Original Articles

Effects of Oral Fructose in Normal, Diabetic, and Impaired Glucose Tolerance Subjects

PHYLLIS A. CRAPO, ORVILLE G. KOLTERMAN, AND JERROLD M. OLEFSKY

We studied the acute effects of oral ingestion of 50-g loads of dextrose, sucrose, and fructose on postprandial serum glucose, insulin, and plasma glucagon responses in 9 normal subjects, 10 subjects with impaired glucose tolerance, and 17 non-insulin-dependent diabetic subjects. The response to each carbohydrate was quantified when the respective carbohydrate was given alone in a drink or when given in combination with protein and fat in a test meal. The data demonstrate that (1) fructose ingestion resulted in significantly lower serum glucose and insulin responses than did sucrose or dextrose ingestion in all study groups, either when given alone or in the test meal; (2) although fructose ingestion always led to the least glycemic response compared with the other hexoses, the serum glucose response to fructose was increased the more glucose intolerant the subject; (3) urinary glucose excretion during the 3 h after carbohydrate ingestion was greatest after dextrose and least after fructose in all groups. In conclusion, fructose ingestion results in markedly lower serum glucose and insulin responses and less glycosuria than either dextrose or sucrose, both when given alone or as a constituent in a test meal. However, as glucose tolerance worsens, an increasingly greater glycemic response to fructose is seen. DIABETES CARE 3: 575–582, SEPTEMBER–OCTOBER 1980.

The role of fructose in the dietary treatment of diabetes has been debated for many years. Fructose is used in a number of European countries, but to date, has not been widely accepted or used in the United States. However, the ban of cyclamates by the U.S. Food and Drug Administration, the questionable future of saccharin, and increased commercial fructose availability have renewed interest in the use of fructose as an alternative sweetener for individuals with diabetes. In spite of the long history of fructose research, major questions about the use and metabolism of oral fructose still remain unanswered.[1,2]

Fructose has been commonly compared with glucose[3–12] and starch[6,12,13] but not with sucrose (50% glucose and 50% fructose), which is one of the sugars most commonly excluded from the diabetic diet. Also, studies of fructose substitution into meals containing a variety of carbohydrates have not allowed for the calculation of the contribution of fructose to the results compared with other carbohydrates.[14] In addition, comparative insulin values following glucose and fructose have only been reported in normal individuals.[10,11] We therefore studied and quantified the postprandial effects of dextrose, sucrose, and fructose on serum glucose, insulin, and glucagon responses in normal subjects and a broad range of non-insulin-dependent diabetic patients. These responses to the various sugars were investigated when the sugars were given alone as drinks or in combination with protein and fat in a liquid formula meal.

MATERIALS AND METHODS

We studied 9 normal subjects, 10 subjects with impaired glucose tolerance,* and 17 non-insulin-dependent diabetic subjects with fasting hyperglycemia (>140 mg/dl). The clinical characteristics of the study groups are displayed in Table 1. No subject was ingesting any drug known to affect glucose or insulin metabolism during the course of the study. None of the diabetic subjects had been treated with insulin. Those diabetic subjects on oral hypoglycemic agents had discontinued the drug 2 wk before testing. Each person consumed a

*** Seven of the 10 subjects had chemical diabetes as previously defined by the criteria of the American Diabetes Association.[15] The remaining 3 had impaired glucose tolerance by previously published criteria,[16] i.e., a 1-h serum glucose >165 mg/dl and/or a 2-h value >135 mg/dl after the oral ingestion of 50 g dextrose.**

TABLE 1
Clinical characteristics of the study groups

	No.				
	Men	Women	Age (yr)*	Relative weight*†	Fasting serum glucose* (mg/dl)
Normal	2	7	56 ± 2 (24–66)	1.18 ± 0.07 (0.78–1.76)	90 ± 3 (74–100)
Impaired glucose	2	8	51 ± 3 (28–64)	1.19 ± 0.08 (0.89–1.67)	106 ± 5 (81–130)
Fasting hyperglycemia	6	11	42 ± 5 (30–69)	1.13 ± 0.10 (0.76–1.77)	250 ± 21 (144–453)

* Values represent mean (±SE), and the numbers in parentheses indicate the ranges.
† Relative weight was determined according to the Metropolitan Life Tables.

weight-maintenance, solid food diet that contained at least 150–200 g of carbohydrate each day throughout the period of investigation. Three sugars (dextrose, sucrose, and fructose) were tested alone (drinks) and in combination with other nutrients (meals). The compositions of the test loads are outlined in Table 2. All tests were conducted after an overnight fast, and their order was randomized for each subject. At 8 a.m. the subject was given one of the solutions to drink over a 15-min period. Blood samples were timed from the initiation of consumption. Three-hour urine samples for determining urinary glucose excretion were obtained during each of the studies in nine of the subjects with impaired glucose tolerance and five of the diabetic subjects.

Analytic methods. Samples for serum and urinary 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.[17] Plasma glucagon was collected in Traysolol on ice and determined in duplicate by radioimmunoassay using antibody G1-5.[18] Statistical analysis was carried out utilizing the Student's *t* test for dependent and independent means as indicated.

RESULTS

In Figure 1 the serum glucose and insulin responses of the normal individuals to the drinks and meals can be seen. Dextrose and sucrose drinks or meals resulted in similar serum glucose responses, whereas the fructose elicited flat response curves. Likewise, the serum insulin responses to dextrose and sucrose were comparable, but the insulin response to fructose was reduced.

In Figure 2 the serum glucose and insulin responses to the carbohydrate drinks and meals in the subjects with impaired glucose tolerance are shown. It can be seen in Figure 2A that the serum glucose responses to the dextrose and sucrose drinks are significantly greater than the flattened response to fructose. Additionally, the responses to dextrose are somewhat greater than the responses to sucrose. Serum insulin responses (Figure 2B) are greater after the dextrose and sucrose drinks than after the fructose drink, while the serum insulin responses to dextrose and sucrose are not significantly different from each other. Fructose meal ingestion leads to flattened and significantly lower serum glucose responses (Figure 2C) compared with dextrose and sucrose meals. The serum insulin responses to the meals (Figure 2D) show that similar responses are elicited by dextrose and sucrose, while the fructose meal insulin response is flattened.

The mean Δ serum glucose and the insulin responses of the non-insulin-dependent diabetic patients to the carbohydrate drinks and meals are shown in Figure 3. Twelve of the 17 patients had only the dextrose and fructose drink tests, whereas 5 participated in all six tests. The values plotted in Figure 3 and statistical analysis are from the 5 subjects who completed all the tests. Since fasting serum glucose values differed among the individual diabetic patients, the Δ serum glucose responses were plotted. The actual fasting glucose values and the peak serum glucose values during each test are shown in Table 3. It can be seen in Figure 3A that the mean serum glucose responses to dextrose and sucrose drinks were similar, whereas the response curve to fructose was much lower. The serum glucose response to the sucrose meal (Figure 3C) was lower than that to the dextrose meal at 60 and 120 min, but the dextrose and sucrose meal responses are both significantly greater than the fructose meal response.

Since subjects with fasting hyperglycemia are usually characterized by decreased postprandial insulin responses, the curves in Figure 3B and 3D are all essentially flat. Although a

TABLE 2
Composition of tolerance tests

	Dextrose (g)	Sucrose (g)	Fructose (g)	Corn oil (g)	Egg albumin (g)	Lemon flavoring (ml)	Total volume (ml)
A. Dextrose (drink)	50					15	500
B. Sucrose (drink)		50				15	500
C. Fructose (drink)			50			15	500
D. Dextrose (meal)	50			20	20	15	500
E. Sucrose (meal)		50		20	20	15	500
F. Fructose (meal)			50	20	20	15	500

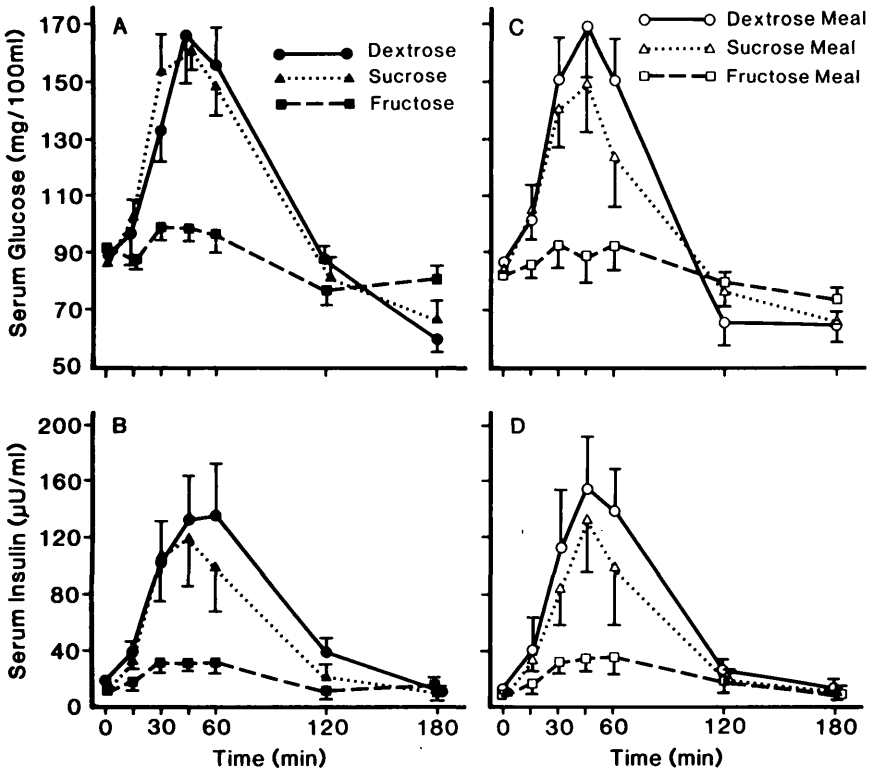

FIG. 1. Mean (±SE) serum glucose and insulin responses to the dextrose, sucrose, and fructose drinks and meals in the nine normal individuals.

	Serum glucose				Serum insulin			
	Sucrose:fructose		Dextrose:fructose		Sucrose:fructose		Dextrose:fructose	
	Drinks	Meals	Drinks	Meals	Drinks	Meals	Drinks	Meals
Time								
F	NS	NS	NS	NS	NS	NS	NS	NS
15	$P < 0.01$	$P < 0.05$	$P < 0.05$	$P < 0.025$	$P < 0.005$	$P < 0.025$	$P < 0.025$	NS
30	$P < 0.001$	$P < 0.005$	$P < 0.005$	$P < 0.0005$	$P < 0.025$	$P < 0.025$	$P < 0.01$	$P < 0.05$
45	$P < 0.0001$	$P < 0.0005$	$P < 0.0005$	$P < 0.0005$	$P < 0.025$	$P < 0.025$	$P < 0.005$	$P < 0.025$
60	$P < 0.005$	$P < 0.025$	$P < 0.0001$	$P < 0.0005$	$P < 0.05$	$P < 0.05$	$P < 0.005$	$P < 0.005$
120	NS	NS	$P < 0.05$	NS	NS	NS	$P < 0.025$	NS
180	$P < 0.025$	NS	$P < 0.005$	NS	NS	NS	NS	NS

few significantly different values can be seen, no obvious trends are apparent.

The comparative Δ serum glucose responses to the fructose drinks in the normal, impaired glucose tolerance, and diabetic (NIDDM) groups are shown in Figure 4. Normal individuals have a flat response to the fructose, which dips slightly below baseline at 2 and 3 h. The peak Δ glucose response in the impaired glucose tolerance group is 3.3 times greater than in the normal group and the peak Δ glucose response of the diabetic (NIDDM) group is 1.7 and 5.6 times greater than in the impaired glucose tolerance and normal groups, respectively. The Δ serum glucose responses of the three groups to the fructose meals show similar but somewhat attenuated differences (data not shown). The diabetic (NIDDM) group Δ peak glucose response to the fructose meal is 1.6 times greater than the response of the impaired glucose tolerance group and 4.7 times greater than the response of the normal group. The Δ peak serum glucose response to the fructose meal in the impaired glucose tolerance group is 2.8 times greater than the response of the normal group. Therefore, although the serum glucose response to fructose is flattened in all groups compared with dextrose and sucrose, fructose causes an increasingly greater glucose excursion as glucose tolerance worsens.

Urinary glucose excretion over the 3-h test period in the subjects with impaired glucose tolerance and the patients with NIDDM was greatest after dextrose consumption and least after fructose ingestion either when given alone or when given in a meal.

Fasting and postprandial plasma glucagon values in 12 of the diabetic subjects after ingestion of oral dextrose and fructose drinks are presented in Table 4. As can be seen, gluca-

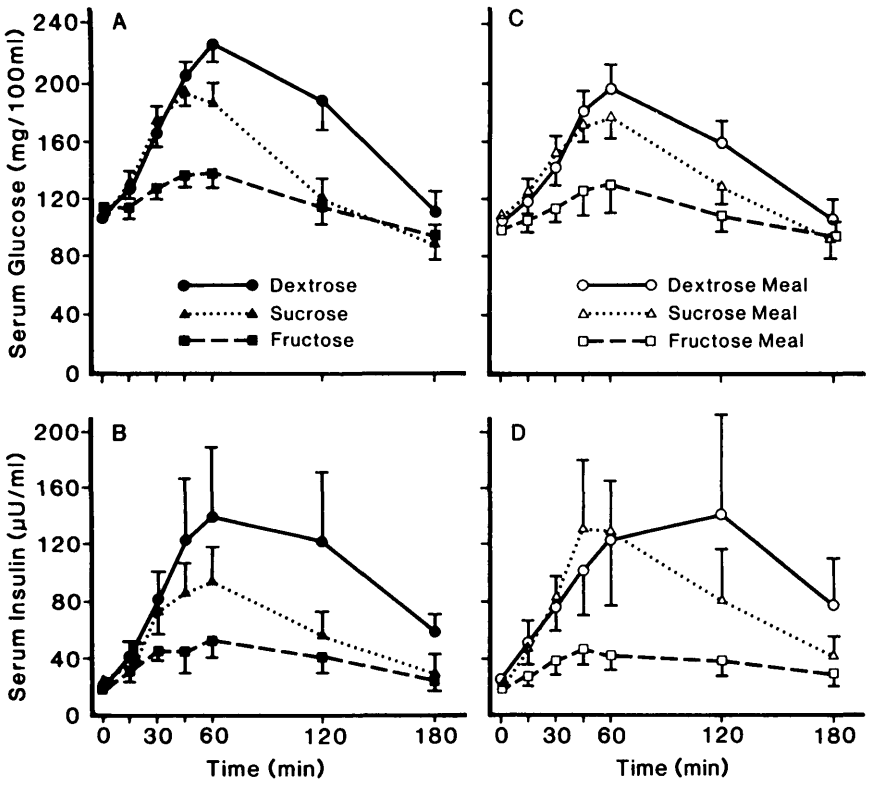

FIG. 2. Mean (±SE) serum glucose and insulin responses to the dextrose, sucrose, and fructose drinks and meals in the 10 subjects with impaired glucose tolerance.

	Serum glucose				Serum insulin			
	Sucrose : fructose		Dextrose : fructose		Sucrose : fructose		Dextrose : fructose	
	Drinks	Meals	Drinks	Meals	Drinks	Meals	Drinks	Meals
Time								
F	NS	NS	NS	NS	NS	NS	NS	NS
15	$P < 0.025$	$P < 0.025$	$P < 0.025$	$P < 0.025$	NS	$P < 0.05$	NS	NS
30	$P < 0.0005$	$P < 0.005$	$P < 0.0005$	$P < 0.01$	$P < 0.005$	$P < 0.025$	$P < 0.01$	$P < 0.025$
45	$P < 0.0005$	$P < 0.005$	$P < 0.0005$	$P < 0.005$	$P < 0.005$	$P < 0.05$	$P < 0.01$	$P < 0.025$
60	$P < 0.0005$	$P < 0.005$	$P < 0.0005$	$P < 0.005$	$P < 0.005$	$P < 0.025$	$P < 0.01$	$P < 0.05$
120	NS	$P < 0.01$	$P < 0.0005$	$P < 0.005$	$P < 0.025$	NS	$P < 0.05$	$P < 0.05$
180	NS	NS	$P < 0.05$	$P < 0.05$	NS	NS	$P < 0.05$	NS

gon levels are relatively nonsuppressible after glucose and increase somewhat ($P < 0.05$ at 15 and 180 min and $P < 0.025$ at 30, 45, and 120 min) after fructose. Therefore, on the basis of the data in the diabetic subjects, it can be concluded that changes in the glucagon level cannot explain the markedly lower glycemic response to fructose compared with dextrose.

DISCUSSION

We studied the effects of orally administered 50-g loads of dextrose, sucrose, and fructose on the postprandial serum glucose and insulin and plasma glucagon responses when given alone in a drink, or when given in combination with protein and fat in a liquid test meal, to normal individuals, individuals with impaired glucose tolerance, and diabetic (NIDDM) subjects. The results show that the serum glucose responses to oral fructose are significantly lower than the responses to dextrose and sucrose, when given alone and when given in a formula meal with other nutrients. The serum insulin responses to fructose are also significantly lower than the responses to dextrose and sucrose in the normal and impaired glucose tolerance groups. In the diabetic group, insulin responses to all three sugars are flat and not significantly different from each other.

These results correspond to previously published acute and chronic studies of fructose consumption. Thus, in acute comparisons of pure dextrose to fructose, significantly lower plasma glucose levels,[6–11] lower plasma insulin levels,[10,11]

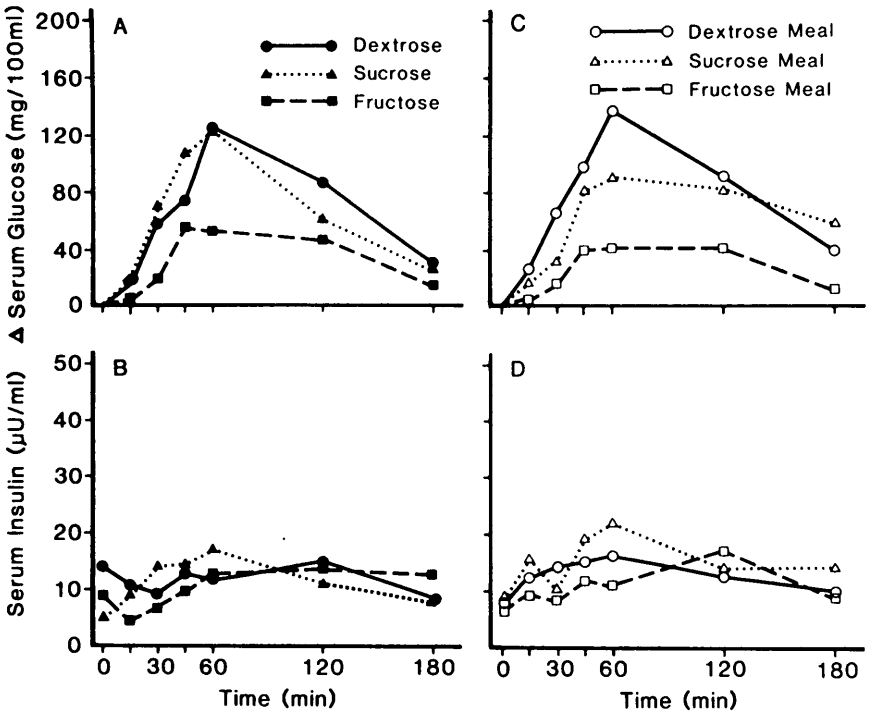

FIG. 3. Mean Δ serum glucose and mean insulin responses to the dextrose, sucrose, and fructose drinks and meals in five subjects with non-insulin-dependent diabetes.

	Serum glucose				Serum insulin			
	Sucrose : fructose		Dextrose : fructose		Sucrose : fructose		Dextrose : fructose	
	Drinks	Meals	Drinks	Meals	Drinks	Meals	Drinks	Meals
Time								
F	NS	NS	NS	NS	NS	NS	NS	NS
15	$P < 0.05$	NS	NS	$P < 0.025$	NS	NS	$P < 0.025$	NS
30	$P < 0.025$	NS	$P < 0.005$	$P < 0.025$	NS	NS	NS	NS
45	$P < 0.025$	$P < 0.025$	NS	$P < 0.025$	NS	NS	NS	NS
60	$P < 0.005$	$P < 0.025$	$P < 0.025$	$P < 0.0005$	NS	NS	NS	NS
120	NS	$P < 0.005$	$P < 0.05$	$P < 0.005$	NS	NS	NS	NS
180	NS	$P < 0.01$	NS	NS	$P < 0.05$	$P < 0.025$	NS	NS

and less glycosuria[8] have been described in diabetic[6–9] and nondiabetic[7,8,10,11] individuals.

In short-term feeding studies, reductions in blood glucose, glycosuria, and ketonemia following the isocaloric substitution of fructose for glucose in diets of controlled diabetic subjects have been shown.[3–5] In addition, the isocaloric substitution of fructose for starch in the diets of moderately controlled insulin-dependent diabetic subjects[13] or diabetic children[6] did not alter diurnal blood glucose levels[13] or urinary glucose output.[6,13] However, beneficial effects are not seen in severe or uncontrolled diabetes.[3,4] The reason for this is most likely an accelerated rate of hepatic conversion of fructose to glucose and hepatic glucose release.

Fructose is more slowly absorbed from the gastrointestinal tract than glucose[19] and is primarily and rapidly taken up by the liver.[20] Consequently, blood fructose levels rise only minimally after fructose ingestion.[21–23] The entry of fructose into liver cells and its initial steps of metabolism are insulin independent. It is converted predominantly into glucose or triglyceride by the liver and, in normal animals and man, most of the glucose formed is stored as glycogen, resulting in only a modest increase in the blood glucose concentration.[24] However, with insulin deficiency glycogen synthesis is impaired, and the fructose, which is converted to glucose in the liver, is rapidly released, leading to a considerable rise in plasma glucose concentration. This has been demonstrated after 2 h of intravenous fructose administration (1.2 g/kg body wt/min) in insulin-dependent diabetes.[25] The degree of insulin deficiency necessary to impair glycogen synthesis is not known. Our data in Figure 4 show substantial increases in serum glucose response in non-insulin-dependent diabetic subjects as well as smaller but notable increases in the sub-

TABLE 3
Individual fasting serum glucose levels and peak serum glucose responses in the five patients with non-insulin-dependent diabetes mellitus* during each of the tests

	Patients				
	1	2	3	4	5
Dextrose					
Fasting glucose	468	289	278	146	268
Peak glucose	573	398	418	261	417
Sucrose					
Fasting glucose	441	267	274	152	266
Peak glucose	606	394	403	264	349
Fructose					
Fasting glucose	438	259	263	141	248
Peak glucose	519	388	299	196	283
Dextrose meal					
Fasting glucose	414	289	274	146	251
Peak glucose	564	432	426	260	370
Sucrose meal					
Fasting glucose	381	230	251	136	208
Peak glucose	525	360	333	212	325
Fructose meal					
Fasting glucose	375	388	267	147	223
Peak glucose	465	448	292	168	279

* In these five patients who completed all the tests, the relative weights were 1.30, 0.91, 1.08, 0.99, and 1.42; ages were 69, 48, 50, 62, and 62 yr; and duration of diabetes was 14, 6, 7, 1, and 1 yr for patients #1–5, respectively.

jects with impaired glucose tolerance after fructose ingestion. Thus, it is possible that this moderate or relative degree of insulin deficiency is enough to impair glycogen synthesis and cause a rise in serum glucose. Alternatively, gastrointestinal conversion of fructose to glucose (10–20% in normal individuals[26]) could be increased in these subjects, or decreased peripheral glucose disposal rates could be responsible for the greater serum glucose responses to fructose.

TABLE 4
Mean (±SE) Δ plasma glucagon responses in 12 patients with non-insulin-dependent diabetes mellitus to dextrose and fructose drinks*

	Δ Plasma glucagon (pg/ml)		
Time	Glucose	Fructose	
15	−21 ± 10	19 ± 11	(P < 0.025)
30	−7 ± 13	37 ± 12	(P < 0.005)
45	2 ± 16	26 ± 11	(NS)
60	2 ± 21	18 ± 12	(NS)
120	−17 ± 24	36 ± 15	(P < 0.05)
180	−10 ± 20	35 ± 19	(P < 0.05)

* Statistical comparisons indicate the significant differences between glucose and fructose. The mean fasting plasma glucagon level was 166 ± 21 pg/ml before the dextrose drink and 147 ± 18 pg/ml before the fructose drink.

On the basis of some animal experiments, it has been suggested that fructose ingestion can lead to hypertriglyceridemia. However, studies in man have not supported this notion. When normal or hypertriglyceridemic individuals, diabetic or nondiabetic, are fed moderate amounts of fructose in their daily diet for periods ranging from 2 wk to 2 yr, no increase in plasma triglyceride level has been detected.[27–29] On the other hand, little or no data are available regarding postprandial triglyceride levels with fructose feeding in diabetic individuals.

Studies involving the use of fructose in combination with varying kinds and amounts of other carbohydrates, proteins, and fats in normal food products and normal meals must be performed before the daylong quantitative reduction of hyperglycemia, which may result from substitution of fructose into the diet, can be established. Since it is possible that adaptation to fructose may occur, further studies are also needed to define the long-term effectiveness on reduction of hyperglycemia that may result when fructose is substituted into the diet for other sugars or nonnutritive sweeteners.

Fructose appears to be an acceptable nutritive sweetener for mild or moderately well-controlled diabetic patients in whom further control of hyperglycemia is felt to be of therapeutic importance. Indeed, fructose may provide some advantages in the dietary management of these patients. Fructose is, of course, a nutritive sweetener, and thus provides calories. This must be recognized when incorporating fructose in the diet. It should also be recognized that, like all sugars and highly refined carbohydrates, fructose is not nutritionally comparable to natural foodstuffs in terms of vitamin and mineral content.

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From the Department of Medicine, Division of Endocrinology, University of Colorado Health Sciences Center, Denver, Colorado 80262.

Address reprint requests to Phyllis A. Crapo, Department of Medicine, B151, 4200 E. Ninth Avenue, University of Colorado Health Sciences Center, Denver, Colorado 80262.

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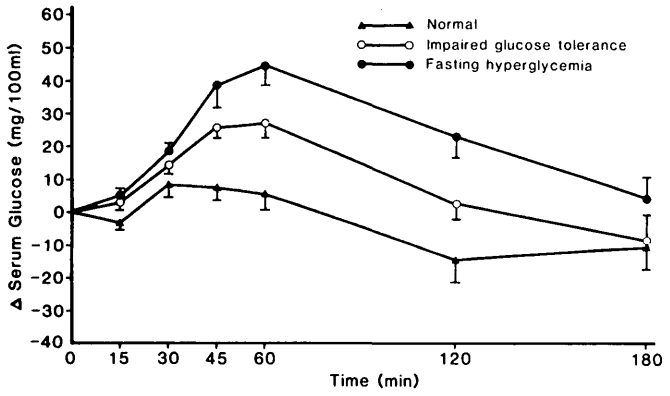

Time	Normal : impaired glucose tolerance	Normal : diabetes	Impaired glucose tolerance : diabetes
15	NS	$P < 0.025$	NS
30	NS	$P < 0.05$	NS
45	$P < 0.005$	$P < 0.01$	NS
60	$P < 0.005$	$P < 0.0005$	$P < 0.025$
120	$P < 0.05$	$P < 0.005$	$P < 0.025$
180	NS	NS	NS

FIG. 4. Mean (±SE) Δ serum glucose responses to fructose drinks in 9 normal individuals (▲), 10 subjects with impaired glucose tolerance (○), and 17 subjects with non-insulin-dependent diabetes (●). Statistical analysis was carried out by Student's t test for two means.

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