Short-Term Effects of Alterations in Dietary Fat on Metabolic Control in IDDM

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OBJECTIVE — Two experimental diets were evaluated to investigate the hypothesis that dietary fat has an independent influence on metabolic control in IDDM.

RESEARCH DESIGN AND METHODS — The diets had similar CHO contents (26 and 22% of energy intake) but differed markedly in fat (53 vs. 16% energy) and protein (20 vs. 62% energy). We had 10 subjects follow the low-CHO, high-fat diet, and 8 subjects follow the low-CHO, low-fat, high-protein diet. In each case, markers of glycemic and lipid control obtained after adherence to the experimental diet for 2 wk were compared with corresponding data from a preceding control period during which subjects had followed their usual diet (protein 18–19%, CHO 41–46%, fat 33–37%).

RESULTS — Despite the low CHO content of the high-fat diet, insulin requirements were unchanged relative to the control diet. Moreover, the glycemic response to a standard breakfast was elevated significantly ($P < 0.001$), suggesting that insulin resistance had either been induced or exacerbated. The small rise in total cholesterol concentration in response to the high-fat diet was accounted for by a rise in HDL cholesterol. Glycemic control and lipid metabolism were unchanged after the low-CHO, low-fat diet, although insulin requirements fell by an average of 6 U/day ($P < 0.05$) relative to those recorded during the 2-wk control period.

CONCLUSIONS — Diets high in fat are deleterious to glycemic control in IDDM, but general applicability is limited by the small sample size and short duration of this study.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; HDL, HIGH-DENSITY LIPOPROTEIN; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; CHO, CARBOHYDRATE; BMI, BODY MASS INDEX; SMBG, SELF-MONITORING OF BLOOD GLUCOSE; FFA, FREE FATTY ACID; LDL, LOW-DENSITY LIPOPROTEIN; CI, CONFIDENCE INTERVAL.

A key objective in the management of IDDM is avoidance of hyperglycemia. Individual insulin regimens are designed to suppress acute postprandial hyperglycemia and chronic elevations of blood glucose resulting from unsuppressed endogenous glucose production. The risk of hyperglycemia and/or hypoglycemia associated with exogenous insulin therapy has ensured that the focus of dietary instruction for IDDM has been on dietary CHO and its regular distribution throughout the day (1). Notwithstanding the importance of CHO restriction in reducing postprandial excursions, little data are available relating to its effect on glycemic control in the fasting state. Recent data from this laboratory (2) in NIDDM show deterioration in metabolic control on a low-CHO, high-fat diet, but improved metabolic control on both a low-CHO, low-fat and a high-CHO, low-fat diet suggests that it is the fat, rather than the CHO, content of the diet that might be critical in determining long-term glycemic control in diabetes. The aim of this study was to determine whether IDDM has a similar metabolic response to NIDDM when following two low-CHO diets that differ in fat content.

RESEARCH DESIGN AND METHODS

— Thirteen patients (8 women, 5 men, age 30.3 ± 1.6 yr, BMI 23.1 ± 0.6) were recruited from the outpatient clinic of the Royal Melbourne Hospital. The protocol had been approved by the Hospital's Ethics Committee, and all subjects gave their voluntary written consent before participation. All subjects met the composite clinical criteria of IDDM, namely, being ≤40 yr of age and being <120% of desirable body weight at the time of diagnosis, and having been placed on insulin therapy within 2 yr of diagnosis (3).

Five subjects took part in both of the experiments described, another 5 followed the high-fat diet only, and the remaining 3 followed the low-fat, low-CHO diet only (Table 1). All subjects followed conventional twice-daily insu-

Table 1—*Characteristics of subjects*

Subjects, by diet and sex	Age (yr)	BMI (kg/m^2)	Duration of IDDM (yr)	Insulin (U/day)	Sequence of diets	
					High fat	Low fat
Both diets						
W	31	25.7	21	38	1st	2nd
M	26	21.8	4	46	1st	2nd
W	26	24.6	22	47	2nd	1st
M	36	22.2	2	22	2nd	1st
W	38	18.3	35	44	2nd	1st
Mean ± SE	31.4 ± 2.5	22.5 ± 1.3	16.8 ± 6.2	39.4 ± 4.6		
High-fat diet only						
M	28	22.6	17	40	1st	—
M	23	20.6	11	52	1st	—
W	25	24.9	16	45	1st	—
M	26	24.0	3	42	1st	—
W	27	23.2	15	54	1st	—
Mean ± SE	25.8 ± 0.9	23.1 ± 0.7	12.4 ± 2.6*	46.6 ± 2.8		
Low-fat diet only						
W	43	26.4	28	44	—	1st
W	34	22.0	24	33	—	1st
W	31	23.4	19	40	—	1st
Mean ± SE	36.0 ± 3.6	23.9 ± 1.3	23.7 ± 2.6	39.0 ± 3.2		

*$P < 0.05$ unpaired Student's t test between the subjects completing the high-fat and low-fat diets. All other tests were NS.

lin regimens with a mean dose of 42 U/day. All subjects practiced SMBG, usually performing ~10 tests/wk. SMBG was used for the purpose of self monitoring only.

All subjects had received previous dietary instruction with the emphasis on regularity in the timing of 3 main meals with small intervening snacks to balance the action of insulin on blood glucose levels. All avoided sucrose, and most had been attempting to increase their intake of complex CHO and dietary fiber. They were advised to continue with their present diet throughout the course of the study, only altering their eating pattern during the experimental diet periods.

The detailed composition of the baseline diets and the two experimental diets is given in Table 2. For both experimental diets, the change in composition of the diet was compared with the self-selected (control) diet consumed in the 2-wk period before commencing the 2-wk experimental diet.

The two experimental diets were

Table 2—*Nutrient composition of the diets obtained from weighed food records and calculated using the Microdiet software package*

	Energy (kcal/day)	Protein (% energy)	CHO (% energy)	Dietary fiber (g/day)	Fat (% energy)	P:S ratio	Cholesterol (mg/day)
High-fat experiment							
Control	1883 ± 153	19.3 ± 1.1	41.1 ± 1.1	23.4 ± 2.2	37.4 ± 1.5	0.35 ± 0.04	247 ± 17
High fat, low CHO (N = 10)	1887 ± 139	20.3 ± 1.0	26.2 ± 1.5	17.1 ± 1.6	53.1 ± 1.3	0.29 ± 0.03	470 ± 42
	NS	NS	$P < 0.001$	$P < 0.05$	$P < 0.001$	NS	$P < 0.001$
Low-fat experiment							
Control	1627 ± 126	18.9 ± 0.9	46.3 ± 1.4	20.4 ± 2.2	33.2 ± 1.6	0.36 ± 0.04	208 ± 24
Low fat, low CHO (N = 8)	1617 ± 109	61.9 ± 1.2	21.6 ± 1.6	12.9 ± 1.5	15.7 ± 0.8	0.47 ± 0.03	578 ± 64
	NS	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P < 0.001$	$P < 0.05$	$P < 0.001$

Values are mean daily intake ± SE. The significant differences in CHO, fat, and protein content were intended. Accompanying changes in dietary fiber, cholesterol, and P:S ratio (ratio of polyunsaturated to saturated fatty acids) were unavoidable consequences of the planned modifications. The Composition of Foods, Paul AA and Southgate DAT (4–6).

designed to be low in CHO: one was high in fat, the other was low in fat and high in protein. Food was not supplied during the control periods nor during the high-fat diet. All major meals were supplied during the low-fat diet to facilitate compliance with what was a very different diet for the subjects. All food and liquid intake was weighed and recorded throughout both study periods. The composition of the diets was determined using the MICRODIET software package based on *McCance and Widdowson's The Composition of Foods* (4). The composition of local foods not included in the database was added and used in the calculation of dietary composition (5).

In both experimental diets, breads and cereals were restricted to 100 g/day, nonstarchy vegetables were eaten as desired, but starchy vegetables and fruits were restricted severely. The high-fat diet was achieved by using full-cream milk and yogurt (restricted to a combined total of 500 ml/day), eggs, fatty meats, butter, margarine, and oil. The low-fat diet was designed to be low in fat and CHO yet isocaloric with the control diet. Each subject ate a total of 1 kg/day (raw weight) of lean meat (beef, fish, poultry, or pork) as a large grilled steak at breakfast, with large casseroles at lunch and dinner. In addition, they ate cold roast beef, steamed chicken, and nonfat cottage cheese as snacks between meals. Skim milk and nonfat yogurt were restricted to a combined total of 500 ml/day on the low-fat diet.

The lower mean energy intake on the low-fat diet relative to the high-fat diet was not coincidental. It reflected the older age and greater proportion of women to men on this diet, as only those subjects with the lowest energy requirements were invited to take part in this phase of the experiment (Table 1). The maximum level of dietary protein that can be metabolized daily is ~300 g (6), so only people with an energy requirement <2000 kcal/day could safely fulfill the precondition that 60% of energy be derived from protein. Furthermore, our previous experience with this diet in a group of NIDDM patients (2) taught us that weight maintenance might be difficult to achieve, and the diet was unlikely to be well tolerated by those with energy requirements >2000 kcal/day.

The study was conducted on an outpatient basis. As most subjects were employed full-time, all tests were performed on Saturday mornings between 0700 and 1130 to minimize disruption to the subjects' normal routine. The protocol was as follows:

Days 1–14

For 2 wk before the commencement of either experimental diet, the subjects weighed and recorded all food and liquid intake on their usual self-selected diet. They were supplied with Soehnle (model 123100, Murrhardt, Germany) dietetic scales for that purpose. In addition, they recorded their daily insulin dose and any hypoglycemic episodes. This provided the baseline or predietary intake (mean of 14 days).

Day 15

The subjects came fasted (at least 9 h) to the Health Education Centre of the Royal Melbourne Hospital between 0700 and 0730, and the height and body weight of each subject was recorded. A soft indwelling catheter then was placed in the ante-cubital fossa, or another convenient vein, to enable repeated blood collection during the morning. A 10-ml sample was taken immediately from each subject: 2 ml was collected into an EDTA tube for subsequent HbA_1 analysis, another 2 ml was collected into a fluoride oxalate tube for the measurement of plasma glucose, and 6 ml was collected into a plain tube for serum triglyceride, cholesterol, HDL-cholesterol, and FFA analysis. Cannulae were kept patent by flushing regularly with isotonic saline. Subjects then gave themselves their usual morning subcutaneous insulin injection. Then, 15 min later, another 2-ml fasting blood sample was taken (0 time) for glucose measurement.

A standard breakfast was eaten within the next 10 to 15 min, providing 71 g carbohydrate, 17 g protein, and 13 g fat. It consisted of 40 g wheat-flake breakfast cereal, 200 ml reduced fat (1.5%) milk, two 27 g slices of toasted whole-meal bread, 10 g polyunsaturated margarine, 7 g yeast extract spread, and 170 ml unsweetened orange juice. Further 2-ml blood samples were taken over the next 3 h (15, 30, 45, 60, 90, 120, 150, and 180 min from the beginning of eating).

Days 15–28

The subjects consumed either of the experimental diets, weighing and recording all food and liquid intake. This provided the data for the calculation of dietary composition during the test phase of the experimental diets (mean 14 days). Although it would be desirable from a scientific perspective for each subject to continue taking the identical daily insulin dose during the diet phase, allowance was made for subjects to make appropriate adjustments, through regular SMBG, to avoid hypoglycemia and excessive hyperglycemia.

Day 29: identical to day 15 (postmetabolic profile)

The subjects weighed themselves at least twice per week during the control and diet periods. Although physical activity was not recorded, the study did not interfere with work or leisure routines.

Glucose concentrations were measured in fluoride oxalate plasma by the glucose oxidase method using a YSI model 23 AM glucose analyzer (YSI, Yellow Springs, OH). Fasting cholesterol and triglyceride concentrations were measured enzymatically after enzymatic hydrolysis on a COBAS-BIO centrifugal analyzer using commercially available kits, Merckotest (cholesterol enzymatic, Merck, Darmstadt, Germany) and Roche Triglycerid Rapid Test (Basel, Switzerland), respectively. Within 2 h of blood collection, HDL was separated from other plasma lipoproteins that had been

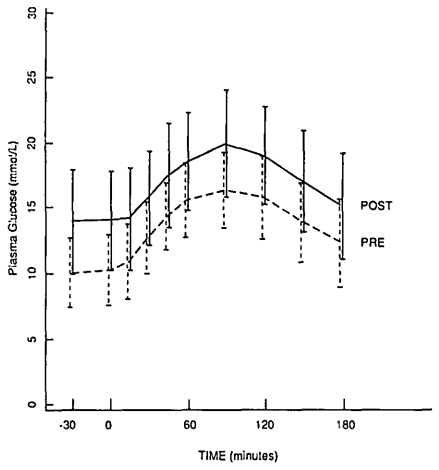

Figure 1—*Glycemic responses to a standard breakfast before (– – –) and after (——) 2 wk on the high-fat, low-carbohydrate diet (mean ± 95% CIs) (n = 10).*

precipitated by heparin-manganese chloride (2). LDL-cholesterol concentrations were computed by using a standard formula incorporating triglyceride, HDL cholesterol, and total cholesterol (7). The WAKO NEFA-C kit (Osaka, Japan), an enzymatic colorimetric method, was used for quantification of FFA in serum (8). The Corning Glytrac kit (Palo Alto, CA) was used to measure total GHb (9).

Wilcoxon's matched-pairs signed-ranks test was used to compare pre- and postdiet data for body weight and all biochemical tests performed in the fasting state. The same nonparametric test was used to compare the control and experimental phase nutrient intake data. Values are expressed as mean ± SE. Wilcoxon's test also was used to compare the area under the glucose curve to test for a difference between pre- and postdiet glycemic response to a standard breakfast after subcutaneous insulin injection.

RESULTS — After the high-fat, low-CHO diet, mean fasting plasma glucose concentration rose by 3.8 mM relative to the control diet, but this difference was not statistically significant. However, when the glycemic responses to a standard meal were compared, a significant elevation ($P < 0.05$) was observed after 2 wk on the high-fat diet (Fig. 1). Insulin doses remained unchanged relative to the control period (Table 3). In addition to its adverse effect on glycemic control, the high-fat diet also caused a significant rise in the level of total cholesterol (Table 4), which was fully accounted for by a rise in HDL-cholesterol concentration: the concentration of LDL cholesterol went down slightly ($P < 0.05$) after the low-CHO, high-fat diet.

No effect was observed on fasting glucose, lipid profile (Table 4), or postprandial glycemic response to the standard meal (Fig. 2) after the 2-wk low-fat, low-CHO dietary intervention. Mean insulin dose decreased during the dietary intervention phase (Table 3). The patients initially were advised to substantially reduce their insulin dose as a precaution against possible hypoglycemic reactions. This empirical advice was considered appropriate because the CHO content of the diet had been halved, and insulin sensitivity had appeared to improve in NIDDM subjects when consuming a similar diet (2). Once the dietary intervention had commenced, however, it soon became apparent that the risk of hypoglycemia was not at all as had been anticipated, and towards the completion of the dietary intervention phase most subjects required their usual insulin dose to achieve satisfactory glycemic control.

CONCLUSIONS — The elevated glycemic response to a standard meal after 2-wk on a high-fat, low-CHO diet suggests that insulin resistance either had been induced or exacerbated. Insufficient data are available upon which to draw conclusions regarding the site (liver versus muscle or adipose tissue) of increased insulin resistance in IDDM related to the feeding of a high-fat diet. Considerable evidence exists to suggest that hepatic insulin sensitivity is relatively normal in well-controlled IDDM patients (10), and as insulin regimens remained unchanged in that phase of this study, it is tempting to speculate that high-fat diets may induce peripheral insulin resistance in IDDM. However, more direct measures of insulin sensitivity should be used in future studies, so that its relationship to dietary composition can be defined more precisely.

The amount of CHO in the diet

Table 3—*Changes in body weight, insulin requirement, GHb, and fasting glucose*

	Body weight (kg)	Daily insulin dose (U)	HbA_1 (%)	Fasting plasma glucose (mM)
High-fat experiment				
Control	65.5 ± 2.8	43.4 ± 2.2	11.8 ± 0.8	10.1 ± 1.3
High fat, low CHO (n = 10)	65.6 ± 2.8	42.8 ± 2.6	12.2 ± 0.8	13.9 ± 2.0
Low-fat experiment				
Control	62.1 ± 3.1	41.1 ± 3.5	11.1 ± 0.6	12.9 ± 2.3
Low fat, low CHO (n = 8)	61.9 ± 3.1	35.3 ± 4.1*	11.6 ± 0.8	11.1 ± 1.3

Values are means ± SE.
*$P < 0.05$ Wilcoxon's matched-pairs test. All other tests were NS.

Table 4—*Fasting lipid levels*

	TOTAL TRIGLYCERIDE (MM)	TOTAL CHOLESTEROL (MM)	HDL CHOLESTEROL (MM)	LDL CHOLESTEROL (MM)	FFA (MM)
HIGH-FAT EXPERIMENT					
CONTROL	1.17 ± 0.11	6.17 ± 0.28	1.66 ± 0.06	4.07 ± 0.25	0.63 ± 0.13
HIGH FAT, LOW CHO (N = 10)	1.24 ± 0.18	6.35 ± 0.28*	2.00 ± 0.11*	3.88 ± 0.19*	0.68 ± 0.09
LOW-FAT EXPERIMENT					
CONTROL	1.10 ± 0.14	5.41 ± 0.20	1.77 ± 0.15	3.23 ± 0.14	0.66 ± 0.12
LOW FAT, LOW CHO (N = 8)	1.04 ± 0.23	5.35 ± 0.30	1.55 ± 0.16	3.41 ± 0.31	0.93 ± 0.14

Values are means ± SE.
*P < 0.05 Wilcoxon's matched-pairs test. All other tests were NS.

does not appear to be the critical factor in determining glycemic control in IDDM. Insulin dosage is probably more important in regulating glycemic control acutely.

Thirty years ago Ernest, Hallgren, and Svanborg (11) conducted a study into the effect of dietary composition on metabolic control in IDDM. The three diets used were either high in protein, fat, or CHO. The authors expressed their surprise that such different diets did not lead to greater variations than were observed in subjective symptoms, plasma glucose level, or insulin requirement. The reason why a high-protein, low-fat, low-CHO diet improves glucose tolerance and insulin sensitivity in NIDDM but not IDDM remains to be established. The most plausible explanation for the conflicting results is the fact that protein is a secretagogue for both glucagon and insulin. Mole for mole, the secretion of insulin in response to amino acids is greater than that of glucagon. In IDDM, the augmented postprandial glucagon secretion would be relatively unopposed such that the potential hypoglycemic effect of dietary CHO reduction would be negated by an increase in hepatic glucose output (12,13).

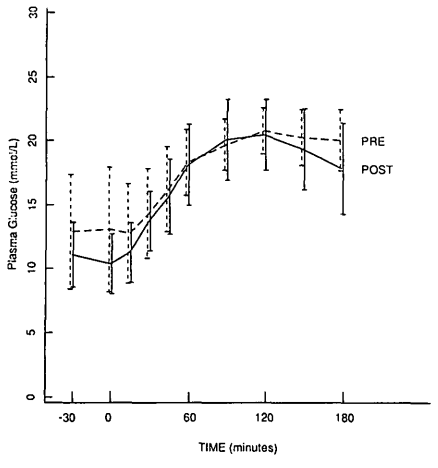

Figure 2—*Glycemic responses to a standard breakfast before (– – –) and after (——) 2 wk on the low-fat, low-carbohydrate diet (mean ± 95% CIs) (n = 8).*

As diabetic nephropathy is a common complication of IDDM, protein restriction has been suggested to reduce subclinically raised albumin secretion—a marker of incipient nephropathy. Cohen, Dodds, and Viberti (14) demonstrated a 35% reduction in median overnight albumin excretion rate among 8 subjects after a 40-g protein, low-fat, high-CHO diet for 3 wk. Blood pressure and serum fructosamine, an integrated index of short-term glycemic control, were unchanged after dietary intervention. The authors concluded that protein restriction significantly reduced albuminuria and should complement other preventive treatment in subjects prone to diabetic nephropathy. It is pertinent that 3 of 8 subjects had to reduce their insulin dose by up to 10 U/day during the low-protein diet to maintain comparable glycemic control. This provides further indirect evidence that protein has considerable potential to raise plasma glucose in IDDM, perhaps to the same or an even greater degree than CHO.

In our related study (2), both fasting triglycerides and cholesterol were reduced significantly in NIDDM after a high-protein, low-fat, low-CHO diet, but no such changes were observed in IDDM in this study.

Previously, we have shown that a high-CHO, high-fiber, low-fat diet reduces plasma lipids without having a significant impact on glycemic control in IDDM (15). The results of this study provide further support for the major conclusion that CHO is not the most critical factor in determining glycemic control in IDDM, and that high-fat diets are deleterious to metabolic control in IDDM, as in NIDDM.

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