Higher Intakes of Fish Protein Are Related to a Lower Risk of Microalbuminuria in Young Swedish Type 1 Diabetic Patients

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OBJECTIVE — To examine the influence of dietary intake from various protein and fat sources on the occurrence of microalbuminuria in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — In this nested case control study, 1,150 patients with diabetes duration >5 years reported dietary habits for the previous 12 months and submitted urinary samples for the analysis of albumin excretion rate (AER). A total of 75 cases of albuminuria (overnight AER ≥15 μg/min) were identified and compared with 225 duration-matched control subjects.

RESULTS — Neither mean protein, fat intake, average fish protein intake (control subjects 4.56 ± 3.83 g/day and cases 3.82 ± 2.87 g/day; $P = 0.12$), nor intake of meat and vegetable protein differed between the cases of albuminuria and the control subjects. High consumers of fish protein (greater than the 75th percentile) (12 cases and 63 control subjects, mean intake 9.35 g fish protein/day, i.e., ~53 g fish/day) had lower odds ratios (ORs) for microalbuminuria than individuals consuming less fish protein (mean 2.72 g/day) (crude OR 0.49 and 95% CI 0.25–0.97). When adjusted for known confounding factors, such as HbA_{1c}, mean arterial pressure, diabetes duration, age, sex, smoking, BMI, country region, and total energy, individuals with a high intake of fish protein and fish fat showed a reduction in the risk for microalbuminuria (OR 0.22 and 0.31, respectively; 95% CI 0.09–0.56 and 0.13–0.76, respectively). When fish protein and fat were adjusted for each other, a high intake of fish protein but not of fish fat was still significantly associated with a decrease in the risk for microalbuminuria.

CONCLUSIONS — Total protein and fat intake were not associated with the presence of microalbuminuria, but a diet including a high amount of fish protein seemed to lessen the risk.

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Prevention of diabetic nephropathy (DN) is one of the most important challenges in the treatment of type 1 diabetes. Most certainly, improved long-term glycemic control has reduced the risk of developing DN in childhood-onset diabetic patients (1,2). Still, the prevalence of DN is as high as 10–30% (1,2). Additional treatment modalities are needed to prevent this serious complication and to prevent cardiovascular disease (CVD), which is closely linked (3–6).

Persistent microalbuminuria is a sign of ongoing glomerular injury in diabetes and a strong predictor of clinical nephropathy (7). Elevated glomerular filtration rate (GFR) has been indicated as predictive of microalbuminuria (8). A high-protein intake increases renal workload and GFR (9) and may enhance the progression of DN in microalbuminuric patients (10,11). Accordingly, the use of a low-protein diet in normoalbuminuric type 1 diabetic patients normalizes glomerular hyperfiltration (12); in addition a meta-analysis by Pedrini et al. (13) showed retarded progression of renal disease in type 1 diabetic patients independent of blood glucose or blood pressure levels. However, there is accumulating evidence to suggest that not all kinds of dietary proteins are equal in relation to their renal effects. Dietary protein of animal origin is proposed to exert a heavier burden on renal hemodynamics than vegetable protein (9,14). In addition, a substitution of red meat with white meat (chicken and fish), in otherwise normal amounts of dietary protein, reduces GFR in hyperfiltrating patients (15).

The relative roles of other dietary components, such as fat, fiber, and certain vitamins and minerals, in the development of diabetes-associated complications also have been discussed (16–22). To reduce the risk for CVD in diabetes, a limited intake of saturated fat and cholesterol is recommended (23). On the other hand, polyunsaturated fatty acids of the n-3 type, provided by fat in fish and seafood, may not only correct hypertriglyceridemia, but also reduce blood pressure and albuminuria in patients with chronic renal disease (18,24,25). It is controversial whether fish oil supplements in albuminuric diabetic patients are beneficial (16,20).

Little is known about the effects of long-term protein or fat intake (from various sources) on the development of diabetic renal disease. Therefore, in the present nested case-control study, we have investigated the influence of reported dietary intake habits on the occurrence of micro- and macroalbuminuria in young patients with type 1 diabetes, while

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Abbreviations: AER, albumin excretion rate; CVD, cardiovascular disease; DN, diabetic nephropathy; GFR, glomerular filtration rate; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

taking into account other known confounding factors.

RESEARCH DESIGN AND METHODS

— In the Swedish Health Care System, all children aged 0–14 years with suspected diabetes are referred to pediatric departments. Since 1 July 1977, all incident cases of diabetes are reported from the pediatric departments to a central register in Umeå, Sweden. In the present study, children registered between 1 July 1977 and 31 December 1987 with a diabetes duration ≥5 years were invited to participate (n = 3,858). Responses were obtained from 1,150 patients. Nonparticipants did not differ from participants with regard to sex, but were older (20.3 ± 4.5 vs. 17.9 ± 4.9 years) and had a slightly longer duration of diabetes (10.9 ± 3 vs. 10.2 ± 3 years). After careful instruction, the participants were asked to deliver two timed overnight urinary samples to be assayed for albumin excretion rate (AER). Collection was not performed during menstruation, and if one of two samples screened positive for microalbuminuria (i.e., ≥15 μg/min), a third sample was requested. We used a definition of persistent microalbuminuria based on at least two urine samples of 15–200 μg/min. AER was determined at the Department of Clinical Chemistry, Umeå University Hospital, using an immunoturbidimetric method (26) and a Hitachi 911 automated spectrophotometer. Intra- and interassay coefficients of variation were 2.40 and 5.84%, respectively. Based on the cohort of the 1,150 patients, a nested case-control design was applied. A total of 75 type 1 diabetes cases with microalbuminuria (AER 15–200 μg/min, n = 69) or macroalbuminuria (AER >200 μg/min, n = 6) were identified in this cohort. Three control subjects per case, matched for diabetes duration, were chosen among the remaining 1,075 normoalbuminuric diabetic patients.

Collection of data

All subjects in the cohort were asked to answer a mailed semiquantitative food frequency questionnaire concerning mean nutritional intake during the previous 12 months. The questionnaire contained detailed instructions and clarifying pictures for the participants. The subjects answered questions concerning how often they consumed different kinds of dishes, drinks, and sandwiches. Specifically, they were asked the following two questions: How often do you eat fish (times per day, week, month)? And, how was it prepared (boiled, fried, smoked, baked, with breading)? With the help of photographs of standard-sized dishes, they also estimated the amount of food eaten. This questionnaire has been developed and evaluated (27) by the Swedish National Food Administration in Uppsala, Sweden. A specially developed computer program converted the precoded alternatives into amounts of macronutrients, vitamins, and minerals. In collaboration with the Swedish National Food Administration and their software consultants, this program was further adjusted to the questionnaire. Protein sources were divided into fish, meat (chicken or red meat), milk, and vegetable protein. Fats (cholesterol, saturated, monounsaturated, and polyunsaturated) were also divided into groups according to origin.

Information regarding current metabolic control (HbA_{1c}), blood pressure levels, prevailing insulin dose, and weight and height were obtained from the medical records of all participants. Laboratory methods and reference levels of HbA_{1c} differed throughout the country, but the mean coefficient of variation was estimated at 7% (EQUALIS Reference Lab, unpublished data). Within each of the 24 counties and often within the six regions, usually the same method is used.

The Ethics Committee of the Karolinska Institute and the Swedish Data Inspection Board approved the study, and informed consent was obtained from all participants.

Statistical analyses

Comparisons between the groups were made by Student's t test or χ^2 analysis. Crude odds ratios (ORs) and 95% CIs were calculated using the Mantel-Haenszel method. Conditional logistic regression analyses were performed using the following confounding factors: age, BMI, duration of diabetes, HbA_{1c}, smoking, sex, and mean arterial blood pressure. The distribution of cases and control subjects was similar throughout the 24 counties by Mann-Whitney rank test (P = 0.63) and did not differ within regions by χ^2 test. In the logistic regression analyses performed to correct for confounding factors, we also adjusted for region. Data are expressed as means ± SD. $P \leq 0.05$ was considered statistically significant. The statistical program used was SPSS 10.0 for windows.

RESULTS

— Median AER (μg/min) was 4.8 in control subjects (25th percentile 3.1 μg/min and 75th percentile 7.1 μg/min) and 40.9 in cases (25th percentile 26.2 μg/min and 75th percentile 75.3 μg/min). Current age, female/male ratio, and blood pressure were higher in cases than in control subjects (Table 1). Mean energy, fat, protein, and carbohydrate intakes were not different (Table 1). Mean daily intake of vitamins and minerals was not different between cases and control subjects, and daily intake of antioxidants (vitamin E, vitamin C, carotenoids, and selenium) did not differ between the groups (data not shown). In Tables 2 and 3, the mean daily intake of protein and fat from different sources (fish, meat, milk, and vegetable) are shown.

Protein intake

The mean protein intake did not differ between cases and control subjects and contributed to 16.3 ± 2.0 and 16.6 ± 2.2% of total energy intake, respectively (P = 0.30). Among the participants, 3 cases and 17 control subjects had a protein intake ≥20% of energy. For cases, the mean intake of protein was 1.55 ± 0.64 g/kg body wt, and for control subjects it was 1.58 ± 0.57 g/kg body wt (P = 0.66); 63 cases and 193 control subjects had a daily intake of >0.8 g protein/kg body wt. When dividing the protein into groups depending on origin (fish, meat, milk, or vegetable protein), control subjects tended to have a higher mean intake of fish protein than cases and a higher milk protein intake. Meat and vegetable protein did not show any differences (Table 2). When analyzing a high protein intake, defined as more than the 75th percentile (≥120.1 g/day) as a risk factor for micro- and macroalbuminuria, it did not differ significantly between cases and control subjects (Table 2). A high meat and vegetable protein intake (75th percentile ≥32.3 and ≥43.2 g/day, respectively) also did not affect the odds for having micro- or macroalbuminuria. A high intake of fish protein (in this study the 75th percentile corresponded to 6.50 g/day) was associated with a significant risk decrease for micro- and macroalbuminuria in young type 1 diabetic patients (Table 2). The mean fish protein intake in

Table 1—*Clinical data of micro- and macroalbuminuria cases and normoalbuminuric control subjects*

	Cases (n = 75)		Control subjects (n = 225)		P
	Female	Male	Female	Male	Both sexes
n	44	31	98	127	—
Age (years)	21.3 ± 4.4	18.7 ± 2.7	20.2 ± 5.1	17.6 ± 4.9	0.02
Age at onset (years)	9.5 ± 3.0	8.4 ± 2.9	8.3 ± 3.8	7.0 ± 3.9	<0.01
Duration of diabetes (years)	11.7 ± 2.9	10.3 ± 2.8	11.9 ± 3.0	10.6 ± 2.8	1.00
BMI (kg/m^2)	22.7 ± 2.4	22.0 ± 2.2	22.4 ± 2.7	22.3 ± 3.1	0.88
HbA_{1c} (%)	7.9 ± 3.1	8.0 ± 2.3	7.6 ± 1.8	7.4 ± 1.9	0.13
Systolic blood pressure (mmHg)	123.9 ± 9.4	126.4 ± 11.9	115.6 ± 9.7	117.4 ± 10.9	<0.01
Diastolic blood pressure (mmHg)	78.5 ± 8.4	76.7 ± 7.7	74.2 ± 8.5	72.1 ± 7.9	<0.01
Mean arterial pressure (mmHg)	93.6 ± 7.2	93.3 ± 8.0	88.0 ± 7.6	87.2 ± 7.4	<0.01
Energy intake (kcal)	2,002 ± 698	2,834 ± 731	1,995 ± 705	2,658 ± 706	0.82
Fat intake (g/day)	59.2 ± 23.5	90.1 ± 31.5	61.9 ± 30.3	85.3 ± 29.5	0.46
Protein intake (g/day)	80.8 ± 27.9	115.5 ± 29.6	82.32 ± 32.7	110.9 ± 32.5	0.48
Carbohydrate intake (g/day)	279.6 ± 111.9	374.6 ± 102.5	270.4 ± 96.9	354.1 ± 109.8	0.90
Smoking (n)					0.12
yes	7	2	11	3	—
no	37	28	85	118	—

Data are means ± SD. P values are calculated for cases, control subjects, and both sexes together.

the high consumer group was 9.35 g/day (~53 g fish), whereas mean fish protein intake in the low consumer group was 2.72 g/day (~15 g fish). Because the mean daily intake of milk protein tended to be higher among control subjects than cases, we also analyzed the OR for micro- or macroalbuminuria when milk intake exceeded the 75th percentile versus intake below the 75th percentile (OR 0.55, 95% CI 0.28–1.07; P = 0.08).

Fat intake

The mean fat intake was similar for cases and control subjects, and fat supplied on average 27.4 ± 5.9% of energy in cases and 28.9 ± 6.6% of energy in control subjects (P = 0.24). There was no significant difference between cases and control subjects in the intake of cholesterol, saturated, monounsaturated, or polyunsaturated fat. When dividing the consumed fat into groups according to origin (the same categories as for protein), there was a difference between cases and control subjects regarding mean intake of fish fat (2.4 ± 2.3 and 2.8 ± 2.7 g/day, respectively; P = 0.20) and milk fat (27.1 ± 18.6 and 30.5 ± 19.9 g/day, respectively; P = 0.20). Meat and vegetable fat did not show any differences (Table 3). An intake above the 75th percentile of total fat (≥93.3 g/day), saturated fat (≥39.9 g/day), monounsaturated fat (≥32.0 g/day), polyunsaturated fat (≥14.1 g/day), or cholesterol (≥0.4 g/day) did not increase or decrease the risk for DN. When comparing fat from different sources, an intake above the 75th percentile of fat from fish (≥3.7 g/day) had a significant protective effect, but fat from any other source (meat, milk, or vegetable) did not (Table 3).

Multivariate analyses

In a logistic regression analysis (Table 4) including age, sex, BMI, duration of diabetes, smoking, mean arterial blood pressure, HbA_{1c}, energy intake, and country region as confounding factors, a high intake of fish protein was still an independent protective determinant (OR 0.22, 95% CI 0.09–0.56). When including a high fish fat intake instead of fish protein, fat also turned out to be an independent protective determinant (0.31, 0.13–0.76). When adjusting fish fat and fish protein for each other, only fish protein was a significant protective factor (0.26, 0.09–0.76), not fish fat (0.77, 0.27–2.20). Children in Sweden drink more milk than older individuals, and cases were older than control subjects. To evaluate whether the putative protective effect in drinking milk was an age-dependent effect, we adjusted the milk protein intake for age, which gave a minor change in the OR (0.57, 0.29–1.11; P = 0.10).

Table 2—*Mean intake of protein (gram/day) and P values of mean differences between all micro- and macroalbuminuria cases and normoalbuminuric control subjects, including crude ORs for intake ≥75th percentile and 95% CI intervals*

	Cases (n = 75)	Control subjects (n = 225)	P	OR*	95% CI*
Total protein	95.17 ± 33.23 (20)	98.44 ± 35.49 (55)	0.48	1.12	0.62–2.04
Fish protein	3.82 ± 2.87 (12)	4.56 ± 3.83 (63)	0.12	0.49	0.25–0.97
Meat protein	24.97 ± 14.76 (19)	24.09 ± 16.44 (56)	0.68	1.02	0.56–1.87
Milk protein	29.68 ± 15.45 (13)	34.11 ± 17.84 (62)	0.06	0.55	0.28–1.07
Veg. protein	35.19 ± 14.97 (19)	34.38 ± 13.77 (56)	0.66	1.02	0.65–1.87

Data are means ± SD and (n) ≥75th percentile, unless otherwise indicated. Numbers of individuals representing ≥75th percentiles are given. *Crude ORs and 95% CIs are calculated with intake ≥75th percentile defined as exposure versus <75th percentile.

Table 3—*Mean intake of fat (gram/day) and P values of mean differences between all micro- and macroalbuminuria cases and normoalbuminuric control subjects, including crude ORs for intake ≥75th percentile and 95% CI intervals*

	Cases (n = 75)	Control subjects (n = 225)	P	OR*	95% CI*
Total fat	71.95 ± 30.94 (20)	75.11 ± 31.97 (55)	0.46	1.12	0.62–2.04
Saturated fat	30.09 ± 14.32 (18)	32.34 ± 15.28 (57)	0.26	0.93	0.51–1.71
Monounsaturated fat	24.88 ± 10.73 (21)	25.66 ± 11.10 (54)	0.60	1.23	0.68–2.22
Polyunsaturated fat	11.05 ± 4.83 (19)	10.95 ± 4.86 (56)	0.88	0.76	0.41–1.43
Cholesterol	0.30 ± 0.12 (15)	0.30 ± 0.15 (60)	0.20	0.69	0.36–1.30
Fish fat	2.39 ± 2.32 (12)	2.84 ± 2.67 (63)	0.20	0.49	0.25–0.97
Meat fat	21.85 ± 13.45 (20)	20.74 ± 13.72 (19)	0.54	1.12	0.62–2.04
Milk fat	27.06 ± 18.58 (16)	30.44 ± 19.95 (59)	0.20	0.76	0.41–1.43
Vegetable fat	20.63 ± 1.43 (20)	21.00 ± 0.86 (55)	0.83	1.12	0.62–2.04

Data are means ± SD and (n) ≥75th percentile, unless otherwise indicated. Numbers of persons representing ≥75th percentile are given. *Crude ORs and 95% CIs are calculated using intake ≥75th percentile defined as exposure versus <75th percentile.

CONCLUSIONS — The major finding of this study was that individuals consuming ~9.3 g of fish protein per day (~53 g fish/day) had lower ORs for microalbuminuria compared with individuals consuming less fish protein (~2.7 g/day, equaling 15 g fish/day) (Table 2). This indicates a protective effect of fish intake on diabetic renal disease. Although in our analysis the effects of fish protein seemed stronger than that of fish fat, it cannot be determined whether fish fat gave the protective effect or other components in fish contributed to our results. A high content of n-3 polyunsaturated fatty acids have been reported, though not unambiguously, to have beneficial effects on arterial blood pressure, transcapillary escape rate of albumin, albuminuria, and kidney function in diabetic and nondiabetic patients (16,20,25,28,29).

The effect of dietary protein on the progression of overt diabetic renal disease in adults has been closely examined (30,31). A low protein diet has been shown to normalize glomerular hyperfiltration in short-term experiments (12) and to slow the progression of diabetic as well as nondiabetic renal disease (13). In this study, we have focused on young diabetic patients to investigate whether dietary intake of protein and other nutrients may affect onset of diabetic nephropathy, but we did not find a significant risk with a diet rich in protein of any kind. In most studies dealing with the effect of dietary protein on renal function, the design has been experimental, i.e., based on an introduction of a low-protein diet or acute protein loads (32–34). In our study, we analyzed reported long-term protein intake and evaluated the risk to have microalbuminuria for high-protein eaters, defined as individuals with an intake above the 75th percentile (in this case >120.1 g/day protein), compared with individuals with an intake below this level. None of the patients were restricted to a low-protein diet. Although it has been shown in several studies that different protein sources may have different effects on renal function (9,14,15), not many epidemiological reports have analyzed the risk of different eating habits on the presence of microalbuminuria in young type 1 diabetic patients. The European IDDM Diabetes Complications Study Group (35) found an association between dietary protein intake and urinary AER in 2,696 patients with type 1 diabetes. In that study, the statistically significant relationship between intake of total protein and AER was observed for animal protein but not for vegetable protein; the animal protein was not grouped according to origin. In our study, we could not confirm an association between a high total animal protein intake and having microalbuminuria. The different results could be caused by a relatively low power in our study, which could make it difficult to find significant associations between different nutrients and AER. In contrast, in a population-based cross-sectional Australian study, energy-adjusted protein intake was inversely related to microalbuminuria when taking other known confounding factors into account (36). In addition, several smaller studies of type 1 diabetic patients have indicated that dietary protein is not associated with the occurrence or progression of diabetic renal disease (37–39). Our findings are also in agreement with those of Pecis et al. (15), who found that GFR was reduced in hyperfiltrating patients not only after a low-protein diet, but also after a switch from a red meat to a fish and chicken diet, still containing the usual amounts of protein. Thus, fish protein may decrease renal workload, thereby reducing the risk for future development of diabetic nephropathy. Because the data collected only included information on nutritional intake over the last year, it is not possible to conclude how long a period of high fish intake is necessary to reach the positive effect observed.

Somewhat unexpectedly, we found that cases with microalbuminuria had a lower milk intake than normoalbuminuric control subjects, and in the univariate analysis, a high milk protein intake was almost as significant as a protective factor against microalbuminuria. However, because cases were older than control subjects and because young children in Sweden may drink more milk than older individuals, it was necessary to correct for age in the statistical analysis. This revealed that milk consumption was related to age.

Data on daily, weekly, or monthly intake of different foods and drinks were retrospectively collected in this study. The participants used photographs of

Table 4—*Logistic regression model, analyzing high fish protein and high fish-fat intake (≥75th percentile vs. <75th percentile), adjusting for possible confounding factors*

Variable	OR	95% CI	P
Age	1.06	0.97–1.16	0.23
Duration	0.94	0.81–1.09	0.45
Sex	1.49	0.72–3.15	0.29
HbA_{1c}	1.16	0.97–1.38	0.10
Mean arterial pressure	1.13	1.08–1.18	<0.01
BMI	0.97	0.86–1.09	0.58
Region	0.88	0.71–1.07	0.25
Smoking	1.36	0.44–4.18	0.60
Energy intake*	1.00	1.00–1.00	0.13
Fish protein†	0.26	0.09–0.76	0.01
Fish fat†	0.77	0.27–2.20	0.63

*The exact figures are OR 1.000 and 95% CI 1.000–1.001; †fish protein and fish fat intake ≥75th percentile (12 cases and 63 control subjects) versus <75th percentile (63 cases and 162 control subjects).

standard-sized dishes to estimate the amount of food eaten. They reported their dietary intake during the last 12 months in a validated semiquantative food frequency questionnaire developed by the Swedish National Food Administration. Becker et al. (27) validated this type of diet recording by comparing it with the weight of the food eaten and showed a high agreement between the two methods. In this study, the participants had a relatively low protein and fat intake and high carbohydrate intake, which is in accordance with the Swedish and international recommendations (23). It is unlikely that the data collected had a disease-dependent bias, because cases and control subjects were unaware of their allocation to the case or control group, which was determined centrally, after returning the questionnaires. In addition, if cases are aware of the microalbuminuria, it is unlikely that they would have any idea that fish diet might affect the risk, and thus offer a biased response. On the other hand, negative results regarding associations between the certain dietary variables and the occurrence of microalbuminuria should be interpreted with caution; a nondifferential misclassification of exposure (i.e., the same between cases and control subjects) cannot be excluded for certain, thus diluting the ORs.

Low-grade microalbuminuria may revert to normal in ~30% of young type 1 diabetic patients, and the renal fate of these cases is unknown (40). Still, persistently elevated AER (in two of three consecutive urine tests) is the strongest predictor of overt diabetic nephropathy (7,41), and increased AER correlates well with glomerular structural changes in type 1 diabetes (42). Thus, it is justified to use microalbuminuria as a marker of incipient diabetic nephropathy. The participants in the present study had a mean diabetes duration of 11 years. It cannot be definitely excluded that some of the normoalbuminuric subjects later may develop microalbuminuria. Therefore, interpretation of these results must be restricted to populations of this diabetes duration. On the other hand, the prevalence of microalbuminuria in the present cohort (6.5%) accords well with the prevalence of diabetic nephropathy in young patients with an onset of type 1 diabetes from 1971 to 1975 followed for 20 years in Sweden (~6%) (2).

In conclusion, our results do not give evidence for the suggestion that a high-protein diet increases the risk for incipient diabetic nephropathy. Rather, a diet rich in fish protein seems to provide protection from this complication.

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