Protein intake and urinary albumin excretion rates in the EURODIAB IDDM Complications Study

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Summary For people with insulin-dependent diabetes mellitus (IDDM) renal disease represents a life-threatening and costly complication. The EURODIAB IDDM Complications Study, a cross-sectional, clinic-based study, was designed to determine the prevalence of renal complications and putative risk factors in stratified samples of European individuals with IDDM. The present study examined the relationship between dietary protein intake and urinary albumin excretion rate (AER). Food intake was assessed centrally by a standardized 3-day dietary record. Urinary AER was determined in a central laboratory from a timed 24-h urine collection. Complete data were available from 2696 persons with IDDM from 30 centres in 16 European countries. In individuals who reported protein consumption less than 20% of total food energy intake, mean AER was below 20 µg/min. In those in whom protein intake constituted more than 20%, mean AER increased, a

trend particularly pronounced in individuals with hypertension and/or poor metabolic control. Trends reached statistical significance for intakes of total protein (% of energy, $p = 0.01$) and animal protein (% of energy, $p = 0.02$), while no association was seen for vegetable protein ($p = 0.83$). These findings support the current recommendation for people with diabetes not to exceed a protein intake of 20% of total energy. Monitoring and adjustment of dietary protein appears particularly desirable for individuals with AER exceeding 20 µg/min (approximately 30 mg/24 h), especially when arterial pressure is raised and/or diabetic control is poor. [Diabetologia (1997) 40: 1219–1226]

Keywords Insulin-dependent diabetes mellitus, protein intake, urinary albumin excretion rate, diabetic nephropathy, diet recommendations, Europe.

Kidney disease is a common and costly complication [1, 2] of diabetes mellitus, with individuals often requiring dialysis or renal transplantation. More than 30% of people with insulin-dependent diabetes

mellitus (IDDM) are at risk of manifest renal disease [3–5]. In the EURODIAB IDDM Complications Study 30.6% of a stratified European sample of individuals with IDDM aged 15–60 years (mean diabetes duration: 15 years) had albumin excretion rates (AER) of 20 µg/min or higher. In persons with a diabetes duration of 1–5 years the rate of elevated AER was 19.3% [6]. This high prevalence of micro- and macroalbuminuria even early in IDDM and its predictive association for both clinical nephropathy [7–12] and increased cardiovascular disease risk [6, 13–15] highlight the potential for early detection and effective prevention of diabetic vascular complications.

The use of low protein diets has been shown to reduce the progression of nephropathy in patients with clinically overt diabetic nephropathy [16–19]. In

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; AER, albumin excretion rate; DNSG, Diabetes and Nutrition Study Group; ADA, American Diabetes Association; CI, confidence interval.

Table 1. Characteristics of IDDM patients

Characteristics	Total (<i>n</i> = 2696)	Males (<i>n</i> = 1364)	Females (<i>n</i> = 1332)
Age (years)	32.8 ± 10.2 (14–61)	32.8 ± 10.2 (14–60)	32.7 ± 10.3 (15–61)
Diabetes duration (years)	14.7 ± 9.3 (1–56)	14.5 ± 9.3 (1–56)	14.9 ± 9.4 (1–47)
BMI (kg/m ²)	23.5 ± 2.9 (15–39)	23.5 ± 2.7 (15–34)	23.4 ± 3.1 (15–39)
HbA _{1c} (%) ^a	6.4 (6.3, 6.4)	6.3 (6.2, 6.5)	6.4 (6.3, 6.5)
Albumin excretion rate (µg/min) ^a	16.6 (15.7, 17.6)	18.4 (17.0, 20.0)	15.0 (13.9, 16.1)
AER < 20 µg/min (<i>n</i> (%))	1887 (70.0)	916 (67.2)	971 (72.9)
AER 20 to 200 µg/min (<i>n</i> (%))	579 (21.5)	320 (23.5)	259 (19.4)
AER > 200 µg/min (<i>n</i> (%))	230 (8.5)	128 (9.4)	102 (7.7)
Total protein intake (% of energy)	17.6 ± 3.5	17.4 ± 3.4	17.9 ± 3.7
(g/kg body weight) ^a	1.46 (1.44, 1.48)	1.53 (1.51, 1.56)	1.39 (1.36, 1.41)
Animal protein intake (% of energy)	12.2 ± 3.7	12.0 ± 3.6	12.4 ± 3.8
Vegetable protein intake (% of energy)	5.2 ± 1.3	5.2 ± 1.3	5.2 ± 1.2

Data are mean ± SD (range) or number of patients (%).

^a Geometric mean (95 % CI)

individuals with normo- and microalbuminuria restriction of protein intake has been found to reduce elevated glomerular filtration rate and albuminuria independently of control of blood glucose or blood pressure [20–24]. The level to which protein intake should be modified in order to achieve these beneficial effects has been examined in studies conducted in individuals with micro- [21, 25] and macroalbuminuria [16–19, 26]. However, a uniform therapeutic approach has not yet been established and the question as to whether even normoalbuminuric individuals with diabetes should decrease or modify their current protein intake to avoid the development of renal disease remains to be clarified [27, 28]. The Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes (EASD) [29] and the American Diabetes Association (ADA) [30] have recently recommended that protein intake in people with diabetes should range between 10 and 20 % of total energy. For patients with incipient or manifest nephropathy a protein intake at the lower end of this range ($\approx$ 0.7–0.9 g/kg body weight) is recommended [29].

The present paper aims to analyse the relationship between dietary protein intake and urinary AER in people with IDDM included in the cross-sectional, clinic-based EURODIAB IDDM Complications Study.

Patients and methods

Patients. The EURODIAB IDDM Complications Study was a cross-sectional clinic-based study in 31 European centres, designed to measure the prevalence of diabetic complications and to examine established and putative risk factors for these complications. Within each centre a stratified sample of up to 140 individuals with IDDM aged 15–60 years was selected. Stratification was based on sex, age and duration of diabetes;

details of the selection procedure have already been published [31]. IDDM was defined as the onset of diabetes before the age of 36 years with continuous insulin treatment initiated within 1 year of diagnosis. Of the 3250 individuals with IDDM participating in the EURODIAB IDDM Complications Study a total of 2868 patients from 30 centres could be included in the nutritional analyses [32].

In the present analysis of the relation between dietary protein intake and urinary AER patients requiring dialysis (*n* = 11) were excluded. For 161 subjects no AER measurements were available. Therefore, data from 2696 persons (1364 males, 1332 females) were included in the present analysis of protein intake and AER. The characteristics are presented in Table 1.

The study conformed to the Declaration of Helsinki, and the study protocol was approved by local ethical committees in each centre. Informed consent was given by all individuals with IDDM.

Methods. A standardized 3-day dietary record was employed for nutrition assessment. For this dietary method a good repeatability has already been documented [33]. The procedure used for nutrition assessment is described in detail elsewhere [32]. In brief, individuals were provided with instructions from their local dietitian on how to record all foods and beverages consumed over 3 days (2 workdays and a Sunday). A standardized list of food portion sizes and common household measures designed for this study was given to each person. The local centre dietitian carefully reviewed the completed 3-day dietary record with each individual, in order to clearly identify and quantify all foods and beverages. Then the dietitian coded the food records using a centrally prepared EURODIAB food list. At the nutrition co-ordinating centre, food records were checked once again. Food records were then computer analysed using a nutrient database carefully compiled from a range of existing European food tables, with additional information from food companies. Dietary records were analysed for total protein, animal and vegetable protein, total fat, saturated fat and cholesterol, carbohydrate, fibre and alcohol. Total energy intake was calculated using Atwater factors [34].

The level of AER was measured in London (Guy's Hospital, Medical School) by an immunoturbidimetric method

(Sanofi, Pasteur, Minn., USA) from a timed 24-h urine collection. Samples with proteinuria due to urinary tract infections (Nephur-Test + Leuco, Boehringer, Mannheim, Germany) were excluded from analysis. AER was defined as normal below 20 µg/min, as microalbuminuria at AER of 20 to 200 µg/min, and macroalbuminuria for AER above 200 µg/min.

HbA_{1c} values were determined in London (The Royal London Hospital) using an enzyme immunoassay with a notably low normal range of 2.9 to 4.8%. Resting blood pressure was measured with a random zero sphygmomanometer. The mean of two readings to the nearest 2 mmHg was used for analysis. Information as to whether persons were smokers (current or ex-) or non-smokers was available from a questionnaire completed by all individuals [35].

Statistical analysis. Mean daily intake of energy and nutrients was calculated from the 3-day record of each individual. The distributions of AER and HbA_{1c} as well as the dietary intake of energy, protein/kg body weight, cholesterol/1000 kcal and fibre/1000 kcal were skewed. Thus, these variables were log transformed and geometric means were calculated.

The relationship between AER and protein is presented for all individuals and for groups stratified by glycaemic control or the presence of hypertension. For stratification by glycaemic control, the sample was divided in two groups, according to whether HbA_{1c} was below 6.4% (median HbA_{1c} value for the total study population) or greater. The presence of hypertension was defined as a blood pressure of 140/90 mmHg or above and/or taking blood pressure lowering drugs.

Protein intake was treated as a series of dummy variables, where a separate variable was assigned for each level of protein intake ($\leq 12\%$, 12–14% ... to $> 24\%$). Mean AER calculated for each level of protein intake was adjusted for age, diabetes duration and total energy intake employing the multivariate nutrient density model [36]. In this least square regression model protein intake is expressed as nutrient density and entered in the model simultaneously with total energy intake. The adjusted means were the values predicted by the model when the other variables were held at their mean values. Furthermore, a test for interaction was carried out to investigate whether the relationship between protein intake and AER differed between the defined strata.

Statistical significances in the relationship between protein intake and AER were determined by a trend analysis using the multivariate nutrient density model adjusting for total energy intake. In a further step, other parameters possibly related to the development of early nephropathy (age, diabetes duration, HbA_{1c}, diastolic blood pressure and smoking) were entered in the model. Due to missing data only 1998 individuals (1011 males, 987 females) could be included in the models when adjusting for centrally measured HbA_{1c} concentrations.

Comparison of protein intakes between patients with micro- or macroalbuminuria and subjects with normoalbuminuria was carried out calculating adjusted nutrient intakes separately for each group and testing for differences using intakes in normoalbuminuric individuals as the reference category. Since the distribution of alcohol intake was highly skewed in place of geometric means adjusted percentages of alcohol consumers are given for the groups of persons with normo-, micro- and macroalbuminuria.

All statistical analyses were carried out using the SAS program [37].

Results

Mean protein intake and mean AER for the 2696 individuals with IDDM are given in Table 1. Protein intakes above the recommended upper level of 20% of energy were found in 22% of the persons with diabetes ($n = 601$). Of the patients with macroalbuminuria 32% consumed more than 20% of protein, while this percentage was 23% for the micro- and 20% for the normoalbuminuric individuals with IDDM.

The relation between protein intake and AER for all individuals is illustrated in Figure 1 (top). In categories of persons with protein intakes below 20% of energy mean AER remained at levels of 13.5 to 16.6 µg/min, thereafter approaching mean AER values of 18.9 to 23.6 µg/min in categories of individuals consuming more than 20% of protein. Figure 1 (middle) compares the relation of protein intake with AER between the two strata of glycaemic control. Overall, mean AER was increased in subjects with a higher HbA_{1c} (range of mean AER: 6.7 to 33.4 µg/min) as compared to individuals with lower HbA_{1c} values (range of mean AER: 11.7 to 16.5 µg/min). The trend of AER to rise in categories with protein intakes above 20% could be found for the strata of persons with a higher HbA_{1c}, while this association was not observed for the stratum of individuals with HbA_{1c} below 6.4% (test for interaction between strata, $p = 0.03$). The lowest panel of Figure 1 illustrates that subjects with hypertension generally had a higher AER (range of mean AER: 27.7 to 86.8 µg/min) as compared to normotensive individuals (range of mean AER: 9.1 to 17.7 µg/min). A notable increase in mean AER was seen for hypertensive patients with protein intakes above 20%, while this trend was not pronounced in the stratum of subjects without hypertension (test for interaction between strata, $p = 0.0001$).

Figure 2 illustrates that adjusted mean AER was appreciably greater when protein provided more than 20% of energy as compared to the mean AER in patients consuming up to 20% of protein. This tendency was most pronounced in patients with hypertension or in those with both hypertension and poor diabetes control. Hypertension was not found to be more frequent in patients with a high protein intake.

The test for a linear relationship between protein intake and AER revealed a significant trend of energy adjusted AER to rise with higher intakes of total protein (% of energy, $\beta = 0.02$ [CI 0.01, 0.04], $p = 0.01$) or animal protein (% of energy, $\beta = 0.02$ [CI 0.003, 0.03], $p = 0.02$), while trends were not significant for vegetable protein (% of energy, $\beta = 0.01$ [CI -0.04, 0.05], $p = 0.83$) or protein related to body weight (g/kg body weight, $\beta = 0.1$ [CI -0.1, 0.3], $p = 0.38$). After inclusion of diabetes duration, age, HbA_{1c}, diastolic blood pressure (mean $\pm$ SD:

Fig. 1. *Top:* Geometric mean AER (—●—) for different categories of protein intake ($\leq 12\%$... $> 24\%$ of total food energy) in 2696 individuals with IDDM. Columns indicate percentage of individuals with IDDM in different categories of protein intake. *Middle:* Geometric mean AER in 999 individuals with $\text{HbA}_{1c} < 6.4\%$ (—△—) compared to 1007 subjects with $\text{HbA}_{1c} \geq 6.4\%$ (—●—). *Bottom:* Geometric mean AER in 2050 normotensive individuals (—△—) compared to 619 hypertensive patients (—●—). All geometric means with 95% confidence intervals ($\perp$) are adjusted for total energy intake, age, and diabetes duration

75.4 ± 11.3 mmHg) and smoking (50% were current or ex-smokers) in the model, the trends observed for total protein and animal protein remained significant ($\beta = 0.03$ [CI 0.01, 0.05], $p = 0.001$ and $\beta = 0.02$ [CI 0.01, 0.04], $p = 0.01$, respectively). Furthermore, AER adjusted for these confounding factors was significantly associated with protein intakes related to body weight ($\beta = 0.25$ [CI 0.01, 0.5], $p = 0.045$), while a positive relationship with vegetable protein could not be established ($\beta = 0.032$ [CI -0.02, 0.08], $p = 0.25$).

In Table 2 nutritional intakes of individuals with macro- and microalbuminuria are compared with intakes of persons with normoalbuminuria. Nutritional intakes were also adjusted for age, diabetes duration, HbA_{1c} , diastolic blood pressure and smoking, variables which were all found to be

Fig. 2. Geometric mean AER in individuals with protein intakes up to 20% of total energy ($\triangle$) compared to subjects consuming more than 20% of protein ($\bullet$): by strata of glycaemic control and presence of hypertension. The geometric means with 95% confidence intervals ($\perp$) are adjusted for total energy intake, age, and diabetes duration

significantly increased in subjects with macro- and microalbuminuria as compared to patients with normoalbuminuria. Patients with macroalbuminuria consumed significantly more total protein, animal protein and g protein per kg body weight than normoalbuminuric individuals. Non-significant trends in the same direction were found between subjects with microalbuminuria and those with normoalbuminuria.

Findings were similar whether the relationship between protein intake and AER was analysed adjusting for systolic blood pressure or for diastolic pressure. Addition of a term for height, BMI or blood lipids did not account for the correlation between protein intake and AER (data not shown).

Discussion

Dietary protein intake may influence renal disease in individuals with diabetes [38]. Therefore, the present study analysed the relationship between reported dietary protein intake and urinary AER in 2696 IDDM individuals from the EURODIAB Complications Study. The dietary intake of protein expressed as a percentage of total food energy intake was found to be related to urinary AER. For persons with protein intakes up to 20%, mean AER did not exceed the upper level of normoalbuminuria, while elevated mean AER levels were observed in individuals with a protein consumption above 20% of food energy intake. Protein intakes at the lower end of the recommended range were not associated with lower AER values; but few subjects had a protein consumption below 12% of energy, some of whom may have followed advice to

Table 2. Nutritional intake in IDDM patients with normo-, micro- and macroalbuminuria

Nutritional intake	AER < 20 µg/min (<i>n</i> = 1887)	AER 20–200 µg/min (<i>n</i> = 579)	AER > 200 µg/min (<i>n</i> = 230)
Total protein (% of energy)	17.6 (17.4, 17.8)	17.8 (17.5, 18.1)	18.5 (18.0, 19.0) ^a
Animal protein (% of energy)	12.2 (12.0, 12.4)	12.5 (12.2, 12.8)	12.9 (12.4, 13.5) ^a
Vegetable protein (% of energy)	5.2 (5.1, 5.2)	5.1 (5.0, 5.3)	5.3 (5.1, 5.5)
g Protein/kg body weight	1.46 (1.44, 1.48)	1.46 (1.42, 1.50)	1.52 (1.47, 1.59) ^a
Fat (% of energy)	37.8 (37.4, 38.2)	38.4 (37.7, 39.0)	36.7 (35.6, 37.8)
Saturated fatty acids (% of energy)	13.8 (13.6, 13.9)	13.8 (13.5, 14.2)	13.0 (12.5, 13.6) ^a
Cholesterol (mg/1000 kcal)	141 (138, 144)	144 (138, 150)	151 (141, 161)
Carbohydrate (% of energy)	42.5 (42.1, 42.9)	41.5 (40.8, 42.2) ^a	43.1 (42.0, 44.2)
Fibre (g/1000 kcal)	7.4 (7.3, 7.6)	7.1 (6.8, 7.4) ^a	7.5 (7.1, 7.9)
Energy (kcal)	2270 (2235, 2306)	2331 (2264, 2399)	2250 (2148, 2356)
Alcohol consumers (% of patients recording alcohol intake over 3-days)	49.1 (46.4, 51.7)	54.6 (49.9, 53.4) ^a	44.5 (36.8, 52.1)

Data are geometric means (95 % CI).

Energy intakes are adjusted for age, duration, HbA_{1c}, diastolic blood pressure and smoking.

Nutrient intakes and percentages of alcohol consumers are adjusted for energy, age, duration, HbA_{1c}, diastolic blood pressure and smoking.

^a Intakes significantly different from intakes in patients with normoalbuminuria, *p* < 0.05

reduce their protein intake because of high levels of AER.

Other smaller cross-sectional epidemiological studies in people with both insulin- and non-insulin-dependent diabetes have not found associations between protein intake with urinary AER [39, 40] or with the presence of clinical proteinuria [41]. Our contrasting results may be partly attributable to the size and structuring of the EURODIAB IDDM Complications Study. Furthermore, most studies investigating the role of protein intake as a risk factor for renal disease did not allow for total energy intake. Despite the fact that correct adjustment for total energy intake in epidemiological analyses of dietary data is increasingly recognised as an important aspect of the interpretation of nutritional studies [36, 42] the concept of energy adjustment has not yet been widely adopted.

High intakes of protein require increased renal excretory function and are associated with higher glomerular filtration rates [16, 25, 43, 44]. High protein intakes are therefore postulated as determinants of the deterioration of clinically overt diabetic nephropathy [26] and perhaps of the progression from stages of diabetic nephropathy without clinical signs to incipient diabetic nephropathy [28, 44]. However, a clear level of undesirably high protein intake has not been established for persons with diabetes. The Diabetes and Nutrition Study Group of the EASD and the ADA have chosen an upper limit of 20 % of energy intake for protein in their nutritional recommendations [29, 30], a level considered to be the upper limit of protein consumption commonly observed in the general population [30]. This recommendation finds some support in our finding that protein intakes above 20 % are associated with elevated levels of AER in European individuals with IDDM.

Diabetic patients with incipient or manifest nephropathy (i.e. presence of micro- or macroalbuminuria [45]) are recommended to reduce their protein intake to 0.7–0.9 g/kg body weight (approximately 10 % of food energy) [29]. However, in the present study individuals with micro- or macroalbuminuria were found to consume even more total protein and animal protein than persons with normoalbuminuria. Other studies reported that in comparison to individuals with normoalbuminuria, protein intakes found in patients with micro- or macroalbuminuria were similarly high [46, 47].

Current therapeutic approaches focus primarily on optimisation of blood pressure and glycaemic control. For these factors clear associations with the progression of nephropathy have already been shown [4, 5, 8, 39, 48–55]. Reduction of dietary protein is considered only when renal function is reduced and declining. In the present study we observed that AER was strongly associated with the presence of hypertension or higher HbA_{1c} values, while a weaker relationship was seen with dietary intake of protein. The association between higher AER and higher dietary protein intake that we demonstrated was of particular importance for patients with hypertension and/or higher HbA_{1c} values, with the presence of hypertension having a greater impact than that of a poorer diabetes control.

The statistically significant relationship between intakes of total protein and AER was observed for animal protein, but not for vegetable protein, a finding which supports other evidence of the specially deleterious effect on renal function of animal protein [21, 24, 27, 56]. Since long-term compliance to low-protein diets is often poor [21, 22] a modification of protein intake [22, 25, 27, 28, 56, 57], substituting vegetable protein for protein from animal sources, should be more fully explored as a feasible

therapeutic approach which would also reduce total fat and saturated fatty acid consumption. While high protein intakes were a unanimous finding in all EU-RODIAB centres [32] the pattern of food groups providing protein/animal protein may vary considerably across European countries. It may be that specific components of animal protein (e.g. meat) exert particularly deleterious effects. Further detailed analyses of the food intake reported by the EU-RODIAB cohort might help to clarify these important issues.

In conclusion the present study demonstrates a significant relationship between dietary protein intake and urinary AER in European individuals with IDDM. This is largely restricted to those consuming more than 20% of their dietary food energy as protein, particularly perhaps if this is of animal origin. Our data provide some support for current nutritional recommendations for people with IDDM not to exceed a protein intake of 20%. In diabetic persons whose urinary AER falls into the micro- or macroalbuminuric range more attention should be directed towards the avoidance of protein intakes higher than 20% of total energy, particularly in the presence of elevated blood pressure and/or poor glycaemic control, both of which require corrective action in their own right.

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