Dietary Fat Predicts Conversion From Impaired Glucose Tolerance to NIDDM

The San Luis Valley Diabetes Study

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OBJECTIVE — To determine if dietary fat intake measured at a baseline exam in subjects with impaired glucose tolerance (IGT) predicted the subsequent development of non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS — Based on an oral glucose tolerance test (OGTT) (World Health Organization criteria), we identified 134 eligible subjects with IGT from a geographically based sample of subjects with no prior history of diabetes. One to three years after the baseline exam, 123 subjects (92%) had a repeat OGTT. Diet was assessed by a 24-h diet recall reported before the baseline OGTT.

RESULTS — The mean percentage of energy eaten as fat was 43.4% in 20 people subsequently developing NIDDM compared with 40.6% in 43 people remaining IGT and 38.9% in 60 subjects who subsequently reverted to normal glucose tolerance. In comparing the 20 subjects who developed NIDDM with the 103 who remained IGT or normal, an increase in fat intake of 40 g/day was associated with an increase in risk of NIDDM of 3.4-fold (95% confidence interval [CI] 0.8–13.6) adjusted for energy intake, age, sex, ethnicity, and obesity. The odds ratio increased to sixfold (95% CI 1.2–29.8) after adjustment for fasting glucose, insulin, and 1-h insulin.

CONCLUSIONS — Fat consumption significantly predicts NIDDM risk in subjects with IGT after controlling for obesity and markers of glucose metabolism.

People with impaired glucose tolerance (IGT) have an increased risk of developing non-insulin-dependent diabetes mellitus (NIDDM) when compared with those with normal glucose tolerance (NGT) (1). Environmental factors that can be altered to decrease an individual's risk of conversion from IGT to NIDDM could lead to public health measures for the primary prevention of NIDDM. Diet is a modifiable environmental factor that has long been believed to be a risk factor for NIDDM, but epidemiological data have been inconclusive (2). Recently, we reported the observation that people with previously undiagnosed NIDDM and IGT report higher fat, lower carbohydrate (CHO) diets than those with confirmed NGT when diet assessments were made before the diagnostic oral glucose tolerance test (OGTT) (3). To further investigate whether high-fat diets precede the development of NIDDM, we hypothesized that a high-fat, low-CHO diet would increase the risk of subsequently developing NIDDM among individuals with IGT at their baseline visit.

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IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus; CHO, carbohydrate; OGTT, oral glucose tolerance test; BMI, body mass index; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.

RESEARCH DESIGN AND METHODS

Study population

The San Luis Valley Diabetes Study was designed to determine the prevalence and incidence of NIDDM, its complications among Hispanic and non-Hispanic white adults, and to study etiological and prognostic risk factors associated with NIDDM. In addition to seeing all known diabetic patients in the study area, a geographically based sample of 1,321 people 30–74 years of age and without a prior history of diabetes were seen for a baseline visit during the period May 1984 to August 1988. Detailed methods are reported elsewhere (4). The analyses reported in this study are based on 134 subjects without a prior diagnosis of diabetes who were determined to have IGT at their initial visit. These subjects were then followed for an average of 22.6 months (range 11–40 months), and glucose tolerance status was re-evaluated.

Interview and examination

Subjects attended the clinic after an overnight fast. Fasting blood samples were

drawn and then the subject was given 75 g of glucose (Koladex, Orangedex, Custom Laboratories, Baltimore, MD). One- and two-hour blood samples were drawn, and interviews and a physical examination were conducted. Glucose was measured using the glucose oxidase method (5) on venous plasma. The 1985 World Health Organization criteria for diabetes (6) were used to classify subjects with NGT (n = 1,077), IGT (n = 173), and previously undiagnosed diabetes (n = 71). Of the 173 subjects with IGT, 134 were invited for follow up before 1 January 1990 when the clinic was closed for a 6-month period. The remaining 39 subjects were invited to the clinic >4 years after their initial visit. These subjects are excluded because of the longer interval and unavailability of complete data when these analyses were completed. Of the invited subjects, 92% (n = 123) had a repeat OGTT.

The 1980 U.S. Census self-assessment question on Spanish origin was used to determine ethnicity (7). Education and income were reported by the subject as the highest grade completed and total family income before taxes in the year before the clinic visit. Family history of diabetes was positive if the subject reported that either biological parent or any sibling had been diagnosed with diabetes (8).

Body mass index (BMI) was calculated as current measured weight in kilograms divided by height in meters squared. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by iliac circumference. Waist circumference was measured at the bottom of the tenth rib at midinspiration, and the iliac circumference was measured at the most lateral tip of the iliac crest. Skin-fold measurements at the tip of the right scapula (subscapular) and at the midpoint between the acromial process and the lateral epicondyle of the elbow (triceps) were made by the same observer twice at each location and averaged (Lange skin-fold calipers, Cambridge, MD). Central obesity (the centrality index) was estimated as the ratio of subscapular to triceps skin folds. To determine the repeatability of selected anthropometric measurements, the same observer remeasured each variable without knowledge of the first result within 2 weeks on a random sample of 36 subjects seen for a baseline visit. The intraclass correlation coefficients were: BMI 0.99 kg/m^2; WHR 0.83; triceps skin fold 0.88; and subscapular skin fold 0.81, which indicated a good to excellent agreement beyond chance.

For the diet assessments, subjects were administered a 24-h diet recall (9) by bilingual interviewers trained and certified by the Nutrition Coordinating Center at the University of Minnesota (10). A two-dimensional food portion visual (11,12) and three-dimensional aids (e.g., ruler, cups, bowls, glasses, plates, measuring spoons) were used to estimate portion sizes. The nutrient analysis was based on version 14 of the Nutrition Coordinating Center's nutrient database released in 1987. Total energy includes energy from alcohol. CHO excludes dietary fiber.

Statistical analysis

Mean levels and percentage distribution of baseline risk factors for converters and nonconverters to NIDDM were compared using the Statistical Analysis System (13). Adjusted odds ratios (ORs) were estimated by multiple logistic regression (14) using Generalized Linear Interactive Modelling software (15). Baseline dietary risk factors were entered into multiple logistic regression models to evaluate their importance after controlling for age, sex, ethnic group, BMI, WHR, central obesity, fasting and 1-h postload insulin levels, and fasting glucose to predict the development of diabetes. Age, BMI, centrality, WHR, insulin and glucose levels, and diet variables were evaluated as continuous variables. ORs were calculated from logistic regression (16) to estimate the relative increase in risk associated with a 40 g/day increase in fat intake. The magnitude of the OR depends on the unit change used for comparison. Forty grams of fat was chosen to represent a change that was ~1 SD for reported 24-h fat intakes in this population (3). The effect of total energy was evaluated by replacing grams of fat with the energy-adjusted residuals for dietary fat intake (17). Finally, using maximum likelihood estimation in comparing two logistic regression models with the same number of parameters, the model with the higher likelihood (lower −2 ln likelihood) is the model that provides the better fit to the data. Likelihoods were used to determine which of the highly correlated nutrients provided a better fit to the data.

RESULTS— Subjects with IGT who subsequently developed NIDDM were more often Hispanic, and more often female, but of similar age to those not developing NIDDM (Table 1). A greater proportion of those developing diabetes had less than a high school education and a positive family history of diabetes. They had a higher BMI and more central obesity. The unexpected lower average WHR among converters was not accounted for by the higher proportion of females in this group. In females, the average WHR was not different in converters and nonconverters (0.88 vs. 0.88), whereas in males, converters had slightly lower but not statistically significant differences in WHRs (0.96 vs. 0.99). A significant increasing trend was observed in glucose levels and fasting insulin levels across categories from reverting to normal to converting to NIDDM.

The mean percentage of energy from fat was 43.9% in individuals who converted to NIDDM compared with 38.9% in those reverting to NGT (Table 2). Saturated and monounsaturated fat intake was also higher in converters, whereas CHO and fiber intake was somewhat lower. Energy intake per kilogram of body weight was not different across the three groups.

We next examined the relation-

Table 1—*Mean levels and percentage of distribution for selected risk factors at baseline by follow-up glucose tolerance status*

	Reverted to normal	Remained IGT	Converted to NIDDM	Test for trend, *P* value
n	60	43	20	
Hispanic (%)	46.7	46.5	60.0	0.39
Female (%)	48.3	67.4	75.0	0.02
Age (years)	58.6 ± 1.3	60.0 ± 1.5	58.6 ± 2.2	0.81
Education level < 12 years (%)	37.3	39.5	50.0	0.36
Income (annual family) (%)				
<$15,000	45.5	55.3	52.9	0.58
$15–25,000	23.6	26.3	11.8	—
>$25,000	30.9	18.4	35.3	—
Family history of diabetes (%)	31.0	38.5	52.6	0.10
BMI (kg/m^2)	27.0 ± 0.6	29.8 ± 0.8	29.2 ± 1.1	0.02
WHR	0.93 ± 0.01	0.92 ± 0.01	0.90 ± 0.02	0.10
Centrality index	1.30 ± 0.06	1.18 ± 0.07	1.33 ± 0.11	0.83
Vigorous activity (%)				
None	47.5	46.5	45.0	0.66
<20 min, 3 times/week	28.8	25.6	25.0	
>20 min, 3 times/week	23.7	27.9	30.0	
Glucose levels				
Fasting glucose (mM)	5.6 ± 0.1	5.8 ± 0.1	6.1 ± 0.1	<0.01
1-h glucose (mM)	10.1 ± 0.3	10.6 ± 0.3	12.6 ± 0.4	<0.01
2-h glucose (mM)	8.6 ± 0.1	9.3 ± 0.1	9.5 ± 0.2	<0.01
Insulin levels				
Fasting insulin (pM)	99.6 ± 8.7	130.8 ± 10.2	145.3 ± 15.0	<0.01
1-h insulin (pM)	749.9 ± 67.5	926.9 ± 79.7	711.0 ± 116.9	0.74
2-h insulin (pM)	805.0 ± 78.9	969.8 ± 93.2	809.0 ± 136.6	0.63
1-h fasting insulin	8.1 ± 0.7	8.6 ± 0.8	5.8 ± 1.2	0.22

Data are means ± SE except for values given in percent.

ship of total dietary fat with the development of NIDDM in multiple logistic models comparing individuals converting to NIDDM with those remaining IGT or reverting to normal. This dichotomization of the study group based on an NIDDM diagnosis at follow-up is consistent with the bimodal distribution of plasma glucose levels. In model 1 (Table 3), a threefold excess risk of NIDDM is associated with a 40-g increase in the intake of dietary fat after adjusting only for total energy intake. This association approached statistical significance at an α of 0.05 ($P = 0.09$). Demographic and obesity variables alone and in combination (Table 3, model 2) were not statistically significant predictors of conversion to NIDDM and also did not alter the association between dietary fat and NIDDM. Next, the effect of dietary fat controlling for markers of glucose metabolism at baseline was evaluated both with (model 3) and without (model 4) the statistically nonsignificant but potentially confounding demographic- and obesity-related variables. Fasting glucose, fasting insulin, and 1-h postload insulin levels were entered as markers of insulin resistance and insulin secretion and as important predictors of the subsequent development of NIDDM. Among subjects with similar insulin and glucose levels at baseline, a 40-g increase in dietary fat intake was associated with a sixfold excess risk of converting from IGT to NIDDM.

The length of the interval between the baseline and follow-up exam, family history of diabetes, reported vigorous activity, and protein, sucrose, and fructose intake did not alter the dietary fat effect seen in Table 3, models 3 and 4 (data not shown). Dietary variables that are highly correlated with total fat (saturated fat, total CHO, and dietary fiber) were evaluated in place of total fat in models 3 and 4. Saturated fat was not a statistically significant predictor of conversion to NIDDM, and total fat provided a better fit to the data using −2 ln likelihood criteria. Although low total CHO intake approached statistical significance (data not shown), high total fat intake provided a marginally better fit to the data than CHO.

We also explored subgroup-specific relationships. The relationship between total fat intake and conversion to NIDDM was of a similar magnitude in

Table 2—*Adjusted nutrient intakes at baseline by follow-up glucose tolerance status*

	Reverted to normal	Remained IGT	Converted to NIDDM	Test for trend, P value
n	60	43	20	
Percentage of energy from				
Fat	38.9 ± 1.0	40.6 ± 1.3	43.9 ± 1.8	0.02
Saturated fat	14.0 ± 0.5	14.6 ± 0.6	16.1 ± 0.9	0.06
Monounsaturated fat	14.9 ± 0.5	16.3 ± 0.6	17.1 ± 0.9	0.03
Polyunsaturated fat	7.0 ± 0.5	6.8 ± 0.5	7.5 ± 0.8	0.74
CHO	45.1 ± 1.3	43.5 ± 1.5	40.5 ± 2.3	0.08
Starch	21.8 ± 1.0	19.5 ± 1.2	20.5 ± 1.7	0.30
Sucrose	8.0 ± 0.8	8.9 ± 0.9	6.9 ± 1.4	0.70
Protein	16.7 ± 0.62	16.4 ± 0.76	15.8 ± 1.1	0.47
Grams per 4.184 kJ(/1,000 kcal)				
Fiber	10.1 ± 0.7	9.0 ± 0.8	7.6 ± 1.2	0.06
Fat to CHO ratio	0.46 ± 0.03	0.54 ± 0.04	0.58 ± 0.06	0.05
J/kg body weight	104.04 ± 5.77	83.38 ± 6.99	97.92 ± 10.22	0.25

Data are means ± SE.
Adjusted for age, sex, and ethnicity by analysis of covariance.

Hispanics and non-Hispanic whites and by whether or not there was a family history of diabetes. Because of the small numbers, we were unable to evaluate whether the observed relation between dietary fat and conversion to NIDDM was similar at all levels of physical activity and obesity or by sex.

CONCLUSIONS — To further investigate the role of fat and CHO in the etiology of NIDDM in humans, we measured diet at a baseline exam and prospectively followed individuals with previously undiagnosed IGT from the San Luis Valley Diabetes Study to determine who converted to NIDDM. We hypothesized that dietary intake high in total fat and low in total CHO would be associated with conversion to NIDDM after controlling for other potential risk factors. The data presented here suggest that a 40-g increase in fat intake is associated with a sixfold excess risk of NIDDM among individuals with similar baseline levels of obesity and markers of glucose metabolism.

These results add support to our previously reported findings that a high-fat/low-CHO diet is associated with the onset of NIDDM (3). In the previous study, diet was measured immediately before the diagnostic OGTT, and in this

Table 3—*Logistic regression models: risk factors associated with NIDDM development among 123 individuals with IGT followed 1–3 years*

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Total fat (40 g/day increase)	3.0 (0.8–10.6)	3.4 (0.8–13.6)	7.4 (1.3–40.6)	6.0 (1.2–29.8)
Energy (4.184 kJ(1000 kcal)/day increase)	1.2 (0.7–2.0)	1.1 (0.6–2.1)	1.2 (0.6–2.7)	1.2 (0.6–2.6)
Sex (Female vs. male)		1.9 (0.3–12.2)	5.2 (0.6–45.3)	11.6 (2.0–68.4)
Age (10 years)		0.8 (0.5–1.5)	0.9 (0.5–1.7)	
Ethnicity (Hispanic vs. non-Hispanic white)		1.7 (0.6–5.4)	1.6 (0.4–6.3)	
BMI (5 kg/m^2)		1.2 (0.7–2.0)	0.8 (0.4–1.7)	
WHR (0.15)		0.4 (0.8–1.6)	0.3 (0.04–1.6)	
Centrality (0.25)		1.2 (0.9–1.7)	1.5 (0.98–2.2)	1.5 (1.0–2.1)
Fasting insulin (25 pM)			1.4 (1.0–2.0)	1.4 (1.0–2.8)
1-h insulin (50 pM)			0.89 (0.81–0.98)	0.90 (0.83–0.98)
Fasting glucose (0.5 mM)			2.3 (1.3–4.4)	2.2 (1.3–3.8)

study, diet was assessed 1–3 years before the diagnosis of NIDDM. Even though the 24-h recall is an imprecise measure of average intake, a statistically significant sixfold excess risk of NIDDM was associated with a 40-g increase in fat intake as assessed by a 24-h diet recall. Because the conversion status was unknown when the diet was assessed and because any systematic differences in dietary reporting by age, sex, ethnicity, or obesity should largely be accounted for by the inclusion of these variables as covariates, the remaining measurement error is expected to be random. Random error drives the association toward the null (18) and suggests that the sixfold excess risk of NIDDM is associated with a smaller difference in fat intake than the 40 g/day reported here.

Other potential limitations of this study include the variable diagnosis of IGT, combining subjects who remained IGT and those who reverted to NGT as the reference group in Table 3, misclassification of IGT because of inadequate preparation for the OGTT, or the possibility that subclinical disease pathology may increase preference for fat intake over CHO. IGT is defined as a 2-h postload blood glucose concentration in the relatively narrow range above 7.7 mM and below 11.1 mM (6). As a group, individuals with IGT are at increased risk for developing NIDDM, but a large number revert to normal on repeat testing within a week and after longer periods of follow up (1). Nonselective misclassification of glucose tolerance status and the small number of subjects converting to NIDDM in this study would work against identifying a statistically significant association between diet and conversion to NIDDM. The association between high fat intake and subsequent NIDDM (Table 3, models 1 and 2) was statistically significant in similar models comparing subjects who developed NIDDM with those reverting to normal, excluding subjects with IGT (data not shown). Selective misclassification of IGT because of inadequate CHO preparation on the day before the initial OGTT would also tend to work against finding an association between high-fat/low-CHO diets and the subsequent development of NIDDM. It remains possible that subclinical disease pathology may increase an individual's preference for dietary fat intake before diagnosis. However, to the extent that initial fasting glucose levels, insulin levels, and 1-h postload insulin levels reflect subclinical disease severity, the association between high fat intake and NIDDM was strengthened when these variables were taken into account (Table 3, models 3 and 4).

High-fat diets have been shown to cause insulin resistance in rats (19). Plausible mechanisms have been proposed for how high-fat diets may lead to obesity (a strong risk factor for the development of NIDDM) in humans (20) and for how subtypes of fat, either an excess of saturated fat or deficits of long-chain ω-3 fatty acids, may alter cell membrane composition, signal transduction across the cell membrane, and subsequent insulin action (21–27). It has been proposed that during most of evolutionary time, it would have been a selective advantage to have a thrifty genotype (28). Adaptive mechanisms that allowed for effective storage of energy during times of feast and efficient use of energy during times of famine would have increased the likelihood of survival. These same attributes may lead to obesity and NIDDM under conditions where energy-dense foods are readily available and do not require significant energy expenditure. Information on the traditional foods and the life-style of Australian aborigines suggests that their feasts would have been high in protein and low in CHO and fat. This has led to the hypotheses that it would have been a survival advantage to have an active system for hepatic gluconeogenesis, which was not suppressed by insulin, and a high capacity for lipogenesis and fat accumulation, which were both sensitive to insulin (29). Mild glucose intolerance and hyperinsulinemia would have conferred an advantage when the irregular diet was coupled with high physical activity and low BMI. Subpopulations with different food supplies and requirements for energy expenditure may have adapted in many additional ways. For example, reduced energy expenditure (30) or a slow or sluggish adjustment of fat oxidation to increased fat intake (19) would allow increased storage of irregular food supplies. This study does not attempt to further define any one of the possible mechanisms by which a high-fat diet could lead to NIDDM but rather looks on a population level for evidence supporting the hypothesis that reducing fat intake would decrease the incidence of NIDDM, which is an increasing public health concern.

A previous review of epidemiological studies (3) found that reported ecological, cross-sectional, and case-control studies generally support a relation between high-fat/low-CHO diets and occurrence of NIDDM. Prospective studies, however, had most often reported no association. These previous negative findings may be explained by small numbers of incident cases, lack of control for potentially confounding variables, inclusion of highly correlated variables in the same models, and design issues related to the timing and temporal stability of dietary exposures as reviewed in more detail elsewhere (3). Recently, Stern (31) and Tsunehara et al. (32) reported prospective observations that support the findings reported in this study.

Epidemiological studies of modifiable risk factors offer the potential for prevention even if the disease mechanism is unknown. Relatively recent reviews have stated that there are no consistent data to support the hypothesis that diet modifies the risk of developing NIDDM (2). However, evidence from animal and clinical studies, epidemiological studies, and evolutionary perspectives increasingly supports the hypothesis that the high-fat/low-CHO diets prevalent in Westernized societies today are contrib-

uting to the excess obesity and NIDDM seen in these same groups. In epidemiological studies, multiple prospective assessments of diet and glucose tolerance are still needed to rule out the possibility that early subclinical disease is altering dietary preferences and to better understand whether dietary composition is acting to increase risk for NIDDM during all stages of the natural history of the disease and in all subgroups (e.g., lean and obese, active and inactive).

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