

Microalbuminuria is positively associated with usual dietary saturated fat intake and negatively associated with usual dietary protein intake in people with insulin-dependent diabetes mellitus¹⁻³

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ABSTRACT Microalbuminuria has a cumulative incidence of > 30% in persons by 25 y duration of insulin-dependent diabetes mellitus (IDDM) and is a strong predictor of renal disease and mortality. Although improved glycemic control, maintenance of normal blood pressure, and use of angiotensin-converting enzyme inhibitors are important strategies to avoid developing microalbuminuria, dietary macronutrient intake may also play a role. A cross-sectional population-based study of Tasmanian adults with IDDM and no previous diagnosis of microalbuminuria was conducted by measuring usual dietary macronutrient intake with a food-frequency questionnaire and defining microalbuminuria as an average urinary albumin excretion rate between 20 and 200 μg albumin/min in at least two of three timed overnight urine collections. After sex, age, duration of diabetes, daily number of insulin injections, body mass index, glycated hemoglobin, serum high-density-lipoprotein cholesterol, frequency of exercise, and smoking status were adjusted for, the adjusted odds ratio for microalbuminuria for the highest quintile of energy-adjusted usual saturated fat intake compared with the lowest quintile was 4.9 (95% CI: 1.2, 20.0; $P = 0.03$). The adjusted odds ratio for microalbuminuria for the highest quintile of energy-adjusted usual protein intake compared with the lowest quintile was 0.10 (95% CI: 0.02, 0.56; $P = 0.01$). There was no significant association between microalbuminuria and energy-adjusted carbohydrate intake, energy-adjusted monounsaturated fat intake, or energy-adjusted polyunsaturated fat intake. *Am J Clin Nutr* 1998;67:50-7.

KEY WORDS Insulin-dependent diabetes mellitus, IDDM, saturated fat, protein intake, microalbuminuria, carbohydrate intake, Tasmania, Insulin-Treated Diabetes Register, humans

INTRODUCTION

Insulin-dependent diabetes mellitus (IDDM) is a condition associated with excess mortality (1, 2) and for which there is currently no cure (3). Of those with IDDM, a substantial subgroup accounts for most of the excess mortality—the group that develops a persistently raised urinary albumin excretion rate (UAER) (4, 5). A persistently raised UAER is also associated with increased mortality in people with non-insulin-dependent diabetes mellitus (NIDDM) (6, 7) and in elderly people without diabetes (8).

The proportion of people with IDDM who develop a persis-

tently raised UAER has been estimated to be >30% (9) and efforts to decrease the mortality rate of persons with IDDM are rationally directed to this group. Optimal control of blood glucose (10) and close regulation of systemic blood pressure (11) are promising strategies for both the prevention of a persistently raised UAER and limiting the progression of the disorder. The use of angiotensin-converting enzyme (ACE) inhibitors prevents the progression from microalbuminuria to overt nephropathy even in normotensive patients with IDDM (12, 13). However, there may be other possibilities for the prevention of persistently raised UAERs. Other factors that have been observed to be associated with albuminuria in people with IDDM are sex (14-16), diabetes duration (9, 15, 17), age at diabetes diagnosis (9), cigarette smoking (18, 19), and serum HDL cholesterol (20, 21).

Others have speculated that dietary macronutrient intake may be important in the development of raised UAERs (22, 23). Generally, attention has been directed toward dietary protein as a factor that results in sustained renal hyperfiltration preceding the loss of nephron units in IDDM (24). However, fat has also been suggested (25, 26) as a macronutrient that might be important in the development of renal disease. Attention to diet is already a keystone of treatment for persons with IDDM. The identification of dietary intake as a cause of the development of diabetic renal disease could also provide insight into the causal mechanism of renal disease in diabetes.

The purpose of this study was to determine whether dietary macronutrient intake was associated with the presence of early stages of raised UAERs in people with IDDM. Unlike other studies that have examined this question (22, 23), this study was conducted in a population-based IDDM case series in which atten-

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dance at any particular health facility did not form any part of the selection procedure.

SUBJECTS AND METHODS

Study population

Tasmania is an island state of Australia with a population of $\approx 470\,000$ in December 1992 (27). A prevalence survey of all people resident in Tasmania who were diagnosed with diabetes and using insulin daily was conducted in 1984–1985; this initiated the Tasmanian Insulin-Treated Diabetes Register (TITDR) (28). For May 1, 1984, the register was estimated to be 94% complete by comparison with insulin prescription information. The methods of operation of the register are described elsewhere (29).

In the period from March 1991 to December 1992, all persons eligible for the TITDR who were resident in Tasmania and defined as having IDDM on May 1, 1984, were sought and invited to participate in the study. The operational definition of IDDM was age <30 y at the time of diabetes diagnosis and commencement of daily insulin treatment within 12 mo from the date of diagnosis. Eligibility criteria also required that subjects were alive, without severe mental or physical handicap, resident in Tasmania (but excluding the associated islands and remote west coast region that together contain $<5\%$ of the Tasmanian population), noninstitutionalized, and over the age of 18 y at the time of data collection. Follow-up of persons listed on the TITDR for a mortality study (1) indicated that 352 subjects met the eligibility criteria for this study and a further 6 subjects were located who met all the criteria except that they had not been listed previously on the TITDR. Thus, the study cohort was 358 adult subjects who had been diagnosed with IDDM ≥ 7 y previously.

Despite comprehensive searches of the electoral roll and the telephone directory and questioning Tasmanian residents with the same surname, 46 subjects (12.8%) could not be located ≈ 7 y after they were listed with the TITDR. An additional 6 subjects in whom diabetes was diagnosed at 29 y of age were inadvertently excluded from the field study list, 54 eligible subjects (15.1%) declined to take any part in the study, 32 subjects (8.9%) did not provide any timed overnight urine samples, and 1 subject did not complete the food-frequency questionnaire (FFQ). Thus, the response rate for full participation was 61.2% (219/358). The procedures followed in this study were approved by the University of Tasmania Ethics Committee.

Data collection and laboratory procedures

For collection of data, subjects were visited in their homes or requested to attend a clinic at a central site near their homes. A questionnaire was administered covering medical history, health-related behavior, usual physical activity, and attitudes toward health. In addition, a 152-item FFQ (described later) was administered by a dietitian. Height and weight were measured with subjects without shoes and in light clothing by using transportable combined scales and a stadiometer (model 707, capacity 200 kg; Seca, Hamburg, Germany). Three repeated measurements of blood pressure were taken with an automated instrument (Dinamap 1846SX vital signs monitor; Critikon, Tampa, FL) after the subject had been seated for ≥ 15 min. A nonfasting venous blood sample was drawn and divided into a plain tube and an EDTA-coated tube. Subjects were instructed in the

method for keeping a series of three timed overnight urine collections within a 3-mo period, and these were retrieved on the morning after each collection.

Each blood sample was centrifuged and the serum or plasma supernate drawn off and refrigerated within 4 h of sample collection. The volume of urine from the overnight collections was measured and a 50-mL sample refrigerated for subsequent analysis.

All blood sample analyses were conducted at a single hospital laboratory that participates in the Australian Quality Assurance Programme and is accredited by the National Association of Testing Authorities. Total serum cholesterol was measured by enzymatic colorimetric methods (Trace Reagents, Clayton, Australia). Serum HDL cholesterol was measured after precipitation of non-HDL lipoproteins with polyethylene glycol 6000 (30). Plasma glycolated hemoglobin was measured by using a cation-exchange column (A1c Micro Column Test; Bio-Rad, Hercules, CA).

The albumin concentration of the urine samples was measured by using an immunoturbidometric method (Reply Automated Chemistry Analyser; Olympus, Tokyo) with antisera (Dako A/S, Glostrup, Denmark). Creatinine concentration was measured in urine by using a Rate-Jaffé reaction (31) (Syncon CX3 analyzer; Beckman Instruments, Los Angeles).

Measurement of dietary intake

The 152-item FFQ was modified from a widely used Australian FFQ (32) and was designed to estimate usual food and nutrient intakes over the previous 12 mo. Information from the FFQ is converted to an estimated daily nutrient intake by using a food-composition database that is based on data from British tables of food composition (33), with supplementary data from Australian sources. Estimated macronutrient intake was adjusted for energy intake by using the residual of the regression of macronutrient intake on energy intake as described by Willett and Stampfer (34). Subjects were categorized into quintiles of energy-adjusted macronutrient intake. The validity of the FFQ has been assessed by comparison with weighed dietary records in the source IDDM population (35); Pearson correlation coefficients with true dietary intake were estimated to be 0.36, 0.72, 0.60, and 0.55 for energy-adjusted protein, carbohydrate, fat, and saturated fat, respectively. The Pearson correlation coefficient for estimated energy intake between weighed dietary records and the FFQ was 0.46. The critical values determining the energy-adjusted macronutrient intake quintiles measured by the FFQ are not readily interpretable; however, for energy from protein as a percentage of energy they were 16.5%, 17.6%, 19.2%, and 20.5%; for carbohydrate as a percentage of dietary energy they were 36.2%, 39.7%, 43.8%, and 47.0%; for fat as a percentage of dietary energy they were 36.5%, 39.6%, 42.1%, and 45.0%; and for saturated fat as a percentage of energy they were 13.1%, 15.0%, 17.2%, and 19.2%.

Definition of microalbuminuria

Microalbuminuria was defined as a UAER of 20–200 $\mu\text{g}/\text{min}$ in at least two of three timed overnight urine collections. This definition is used commonly (17, 36). Nine subjects provided one timed overnight urine sample only. These subjects were defined as having microalbuminuria ($n = 5$) when the single UAER was >50 $\mu\text{g}/\text{min}$ (range: 51–2856 $\mu\text{g}/\text{min}$). The other subjects ($n = 4$) providing only one urine sample had a single UAER <20 $\mu\text{g}/\text{min}$ (range: 0.6–18.6 $\mu\text{g}/\text{min}$) and were defined

as having normal urinary albumin excretion. For 12 subjects it was not possible to calculate a UAER because of failure to record the time period of the sample collection or the collection of an incomplete sample as a result of spillage. These subjects were categorized as having normoalbuminuria or microalbuminuria on the basis of the mean urinary ratio of albumin to creatinine in their samples. By linear regression analysis of data from those subjects who had both measures taken ($n = 207$), mean urinary ratios of albumin to creatinine of 2.5 and 45 corresponded to mean UAERs of 20 and 200 $\mu\text{g}/\text{min}$ respectively. For the 12 subjects with a measurement for urinary ratio of albumin to creatinine only, microalbuminuria was defined as a mean ratio between 2.5 and 45.

Subjects who reported a diagnosis of raised UAER before this study were excluded from the analysis because their diagnosis may have affected their dietary intake. Similarly, subjects with a UAER $>200 \mu\text{g}/\text{min}$ were also excluded from the analysis because this advanced renal dysfunction could have unpredictable effects on dietary intake.

Statistical analysis

The distributions of characteristics for subjects with microalbuminuria and subjects without microalbuminuria were described by using means and SDs for continuous variables and percentages for categorical variables. Evidence for a difference between groups was tested by using the *t* test for independent samples for continuous variables and the chi-square test for percentages.

Because of our concern about potential confounding of the relation of central interest, we examined the relation between each energy-adjusted macronutrient variable and other factors that may be related to microalbuminuria by using linear regression models. Energy-adjusted macronutrient values were entered as continuous dependent variables and the independent variables included one at a time. The factors included as continuous independent variables were age, age at diagnosis, duration of diabetes, body mass index, serum HDL cholesterol, serum glycated hemoglobin, systolic blood pressure, diastolic blood pressure, and serum cholesterol. Factors added as dichotomous independent variables were sex (male or female) and current smoking status (smoking or nonsmoking). Exercise frequency (not at all, less than once per week, once or twice per week, or three times per week or more), and number of daily insulin injections (one, two, three, or four) were entered as ordered categorical variables. The particular factors considered in the analysis were selected because either they have been shown to be related to microalbuminuria by other investigators or there is reason to think they could be related to both macronutrient intake and the presence of microalbuminuria.

Logistic regression modeling was used to examine the relation between microalbuminuria and dietary macronutrient intake. The dichotomous dependent variable was albuminuria status (microalbuminuria or normoalbuminuria) and dummy variables were used for each of the top four quintiles of macronutrient intake. The other factors described above that are potential confounders were included as independent variables in the same form as for the linear regression models. These variables were included one at a time with the macronutrient dummy variables and the effect on the parameter estimates for the extreme macronutrient quintile noted. Each factor that caused a change of $>10\%$ in the odds ratio for the extreme quintile of a particular

macronutrient was included in a multiple-logistic-regression model for that macronutrient (37). Finally, all the factors considered were included simultaneously (excluding age, which becomes redundant with the addition of age at diagnosis and duration of diabetes) in each regression model. Dummy variables for different energy-adjusted macronutrient variables were also included simultaneously in logistic regression models. As a test for trend of quintiles of energy-adjusted macronutrients with microalbuminuria, the difference from 0 of the parameter estimate of the five-level macronutrient variable in a logistic regression model was tested. All statistical analyses were conducted with SAS software (38).

RESULTS

The number of subjects providing at least two timed overnight urine samples and responses to the FFQ was 210. An additional nine persons provided one timed overnight urine sample only, five of these subjects were classified as having microalbuminuria. This represents 61.2% of the eligible target population. Thirteen of these subjects had been diagnosed with raised UAERs before this study and an additional 28 subjects had a mean UAER $>200 \mu\text{g}/\text{min}$. The subjects forming the basis of this analysis were 48 persons classified as having newly diagnosed microalbuminuria and 130 persons classified as having normoalbuminuria.

The mean age of the participants of this study ($n = 178$) was 39.4 ± 12.8 y ($\bar{x} \pm \text{SD}$) and their mean duration of diabetes was 22.6 ± 11.3 y. The percentage who were male was 52.2%. The mean age of eligible subjects who declined to participate ($n = 54$) was 34.9 ± 13.5 y (significantly different from participants, $P = 0.03$), their mean duration of diabetes was 19.6 ± 10.7 y (NS) and 66.7% of them were male (NS). Otherwise-eligible subjects who could not be traced ($n = 46$) had a mean age of 33.7 ± 11.2 y (significantly different from participants, $P = 0.003$), they had a mean duration of diabetes of 19.5 ± 10.1 y (NS), and 50% of them were male (NS). Characteristics of the 178 participants are shown in **Table 1**.

Factors that are possible confounders of the relation between dietary intake and raised UAERs were considered. Factors that have been shown by others to be associated with albuminuria status include sex (14–16), smoking status (18, 19), age at diagnosis of diabetes (9), duration of diabetes (9, 15, 17), glycemic control (10), and serum HDL cholesterol (20, 21). Higher systemic blood pressure (39) and abnormal plasma lipid and coagulation factor concentrations (21, 40) have also been observed to be associated with microalbuminuria in IDDM; however, it is not clear whether changes in these factors precede or follow the initial rise in UAER. If these factors are an effect of the disease (or an intervening factor between exposure and disease), it is inappropriate to control for them in the analysis of the relation between energy-adjusted macronutrient intake and microalbuminuria. Serum HDL cholesterol may be related to aerobic fitness, the extent of a sedentary lifestyle, or obesity; self-reported frequency of sustained exercise may be related to other health behavior, blood pressure, and glycemic control; and the number of daily insulin injections may also be related to glycemic control. Body mass index was observed to be related to the progression of microalbuminuria in a longitudinal study (41).

The association of those factors for which measurements were available with energy-adjusted saturated fat and energy-adjusted



TABLE 1
Characteristics of study participants¹

Characteristic	Subjects with MA (n = 48)	Subjects without MA (n = 130)	P for difference
Current cigarette smokers (%)	27.1	18.5	0.208
Sex (% male)	52.1	52.3	0.979
Age (y)	38.1 ± 14.3 ²	39.9 ± 12.2	0.415
Duration of diabetes (y)	23.6 ± 11.4	22.3 ± 11.2	0.483
Age at diabetes diagnosis (y)	14.5 ± 8.4	17.6 ± 7.4	0.018
Percentage who usually consult with a dietitian ≤ 1 time/y (%)	97.9	98.4	0.794
Systolic blood pressure (mm Hg)	141.5 ± 18.4	137.1 ± 20.9 [125] ³	0.202
Diastolic blood pressure (mm Hg)	80.2 ± 9.8	78.0 ± 9.2 [125]	0.156
Serum HDL cholesterol (mmol/L)	1.38 ± 0.41 [35]	1.59 ± 0.43 [103]	0.015
Serum cholesterol (mmol/L)	5.9 ± 1.2 [35]	5.7 ± 1.1 [106]	0.345
Glycated hemoglobin (%)	8.9 ± 1.5 [36]	8.5 ± 1.7 [107]	0.243
Subjects having ≤ 2 insulin injections/d (%)	85.4	76.2	0.181
Subjects reporting no regular exercise (%)	20.8	13.1	0.200
Dietary intake			
Fat (% of energy)	41.6 ± 5.7	40.2 ± 5.5	0.135
Protein (% of energy)	18.2 ± 2.1	18.9 ± 3.0	0.131
Carbohydrate (% of energy)	41.3 ± 6.5	41.8 ± 6.1	0.690
Saturated fat (% of energy)	17.2 ± 3.7	16.0 ± 3.2	0.031

¹MA, microalbuminuria.² $\bar{x} \pm SD$.³n in brackets.

protein is indicated by regression coefficients from a linear regression in **Table 2**. A complete set of measurements was not available for all subjects. In particular, glycated hemoglobin was not measured in 35 subjects, serum HDL cholesterol was not measured in 40 subjects, serum cholesterol was not measured in 37 subjects, systemic blood pressure was not measured in 5 subjects, and weight was not known for 4 subjects. A total of 132 subjects had complete data for all variables. There was no significant linear relation between energy-adjusted protein intake and energy-adjusted saturated fat intake ($\beta = 0.089$, $P = 0.135$)

The odds ratios calculated from logistic models with microalbuminuria status as the dependent variable and dummy variables representing quintiles of energy-adjusted macronutrient intake as the independent variables are shown in **Table 3**. The odds ratio

of having microalbuminuria in the highest quintile of energy-adjusted saturated fat compared with the lowest was significantly > 1.0 ($P = 0.02$). A test for trends was not significant for quintiles of energy-adjusted saturated fat ($P = 0.05$), quintiles of energy-adjusted protein ($P = 0.11$), or quintiles of energy-adjusted carbohydrate intake ($P = 0.85$).

With use of logistic regression, the odds ratio for the relation between quintiles of energy-adjusted dietary protein and presence of microalbuminuria (relative to the lowest quintile of intake) was calculated both unadjusted and adjusted for each factor mentioned above. Only age at diabetes diagnosis altered the odds ratio for the highest quintile of energy-adjusted protein intake by $> 10\%$. A similar process was carried out for quintiles of energy-adjusted saturated fat intake. The only factors to alter

TABLE 2
Regression coefficient for the univariate relation between energy-adjusted macronutrient variables and other independent variables

Independent variable	Dependent variable: energy-adjusted protein		Dependent variable: energy-adjusted saturated fat	
	β ($\times 10^{-3}$)	P	β ($\times 10^{-3}$)	P
Sex (n = 178)	24.0	0.243	-6.0	0.843
Age at diagnosis (y) (n = 178)	-1.61	0.226	-0.67	0.732
Age (y) (n = 178)	0.51	0.533	1.19	0.407
Smoking status (n = 178)	37.0	0.144	2.0	0.957
Duration of diabetes (n = 178)	1.43	0.121	1.60	0.238
Body mass index (kg/m ²) (n = 174)	-0.042	0.966	-1.9	0.177
Glycated hemoglobin (%) (n = 143)	0.034	0.996	-5.47	0.594
Serum HDL cholesterol (mmol/L) (n = 138)	6.98	0.803	40.2	0.319
Exercise frequency (n = 177)	14.2	0.127	-27.8	0.042
Number of insulin injections (n = 178)	7.54	0.584	1.21	0.952
Systolic blood pressure (mm Hg) (n = 173)	0.29	0.578	1.17	0.128
Diastolic blood pressure (mm Hg) (n = 173)	0.33	0.772	1.78	0.284
Serum cholesterol (mmol/L) (n = 141)	3.33	0.756	8.51	0.577

TABLE 3

Odds ratios and 95% CIs for microalbuminuria in subjects with insulin-dependent diabetes mellitus according to quintile of energy-adjusted macronutrient intake¹

Dietary quintile	Odds ratio	95% CI	P for odds ratio=1.0
Saturated fat			
1 (lowest)	1.0	Referent	—
2	1.9	(0.59, 5.9)	0.29
3	1.7	(0.52, 5.4)	0.38
4	1.2	(0.35, 3.9)	0.80
5 (highest)	3.9	(1.3, 11.7)	0.02
Protein			
1 (lowest)	1.0	Referent	—
2	0.96	(0.36, 2.6)	0.93
3	0.48	(0.16, 1.4)	0.18
4	0.84	(0.31, 2.3)	0.74
5 (highest)	0.38	(0.12, 1.2)	0.09
Carbohydrate			
1 (lowest)	1.0	Referent	—
2	0.31	(0.09, 1.01)	0.05
3	1.0	(0.37, 2.7)	1.00
4	0.74	(0.27, 2.0)	0.74
5 (highest)	0.64	(0.23, 1.8)	0.64

¹n = 178.

the odds ratio for the highest quintile of energy-adjusted saturated fat intake by >10% were body mass index and serum HDL cholesterol (**Table 4**). Furthermore, adjusting separately for systolic blood pressure, diastolic blood pressure, and serum cholesterol did not alter the odds ratio for the highest quintile of either energy-adjusted macronutrient by >10%.

Adjusting for all the factors did not qualitatively alter the negative relation between energy-adjusted protein intake and microalbuminuria or the positive relation between energy-adjusted saturated fat intake and microalbuminuria (**Table 5**). After the inclusion of both serum cholesterol and diastolic blood pressure, the odds ratio for the highest quintile of energy-adjusted macronutrient intake remained significantly greater than one for saturated fat (5.3, $P = 0.028$) and significantly less than one for protein (0.076, $P = 0.006$). Defining the continuous independent variables as dichotomous variables for inclusion in the logistic models did not substantially alter the results.

When dummy variables for quintiles of energy-adjusted protein intake and for quintiles of energy-adjusted saturated fat intake are included in the same regression model, the relation of each macronutrient variable to microalbuminuria was not substantially altered. There was a significant trend for quintiles of saturated fat ($P = 0.029$) when energy-adjusted protein was included as an independent variable; similarly, there was a significant trend for quintiles of energy-adjusted protein ($P = 0.047$) when energy-adjusted saturated fat was included as an independent variable.

When the eight subjects who reported taking ACE inhibitors (four with normoalbuminuria and four without microalbuminuria) were excluded from the analysis, the odds ratio for the relation between highest quintile of energy-adjusted saturated fat and microalbuminuria for the remaining 170 subjects was 3.7 (95% CI: 1.2, 11.3; $P = 0.021$). The odds ratio for the relation between the highest quintile of energy-adjusted protein intake and microalbuminuria was 0.36 (95% CI: 0.11, 1.2; $P = 0.093$).

From the logistic models there is a suggestion of a threshold effect between quintiles 4 and 5 (the highest quintiles) for both energy-adjusted saturated fat intake and energy-adjusted protein intake. The critical value dividing the highest quintile of percentage of energy as saturated fat from the second-highest quintile in this study population was 18.7% when estimated by 2-d weighed diet record and 19.2% when estimated by FFQ. For protein intake, the critical value for the highest quintile of percentage of energy as protein was 20.5% when estimated by the FFQ and 21.0% when estimated by weighed diet record. An apparent relation between energy-adjusted dietary fat intake and microalbuminuria did not persist after energy-adjusted saturated fat intake was controlled for, and there was no apparent relation for either energy-adjusted monounsaturated fat or energy-adjusted polyunsaturated fat.

DISCUSSION

This study addressed dietary factors that lead to the development of microalbuminuria rather than its progression because the exposure measure used was usual dietary intake and the outcome measure was first detection of persistently raised UAERs. Development of a persistently raised UAER is a strong marker for further increases in the UAER and eventual development of nephropathy (42). In this study of a population-based cohort of persons with IDDM, we found excess microalbuminuria at high relative intakes of saturated fat and a decreased prevalence of microalbuminuria at high relative intakes of protein. These associations were strengthened by controlling for other factors that may have acted as confounders and the associations persisted when one dietary nutrient was controlled for the other. Although the linear associations between the potential confounding factors and the dietary exposure variables were not strong, the increase in the strength of association between exposure and outcome remaining after these factors were controlled for suggested that some confounding was present.

The small number of subjects in each quintile of the macronutrient variables meant that there was low power to detect a significant difference between the outcome groups. This was particularly so for the multivariate analysis, in which the number in each

TABLE 4

Odds ratios and 95% CIs for microalbuminuria in subjects with insulin-dependent diabetes mellitus according to quintile of energy-adjusted macronutrient intake¹

Dietary quintile	Unadjusted		Adjusted	
	Odds ratio	95% CI (P)	Odds ratio	95% CI (P)
Saturated fat				
1 (lowest)	1.0	Referent	1.0	Referent
2	1.9	0.51, 6.7 (0.34)	1.9	0.51, 7.3 (0.33)
3	1.0	0.25, 4.0 (1.00)	0.86	0.20, 1.3 (0.84)
4	1.3	0.33, 4.8 (0.74)	1.2	0.30, 4.7 (0.80)
5 (highest)	2.8	0.82, 9.9 (0.10)	4.4	1.2, 16.6 (0.03)
Protein				
1 (lowest)	1.0	Referent	1.0	Referent
2	0.96	0.36, 2.6 (0.93)	0.94	0.34, 2.6 (0.90)
3	0.48	0.16, 1.4 (0.18)	0.46	0.15, 3.0 (0.17)
4	0.84	0.31, 2.3 (0.74)	0.76	0.27, 2.1 (0.59)
5 (highest)	0.38	0.12, 1.2 (0.09)	0.32	0.10, 1.0 (0.05)

¹Quintiles adjusted for age at diagnosis (protein: $n = 178$) and for BMI and serum HDL cholesterol (saturated fat: $n = 136$).

TABLE 5

Odds ratios and 95% CIs for microalbuminuria in subjects with insulin-dependent diabetes mellitus according to quintile of energy-adjusted macronutrient intake¹

Dietary quintile	Unadjusted		Adjusted	
	Odds ratio	95% CI (P)	Odds ratio	95% CI (P)
Saturated fat				
1 (lowest)	1.0	Referent	1.0	Referent
2	1.9	0.51, 6.7 (0.34)	2.2	0.54, 9.0 (0.27)
3	1.0	0.25, 4.0 (1.00)	0.6	0.14, 3.0 (0.57)
4	1.3	0.33, 4.8 (0.74)	1.1	0.26, 4.6 (0.91)
5 (highest)	3.0	0.87, 10.6 (0.08)	4.9	1.2, 20.0 (0.03)
Protein				
1 (lowest)	1.0	Referent	1.0	Referent
2	0.85	0.28, 2.6 (0.78)	0.88	0.25, 3.2 (0.85)
3	0.49	0.15, 1.6 (0.24)	0.58	0.16, 2.2 (0.42)
4	0.72	0.23, 2.3 (0.56)	0.81	0.23, 2.9 (0.75)
5 (highest)	0.14	0.03, 0.71 (0.02)	0.10	0.02, 0.56 (0.01)
Carbohydrate				
1 (lowest)	1.0	Referent	1.0	Referent
2	0.41	0.11, 1.6 (0.20)	0.31	0.06, 1.5 (0.13)
3	1.0	0.31, 3.3 (1.00)	0.98	0.25, 3.9 (0.98)
4	0.83	0.25, 2.8 (0.76)	0.49	0.12, 2.0 (0.32)
5 (highest)	1.0	0.31, 3.3 (1.00)	0.81	0.22, 3.0 (0.75)

¹*n* = 135.

²Adjusted for sex, age at diagnosis, smoking status, duration of diabetes, BMI, glycated hemoglobin, serum HDL cholesterol, frequency of exercise, and number of daily insulin injections.

quintile dropped to 27. Despite this, the parameter estimates for the relation between microalbuminuria and the highest quintile of energy-adjusted saturated fat or energy-adjusted protein were consistent and stable with the introduction of other variables into the model. Although the study was cross-sectional, the likelihood of the outcome factor (albuminuria status) influencing the dietary exposure measures was minimized by exclusion of subjects who had been diagnosed previously with raised urinary albumin excretion and those who had a UAER > 200 µg/min.

Persons who declined to participate in this study were more likely to be male than female and also more likely to be younger. There are no compelling reasons to believe the findings of this study were biased by nonparticipation. When the 43 subjects who had measurements for dietary intake and microalbuminuria status but not all of the other factors considered in multivariate analysis were excluded, the unadjusted odds ratios for the relation between quintiles of energy-adjusted macronutrient variables and microalbuminuria were not qualitatively different from those including 178 subjects. In the case of energy-adjusted protein intake, the relation was strengthened.

It is possible that the association between the dietary exposure variables and the outcome is an artifact of dietary intake measurement error. The FFQ measurement instrument was compared with weighed diet records for the study population and was found to perform similarly to FFQs used in other populations. Measurement error in FFQs is substantial; however, there is no reason to suspect it is differential with respect to microalbuminuria. Therefore, measurement error is likely to result in an underestimate of the true association between dietary macronutrient intake and microalbuminuria. The estimated correlation between

true dietary intake and the FFQ for energy-adjusted protein intake was relatively poor (0.36), probably because protein intake has a high ratio of within- to between-person variance. The possibility remains that the measurement of dietary protein intake is more strongly correlated with a factor associated with microalbuminuria than with actual usual protein intake although this seems remote. The observed association could be explained if subjects with microalbuminuria had been included who had followed advice to lower their dietary protein intake. This was not the case: all subjects who had knowledge of having microalbuminuria before the study began and all with a UAER > 200 µg/min were excluded.

The exclusion from analysis of subjects who were taking ACE inhibitors daily strengthened the relations observed between microalbuminuria and both energy-adjusted protein intake and energy-adjusted saturated fat intake. ACE inhibition has a strong effect to lower urinary protein excretion in microalbuminuria (43); therefore, failure to control for ACE inhibition would be expected to obscure a relation between dietary saturated fat intake or dietary protein intake and microalbuminuria.

Few previous studies directly addressed the relation between usual dietary intake and the development of microalbuminuria in IDDM (in contrast with the progression of microalbuminuria once established). Two other studies compared the mean dietary intake of subjects with IDDM between those with microalbuminuria and those without microalbuminuria (22, 23). In both studies, estimated dietary energy intake was higher in the group that had microalbuminuria although the difference was not significant. The mean percentage of dietary energy from protein was not significantly different between groups in both studies: it was higher in the group with microalbuminuria in the American study (23) but lower in the British study (22). The percentage of energy from dietary fat was significantly greater in the group with microalbuminuria in the British study (22); the mean intake for the group was 44% of dietary energy. The nonsignificant difference was in the reverse direction in the study from the United States (23). Neither study compared dietary intake of saturated fat between groups. The studies involved small groups of subjects (*n* = 30 and *n* = 32 in the British and US studies, respectively), which resulted in low power to detect differences in nutrient intake. Furthermore, the reference period for assessment of dietary intake in both studies was relatively short.

The present study had more than five times the number of subjects in either of the studies discussed above and controlled for several factors in the analysis. After each factor was controlled for, the strength of association observed between the dietary exposure variables and microalbuminuria tended to increase. The significant nutrient differences found in the two smaller studies (22, 23) were also observed in this study.

The finding in relation to protein intake is surprising. Studies that address the effect of dietary intake (in particular, protein intake) on the progression of microalbuminuria (44–47) show that lower protein intakes result in a mean reduction in the rate of urinary albumin excretion for ≥ 2 y. The findings from these studies are not necessarily relevant to factors influencing the initiation of microalbuminuria. However, recommendations have been made that people with IDDM and normoalbuminuria should moderate their protein intake to prevent the onset of microalbuminuria (48), despite a lack of evidence addressing this specific event.


It is not at all clear how a high relative intake of dietary protein might protect against the development of microalbuminuria.

This result needs to be replicated in other studies, and clearly the issue of differential measurement error is important. Dietary protein restriction lowers the glomerular filtration rate in patients with IDDM who have normal to increased glomerular filtration rates, which may play a part in the reduction of urinary albumin excretion that accompanies protein restriction after the onset of microalbuminuria. It is tempting to speculate that a long-term, sustained, high-protein intake may lead to compensatory mechanisms that ameliorate the harmful effects of a high glomerular filtration rate or high intraglomerular pressure, but a detailed mechanism cannot be proposed.

In a 2-y study of people with IDDM and microalbuminuria (49), replacement of dietary saturated fat with linoleic acid increased the UAER compared with a group in which the total fat component was unchanged. The effect of fat intake in general has not been reported. A mechanism relating a high dietary saturated fat intake to the initiation of microalbuminuria could involve the development of a hypercoagulative circulatory state indicated by raised fibrinogen, increased plasminogen activator inhibitor 1, and increased factor VII coagulant activity (40). Diets rich in fat, and in particular saturated fat, increase factor VII coagulant activity in healthy individuals and may favor the development of a hypercoagulative state (50, 51).

The relation of dietary saturated fat to microalbuminuria may be mediated through elevated serum cholesterol or other lipoprotein abnormalities influenced by diet. If this were the primary causal pathway, the apparent relation between microalbuminuria and energy-adjusted saturated fat would be expected to weaken when serum cholesterol concentration was added as a covariate to the model. We found that the odds ratio for the highest quintile of energy-adjusted saturated fat relative to the lowest decreased marginally by 5% with introduction of serum cholesterol as a covariate. The role of other lipoprotein abnormalities is unknown because they were not measured.

A further possible mechanism may involve the development of an insulin-resistant state by a high saturated fat intake (52). Dietary saturated fat may contribute to peripheral insulin resistance by altering membrane fluidity or by interfering with the cycling of the insulin receptor (53). Different types of dietary fats have been shown to have differing effects on insulin and glucose responses in people with NIDDM (54). In addition, insulin resistance has been observed to be associated with microalbuminuria in human subjects with IDDM (55) and in rats (53, 56); furthermore, insulin resistance is associated with low serum HDL cholesterol in nondiabetic subjects (57). The measurement of insulin resistance in future studies of the relation of dietary macronutrients to microalbuminuria would contribute important information to explore this possibility.

The findings of this study are potentially important because microalbuminuria is associated with greater mortality in IDDM, NIDDM, and nondiabetic populations and because the incidence of microalbuminuria is high in IDDM. Although strict control of blood glucose, maintenance of blood pressure within a normal range, and use of ACE inhibitors in normotensive subjects with IDDM are all likely to be important in preventing the development of microalbuminuria, other lifestyle measures such as following a particular dietary regime may form an important adjunct strategy to avoid microalbuminuria. Therefore, a sound rationale exists for further investigation of the relation between dietary intake and microalbuminuria. 

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