Persistence of Hypertriglyceridemic Effect of Low-Fat High-Carbohydrate Diets in NIDDM Patients

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Although low-fat high-carbohydrate diets are recommended for patients with non-insulin-dependent diabetes mellitus (NIDDM) in an effort to reduce the risk of coronary artery disease (CAD), the results of short-term studies have shown that these diets can lead to changes in carbohydrate and lipid metabolism associated with an increased risk of CAD. This study has extended these earlier observations by determining the metabolic effects of such diets over a longer period in these patients. The comparison diets contained either 40 or 60% of the total calories as carbohydrates, with reciprocal changes in fat content from 40 to 20% consumed in random order for 6 wk in a crossover experimental design. The ratio of polyunsaturated to saturated fat and the total cholesterol intake were held constant in the two diets. Plasma glucose and insulin concentrations were significantly ($P < .001$) elevated throughout the day when patients consumed the 60% carbohydrate diet, and 24-h urinary glucose excretion more than doubled (0.8 vs. 1.8 mol/24 h). Fasting plasma total and very-low-density lipoprotein (VLDL) triglyceride (TG) concentrations increased by 30% ($P < .001$) after 1 wk on the 60% carbohydrate diet, and the magnitude of carbohydrate-induced hypertriglyceridemia persisted unchanged throughout the 6-wk study period. Total plasma cholesterol concentrations were similar after both diets. However, VLDL cholesterol (VLDL-chol) was significantly increased, whereas both low-density lipoprotein (LDL-) and high-density lipoprotein (HDL-) chol concentrations were significantly decreased after consumption of the 60% carbohydrate diet. Consequently, neither total-chol–to–HDL-chol nor LDL-chol–to–HDL-chol ratios changed. The results of this study indicate that high-carbohydrate diets lead to several changes in carbohydrate and lipid metabolism in patients with NIDDM that could lead to an increased risk of CAD, and these effects persist for ≥6 wk. Given these results, it seems reasonable to suggest that the routine recommendation of low-fat high-carbohydrate diets for patients with NIDDM be reconsidered.
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We have recently demonstrated that plasma glucose and triglyceride (TG) concentrations increase and plasma high-density lipoprotein cholesterol (HDL-chol) concentrations decrease when patients with non-insulin-dependent diabetes mellitus (NIDDM) consume low-fat high-carbohydrate diets (1). Because these three changes appear to increase the risk of coronary artery disease (CAD) in patients with NIDDM (2–5), we are concerned that these diets continue to be recommended in an effort to reduce the risk of CAD in these individuals (6). Although the reasons for advocating this type of diet are numerous, one commonly held belief is that the metabolic changes noted to occur in response to a low-fat high-carbohydrate diet, particularly hypertriglyceridemia, are transitory and will recede with time, although not all researchers agree (7–9). Because transitory hypertriglyceridemia has never been shown to occur in patients with NIDDM, we thought it reasonable to pursue this issue by extending the length of this study aimed at defining the effects of low-fat high-carbohydrate diets

Glucose	1 mM = 18 mg/dl	Triglyceride	1 mM = 128 mg/dl
Cholesterol	1 mM = 38.7 mg/dl		

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TABLE 1
Clinical characteristics

Subject	Sex	Age (yr)	BMI (kg/m²)	Glucose (mM)	Cholesterol (mM)	Triglyceride (mM)	Medication
1	M	70	25.8	8.3	5.3	2.3	Glyburide
2	M	73	24.8	9.8	5.7	2.8	None
3	M	50	30.0	12.7	4.4	3.4	Glyburide
4	F	58	27.5	13.0	5.2	1.5	Tolazamide
5	F	71	24.5	7.9	9.0	2.8	Glipizide
6	F	69	23.3	6.3	6.6	1.2	None
7	M	73	22.5	10.1	4.9	1.6	Glipizide
8	M	60	25.6	15.5	5.9	1.8	Chlorpropamide
Means ± SE	5/3	66 ± 3	25.5 ± 0.8	10.5 ± 1.1	5.88 ± 0.50	2.18 ± 0.27	

on carbohydrate and lipid metabolism in patients with NIDDM.

MATERIALS AND METHODS

Subjects. Eight volunteers (3 women, 5 men) who satisfied the criteria for NIDDM (10) were recruited for this study. With the exception of diabetes, all subjects were in good health and not taking any medication, other than sulfonylureas, known to alter glucose, insulin, or lipid metabolism. The clinical characteristics of these patients are presented in Table 1. Patients ranged in age from 50 to 73 yr with a mean ± SE of 66 ± 3 yr. Mean ± SE body mass index (BMI) was 25.5 ± 0.8 kg/m², with a range of 22.5–30.0 kg/m². At entry into the study, the mean ± SE fasting plasma glucose was 10.5 ± 1 mM, plasma TG concentration was 2.18 ± 0.27 mM, and cholesterol was 5.88 ± 0.50 mM. Medical therapy was not altered during the study period.

Experimental design. The study was conducted in a crossover design with two 6-wk dietary periods randomly assigned. All patients completed 42 days on each of the study diets. Informed consent, as approved by the Human Subjects Committee of Stanford University, was obtained from each subject on admission to the General Clinical Research Center (GCRC). Subjects reported daily for their meals and continued their usual level of physical activity. Body weight was maintained within 0.5 kg of admission weight throughout the study.

Diets. All food consumed by the subjects during the 84-day period was provided by the GCRC kitchen. Diets containing (as percent of total calories) 40 and 60% carbohydrate were compared (Table 2). The protein content of the diets was held constant at 20%, and total fat intake varied reciprocally with the carbohydrate from 40 to 20% of total calories. The diets were designed to include no added sucrose, however, the amount of sucrose (5% for the 40% carbohydrate diet and 8% for the 60% carbohydrate diet) was accounted for by the sucrose present in the fruits, vegetables, breads, and cereals selected for the menus. Table 3 describes the meals from one day of a 3-day menu cycle.

Total daily calorie intake was calculated for each subject to achieve weight maintenance. The calories were divided into three meals and afternoon and evening snacks. Twenty percent of the daily calorie requirement was consumed at 0800 and 40% at 1200 and 1700, including the afternoon and evening snacks, respectively.

Biochemical analyses. Fasting glucose samples were obtained weekly during each 6-wk diet phase for the measurement of glucose, insulin, TG, and cholesterol concentrations (11–14). Fasting and postprandial plasma samples were obtained on days 41 and 42 of each diet period at hourly intervals from 0800 to 1600 for determination of glucose and insulin concentrations. Fasting plasma samples from days 41 and 42 were subjected to sequential density ultracentrifugation (15) to isolate very-low-density (VLDL), low-density (LDL), and high-density (HDL) lipoprotein fractions for cholesterol and TG determinations. In addition, 24-h urine collection on day 41 was analyzed for total glucose excretion. The data from the 2 days were averaged for each study phase.

Statistical analysis. The results are expressed as means ± SE. Student's paired *t* test was used to assess statistical significance of the fasting data between the two dietary periods. Postprandial differences were assessed by two-way analysis of variance (16). Wilcoxon's signed-rank test was used to assess statistical difference in urinary glucose excretion.

TABLE 2
Composition of test diets per 1000 kcal

	Carbohydrate diet	
	40%	60%
Carbohydrate (g)	100	150
Sucrose (g)	11.5	19.3
Dietary fiber (g)	14.3	18.1
Protein (g)	50	50
Fat (g)	44.5	22.2
Polyunsaturated-to-saturated ratio	1.0	1.1
Cholesterol (mg)	115	120

Calculations based on U.S. Dept. Agric. handbook, no. 456, p. 8-1–8-11, Washington, DC, Agriculture Research Service, U.S. Govt. Printing Office. Data for sucrose and dietary fiber from USDA preliminary data, 1985.

TABLE 3
Itemized composition of diets per 2000 kcal for typical meal

Carbohydrate diets			
40%		60%	
Food items	Weight (g)	Food items	Weight (g)
Breakfast			
Cornflakes	20.0	Cornflakes	25.0
Nonfat milk	168.6	Low fat milk, 2% fat	127.0
Cheddar cheese	40.0	Cottage cheese, 2% fat	67.7
Whole wheat bread	18.0	Whole wheat bread	25.0
Orange sections	44.9	Orange juice	159.5
Margarine	4.0	Margarine	5.0
Lunch			
Tuna fish, water packed	80.0	Tuna fish, water packed	71.3
Mayonnaise	32.5	Mayonnaise	9.8
Whole wheat bread	65.0	Whole wheat bread	70.0
Lettuce	13.3	Lettuce	15.0
Lowfat milk, 2% fat	120.0	Nonfat milk	179.3
Banana with skin	152.8	Banana with skin	230.2
Snack (afternoon)			
Raisins	16.5	Raisins	27.5
Peanuts	12.8	Plain muffin*	40.0
Dinner			
Sirloin steak	80.0	Sirloin steak	58.0
Baked potato (raw wt)	140.0	Baked potato (raw wt)	203.8
Carrots, cooked	61.3	Carrots, cooked	120.0
Lettuce	40.0	Lettuce	40.0
Tomato, raw	40.0	Tomato, raw	40.0
Canned pears, water packed	70.0	Canned pears, water packed	150.0
Dinner roll	30.0	Dinner roll	45.0
Oil	8.5	Oil	3.4
Margarine	16.4	Egg nog*	39.7
Snack (evening)			
Bran muffin*	17.0	Bran muffin*	55.0
Lowfat milk, 2% fat	100.0	Nonfat milk	120.0

*Special recipe.

RESULTS

Mean plasma glucose and insulin concentrations from 0800 to 1600 in response to the two diets are shown in Fig. 1. Plasma glucose concentrations were higher throughout the day when patients ate the 60% carbohydrate diet and this day-long difference was statistically significant ($P < .001$). The data on the right graph show that the insulin response from 0800 to 1600 was also significantly greater on the 60% carbohydrate diet ($P < .001$). Further evidence that glycemic control deteriorated in the low-fat high-carbohydrate diet is shown in Fig. 2, where 24-h urinary glucose excretion was significantly greater in response to the 60% carbohydrate diet.

Mean fasting plasma TG and VLDL TG concentrations after 6 wk on both diets are shown in Fig. 3. These results demonstrate that both total and VLDL TG concentrations were higher when patients consumed the low-fat high-carbohydrate diet ($P < .001$).

To evaluate the time-related effect of dietary carbohydrate on plasma TG concentration, fasting plasma TG concentrations at weekly intervals are shown in Fig. 4. These results show that plasma TG concentrations were 30% higher after 1 wk of the 60% carbohydrate diet, and the magnitude of the carbohydrate-induced increase in plasma TG concentrations continued unchanged throughout the 6-wk study period.

The effect of variations in dietary carbohydrate on plasma cholesterol concentrations is shown in Fig. 5. Although total plasma cholesterol was similar in both diets, significant differences did occur in the cholesterol concentrations of the various lipoprotein fractions. Specifically, the plasma VLDL-chol concentration increased ($P < .05$) and plasma LDL-chol ($P < .05$) and HDL-chol ($P < .001$) decreased when patients with NIDDM consumed a 60% carbohydrate as compared with the 40% carbohydrate diet.

DISCUSSION

The results presented in this study support our earlier findings that increasing dietary carbohydrate from 40 to 60% in patients with NIDDM will result in a significant elevation of plasma TG concentration (1). More important, it is apparent from Fig. 4 that fasting plasma TG concentrations are 30% higher 1 wk after the initiation of the low-fat high-carbohydrate diet. This increment remained essentially constant throughout the remainder of the 6-wk period when patients with NIDDM consumed the 60% carbohydrate diet. It is apparent that 6 wk is not a lifetime, and it is possible that the increase in plasma TG concentration in response to the 60% carbohydrate diet would eventually disappear. On the other hand, the absence of a tendency for plasma TG levels to fall over the 6-wk low-fat high-carbohydrate dietary period suggests that the burden of proof be shifted somewhat, and future advocacy of low-fat high-carbohydrate diets should require documentation that the increase in risk factors for CAD associated with this approach be shown to disappear with time.

Although the major reason for undertaking this study was to define the effect of time on carbohydrate-induced hypertriglyceridemia in patients with NIDDM, it would be inappropriate not to discuss the other deleterious metabolic effects associated with the 60% carbohydrate diet. For example, it is apparent from Fig. 1 that ambient plasma glucose concentration was higher from 0800 to 1600 when patients consumed the 60% carbohydrate diet, and the observation that 24-h urine glucose excre-

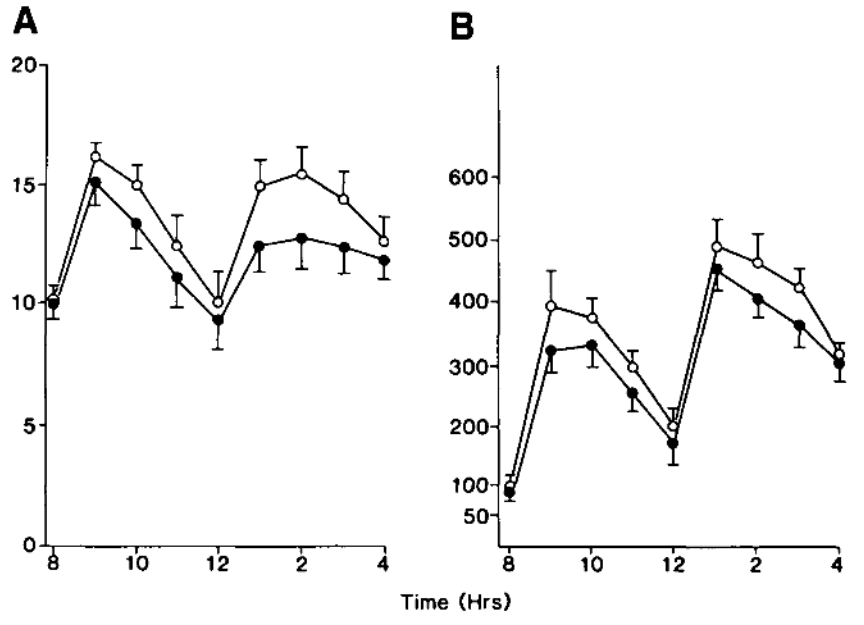

FIG. 1. Mean ± SE fasting and postprandial plasma glucose (mM, *A*) and insulin (pM, *B*) concentrations after 6 wk of diets containing either 40% (●) or 60% (○) of total calories as carbohydrate. Meals were eaten at 0800 and 1200.

tion more than doubled on the low-fat high-carbohydrate diet provides further evidence that glycemic control deteriorates in response to this dietary manipulation. Whether or not hyperglycemia increases the risk of CAD is still not clear (2,4,17), but there is certainly evidence that it plays a role in the development of microangiopathy (18). The view that hyperinsulinemia may be a risk factor for CAD in nondiabetic individuals has recently received support (17,19), and the fact that plasma insulin levels were higher in the low-fat high-carbohydrate diet must also be considered.

In contrast with the several deleterious metabolic changes noted to occur in response to the 60% carbohydrate diet, the only effect that might be viewed as beneficial was the fall in plasma LDL-chol concentration. However, this was associated with an increase in VLDL-chol concentration and a decrease in HDL-chol concentration, which is associated with an increased risk of CAD. Given the disparate effects of the low-fat high-carbohydrate diet on cholesterol metabolism, it is difficult to decide if the overall impact would increase

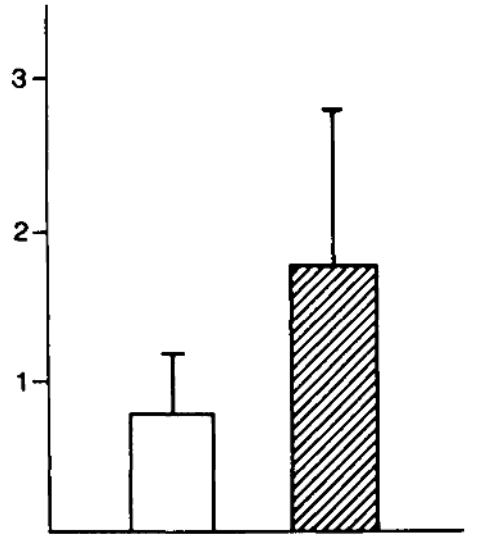

FIG. 2. Mean ± SE 24-h urinary glucose excretion (mM) after 6 wk of diets containing either 40% (*open bar*) or 60% (*hatched bar*) of total calories as carbohydrate. $P < .05$.

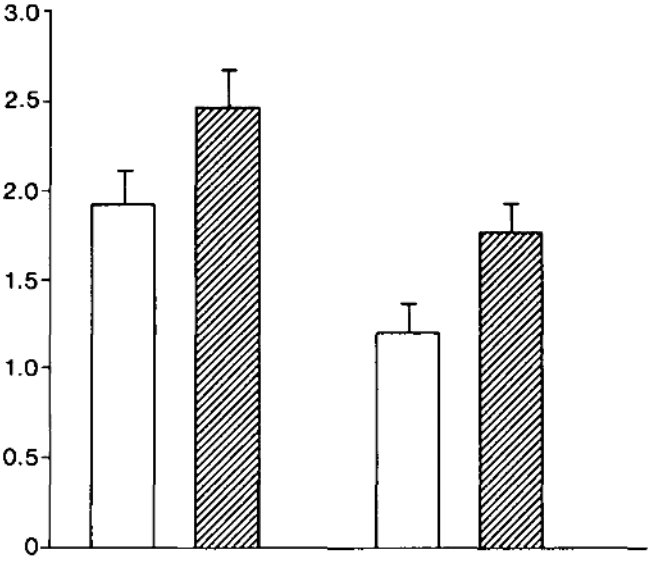

FIG. 3. Mean ± SE fasting plasma and very-low-density lipoprotein triglyceride concentrations (mM) after 6 wk of diets containing either 40% (*open bars*) or 60% (*hatched bars*) of total calories as carbohydrate. $P < .001$.

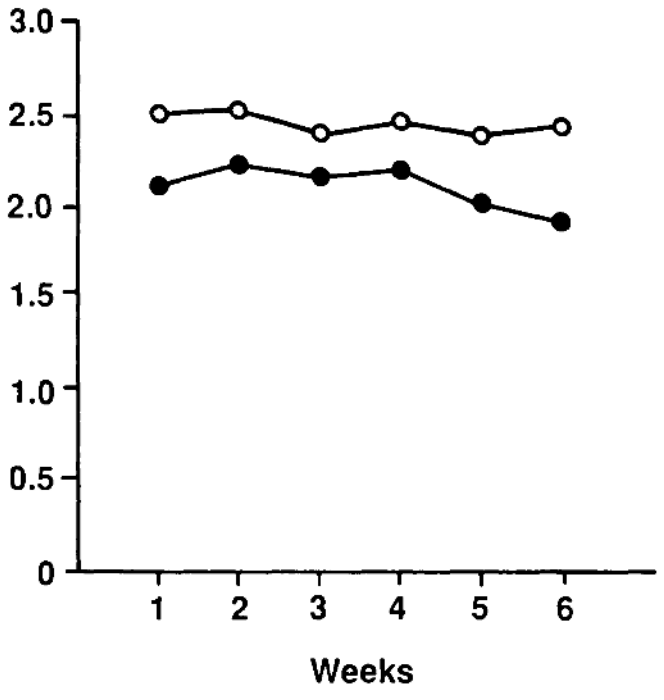

FIG. 4. Mean weekly fasting plasma triglyceride concentrations (mM) after diets containing either 40% (●) or 60% (○) of total calories as carbohydrate.

or decrease the risk of CAD. The use of several ratios has been suggested as an approach to quantify the atherogenic risk of plasma cholesterol concentration, i.e., total chol to HDL-chol, LDL-chol to HDL-chol, or VLDL- plus LDL-chol to HDL-chol. The effects of the two diets used in this study on these ratios are listed in Table 4, and it is apparent that none of the changes were significantly different between the two diets. In other words, the beneficial effects to be derived from lipoprotein cholesterol concentrations, for which high-carbohdyrate diets are recommended, were not observed in this study.

Given these findings, it is necessary to ask why low-fat high-carbohydrate diets are recommended for patients with NIDDM. The theoretical justification for the use of similar diets in the population at large is that they will lead to a fall in plasma LDL-chol concentration and thereby reduce the risk of CAD (20). It is not immediately apparent that this strategy is appropriate for patients with NIDDM. The characteristic defects in lipoprotein metabolism in patients with NIDDM are an increase in plasma VLDL TG concentration and a decrease in plasma HDL-chol concentration (21–24), and both of these changes have been shown to be associated with an increased risk of CAD (3,4,25,26). In contrast, plasma LDL-chol concentrations in patients with NIDDM do not appear to be different from values in the general public (27), and we are unaware of any studies in patients with NIDDM that document any relationship between CAD and plasma LDL-chol. Therefore, it is reasonable to question a dietary strategy that is focused on modulation of plasma LDL-chol concentration in patients with NIDDM and ignores the defects in carbohydrate and lipid metabolism that have been shown to be associated with CAD in these patients.

From another viewpoint, evidence has been published that shows that low-fat high-carbohydrate diets may actually be clinically beneficial (28–32). However, when these reports are examined closely this interpretation can be questioned. For example, Brunzell et al. (28) reported that increasing dietary carbohydrates from 45 to 85% of total calories led to an 8% improvement in response to an oral glucose tolerance test in normal subjects and patients with impaired glucose tolerance. However, these authors did not provide any information concerning either the ambient plasma glucose and insulin levels in these subjects when they were actually consuming the diet containing 85% carbohydrate, or the effects of the high-carbohydrate diet on plasma lipid and lipoprotein concentrations. However, research from our laboratory (1,33–36) on a similar patient population, and with a less dramatic increment in dietary carbohydrate, demonstrates the presence of day-long hy-

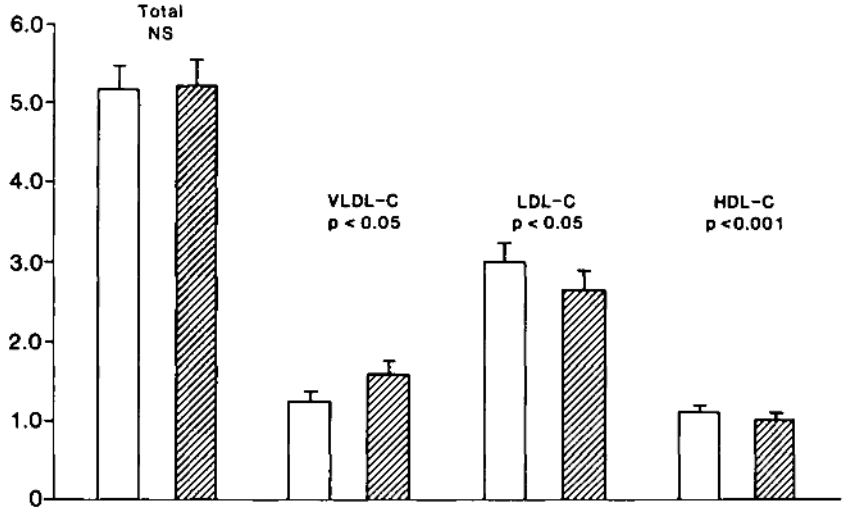

FIG. 5. Mean ± SE fasting plasma total and lipoprotein cholesterol concentrations (mM) after 6 wk of diets containing either 40% (*open bars*) or 60% (*hatched bars*) of total calories as carbohydrate.

TABLE 4
Plasma lipoprotein cholesterol ratios

	Dietary carbohydrate content	
	40%	60%
Total-chol to HDL-chol	4.87 ± 0.52	5.17 ± 0.44
LDL-chol to HDL-chol	2.78 ± 0.36	2.62 ± 0.28
LDL + VLDL-chol to HDL-chol	3.87 ± 0.55	4.18 ± 0.44

P values not significant.

perglycemia and hyperinsulinemia, increased plasma TG concentration, and decreased plasma HDL-chol concentration. More relevant to the issue of low-fat high-carbohydrate diets in the treatment of NIDDM are the findings from the group at Oxford (31,32), which demonstrate that low-fat high-carbohydrate diets lead to a reduction in both plasma glucose and LDL-chol levels in patients with NIDDM. However, the low-fat high-carbohydrate diets used in these studies were enriched to an enormous degree in dietary fiber content, particularly leguminous fiber. For example, in one study 42% of total calories was in the form of legumes, and only 18% of total calories was allocated to foods other than legumes, margarine, whole-meal bread, and skimmed milk (32). In reality, these diets were essentially vegetarian in nature. It would not be unreasonable to suggest that the majority of people in our society would find it difficult to follow such a strict dietary regimen. In fact, patients receiving the high-legume diets in one study were unable to consume these diets for the 1–2 days they were fed in a metabolic unit (31). When more conventional low-fat high-carbohydrate diets were used, there was no improvement in plasma glucose or LDL-chol levels, VLDL TG levels increased, and HDL-chol concentrations fell (30). In addition, it should be emphasized that total cholesterol intake was reduced and the ratio of polyunsaturated to saturated fat increased during the high-carbohydrate phase in these previous studies. Because these alterations could account for the beneficial lowering of total and LDL-chol concentrations, it is difficult to attribute these changes simply to the effects of the increased carbohydrate content of the diets. Indeed, the only study which controls for these latter variables, as well as employing relatively conventional diets, is that of Weinsier et al. (29). These authors noted that increasing dietary carbohydrate from ~40 to 55% did not lead to deterioration in diabetes control in a 20-wk outpatient study. Furthermore, there was no change in plasma TG or cholesterol concentration. The only obvious difference between this study and ours is that we provided all the meals, whereas they simply provided dietary prescriptions. Whether this explains why we did and they did not see any deleterious metabolic effects from increased dietary carbohydrate consumption can only be speculated. In either case, it is apparent that the results from this study do not suggest that decreasing fat and increasing carbohydrate was of any clinical benefit to patients with NIDDM. Their findings must be put into perspective regarding our demonstration in several patient populations that low-fat high-carbohydrate diets can have a deleterious metabolic impact (1,34–37). Until this issue is resolved, we suggest that the recommendation of such diets in the treatment of NIDDM be avoided.

Finally, certain points must be addressed. The mean fasting plasma glucose concentration of the study population was ~10 mM; therefore, it could be argued that the results would have been different if they were in better glycemic control. However, the relationship between glycemic control and plasma lipid levels is far from simple, and this point is clearly evident from inspection of Table 1. For example, patients 1 and 9 had relatively low fasting plasma glucose concentrations and relatively high plasma TG concentrations. Conversely, patients 4 and 8 had elevated fasting glucose concentrations in association with relatively normal TG concentrations. On the other hand, we cannot predict what the effects of the low-fat high-carbohydrate diet would have been if excellent metabolic control with insulin had been achieved. However, we are not aware of any research that low-fat high-carbohydrate diets only be initiated in patients with NIDDM who are in excellent glycemic control. Because the range of fasting glucose concentrations seen in the study population seems to be typical of the average clinic population of patients with NIDDM, the results are likely to be indicative of individuals who followed the advice to reduce fat and increase carbohydrate intake.

It is also important to emphasize that because the majority of patients with NIDDM are overweight, the mainstay of a diabetic diet should be to reduce total calories in all patients who need to lose weight. However, not all patients with NIDDM are overweight. For example, the mean BMI of the study population was 25.5 kg/m^2, and only two patients had a BMI >26.0 kg/m^2. Thus, obesity was not a major issue in this particular group of patients with NIDDM. What effect low-fat high-carbohydrate diets would have on a group of heavier patients with NIDDM, or what would happen if obese patients were advised to follow a diet that was both hypocaloric and low in fat and high in carbohydrate, remains to be determined.

In conclusion, it is apparent that isocaloric diets that are relatively low in fat and high in carbohydrate accentuate the abnormalities in glucose, insulin, VLDL, and HDL metabolism that are present in NIDDM. Because these results were observed in a population typical of those with NIDDM seen in most clinics, it seems reasonable to suggest that it is time to reappraise the clinical benefit of low-fat high-carbohydrate diets in these patients. This is not meant to question the aim of reducing saturated fat and cholesterol intake in patients with NIDDM but rather to indicate that this goal can be accomplished without drastic reductions in total fat intake and reciprocal increases in carbohydrate consumption by simply substituting polyunsaturated and

monounsaturated fat for saturated fat. For example, this can be accomplished in a diet containing 40% of total calories as fat by providing ~33% of fat calories each from monounsaturated, polyunsaturated, and saturated fat, respectively. Although this provides slightly more than the 10% of total calories recommended by the American Diabetes Association (6), we doubt that this difference would have clinical significance. We believe that the results no longer permit us to dismiss the deleterious metabolic effects of low-fat high-carbohydrate diets as purely transitory events in patients with NIDDM and require that dietary regimens that address the defects in carbohydrate and lipid metabolism that exist in these patients be evaluated.

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