admitted to the Vanderbilt University Medical Center General Clinical Research Center the evening before each study and were studied after a 10-h overnight fast. At ~0800 on the day of study, a 20-gauge intravenous cannula was inserted retrograde into a dorsal vein in one hand. The hand was placed in a thermostatically controlled warmed box, where it was kept throughout the study so arterialized venous blood samples could be obtained.

Two basal blood samples were collected, 15 min apart, before the start of each study. After the second sample was drawn, the subject rapidly (within 1 min) drank a solution containing 75 g glucose. On one of the study days (OGTT + F), the subject received 7.5 g fructose in addition to the 75 g glucose, and on the other day, the subject received no fructose (OGTT – F). The carbohydrate drink was followed immediately by the ingestion of 180 ml water. Blood samples were drawn every 15 min for 180 min after ingestion of the carbohydrate.

Analytical methods

Plasma glucose concentrations were measured with the glucose oxidase technique using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin and glucagon were measured by radioimmunoassay (16,17). Lactate and glycerol (18) and fructose (19) were measured in samples of blood deproteinized with perchloric acid. Plasma nonesterified fatty acids (NEFA) and triglycerides were measured with enzymatic colorimetric assays (NEFA C; Wako Chemicals, Richmond, VA, and IL Test Triglyceride; Instrumentation Laboratory, Lexington, MA, respectively) on a Monarch 2000 centrifugal analyzer (Instrumentation Laboratory).

Calculations and statistical analysis

Based on our previous work in nondiabetic adults (15), we predicted an effect (reduction in the area under the curve [AUC] of the excursion in plasma glucose) of ~160 mmol, with a standard deviation of 100 mmol. With $\alpha = 0.05$ and $\beta = 0.10$, the estimated number of subjects required was 4.1.

Data are means ± SEM. The trapezoidal rule was used for calculation of AUCs of substrate and hormone responses. All AUCs are incremental (i.e., change from baseline values). Paired Student's *t* tests were used for analysis of AUC data. Time-course data were analyzed with repeated-measures analysis of variance, with univariate *F* tests used for post-hoc analysis. Data were accepted as significant if $P < 0.05$.

RESULTS

Glucose response

The AUC of the plasma glucose response during OGTT + F was ~14% less than that evident during the OGTT – F ($P <$

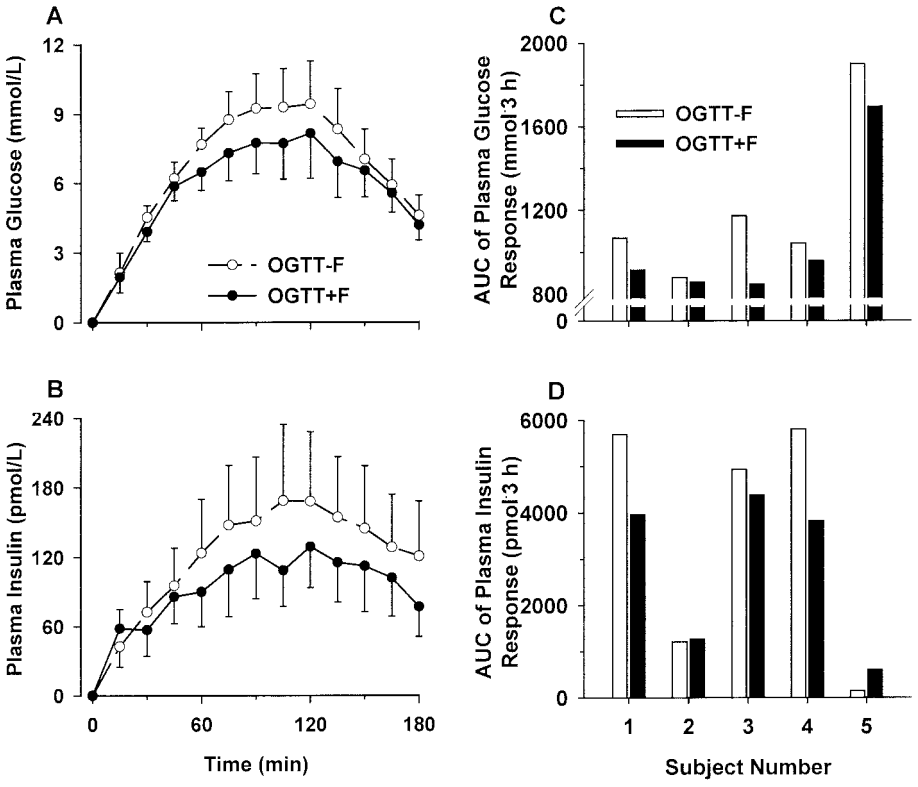

Figure 1—*Change from basal in plasma glucose* (A) *and insulin* (B) *concentrations in five adults with type 2 diabetes during OGTT – F or OGTT + F. Data are means ± SEM. The AUCs of the glucose and insulin responses are 14% (*$P < 0.05$*) and 21% (*$P = 0.2$*), respectively, smaller during the OGTT + F than during the OGTT – F. The histograms on the right show the AUC of the change from basal in plasma glucose* (C) *and insulin* (D) *concentrations in each individual subject during the two OGTTs, which were performed in random order.*

0.05) (Fig. 1). The plasma glucose response was reduced by fructose in all subjects, although the reduction was very modest (~3%) in one subject (subject 2 in Fig. 1*C*). There was no significant effect of order of study on the glycemic response ($P < 0.3$). Moreover, there was no relationship between the prestudy HbA_{1c} concentration and the degree of improvement in the glucose AUC between the two OGTTs ($r = -0.09$, $P = 0.88$).

Insulin and glucagon

Overall, the insulin concentrations were reduced 21% during the OGTT + F versus the OGTT – F (Fig. 1*B*) ($P = 0.2$). Three of the subjects had smaller insulin AUCs (30, 11, and 34%) during the OGTT + F than during the OGTT – F (AUC 33,890 ± 2,000 vs. 24,323 ± 1,234 pmol · 3 h during the OGTT – F and OGTT + F, respectively, in these three subjects; $P < 0.05$). One subject had virtually identical AUCs during both OGTTs (7,661 and 7,628 pmol · 3 h during the OGTT – F and OGTT + F, respectively), and one demonstrated an increase in the insulin AUC during the OGTT + F (884 and 3,594 pmol · 3 h during the OGTT – F and OGTT + F, respectively) (Fig. 1). However, in these last two subjects (subjects 2 and 5 in Fig. 1*D*), there was only a slight increase in insulin concentration over basal after either OGTT. They were also the subjects with the highest prestudy HBA_{1c} levels (9.0 and 10.1%). There was no significant relationship between the glucose and insulin responses during the OGTTs ($F = 0.04$, $P = 0.9$).

Basal glucagon concentrations were 59 ± 3 and 54 ± 4 ng/l during the OGTT – F and OGTT + F, respectively, and the concentrations declined to 48 ± 5 ng/l during both OGTTs (not significant between studies; $P < 0.05$ for change from basal within each OGTT).

Fructose and lactate

The AUC of the blood lactate after carbohydrate ingestion was ~100% greater in OGTT + F than in OGTT – F (106 ± 31 and 50 ± 20 mmol · 3 h, respectively; $P < 0.05$) (Table 1).

The blood fructose concentrations did not change significantly from basal during the OGTT – F (Table 1). During the OGTT + F, the blood fructose concentrations increased more than twofold over basal and were significantly greater than the levels evident during the OGTT – F between 30 and 165 min (mean postingestion levels 30 ± 10 and 64 ± 7 μmol/l in OGTT – F and OGTT + F, respectively; $P < 0.05$).

NEFA, glycerol, and triglycerides

Plasma NEFA, blood glycerol, and plasma triglyceride concentrations did not differ at any time between the two studies (Table 1). NEFA concentrations declined 65–70% in relation to basal values during both OGTTs, and glycerol concentrations declined 35–45%. Triglyceride concentrations did not change significantly during either OGTT.

CONCLUSIONS — Individuals with type 2 diabetes demonstrated a 14% reduction in the AUC of the glucose response to an OGTT when a small dose of fructose was added to the glucose load. This response was similar to the 19% reduction that we observed in 11 normal subjects studied under the same conditions (15). The improvement in glucose tolerance in both diabetic and nondiabetic adults was all the more impressive because the subjects received 10% more carbohydrate during the OGTT + F than during the OGTT – F. The increase in the carbohydrate load during the OGTT + F was, by design, to determine the effect of fructose per se on glucose tolerance rather than the effect of fructose as a replacement for other dietary carbohydrates. The improvement in glucose tolerance with fructose seems to be dependent on the concomitant ingestion of the two monosaccharides. In a randomized crossover study, 10 subjects with type 2 diabetes consumed a high-fructose diet (20% of total energy intake) for 3 weeks and a low-fructose (essentially nil) diet for 3 weeks, with a 4-week washout period between diets. Before and at the end of each diet period, they underwent a 75-g OGTT. The blood glucose profiles after the OGTT were not altered by either the high- or low-fructose diets (4). Meal tolerance tests yielded the same results. All of the

OGTTs and meal tolerance tests were administered after a 12-h fast, and none of them contained fructose. The investigators concluded that fructose has no long-term benefit in reducing the glucose response to an oral glucose load or a mixed meal (4).

The improvement in glucose tolerance with fructose ingestion in the current study did not occur at the expense of increased insulin secretion. The overall insulin response was decreased 21% during the OGTT + F versus the OGTT − F. Three of the five subjects had a reduction in the AUC of the plasma insulin response during the OGTT + F compared with the OGTT-F. Although two of the subjects failed to demonstrate a decrease in insulin concentrations with fructose administration, those two subjects did not exhibit a substantial increase in circulating insulin above basal after either OGTT. In our previous study of nondiabetic adults, almost half had greater insulin responses during the OGTT + F, raising the possibility that improvement of glucose tolerance with fructose was secondary to enhancement of insulin secretion (15). However, in the diabetic individuals, it was clear that the smaller glycemic response during the OGTT + F was independent of any change in insulin release.

Healthy individuals display a limited capacity for intestinal absorption of fructose. Malabsorption of fructose, evidenced by elevated breath hydrogen levels, occurred in 37–80% of healthy adults ingesting a 50-g fructose load (20,21). Therefore, malabsorption may help explain the fructose-induced reduction in the glucose and insulin profiles in studies in which normal subjects or those with diabetes received 50-g fructose versus glucose loads (1,2). However, malabsorption should not have been a problem with the small dose of fructose (7.5 g) used in the current study. Of 21 healthy subjects in whom malabsorption was demonstrated after ingestion of 50 g fructose, only 4 individuals experienced malabsorption after consuming 25 g fructose (21). Moreover, ingestion of glucose with fructose markedly improves fructose absorption (21,22).

The glucose solution ingested during the OGTTs was hyperosmolar (570 mOsm/kg if the water consumed with the carbohydrate is considered); the addition of fructose increased the osmolality by ~10%. It is possible that the additional osmolality or energy content added by the fructose could have delayed gastric emptying (23). However, this possibility seems relatively remote. The $t_{1/2}$ for gastric emptying of even very hypertonic glucose and fructose solutions (2,780 mOsm/kg) was only ~1 h in healthy adults (24), and none of our subjects had any evidence of gastroparesis. A fructose load is emptied more rapidly from the stomach than a similar glucose load (25,26); therefore, the fructose might have actually had a stimulatory effect on gastric emptying. Certainly, the slope of the glucose profiles for the two OGTTs was virtually identical for the last 30–60 min of the experimental period (Fig. 1*A*). Therefore, absorption seemed to have followed much the same pattern during the two OGTTs.

Considering that the insulin response was unable to account for the improvement in glucose tolerance associated with fructose delivery, that malabsorption of fructose was unlikely at this dose and in the presence of a glucose load, and that there is no evidence of a delay in gastric emptying during the OGTT + F, it is probable that fructose itself was responsible for the improvement of glucose tolerance with ingestion of fructose. Glucose phosphorylation by glucokinase is a rate-determining step for hepatic glucose metabolism. Under basal conditions, hepatic glucokinase is localized to the nucleus, where it is bound to the glucokinase regulatory protein (GKRP). Only when glucokinase is released from GKRP can it translocate to the cytosol to allow phosphorylation of glucose (14). In isolated hepatocytes, low levels of fructose have been found to stimulate the release of glucokinase from GKRP, allowing the translocation of glucokinase from the nucleus to the cytoplasm (14). In animal models, administration of fructose has been shown to stimulate translocation of glucokinase (M. Shiota, P. Galassetti, T.L. Jetton, M.A. Magnuson, and A.D. Cherrington, unpublished observations), and in dogs, low-dose fructose administration accompanying intraduodenal glucose infusion has been shown to enhance net hepatic glucose uptake and net hepatic fractional extraction of glucose ~twofold (27). Thus, it is likely that fructose ingestion resulted in improved glucose tolerance via the stimulation of net hepatic glucose uptake secondary to enhanced translocation of glucokinase. It has not been determined whether administration of fructose stimulates glucokinase translocation and hepatic glucose uptake in humans, although the available data suggest that this is the case. In a study of normal humans given fructose at a high rate during a hyperglycemic-pancreatic clamp, fructose stimulated both total glucose output and glucose cycling (28). Because glucose cycling under conditions of

Table 1—*Blood lactate, blood fructose, plasma NEFA, blood glycerol, and plasma triglyceride concentrations during OGTT − F or OGTT + F*

Parameter and treatment	Basal period	Time after ingestion of carbohydrate (min)			
		30	60	120	180
Lactate (mmol/l)					
OGTT − F	1.13 ± 0.16	1.13 ± 0.17	1.42 ± 0.24	1.64 ± 0.16	1.30 ± 0.14
OGTT + F	1.19 ± 0.18	1.38 ± 0.18	1.95 ± 0.14*†	2.04 ± 0.24*†	1.41 ± 0.13
Fructose (μmol/l)					
OGTT − F	24.0 ± 7.7	24.4 ± 7.3	28.5 ± 9.1	32.1 ± 13.4	26.7 ± 10.1
OGTT + F	26.5 ± 3.8	56.2 ± 4.2*†	58.3 ± 5.4*†	64.6 ± 5.6*†	57.7 ± 18.9
NEFA (mmol/l)					
OGTT − F	0.62 ± 0.13	0.61 ± 0.09	0.52 ± 0.15	0.27 ± 0.09*	0.22 ± 0.07*
OGTT + F	0.62 ± 0.09	0.54 ± 0.06*	0.37 ± 0.06*	0.19 ± 0.03*	0.18 ± 0.06*
Glycerol (μmol/l)					
OGTT − F	90.4 ± 6.9	79.2 ± 11.6	70.6 ± 11.2*	55.7 ± 8.8*	48.5 ± 4.7*
OGTT + F	86.1 ± 5.3	74.1 ± 5.2*	59.2 ± 5.2*	58.4 ± 7.1*	56.0 ± 6.4*
Triglycerides (g/l)					
OGTT − F	1.75 ± 0.53	1.76 ± 0.41	1.82 ± 0.38	1.66 ± 0.40	1.64 ± 0.36
OGTT + F	1.73 ± 0.23	1.72 ± 0.24	1.75 ± 0.26	1.77 ± 0.24	1.86 ± 0.23

Data are means ± SEM; each of the five subjects received both OGTT in random order. *$P < 0.05$ vs. basal values during the same OGTT; † $P < 0.05$ versus OGTT − F.

net hepatic glucose release, such as that which occurred in that investigation, is dependent primarily on glucokinase activity, these findings suggest that fructose stimulated glucokinase activity via enhancement of translocation of the enzyme (28). In addition, normal individuals synthesized significantly more hepatic glycogen during an intravenous glucose infusion when low-dose fructose was delivered simultaneously (29). Therefore, the data available in humans are consistent with a stimulation of glucokinase translocation by fructose.

The difference between the AUC of the plasma glucose responses during the OGTT + F and OGTT – F was 158 ± 58 mmol. Blood lactate concentrations were higher after the OGTT + F than the OGTT – F ($P < 0.05$), presumably because of an increase in net hepatic production of lactate (27). The difference in the blood lactate AUC between the two tests totaled 28 ± 12 mmol of glucose equivalents, consistent with a stimulation of glycolysis by fructose. Fructose increases the activities of both pyruvate kinase and phosphofructokinase, which are key regulators of glycolytic flux (30,31). Therefore, the difference in the glucose AUC between the OGTTs was 130 mmol greater than can be accounted for by conversion to lactate. Although the fate of the glucose carbon not converted to lactate could not be determined in these experiments, the findings are consistent with enhancement of hepatic glycogen storage by fructose. Both dogs and humans receiving low-dose fructose infusions along with glucose infusions exhibit enhanced hepatic glycogen storage, as compared with infusion of glucose without fructose (27,29).

During both OGTTs, the hyperglycemic, hyperinsulinemic conditions suppressed lipolysis significantly and to a similar extent, based on the NEFA concentrations (Table 1). Studies of both acute and chronic fructose ingestion (50 g acutely; 10–20% of daily energy intake chronically) have shown increases in triglyceride concentrations among individuals with type 2 diabetes (1,4,6), although increases in triglyceride concentrations have not been universally observed with chronic fructose ingestion (13–20% of total energy intake) (5,32). Nevertheless, at the low levels used in the current study, fructose did not cause any clinically significant change in triglyceridemia.

In conclusion, the addition of small (catalytic) amounts of fructose to a glucose load improves glucose tolerance in adults with type 2 diabetes without enhancing the insulin response. Fructose intake in the U.S. population is relatively high, with fructose providing ~8–10% of total energy intake (33). This raises the question of whether there is need for the addition of catalytic doses of fructose to the diet. However, as much as two thirds of dietary fructose in the U.S. is derived from regular soft drinks and other sweetened beverages in which high-fructose corn syrup is a prominent ingredient, as well as sweetened bakery goods (33). Individuals with diabetes are usually discouraged from frequent use of such products, and therefore, their fructose intake may be much lower than in the general population. More importantly, the timing of fructose intake must be considered. Apparently, fructose must be ingested at or near the time other carbohydrate is consumed to improve carbohydrate tolerance (4). The current data indicate that ingestion of a small amount of fructose concurrent with other carbohydrates may hold promise for the improvement of carbohydrate tolerance in individuals with impaired glucose tolerance and diabetes. The effect of acute catalytic doses of fructose in more physiologic circumstances (e.g., in addition to a mixed meal) is an important question that remains unanswered.

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