Effects of dietary fructose on plasma lipids in healthy subjects[1–3]

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ABSTRACT

Background: About 9% of average dietary energy intake in the United States comes from fructose. Such a high consumption raises concern about the metabolic effects of this sugar.

Objective: The objective of this study was to determine the effect of dietary fructose on plasma lipids.

Design: The study was conducted in the General Clinical Research Center at Fairview-University of Minnesota Medical Center. The participants were 24 healthy adult volunteers (12 men and 12 women; 6 of each sex were aged <40 y and 6 of each sex were aged ≥40 y). All subjects received 2 isoenergetic study diets assigned by using a randomized, balanced crossover design. One diet provided 17% of energy as fructose. The other diet was sweetened with glucose and was nearly devoid of fructose. Each diet was fed for 6 wk. Both diets were composed of common foods and contained nearly identical amounts of carbohydrate, protein, fat, fiber, cholesterol, and saturated, monounsaturated, and polyunsaturated fatty acids. All meals were prepared in the metabolic kitchen of the General Clinical Research Center.

Results: The responses to the study diets differed by sex. In men, the fructose diet produced significantly higher fasting, postprandial, and daylong plasma triacylglycerol concentrations than did the glucose diet. The daylong plasma triacylglycerol concentration after 6 wk of the fructose diet was 32% greater in men than the corresponding concentration during the glucose diet ($P < 0.001$). The fructose diet had no significant effect on fasting or postprandial plasma triacylglycerol concentrations in women. The fructose diet also had no persistent effect on fasting plasma cholesterol, HDL cholesterol, or LDL cholesterol in either men or women.

Conclusions: Dietary fructose was associated with increased fasting and postprandial plasma triacylglycerol concentrations in men. Diets high in added fructose may be undesirable, particularly for men. Glucose may be a suitable replacement sugar. *Am J Clin Nutr* 2000;72:1128–34.

KEY WORDS Dietary fructose, dietary glucose, healthy adults, plasma lipids, plasma glucose, serum insulin

INTRODUCTION

The Sugars Task Force of the United States Food and Drug Administration reported in 1986 that "sugars as they are consumed in the average American diet contribute to the development of dental caries" but that there was "no conclusive evidence" that consumption of sugars caused other adverse health effects (1).

Nevertheless, concern persists about possible adverse effects of dietary sugars because of their high consumption rates. Mean per capita consumption of sugars in the United States was estimated from the US Department of Agriculture Food Consumption Surveys of 1977–1978 and 1987–1988 to be 95 and 94 g/d, respectively (1, 2). Of the sugars consumed, 37 g came from fructose in 1977–1978, accounting for ≈8% of average energy intake, and 39 g came from fructose in 1987–1988, accounting for ≈9% of average energy intake (3). Except for infants, the 90th percentile intakes for population subgroups were 1.5 to 2.5 times the average intakes (4). Approximately one-third of dietary fructose came from fruit, vegetables, and other natural sources and two-thirds was added to beverages and foods in the diet (eg, soft drinks, fruit-flavored drinks, candies, jams, syrups, and bakery products) (4).

Such a significant contribution by fructose to total energy intake raises questions about the metabolic effects of this sugar. Of particular concern are the potential effects of dietary fructose on plasma lipids. Data from animal models suggest that fructose stimulates lipogenesis (5–8). Data from human studies as summarized by Henry and Crapo (9) and Hollenbeck (10) are less conclusive. Whereas some studies in healthy subjects (11–13) and subjects with diabetes (14–18) showed no adverse effects of fructose on lipemia, other studies in healthy (19–21), hyperinsulinemic (20, 22), and diabetic (23) subjects did show such adverse effects. Given this lack of agreement among studies, the dietary guidelines of neither the US Departments of Agriculture and Health and Human Services (24) nor the American Heart Association (25) make any recommendation about fructose intake.

Therefore, to determine whether dietary fructose has adverse effects on plasma lipids, we fed a study diet composed of common foods and providing 17% of energy as fructose to healthy volunteers for 6 wk. With use of a crossover design, the high-fructose diet was compared with an isoenergetic diet sweetened with glucose and that provided only 3% of energy as fructose. To eliminate

TABLE 1
Baseline characteristics of the 24 subjects, grouped by sex and age

	Men		Women	
	<40 y	≥40 y	<40 y	≥40 y
Age (y)	31 ± 3	54 ± 4	29 ± 3	51 ± 2
BMI (kg/m^2)	24.7 ± 0.7	25.8 ± 1.0	24.6 ± 1.3	25.2 ± 1.0
Fasting plasma glucose (mmol/L)[1]	5.1 ± 0.2	5.2 ± 0.3	4.9 ± 0.2	5.01 ± 0.2
Fasting plasma cholesterol (mmol/L)[2]	3.99 ± 0.34	4.45 ± 0.47	4.25 ± 0.31	5.23 ± 0.34
Fasting plasma LDL cholesterol (mmol/L)[2]	2.36 ± 0.39	2.64 ± 0.34	2.36 ± 0.21	3.03 ± 0.21
Fasting plasma HDL cholesterol (mmol/L)[2]	1.14 ± 0.10	1.09 ± 0.10	1.45 ± 0.21	1.61 ± 0.13[3]
Fasting plasma triacylglycerols (mmol/L)[4]	1.12 ± 0.23	1.53 ± 0.40	1.02 ± 0.16	1.31 ± 0.18

[1] To convert to mg/dL, multiply by 18.0.
[2] To convert to mg/dL, multiply by 38.6.
[3] Significantly different from men aged ≥40 y, $P = 0.018$.
[4] To convert to mg/dL, multiply by 88.5.

the confounding effects of other nutrients, the 2 diets were identical in all other respects. In addition to assessing the effects of dietary fructose on fasting plasma lipids, we attempted to determine what effects fructose might have on postprandial lipemia because there is increasing evidence that postprandial lipids are important in the pathogenesis of atherosclerosis (26–30).

SUBJECTS AND METHODS

Subjects

Twenty-four healthy subjects participated in the study. There were 12 women and 12 men; 6 of each sex were aged <40 y and 6 of each sex were aged ≥40 y. Exclusionary criteria were any active medical problem, age ≤18 or ≥80 y, body mass index (BMI; in kg/m^2) >32.0, fasting plasma cholesterol above the 90th percentile for sex and age (31), fasting plasma triacylglycerol concentration >4.5 mmol/L (400 mg/dL), fasting plasma glucose >6.1 mmol/L (110 mg/dL), and evidence of abnormal hepatic, renal, or thyroid function from screening laboratory test results. The baseline characteristics of the subjects are summarized in **Table 1**. None of the subjects took prescription medication except for 3 premenopausal women who took oral contraceptives and 4 postmenopausal women who took estrogens and, in one case, a progestin. In all instances, the doses of these medications were held constant throughout the study. The research protocol was reviewed and approved by the University of Minnesota's Committee on the Use of Human Subjects in Research. Written consent was obtained from all subjects. A stipend of $600 was paid to each subject after satisfactory completion of the protocol.

Study design

All the subjects received 2 study diets in a randomized, balanced crossover design. The study was designed with both sex and age (<40y and ≥40 y) as strata and 6 subjects were recruited into each of the 4 resulting subgroups (younger women, older women, younger men, and older men). The aim of this balanced design was to enable sufficient power to compare endpoints among these subgroups.

The subjects consumed the 2 study diets for 42 d each. The diets were isoenergetic, composed of common foods, and identical except that crystalline fructose was added to one diet and crystalline glucose was added to the other. Both diets provided 55% of energy as carbohydrate, 15% of energy as protein, and 30% of

energy as fat. In addition, both diets contained nearly identical amounts of dietary fiber, cholesterol, saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids. However, in the fructose diet, 17% of total energy was contributed by fructose whereas in the glucose diet only 3% of total energy was contributed by fructose. In the fructose diet, 14% of energy came from added fructose and 3% of energy came from fructose occurring naturally in the foods used in the diet. In the glucose diet, 14% of energy came from added glucose and 3% of energy came from fructose occurring naturally in the foods used in the diet. The crystalline fructose and glucose added to the diets were used in baking and to sweeten breakfast cereals and beverages.

Each subject was matched to an energy intake that was calculated by multiplying resting energy expenditure determined with a DeltaTrac Metabolic Monitor (SensorMedics, Yorba Linda, CA) by an activity factor determined after the subject was interviewed. Breakfast, lunch, dinner, and an evening snack were provided with each diet and contributed, respectively, 20%, 35%, 30%, and 15% of total energy. A 2-d rotating menu was used. All meals were prepared in the metabolic kitchen of the General Clinical Research Center (GCRC), where all foods were weighed during meal preparation. Dinner was eaten in the GCRC. Breakfast, lunch, and the evening snack were packaged and given to the subjects to eat away from the GCRC. The subjects were required to eat all the food provided and nothing else. Consumption of ethanol during study participation was proscribed. Dietary compliance was monitored regularly by study personnel. All subjects reported good compliance with the study diets.

Dietary nutrients were calculated with use of CGRC DIET PLANNER software (University of California, San Francisco). Supplemental data for dietary sugars were obtained from the Nutrition Coordinating Center Database (version 16.0; School of Public Health, University of Minnesota, Minneapolis). A 48-h sample of each 8368-kJ (2000 kcal) study diet was prepared, homogenized, and submitted to an independent reference laboratory (Medallion Laboratories, Golden Valley, MN) for nutrient analysis. The calculated and analyzed nutrient compositions of the diets are summarized in **Table 2**.

On days 7, 14, 21, 28, 35, and 42 of each diet period, fasting blood samples were obtained for determinations of plasma cholesterol, HDL cholesterol, triacylglycerols, and calculated LDL cholesterol. On days 28 and 42, additional fasting blood samples were obtained for direct measurement of plasma LDL cholesterol. Samples for fasting apolipoprotein B were obtained on day

TABLE 2
Calculated nutrient compositions of the 2 study diets[1]

	Fructose diet	Glucose diet
Total energy		
(MJ)	8.0 (8.1)	8.0 (8.0)
(kcal)	2004 (2032)	2001 (1989)
Carbohydrate (g)	276 (275)	276 (268)
Fructose (g)	80 (85)	10 (15)
Glucose (g)	10 (17)	80 (81)
Sucrose (g)	10 (3)	10 (3)
Lactose (g)	11 (20)	11 (10)
Starch (g)	134	134
Fiber (g)	23 (17)	23 (22)
Protein (g)	76 (83)	76 (82)
Fat (g)	66 (59)	66 (59)
Saturated fatty acids (g)	19 (18)	19 (19)
Monounsaturated fatty acids (g)	24 (22)	24 (21)
Polyunsaturated fatty acids (g)	18 (18)	18 (19)
Cholesterol (mg)	241 (238)	241 (265)

[1] Analyzed values in parentheses. Analyzed values were determined from a homogenized 48-h sample of each diet.

42. On day 42 of each diet period, the subjects were admitted to the GCRC for a 24-h metabolic profile. Blood samples were obtained for plasma triacylglycerols, plasma glucose, and serum insulin at 0730 (fasting), 0930, 1130, 1400, 1600, 1900, 2300, 0200, and 0500 h.

Analytic techniques

Plasma total cholesterol, HDL cholesterol, triacylglycerols, and glucose were determined in the Biochemistry Laboratory of the Fairview-University Medical Center (F-UMC) as described previously (21). Calculated plasma LDL cholesterol was estimated (32) as

$$\text{LDL cholesterol} = \text{total cholesterol} - (\text{HDL cholesterol} + \text{triacylglycerols}/2.2) \quad (1)$$

Measured plasma LDL cholesterol was determined after separation of lipoprotein subfractions by density gradient ultracentrifugation at $541\,000 \times g$ for 2.5 h at 10 °C. Serum apolipoprotein B was determined by rate nephelometry. The F-UMC reference range was 0.50–1.0 g/L (50–100 mg/dL) for women and 0.50–1.10 g/L (50–110 mg/dL) for men. Serum insulin was determined by radioimmunoassay. The F-UMC reference range for fasting serum insulin was 0–140 pmol/L (0–20 μU/mL).

Statistical analysis

For each study response variable, mean values were computed for days 7, 14, 21, 28, 35, and 42. For the response variables obtained repeatedly on day 42, the areas under the curves defined by connecting the observations with line segments were computed to estimate daylong values. Comparisons of the study diets and of differential effects of diet on age and sex subgroups were done by repeated-measures analysis of variance (ANOVA) with use of 3 levels: subjects, diet periods within subjects, and weeks within diet periods. The ANOVA provided separate error terms for each level, and the SEs based on the appropriate error terms are given in the tables. Effects of sex and age group were compared between subjects; effects of diets and interactions between diets and age groups and sex were compared within

subjects. Weekly changes and differences in weekly changes by age group and sex were compared within diet periods.

All response variables provided are the sample means ± SEMs, unless noted otherwise. SEMs are based on the appropriate error terms from the repeated-measures ANOVA, so all weekly means for a single response variable have the same SE term. Exact two-sided *P* values are provided in the text and tables. The Bonferroni procedure was used to protect against the effects of multiple comparisons (33); the significance level required within a group of related endpoint comparisons was 0.05 divided by the number of comparisons of that specific endpoint.

RESULTS

The baseline characteristics of the subjects, grouped by age and sex into 4 strata, are summarized in Table 1. In the older age stratum, men had significantly lower fasting plasma HDL-cholesterol concentrations than did women. There were no significant differences based on sex or age in BMI or fasting plasma glucose, cholesterol, LDL cholesterol, or triacylglycerols.

The calculated nutrient contents of the 2 study diets were in close agreement with the values measured by an independent reference laboratory (Table 2). Both diets were well tolerated by all 24 subjects. Mean body weights of the subjects were not significantly different at the start of the study diets (fructose diet, 74.1 ± 2.1 kg; glucose diet, 74.1 ± 2.0 kg) or at the completion of the study diets (fructose diet, 72.8 ± 2.1 kg; glucose diet, 72.7 ± 2.0 kg). The declines in body weight were statistically significant (*P* < 0.001) but clinically unimportant.

Mean fasting plasma lipids during the 2 study diets are shown in **Table 3**. Although fasting plasma cholesterol, calculated LDL cholesterol, and measured LDL cholesterol were all higher on day 28 of the fructose diet than on day 28 of the glucose diet, these differences did not persist at later time points. The measured plasma LDL-cholesterol concentrations on days 28 and 42 agreed closely with the calculated LDL values. Serum apolipoprotein B concentrations were 0.80 ± 0.04 g/L (80 ± 4 mg/dL) on day 42 of the fructose diet and 0.77 ± 0.03 g/L (77 ± 3 mg/L) on day 42 of the glucose diet. Age or sex did not significantly influence the responses of fasting plasma cholesterol, HDL cholesterol, LDL cholesterol, or apolipoprotein B to the diets.

The fasting plasma triacylglycerol responses of the women and the men to the study diets were significantly different (*P* = 0.004). The women showed no significant difference in fasting plasma triacylglycerols in response to the study diets (Table 3). In contrast, the men had significantly higher fasting plasma triacylglycerol values during the fructose diet than during the glucose diet at multiple time points, including days 7, 28, and 42. The response of plasma triacylglycerols during the 24-h metabolic profiles on days 42 of the study diets also differed by sex (*P* = 0.008). Although the women showed no significant difference between the diets in plasma triacylglycerols at any time point, the men showed higher plasma triacylglycerols at multiple time points on day 42 of the fructose diet compared with the glucose diet (**Figure 1**). In addition, the daylong value for plasma triacylglycerols on day 42 of the fructose diet was greater by 32% in men than was the daylong value for plasma triacylglycerols on day 42 of the glucose diet (**Table 4**). Age did not significantly influence the plasma triacylglycerol responses to the study diets.

Mean plasma glucose and serum insulin concentrations during the 24-h metabolic profiles on day 42 of the study diets are shown

TABLE 3
Effects of the 2 study diets on mean fasting plasma lipids[1]

	Day					
	7	14	21	28	35	42
Plasma cholesterol (mmol/L)[2,3]						
Fructose diet	4.66	4.53	4.45	4.61	4.53	4.30
Glucose diet	4.58	4.43	4.33	4.30	4.45	4.22
P[4]	0.174	0.154	0.031	<0.001	0.224	0.169
Plasma LDL cholesterol (mmol/L)[2]						
Calculated[5]						
Fructose diet	2.75	2.67	2.59	2.69	2.69	2.49
Glucose diet	2.69	2.59	2.51	2.49	2.62	2.49
P[4]	0.399	0.256	0.122	<0.001	0.174	0.756
Measured[3]						
Fructose diet	—	—	—	2.75	—	2.54
Glucose diet	—	—	—	2.51	—	2.56
P	—	—	—	<0.001	—	0.658
Plasma HDL cholesterol (mmol/L)[2,6]						
Fructose diet	1.40	1.35	1.37	1.37	1.35	1.30
Glucose diet	1.42	1.40	1.35	1.37	1.35	1.30
P[4]	0.363	0.077	0.516	0.897	0.488	0.965
Plasma triacylglycerols (mmol/L)[7]						
Women						
Fructose diet	0.96	0.97	0.97	1.02	0.94	0.93
Glucose diet	0.93	0.88	0.97	0.99	1.04	0.97
P[4]	0.706	0.298	0.964	0.810	0.226	0.631
Men						
Fructose diet	1.34	1.32	1.21	1.30	1.27	1.25
Glucose diet	1.11	1.12	1.07	1.03	1.10	0.95
P[4]	0.005	0.018	0.105	0.001	0.043	<0.001

[1] The means for each endpoint have a common SE based on the appropriate repeated-measures ANOVA error term.

[2] To convert to mg/dL, multiply by 38.6.

[3] SE = 0.05.

[4] Because 6 paired comparisons of this endpoint were made, only $P < 0.008$ (0.05/6) should be considered significant at the 0.05 level (*see* Statistical analysis section).

[5] SE = 0.04.

[6] SE = 0.03.

[7] To convert to mg/dL, multiply by 88.5. SE = 0.06.

in **Figure 2**. On day 42 of the fructose diet, plasma glucose was lower at 0930 (90 min after breakfast) than at the corresponding time point during the glucose diet, but there was no significant difference in daylong values for plasma glucose estimated from the areas under the response curves (Table 4). Serum insulin was also lower at 0930 on day 42 of the fructose diet and the daylong value for serum insulin on day 42 of the fructose diet was lower by 18% than the daylong value for serum insulin on day 42 of the
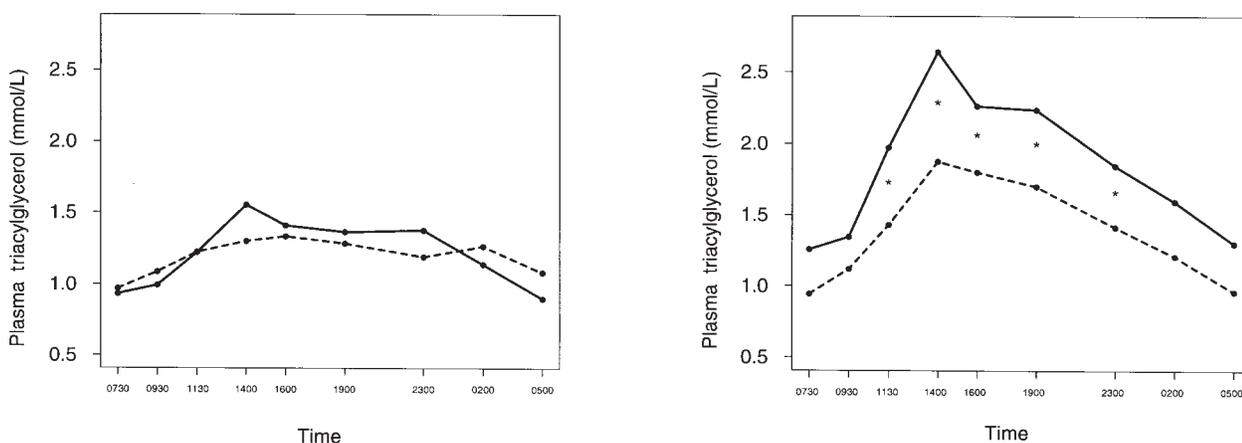

FIGURE 1. Mean plasma triacylglycerol concentrations in women (left) and men (right) during the 24-h metabolic profiles on day 42 of the fructose diet (——) and the glucose diet (----). *Significant difference between the 2 points, $P < 0.006$ (0.05/9; Bonferroni adjustment for multiple comparisons). To convert to mg/dL, multiply by 88.5.

TABLE 4
Daylong values for plasma triacylglycerols, plasma glucose, and serum insulin on day 42 of each of the study diets[1]

	Fructose diet	Glucose diet	P
Plasma triacylglycerols (mmol·h/L)[2]			
Women	30.8	29.9	0.722
Men	46.1	35.0	<0.001
Plasma glucose (mmol·h/L)[3]	139	141	0.446
Serum insulin (pmol·h/L)[4]	3486	4243	0.011

[1] Estimated by determining the area under the curves created by connecting the 9 observations for each variable during the 24-h metabolic profiles on day 42 of each of the study diets. The means for each endpoint have a common SE based on the appropriate repeated-measures ANOVA error term.
[2] SE = 1.7.
[3] SE = 1.6.
[4] SE = 194.

glucose diet. Age or sex did not significantly influence the responses of plasma glucose or serum insulin to the study diets.

DISCUSSION

The objective of our study was to determine whether the fructose content of the American diet produced adverse effects on fasting or postprandial plasma lipids. The reference diet was sweetened with glucose and contained only the fructose that occurs naturally in fruit and vegetables. The fructose study diet provided 17% of energy as fructose, whereas the reference glucose diet provided only 3% of energy as fructose. Although the fructose diet contained nearly twice as much fructose as does the typical American diet (3), Americans at or above the 90th percentile of fructose intake ($\approx$27 000 000 people) probably consume at least this much fructose (4).

Several previous studies showed no adverse effects of dietary fructose on plasma lipids (11–18). However, all of these studies either compared fructose with sucrose (11,12,16) or were outpatient studies that provided subjects with menus or nutrient supplements and not actual meals (13–15, 17, 18). Because sucrose is composed of a fructose and a glucose molecule linked together and is thus 50% fructose, it is not an optimal reference. Similarly, provision of menus and supplements is not optimal

because these do not establish rigorous control of nutrient intake. Such control can be accomplished only by providing subjects with all study meals.

Studies that compared a fructose diet with a diet nearly devoid of fructose and that also attempted to establish rigorous control of nutrient intake by providing all food to the subjects showed consistently that fructose adversely affected plasma lipids (19–23). Consistent with this, we found that a high-fructose diet increased plasma triacylglycerols in men. This was true for both younger and older men. The fructose diet produced significantly higher fasting plasma triacylglycerol values than did the glucose diet in men on days 7, 28, and 42. Moreover, postprandial plasma triacylglycerols were higher at multiple time points on day 42 of the fructose diet than on day 42 of the glucose diet. Daylong plasma triacylglycerols on day 42 were 32% higher in men during the fructose diet than during the glucose diet. No similar effect of fructose was seen in women. The reason for the difference between men and women was not clear, but men were shown previously to have an exaggerated postprandial triacylglycerol response compared with women (34).

We also found that fasting plasma cholesterol and LDL cholesterol on day 28 were significantly higher during the fructose than during the glucose diet. This was true for both calculated and measured plasma LDL cholesterol. However, these differences did not persist at later times, suggesting that the effect of dietary fructose on fasting plasma cholesterol and LDL cholesterol was transient. Nevertheless, we cannot exclude the possibility that fructose has adverse effects on fasting plasma cholesterol, which our study did not have the power to detect.

During the metabolic profiles on day 42, both plasma glucose and serum insulin after breakfast were lower during the fructose than during the glucose diet. In addition, daylong serum insulin was lower during the fructose diet than during the glucose diet. Reduced postprandial plasma glucose and serum insulin responses to dietary fructose were reported previously (35–37). However, the significance of these effects for healthy populations is unknown.

Our results are consistent with those of MacDonald (19), Reiser et al (20), and Hallfrisch et al (22), who found that consumption of high-fructose diets was associated with an increase in fasting plasma triacylglycerols in men. Moreover, our data show that the effect of dietary fructose on plasma triacylglycerols
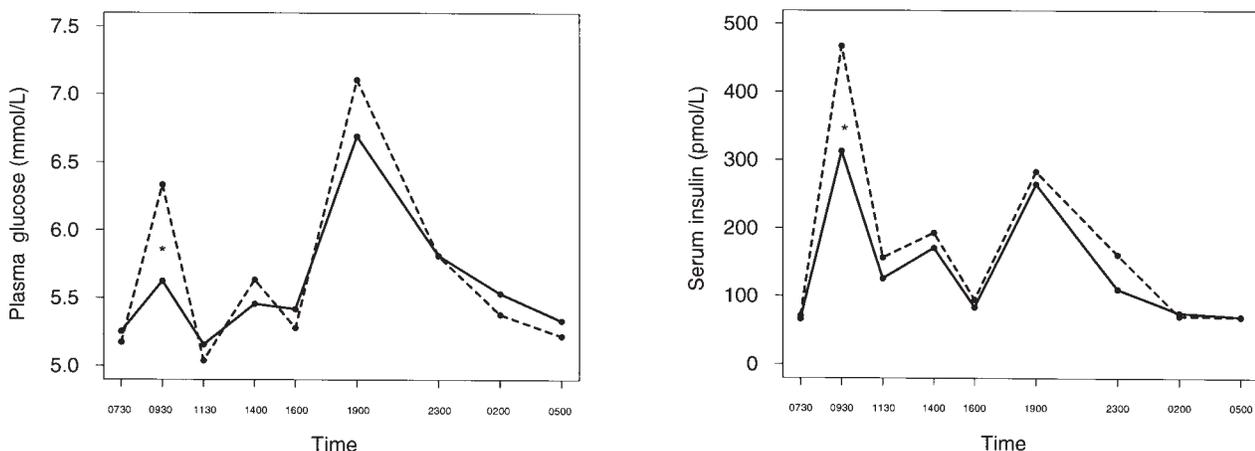

FIGURE 2. Mean plasma glucose (left) and serum insulin (right) concentrations in all subjects during the 24-h metabolic profiles on day 42 of the fructose diet (——) and the glucose diet (----). *Significant difference between the 2 points, *P* < 0.006 (0.05/9; Bonferroni adjustment for multiple comparisons). To convert to mg/dL, multiply by 18.0.

in men was greater in the postprandial than in the fasting state. It was shown previously that the addition of fructose to a fat-containing meal increased postprandial lipemia more so than did glucose (38). Our data suggest that this effect of fructose persists after 6 wk of fructose feeding. The mechanism of the fructose-induced increase in triacylglycerols is uncertain, but the increase may be due to stimulation of triacylglycerol synthesis (39, 40).

The importance of a fructose-induced increase in fasting and postprandial triacylglycerols is uncertain. The National Institutes of Health Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease concluded in 1993 that the evidence for a causal relation between triacylglycerols and coronary artery disease was incomplete (41). However, an increasing body of evidence implicates fasting (42) and postprandial (26–30) plasma triacylglycerols in the pathogenesis of atherosclerosis. Moreover, a recent meta-analysis concluded that plasma triacylglycerols were an independent risk factor for cardiovascular disease (43).

It is not certain whether therapies that lower triacylglycerols reduce cardiovascular risk. However, a recent clinical trial of benzafibrate showed slowing of the progression of focal coronary atherosclerosis in association with a 31% reduction in serum triacylglycerols and no significant change in serum LDL cholesterol (44). Consistent with this, data from the Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial showed that treatment of men with coronary heart disease and low HDL cholesterol with gemfibrozil increased HDL cholesterol, lowered triacylglycerols, and reduced the risk of myocardial infarction without lowering LDL cholesterol (45).

If plasma triacylglycerols are a risk factor for cardiovascular disease, then diets high in fructose may be undesirable, particularly for men. Because the naturally occurring fructose in fruit and vegetables provides only a modest amount of dietary fructose, efforts to reduce fructose intake should focus on reducing the amount of fructose added to beverages and foods in the American diet. A reduction in added fructose would be facilitated by an acceptable replacement sugar. Such a sugar might be glucose.

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