Metabolic Consequence of Two-Week Fructose Feeding in Diabetic Subjects

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We studied the metabolic effects of 2-wk fructose feeding as the sweetener in the diet of seven non-insulin-dependent diabetic individuals. The data demonstrated reduced postprandial hyperglycemia to an oral glucose challenge after 14 days without a significant difference in insulin response. There was no change in the markedly blunted glucose response to a fructose challenge but a significantly lower insulin response (area under the 3-h curve) was observed after 14 days of fructose feeding. There was reduced postprandial hyperglycemia after 14 days of fructose feeding with test meals as compared with baseline, without significant differences in insulin response. We also found no significant difference in free fatty acids, cholesterol, high-density lipoprotein (HDL) cholesterol, pyruvate, lactate, or uric acid after fructose feedings. There was a 13% increase in triglyceride levels after 14 days in 5 subjects with initial fasting hypertriglyceridemia (>150 mg/dl). Insulin receptor binding to isolated adipocytes did not change after 14 days of fructose feeding. DIABETES CARE 1986; 9:111–19.

We have previously found that when normal subjects were fed a diet containing (by calories) 55% carbohydrate, 30% fat, and 15% protein, with fructose as the sole added sweetener (24% of total carbohydrate), for 2 wk, no adverse effects on triglyceride, pyruvate, lactate, or uric acid metabolism occurred. Furthermore, there was no apparent adaptation in the metabolism of fructose, since the metabolic responses seen after 14 days of fructose feeding were similar to those noted after acute ingestion of pure fructose or fructose-containing meals. There was a modest decline in postprandial glucose and insulin levels after ingestion of standard fructose-containing mixed meals as compared with sucrose-containing mixed meals.[1] We anticipate that the beneficial effect on blood glucose and insulin responses to fructose incorporated into mixed meals would be greater in subjects with varying degrees of carbohydrate intolerance, insulin resistance, and hyperinsulinemia. However, the metabolic effects of the longer-term inclusion of fructose as the sweetener in the diet are incompletely understood in diabetic individuals. Consequently, we have studied the metabolic effects of using fructose as the sweetener in mixed meals in the diet of subjects with non-insulin-dependent diabetes mellitus (NIDDM) over a 2-wk period.

MATERIALS AND METHODS

Subjects. Seven volunteers (four women and three men) with NIDDM were studied. The clinical characteristics of the study group are displayed in Table 1. No subject ingested any drug known to affect glucose or insulin metabolism during the course of the study. None of the subjects had been treated with insulin. Those subjects on oral hypoglycemic agents had discontinued the drug 3 wk before testing.

Diet composition. Before entry into the study a diet history was taken from each subject and usual sucrose habits evaluated. Diet patterns were then adjusted to achieve a sucrose intake comparable with that which would be ingested in the study. Subjects were then asked to consume this level of sucrose for 2 wk before admission. During the inhospital course of the study each person consumed a 3-day rotating, weight-maintenance, solid-food diet (range of caloric intake 2400–3500) that contained approximately 55% carbohydrate, 30% fat, and 15% protein. The diet contained an average of approximately 300 mg cholesterol and 25 g dietary fiber, and had a polyunsaturated ratio of approximately 1.0. During the baseline period (the first 3–4 days), 24% of the total carbohydrate was given as sucrose; during the study period, fruc-

TABLE 1
Clinical characteristics of the NIDDM subjects

NIDDM subjects	Sex	Age (yr)	Fasting serum glucose (mg/dl)	Relative weight*	Weight (lb)
1	F	52	179	1.49	220
2	F	55	151	1.50	239
3	F	53	325	1.41	208
4	M	43	197	1.41	206
5	M	66	152	0.87	155
6	M	43	156	1.36	260
7	F	44	135	1.41	197

*Relative weight was determined by dividing the actual weight by average body weight, as determined by the Build and Blood Pressure Study (Society of Actuaries 1959; 1:16).

tose was substituted for sucrose in the diet (the range of fructose given was 80–115 g/day). The sugars were incorporated into standard food products and were also given as an added sweetener, i.e., on cereals, in drinks, as indicated in the sample diet in Table 2. The intent of the diet design was to mimic the way crystalline fructose could currently be substituted into the diet.

Protocol. During the baseline period of 3–4 days, while the subject was consuming sucrose as the sweetener in the diet, glucose, insulin, pyruvate, and lactate responses were measured after oral glucose and oral fructose, and after the subject consumed breakfast and lunch test meals. Three separate fasting measurements were made of triglyceride, cholesterol, high-density lipoprotein (HDL), and uric acid levels. In addition,

TABLE 2
Sample diet

Food	Measure	kcal	Protein (g)	Fat (g)	Carbohydrate (g)	Added sugar (g)
Oatmeal	1 cup	148	5.4	2.8	26.0	—
2% Milk	¼ cup	49	3.6	1.7	4.0	—
Grape juice	½ cup	7	0.3		21.8	—
Whole-wheat muffins	2	354	7.0	20.2	36.2	6.0
Margarine	1 tsp	34		3.8		
Coffee/tea	1 cup	2			0.5	—
Sugar	2 tsp	40			10.0	10.0
Tuna, water pack	½ cup	127	28.0	0.8	—	—
Bread	2 slices	112	4.8	1.4	22.0	—
Lettuce		1	0.1		0.2	—
Mayonnaise	1 tbsp	101	0.2	11.2	0.3	—
Orange	1 medium	71	1.8	0.1	17.8	—
Corn chips	½ oz	77	1.0	5.2	7.3	—
Carrot stick	1 medium	30	0.8	0.1	7.0	—
Cookies	3	213	3.3	7.2	35.1	7.4
Coffee/tea	1 cup	2	—	—	0.5	—
Sugar	2 tsp	36	—	—	9.0	9.0
Rye Krisp	4 squares	88	2.4	0.4	19.6	—
Tenderloin, broiled	1	148	17.2	8.3	—	—
Noodles	1 cup	200	6.6	2.4	37.3	—
Green beans	½ cup	20	1.1	0.1	4.6	—
Roll	1	92	2.4	2.2	15.3	—
Margarine	1 tsp	34	—	3.8	—	—
Coffee/tea	1 cup	2	—	—	0.5	—
Sugar	1 tsp	35	—	—	8.7	8.7
Chocolate brownie	1	160	2.2	9.5	17.1	13.1
Orange gelatin	1 serving	124	2.5	0.2	28.4	15.0
Total		2387	90.6	81.4	330.1	79.2

serum free fatty acid (FFA) levels were measured during a day when the actual test meals were being consumed. The subjects were then switched to the test diet containing fructose. After 3 and 14 days on the fructose-containing diet all baseline tests were repeated. All studies were conducted after an overnight fast, in randomized order at each testing point. For the oral glucose and fructose tolerance tests, the subjects were given 50-g loads of the sugars in 300-ml volumes. The loads were given at 8 a.m. and were consumed over a 15-min period. Blood samples for glucose and insulin were drawn at time 0 and at 15, 30, 45, 60, 120, and 180 min after the beginning of the period of consumption. Blood samples for lactate and pyruvate were drawn at time 0 and at 60 min. On the days when meal responses were measured, the breakfast meal was given at 8 a.m. and the lunch meal was given at 12 p.m., and these meals were ingested over a 30-min period. Each of these meals contained approximately one-third of the day's total calories and approximately 16 g of added fructose (Table 2). Each individual subject was fed the same meals on each of the meal test days. Blood sampling for glucose, insulin, and FFA levels took place at time 0 and at 1, 2, 3, 4, 5, 6, and 7 h after the beginning of the period of consumption. Blood samples for lactate and pyruvate were drawn at time 0 and at 1 and 5 h.

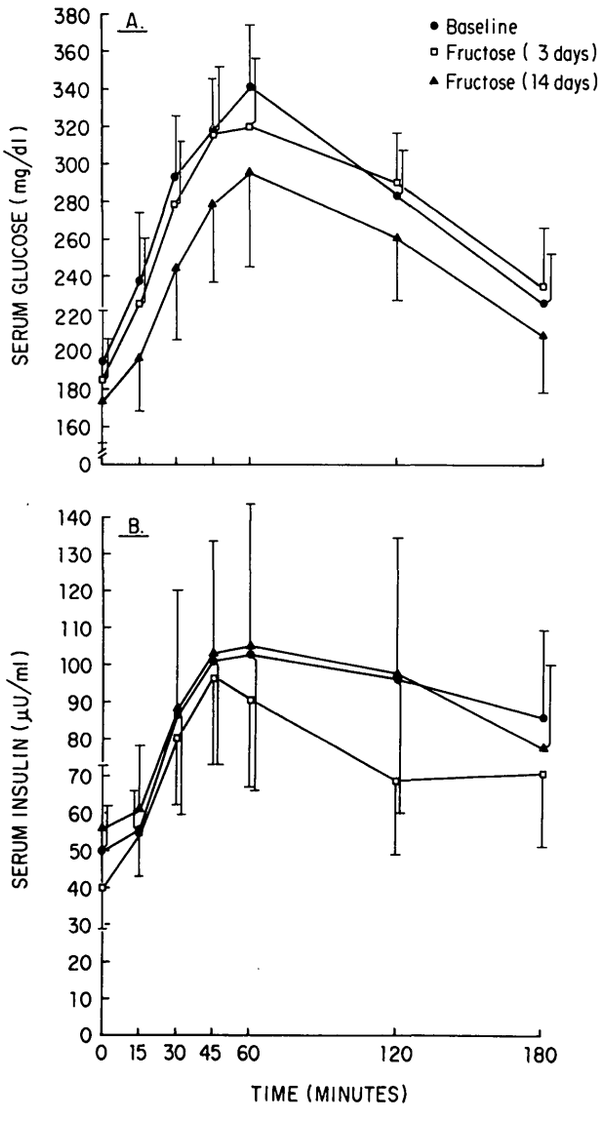

FIG. 1. Mean (±SE) serum glucose (A) and insulin (B) responses of diabetic subjects (N = 7) to oral glucose at baseline and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

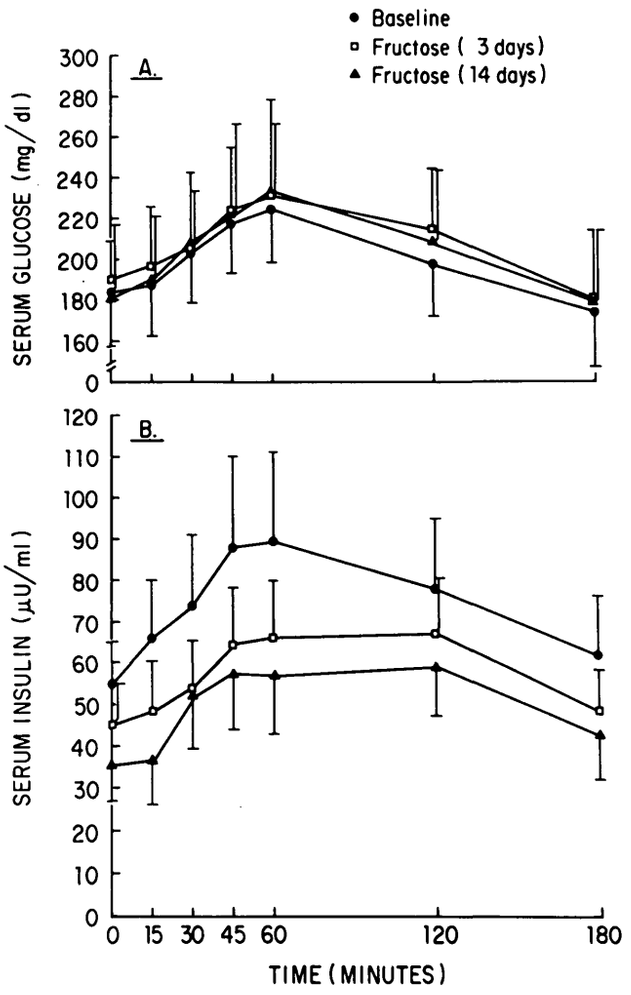

FIG. 2. Mean (±SE) serum glucose (A) and insulin (B) responses of diabetic subjects (N = 7) to oral fructose at baseline and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

Measurement of adipocyte insulin binding. To assess the effects of fructose feeding on insulin receptors, insulin binding to isolated adipocytes was studied before and after the 14-day dietary regimen. Insulin binding to adipocytes was measured in tissue obtained by open biopsy from the lower anterior abdominal wall using 1% Xylocaine without epinephrine (Lidocaine, Astra Pharmaceutical Products, Inc., Worcester, Massachusetts) as the local anesthetic. The operative site was

infiltrated in a 2-in.-square-field fashion and the biopsy specimen (5–10 g) obtained from the center of the square. Isolated adipocytes were incubated at 37°C for 60 min in Krebs-Ringer bicarbonate buffer containing collagenase (3 mg/ml) and albumin (40 mg/ml) by the method of Rodbell.[2] Adipocyte counts were performed by a modification of method III of Hirsch and Gallian,[3] in which the cells are fixed in 2% osmium tetroxide in 0.05 M collidine buffer (made isotonic with saline) for 72 h at 37°C, and were taken up in a known volume of 0.154 M NaCl for counting. Counting was performed with a model ZB Coulter Counter with a 400-m aperture (Coulter Electronics, Inc., Hialeah, Florida). Isolated fat cells were suspended in a buffer containing 35 mM Tris, 120 mM NaCl, 1.2 mM $MgSO_4$, 2.5 mM KCl, 10 mM glucose, 1 mM EDTA, and 1% bovine serum albumin (pH 7.6) and incubated with ^{125}I-insulin (monoiodinated in the ^{14}A position) and unlabeled insulin in plastic flasks in a 24°C shaking water bath, as previously described.[4,5] Details concerning the measurement and calculation of the amount of insulin bound to adipocytes have previously been published.[4,5]

Analytic methods. Samples for serum glucose were measured by the glucose-oxidase method using a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, California). This method measures glucose specifically and does not register increases in serum fructose levels. Serum immunoreactive insulin was measured by the method of Desbuquois and Aurbach.[6] Total cholesterol and triglyceride determinations were measured enzymatically with HDL cholesterol quantified in plasma after dextran sulfate Mg^{2}+ precipitation.[7] Blood for measurement of serum lactate and pyruvate levels was drawn with special precautions[8] and measured enzymatically.[9] Serum FFA levels were measured by use of ^{60}CO as a tracer, which formed a salt complex with available FFA.[10] Statistical analysis was carried out using the Student's *t*-test for dependent means. All data are expressed as mean (±SE) unless indicated otherwise.

RESULTS

Figure 1 depicts the mean serum glucose and insulin responses to a 50-g glucose load during baseline (sucrose) and after 3 and 14 days of the fructose-containing diet. Serum glucose levels were not significantly different from baseline values at 3 days but values at 14 days were significantly lower than baseline at 30 min ($P < 0.05$), and lower than 3-day levels at 15 ($P < 0.01$), 30 ($P < 0.05$), and 180 min ($P < 0.05$). The total area under the glucose curves were 50,735 ± 4929, 50,257 ± 5144, and 45,138 ± 6190 mg/dl · h at baseline, 3 days, and 14 days, respectively, and the difference between the 3- and 14-day values were statistically significant ($P < 0.05$), while the difference between baseline and 14 days just missed significance ($P < 0.08$). The incremental glucose areas were 15,558 ± 1305, 16,957 ± 1658, and 13,869 ± 2560 mg/dl · h at baseline, 3 days, and 14 days, respectively; however, only the difference between 3 and 14 days approached significance ($P < 0.06$). No significant differences in serum insulin responses were observed.

Figure 2 shows the mean serum glucose and insulin responses to a 50-g fructose load during the baseline period and after 3 and 14 days of the fructose-containing diet. The serum glucose responses were all relatively flat, and were essentially identical during each test. Despite the fact that serum glucose levels were unchanged, the insulin responses to oral fructose were significantly decreased at 3 and 14 days compared with baseline. Thus, the total insulin area was 13,714 ± 3074, 10,770 ± 2195, and 9408 ± 1967 μU/ml · h at 0, 3, and 14 days, respectively ($P < 0.05$ baseline to 3 days and 14 days). Incremental insulin areas were 3737 ± 1561, 2619 ± 729, and 3185 ± 933 μU/dl · h at baseline, 3 days, and 14 days, respectively (NS). Thus, the major effect of diet leading to a reduction in insulin response was expressed in a lower basal value.

Figure 3 shows mean serum glucose and insulin responses to breakfast and lunch. Serum glucose responses to fructose-

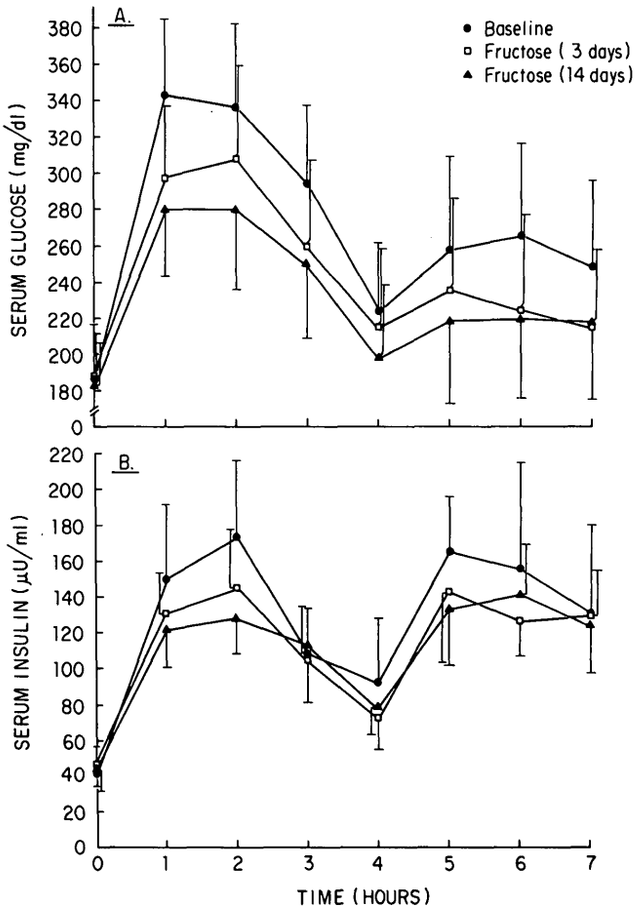

FIG. 3. Mean (±SE) serum glucose (A) and insulin (B) responses of diabetic subjects (N = 7) to actual breakfast and lunch meals consumed by the study subjects during the baseline period and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

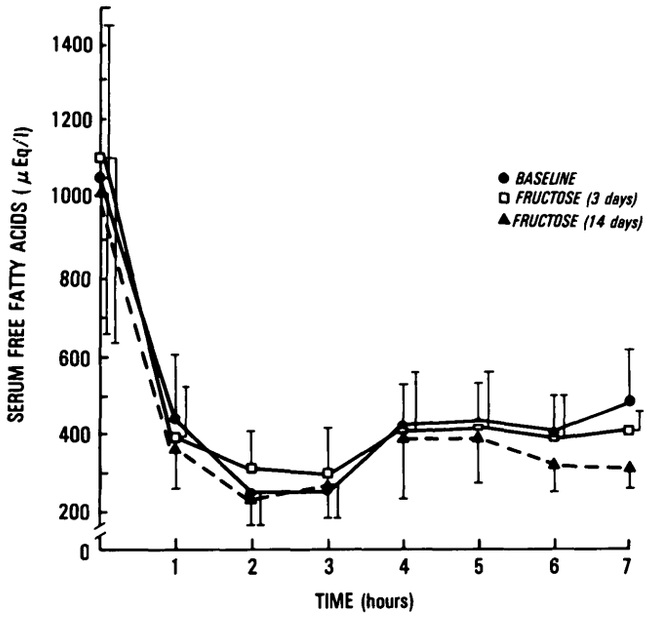

FIG. 4. Mean (±SE) serum free fatty acid (FFA) responses to the actual breakfast and lunch meals consumed by the diabetic subjects (N = 7) during the baseline period and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

containing test meals (3 and 14 days) were significantly lower than those to the sucrose-containing baseline meals ($P < 0.05$ at 1, 6, and 7 h at 3 days and at 1, 2, 3, 5, and 7 h at 14 days). The glucose responses at 3 and 14 days did not differ. The total area under the glucose curves were 116,400 ± 17,940, 104,580 ± 18,900, and 99,000 ± 17,160 mg/dl · h at baseline, 3 days, and 14 days, respectively ($P < 0.05$ baseline to 3 days and $P < 0.001$ baseline to 14 days). Incremental areas under the glucose curves were 37,560 ± 6720, 25,200 ± 9540, and 22,920 ± 6720 mg/dl · h at baseline, 3 days, and 14 days, respectively ($P < 0.05$ baseline to 3 days and $P < 0.001$ baseline to 14 days). Serum insulin responses (Figure 3B) were similar and no significant differences were noted.

The mean serum FFA responses to the breakfast and lunch meals at baseline, 3 days, and 14 days are seen in Figure 4. We observed a marked meal-induced suppression of FFA levels that was comparable at each test period.

Figure 5 demonstrates the mean serum lipid values during baseline and fructose feeding period. As can be seen, there was no significant change in fasting serum triglyceride, cholesterol, or HDL cholesterol levels in the group as a whole. However, although the fasting serum triglyceride levels did not increase significantly on the fructose-containing diet, there was a modest tendency toward rising levels. Kaufman et al.[11] and Halpern[12] have reported that a fructose-containing diet leads to increased triglyceride levels in hypertriglyceridemic subjects. Consequently, we have separately analyzed these results (Figure 6) in the five subjects with preexisting fasting hypertriglyceridemia (>150 mg/dl). The trend toward increasing fasting triglyceride values still existed and resulted in a statistically significant 13% increase between baseline and 14 days.

Serum uric acid levels were measured before (6.0 ± 0.8 mg/dl) and during (5.5 ± 0.06 and 6.1 ± 0.6 mg/dl at 3 and 14 days) the fructose-containing diet and no differences were observed.

Serum pyruvate and lactate responses during the oral glucose tolerance tests, oral fructose tolerance tests, and meal response tests are presented in Figure 7. For each of the three kinds of tests the postprandial serum pyruvate and lactate levels were the same at baseline, 3-day, and 14-day testing periods. The only significant difference was between the fasting serum lactate levels during the oral glucose tolerance test after 3 days of fructose feeding, compared with baseline. For each study period, the postprandial pyruvate and lactate levels were higher after pure fructose and meal ingestion than after glucose ingestion.

The fructose diet led to lower serum glucose levels in the face of unchanged or reduced insulin levels during the oral glucose tolerance test, which is consistent with an improvement in overall insulin sensitivity. One aspect of insulin sensitivity, insulin binding to isolated adipocytes, was measured before and during (14 days) the fructose-containing diet. Competition binding curves (Figure 8) demonstrated no change in insulin receptor binding as a result of the diet.

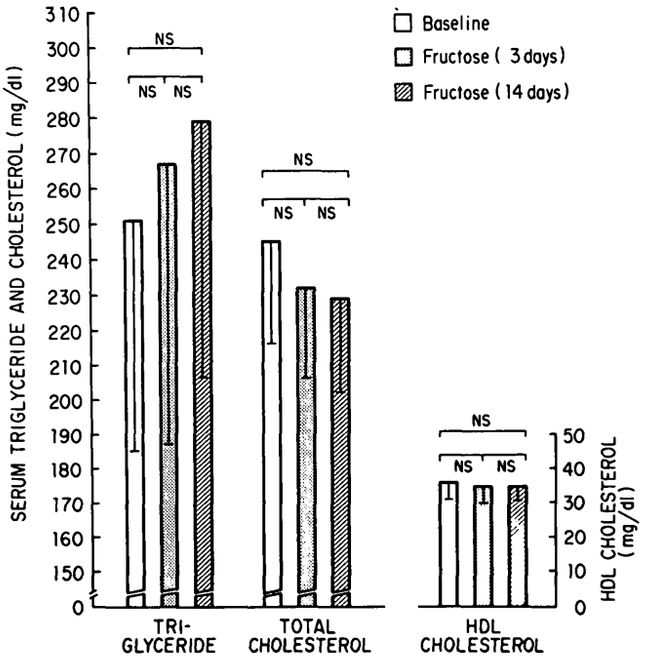

FIG. 5. Mean (±SE) serum triglyceride, total serum cholesterol, and HDL cholesterol levels of diabetic subjects (N = 7) during the baseline period and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

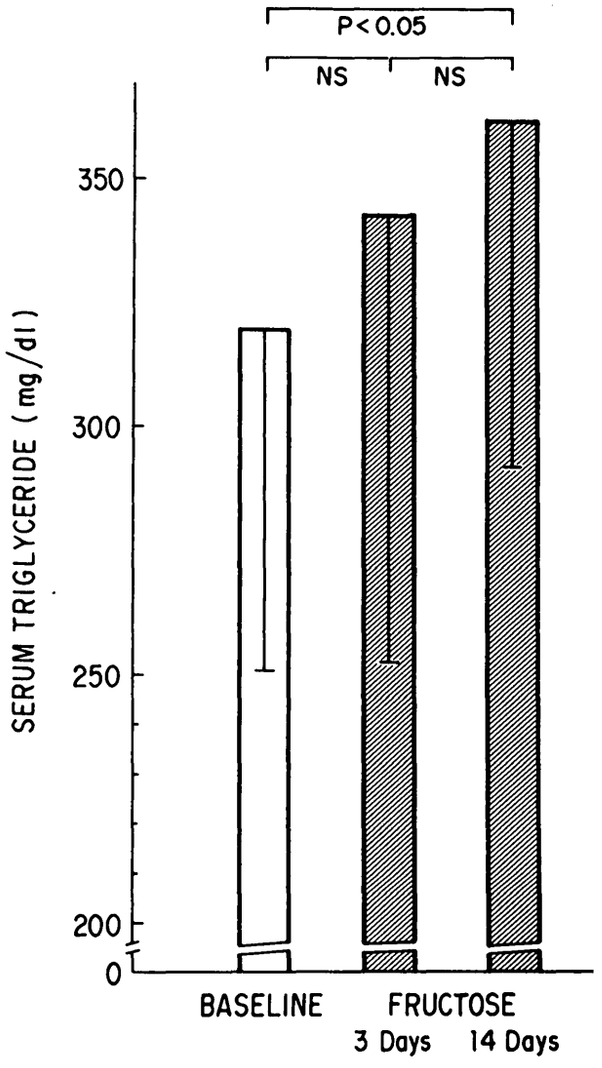

FIG. 6. Mean (±SE) serum triglyceride levels in the five subjects with preexisting fasting hypertriglyceridemia during the baseline period and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

DISCUSSION

Non-insulin-dependent diabetic subjects were fed 80–115 g fructose daily by substituting fructose for the added sucrose in a standard diet; the effect of this dietary modification was measured after 3 and 14 days. Our intent was to create a physiologic situation in which subjects substituted fructose for sucrose in a natural, regular food diet in amounts similar to those that could be achieved if individuals were exchanging fructose for sucrose as the dietary sweetener in the free-living state. Overall, this dietary modification resulted in reduced glucose in the face of unchanged or lower insulin responses. Except for mild elevation of triglyceride levels in the five subjects with preexisting fasting hypertriglyceridemia, no adverse metabolic effects occurred in any of the subjects. The flattened serum glucose levels after ingestion of pure fructose were maintained throughout the 14-day period of fructose ingestion, and there was a trend toward progressive reduction of the serum glucose responses to the fructose-containing test meals over the course of the fructose feeding period. Thus, it is clear that no adaptive change occurs with the substitution of moderate amounts of fructose in the daily diet that would result in a greater rise in blood glucose or insulin levels. Previous studies in diabetic subjects have also reported no change[13] or improvement[14–17] in glucose parameters with fructose feeding.

On the basis of animal experiments, it has been suggested that fructose ingestion can lead to hypertriglyceridemia. In some studies, moderate fructose feeding in hypertriglyceridemic,[11,12] hyperinsulinemic,[18] diabetic,[15] and normal[16] subjects has also been shown to cause increased triglyceride levels. However, we[1] and others[16,19–22] have previously found that ingestion of moderate amounts of fructose in normal,[1,19,20] diabetic,[16] and hypertriglyceridemic subjects[21,22] did not pro-

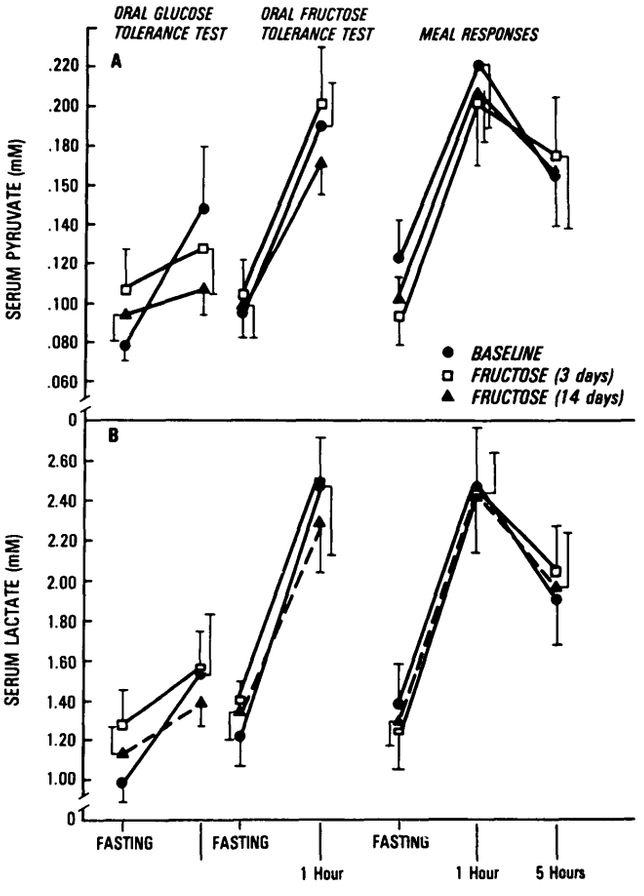

FIG. 7. Mean (±SE) serum lactate and pyruvate responses to oral glucose, oral fructose, and the actual breakfast and lunch meals consumed by the diabetic subjects (N = 7) during the baseline period and after 3 and 14 days of fructose substitution for sucrose as the sweetener in the diet.

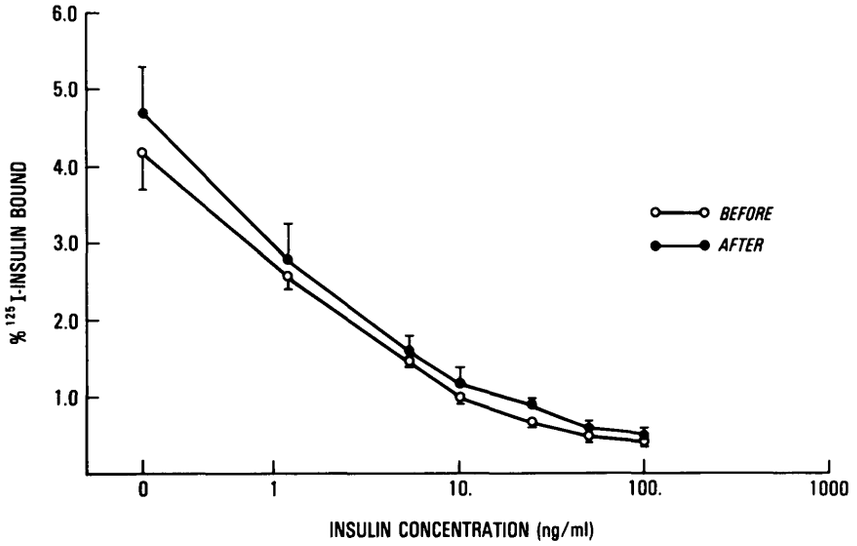

FIG. 8. Mean (±SE) insulin binding to isolated adipocytes from the study subjects (N = 8) during the baseline period and after 14 days of fructose substitution for sucrose as the sweetener in the diet.

duce an increase in fasting triglyceride level. In the current study we found no significant change in serum triglyceride levels when the group of diabetic subjects was assessed as a whole but significant differences were observed when the subjects with preexisting hypertriglyceridemia were separately analyzed. However, it should be noted that although the differences reached statistical significance, the magnitude of the change was quite modest, resulting in a mean increase of only 13% in fasting triglyceride concentration. In those studies in which elevations of triglyceride levels were reported in diabetic and normal subjects, initial triglyceride levels were slightly elevated[16] or not specified. On the other hand, Turner et al.[21] found that fructose feeding did not elevate triglyceride levels in subjects with hypertriglyceridemia; in that study, formula diets containing either fructose (20% of carbohydrate calories) or dextromaltose were compared. Additionally, it has been suggested that the hypertriglyceridemic effect of dietary carbohydrate is temporary in nature and that triglyceride levels will eventually return to baseline levels.[23,24]

It has been previously shown that acute administration of large amounts of fructose can lead to a rise in plasma lactate and pyruvate levels. Our current results and previous results in normal subjects[1] are consistent with this phenomenon since the postprandial rise in plasma lactate and pyruvate levels was greater after the oral fructose tolerance test than after the oral glucose tolerance test. This is most likely due to the fact that during the fructose tolerance test, large amounts of fructose are rapidly taken up by the liver and are converted to lactate and pyruvate, which are subsequently released into the peripheral circulation. On the other hand, it is also possible that fructose ingestion decreases hepatic lactate and pyruvate uptake, resulting in higher serum levels. Regardless of the mechanism, this metabolic phenomenon appears to have little relevance to ingestion of fructose incorporated into mixed meals in a more standard diet setting; that is, after the ingestion of mixed meals on either the sucrose- or fructose-containing diet, the postprandial plasma lactate and pyruvate levels were comparable at all three testing periods, and were higher than during the fructose tolerance tests. Koh and Reiser[25] have also recently reported that 4 wk of fructose feeding (15% of total calories) did not increase pyruvate or lactate levels in diabetic and nondiabetic subjects. Thus, it seems clear that ingestion of moderate amounts of fructose (80–115 g/day) in mixed-meal, natural food diets does not lead to any increase in serum lactate or pyruvate levels in normal or moderately severe NIDDM.

It has also been previously shown that large amounts of intravenous fructose lead to increased circulating serum uric acid concentrations. In the present study and in a previous study in normal subjects,[1] we found no evidence to substantiate the possibility that this phenomenon occurs when moderate amounts of fructose are ingested while patients consume mixed meals in a free-living state. Thus, serum uric acid levels were unchanged throughout the 14-day fructose feeding period.

Results from animal studies in which rats were fed very large amounts of fructose have indicated that fructose can lead to glucose intolerance and insulin resistance.[26–27] It has also been reported that postprandial serum glucose and insulin levels and fasting glucose levels were higher in normal and hyperinsulinemic men after consuming diets containing 7.5% and 15% of total calories as fructose for 5 wk as compared with when they were consuming diets containing no fructose (cooked wheat starch substituted for the fructose).[28] Others have found no change or improvement in glucose or insulin levels after fructose in normal and diabetic subjects.[12–17,19–21,29,30] Our current data in diabetic subjects demonstrate that elevated glucose and insulin levels do not result from the ingestion of the moderate amounts of fructose given. These differences in results between studies may be due to differences in the control diet with which the fructose-containing diet have been compared. Our findings of lowered

plasma glucose levels in the face of unchanged or lower insulin values is consistent with the possibility that insulin action was improved during fructose ingestion. However, this inference must remain speculative in the absence of direct measurements of in vivo insulin action. Nevertheless, since we have found that insulin binding to receptors is unchanged before and after the fructose diet and if adipocyte insulin receptors are reflective of receptors in skeletal muscle and hepatic tissue, then any potential improvement in insulin resistance would be due to a postreceptor modification in insulin action. In an earlier report, Beck-Nielsen et al.[31] found a decrease in insulin binding to circulating monocytes from patients consuming large amounts of fructose (250 g/day) given as a 1000-calorie supplement above the isocaloric diet. The reason for this apparent difference in insulin binding data is unclear but may be related to the fact that in the later study[31] more than twice as much fructose was given and the diets were hypercaloric.

The patterns of postprandial glucose responses to the breakfast and lunch meals are of interest and deserve comment. In our protocol, each meal contained approximately one-third of the day's total calories and therefore the breakfast and lunch meals represent comparable caloric and carbohydrate loads. Despite this difference, the postprandial glucose levels after the lunch meal were considerably lower than those after the breakfast meal for each testing period. In contrast, postprandial insulin levels were comparable after the breakfast, despite comparable carbohydrate and caloric loads and equivalent insulin concentrations. This suggests enhanced insulin sensitivity after lunch compared with breakfast. Although our results do not delineate the mechanisms underlying this phenomenon, the postprandial FFA data seen in Figure 6 suggest a potential explanation. Thus, unlike normal subjects,[1] FFA levels in NIDDM subjects are markedly depressed after food ingestion and remain suppressed for the ensuing 7 h. This prolonged and continuous suppression of FFA levels may lead to a time-dependent improvement in insulin action, since, according to the Randle hypothesis,[32] an inverse relationship should exist between circulating FFA levels and the ability of insulin to mediate overall glucose disposal. Indeed, recent reports have directly demonstrated that when FFA levels are artificially elevated in man an insulin-resistant state occurs.[33] By analogy, it is possible that prolonged lowering of FFA levels leads to the opposite effect.

In summary, the study assessed the metabolic effects of the use of fructose as a natural, caloric sweetener in amounts that are readily achievable (80–115 g/day) in the free-living state in subjects consuming standard mixed meals that contain a normal distribution of carbohydrate, protein, and fat. On this diet, no adverse effects of the fructose-containing diet on pyruvate, lactate, or uric acid metabolism were observed. Adverse effects on serum triglyceride levels were seen only in those subjects with preexisting hypertriglyceridemia. Furthermore, no apparent adaptation to the metabolic effects of fructose occurred. Finally, postprandial glucose levels were lower after ingestion of the standard fructose-containing mixed meals than after ingestion of sucrose-containing mixed meals. Overall, these results suggest that fructose may be an acceptable, perhaps even beneficial, dietary sweetener for individuals with NIDDM. In those individuals who have preexisting hypertriglyceridemia, longer-term studies of the effects of fructose on triglyceride levels are needed.

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