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Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy

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Background. Recent data suggest that dietary protein restriction improves survival and delays the progression to end-stage renal disease (ESRD) in non-diabetic nephropathies. The purpose of our study was to determine the effect of dietary protein restriction on survival and progression to ESRD in diabetic nephropathy.

Methods. A four-year prospective, controlled trial with concealed randomization was performed comparing the effects of a low-protein diet (0.6 g/kg/day) with a usual-protein diet. The study included 82 type 1 diabetic patients with progressive diabetic nephropathy [pre-study mean decline in glomerular filtration rate (GFR) 7.1 mL/min/year (95% CI, 5.8 to 8.5)]. The main outcome measures were decline in GFR and development of ESRD or death.

Results. During the follow-up period the usual-protein diet group consumed 1.02 g/kg/day (95% CI; 0.95 to 1.10) as compared with 0.89 (0.83 to 0.95) in the low-protein diet group ($P = 0.005$). The mean declines in GFR were 3.9 mL/min/year (2.7 to 5.2) in the usual-protein diet group and 3.8 (2.8 to 4.8) in the low-protein diet group. ESRD or death occurred in 27% of patients on a usual-protein diet as compared with 10% on a low-protein diet (log-rank test; $P = 0.042$). The relative risk of ESRD or death was 0.23 (0.07 to 0.72) for patients assigned to a low-protein diet, after an adjustment at baseline for the presence of cardiovascular disease ($P = 0.01$). Blood pressure and glycemic control were comparable in the two diet groups during the follow-up period.

Conclusion. Moderate dietary protein restriction improves prognosis in type 1 diabetic patients with progressive diabetic nephropathy in addition to the beneficial effect of antihypertensive treatment.

Dietary protein restriction slows the progression of renal disease and improves survival in animals with varies glomerulopathies [1, 2]. Recently, a meta-analysis suggested that dietary protein restriction lowers the incidence of end-stage renal disease (ESRD) or death in patients with non-diabetic nephropathies and slows the progression of diabetic nephropathy [3]. However, the latter conclusion was based on 108 type 1 diabetic patients in five studies (mean length of follow-up, 4.5 to 35 months) [4–8] applying changes in urinary albumin excretion rate or the decline in GFR or creatinine clearance as end-points. Flaws in design, randomization procedure, patient selection, methods and end-points in addition to the confounding impact of antihypertensive treatment suggest that the above-mentioned conclusion in relation to diabetes should be interpreted with caution [9–12].

We report the results of a four year, prospective controlled trial with concealed randomization, comparing the effect of a low-protein diet with a usual-protein diet in 82 type 1 diabetic patients with progressive diabetic nephropathy. The study tested the hypothesis that a reduction in dietary protein intake retards the progression to ESRD and improves survival in type 1 diabetic patients with diabetic nephropathy.

Key words: type 1 diabetes, survival, ESRD, GFR, progressive renal disease, protein restriction, diabetic nephropathy.

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METHODS

The study was a prospective, randomized, unmasked, controlled trial carried out at the Steno Diabetes Center. With concealed randomization the patients were in blocks of two according to the level of GFR (≤ 50, $50 < x \leq 75$, $75 < x \leq 100$, > 100 mL/min/1.73 m^2), assigned to receive either a usual-protein diet or a low-protein diet. All patients were recruited at the Steno Diabetes Center and seen by the same physician (HPH) and dietitian (ETL) at each visit. The local ethics committee approved the study, and all patients gave written informed consent.

Patients and randomization

The following inclusion criteria were used: Patients between 18 and 60 years of age with type 1 diabetes mellitus for at least 10 years, with an onset before the age of 35 years, presence of diabetic retinopathy, albuminuria ≥ 300 mg/24 h in at least two out of three sterile urine samples, and no clinical or laboratory evidence of

other kidney or urinary tract disease [13], GFR above 20 mL/min/1.73 m^2 and a pre-study decline in GFR ≥2 mL/min/year (progressive diabetic nephropathy). Since patients continued their usual antihypertensive treatment, reduction in albuminuria even into the normal range was observed in some of the patients at entry, as previously demonstrated by us [14, 15]. Presence of pregnancy, a history of congestive heart failure or myocardial infarction or coronary bypass surgery within the last three months resulted in exclusion. Eighty-two type 1 diabetic patients who fulfilled the inclusion criteria consecutively entered the study between May 1995 and April 1996 (Fig. 1).

Study diet

After randomization an iso-caloric low-protein diet of 0.6 g/kg/day was prescribed to patients in the low-protein diet group. The same dietitian (ETL) gave nutritional advises, based on estimated protein intake, at least every three months during the whole study period (see below). All patients in the low-protein diet group received supplementation of calcium of 500 mg/day. The usual-protein diet consisted of the patients' pre-study diet. In the low-protein diet group ($N = 4$), urine albumin losses ≥2 g/day were replaced by increasing dietary protein on a gram-for-gram basis, only if the patient was compliant with the prescribed low-protein diet.

Procedures and measurements

The planned duration of follow-up was four years in each patient. At randomization and scheduled visits every three-month all patients gave a complete history of medication, underwent examination of weight, urinary albumin-, sodium- and urea excretion, serum albumin, serum urea, hemoglobin, hemoglobin A_{1c} (normal range; 4.1 to 6.4%), blood pressure, serum total-cholesterol and high-density lipoprotein (HDL) cholesterol. GFR, serum triglycerides, calcium and phosphorous, anthropometric measurements, nutritional status and smoking habits were evaluated every six months. Apart from the urine collections, all the measurements were carried out with the patients in the supine position. Chemical and biochemical analyses of serum and urine were performed by standard laboratory techniques.

Dietary protein intake was estimated on the basis of three consecutive 24-hour urine samples completed before each visit, using the urinary excretion of urea nitrogen (UUN) as follows [16]: estimated protein intake (g/day) = 6.25 · [UUN (g/day) + standard body weight (kg) · 0.031 (g/kg/day)]. All consumed protein is reported.

Before randomization, GFR was measured either by the plasma clearance of ^{51}Cr-EDTA ($N = 58$) or the formula of Cockroft and Gault (usual-protein diet group; $N = 11$, low-protein diet group; $N = 13$) [17]. At randomization and during follow-up, GFR was measured on the basis of the plasma clearance of an intravenous injection of ^{51}Cr-EDTA over a four-hour period starting at 8 AM [18]. The results were standardized for 1.73 m^2 body surface area, using the same surface for each patient during the study.

Blood pressure was measured on the right arm with a Hawksley Random Zero Sphygmomanometer. The individual blood pressure level was determined as the mean of at least two measurements. The mean blood pressure was calculated {[(systolic blood pressure + (2 × diastolic blood pressure)]/3}.

Body mass index (BMI) was calculated as weight (kg) per height $(m)^2$. Retinopathy was assessed by fundus photography and graded simplex or proliferative retinopathy. Present smokers were defined as persons smoking more than one cigarette/cigar/pipe per day.

A 12-lead electrocardiogram was recorded and subsequently coded using the Minnesota Rating Scale [19] independently by two trained observers, who were masked to the clinical status of the patients. Coronary heart disease was diagnosed if the electrocardiogram showed signs of myocardial infarction or ischemia, or if patients reported a history of myocardial infarction according to the World Health Organization criteria [20] and validated by hospital records.

Outcome measures

The main outcome measures were the rate of decline in GFR and the cumulative incidence of ESRD requiring dialysis or transplantation, and death. Slopes were calculated on the basis of the baseline GFR and all follow-up values. Before the development of uremic symptoms, patients ($N = 6$) were referred to the department of nephrology at the University Hospital of Herlev or Rigshospitalet, when GFR deteriorated below 10 to 20 mL/min/1.73 m^2, where accepted criteria for initiation of dialysis and transplantation were applied on patients from both diet groups. These patients continued their scheduled visits and treatment in the study until the end of the four-year follow-up. Cause of death was obtained from the death certificate. An independent observer without knowledge of randomization reviewed all death certificates and the primary cause of death was recorded. Conditions requiring withdrawal from the study included intercurrent illness (cancer, $N = 3$; stroke, $N = 1$) that precluded the patients continued participation in the study.

Statistical analysis

Data for blood pressure, hemoglobin A_{1c} and albuminuria during the period before randomization were averaged for each year for each patient and used to determine a mean value for the entire period. Linear regression analysis was used to estimate the rate of decline in GFR for each patient before and during the present study

Table 1. Clinical characteristics of type 1 diabetic patients with diabetic nephropathy at the time of randomization

Variable	Usual-protein diet $N = 41$	Low-protein diet $N = 41$
Sex *female/male*	18/23	11/30
Age *years*	41 (9)	40 (8)
Duration of diabetes *years*	28 (8)	27 (7)
Duration of diabetic nephropathy *years*	10 (5)	9 (5)
Insulin *u/kg/24 h*	0.60 (0.16)	0.67 (0.18)
Dietary protein intake *g/kg/24 h*	1.04 (0.25)	0.97 (0.26)
Standard body weight *kg*	68 (9)	72 (8)
Body mass index kg/m^2	25 (3)	25 (4)
Systolic blood pressure *mm Hg*	138 (18)	142 (17)
Diastolic blood pressure *mm Hg*	79 (10)	81 (9)
Retinopathy *simplex/proliferative*	12/29	9/32
GFR $mL/min/1.73\ m^2$	67 (32)	69 (30)
Albuminuria[a] *mg/24 h*	737 (1.2)	681 (1.2)
Urinary sodium excretion rate *mmol/24 h*	166 (58)	151 (52)
Cardiovascular events *N* (%)		
Coronary heart disease	8 (20)	8 (20)
Stroke	2 (5)	3 (7)
I/D polymorphism in the ACE gene (%)	20/53/27	21/54/25
No. of antihypertensive drugs *0/1/2/3/>3*	7/7/15/9/3	8/6/13/9/5
Smoking *N* (%)	19 (46)	18 (44)
Hemoglobin A_{1c} (%)	9.7 (1.4)	9.8 (1.6)
Blood hemoglobin *mmol/L*	8.2 (1.1)	8.2 (1.3)
Serum total-cholesterol *mmol/L*	5.4 (1.0)	5.5 (1.4)
Serum HDL-cholesterol *mmol/L*	1.43 (0.45)	1.32 (0.49)
Serum triglicerids *mmol/L*	1.17 (0.62)	1.70 (2.03)
Serum creatinine *μmol/L*	139 (62)	133 (48)
Serum urea *mmol/L*	9.1 (4.6)	9.1 (4.2)
Serum albumin *g/L*	36 (4)	37 (3)
Serum calcium *mmol/L*	1.24 (0.05)	1.23 (0.05)
Serum phosphorous *mmol/L*	1.30 (0.18)	1.25 (0.23)

None of the variables differed significantly between diet groups. Abbreviations are: I/D, insertion/deletion; ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate. Data are mean (SD) unless specified.

[a] Geometric mean (antilog SE)

using all the determinations of GFR. A minimum of one year of follow-up with at least three measurements of GFR was required for a patient to be included in the slope analysis. Variables from the first visit after randomization and during the whole study were used to determine the mean value for each patient. Using an intention-to-treat approach, we related the rates of decline in glomerular filtration, and cumulative incidence of ESRD or death to the prescribed diet group. Kaplan-Meier estimates of time to ESRD or death curves were compared by log-rank test. In the analysis of predictors of ESRD or death, the Cox regression model was used. A multiple regression analysis was performed with rate of decline in GFR as the dependent variable and backward selection including variables (dietary protein intake, mean arterial blood pressure, hemoglobin A_{1c}, albuminuria and total cholesterol) with $P < 0.10$ in an univariate analysis. Before the present study, we analyzed the rate of decline in GFR in 106 type 1 diabetic patients with progressive diabetic nephropathy. Applying the obtained standard deviation (3.2) for the rate of decline in GFR (6.8 mL/min/year), in a sample size calculation we found that 34 patients were necessary in each diet group to detect a difference in the rate of decline in GFR of 2.5 mL/min/year between the two groups ($\alpha = 0.05$, $\beta = 0.10$). Data are presented as means (SD or 95% CI) except when indicated. Owing to the skewed distribution values for albuminuria was logarithmically transformed before statistical analysis and given as geometric mean (range or 95% CI). Paired and unpaired *t* tests were used to compare the results within or between the two diet groups. All calculations were made using SPSS for Windows (SPSS Inc., Chicago, IL, USA). *P* values less than 0.05 (two-sided) were considered to indicate significance.

RESULTS

Clinical characteristics of patients in the two diet groups are shown in Table 1. No patients were lost to follow-up (Fig. 1).

Dietary protein intake and nutritional status

After randomization and within the first three months of the study, there was an initial decline in the dietary protein intake of 0.06 g/kg/day ($P = 0.24$) in the usual-protein diet group and 0.15 g/kg/day ($P = 0.01$) in the low-protein diet group ($P = 0.22$ between groups; Fig. 2). After three months and during follow-up, the patients

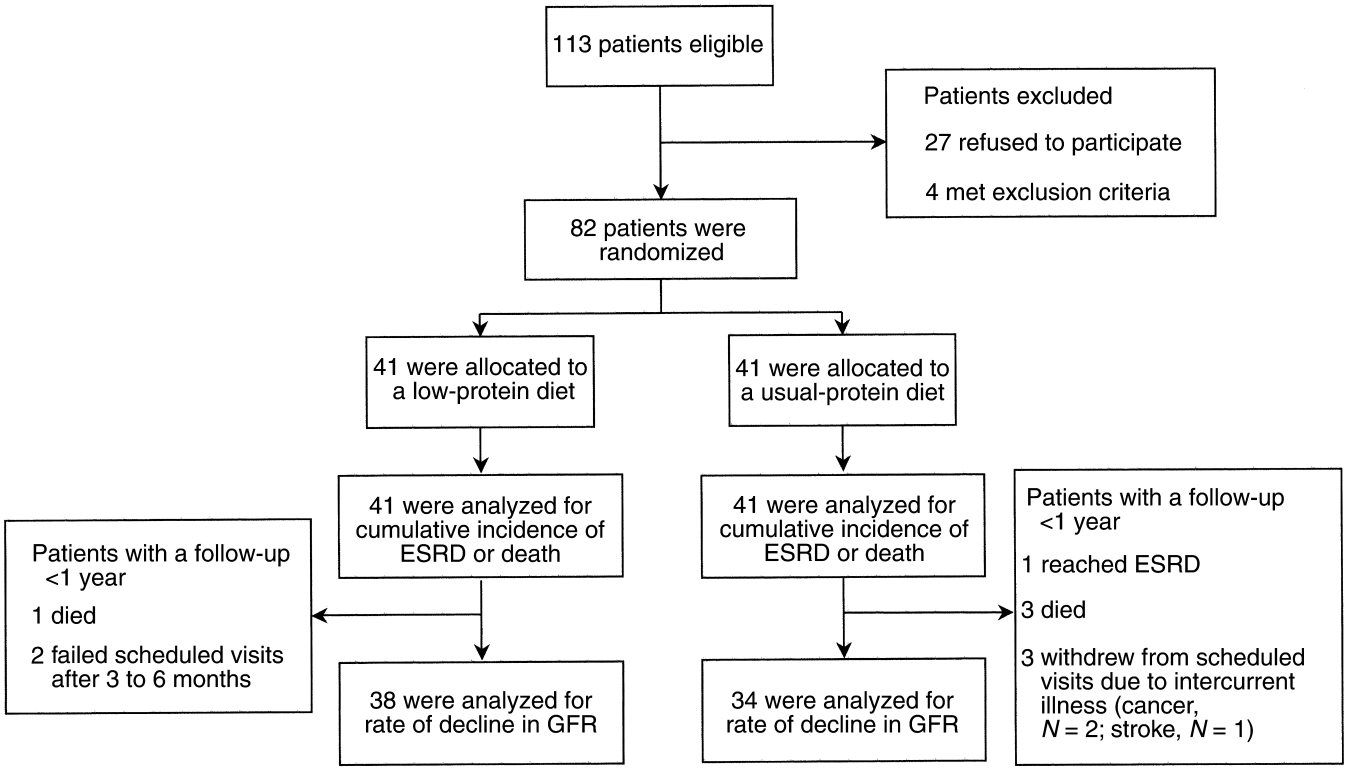

Fig. 1. The study profile.

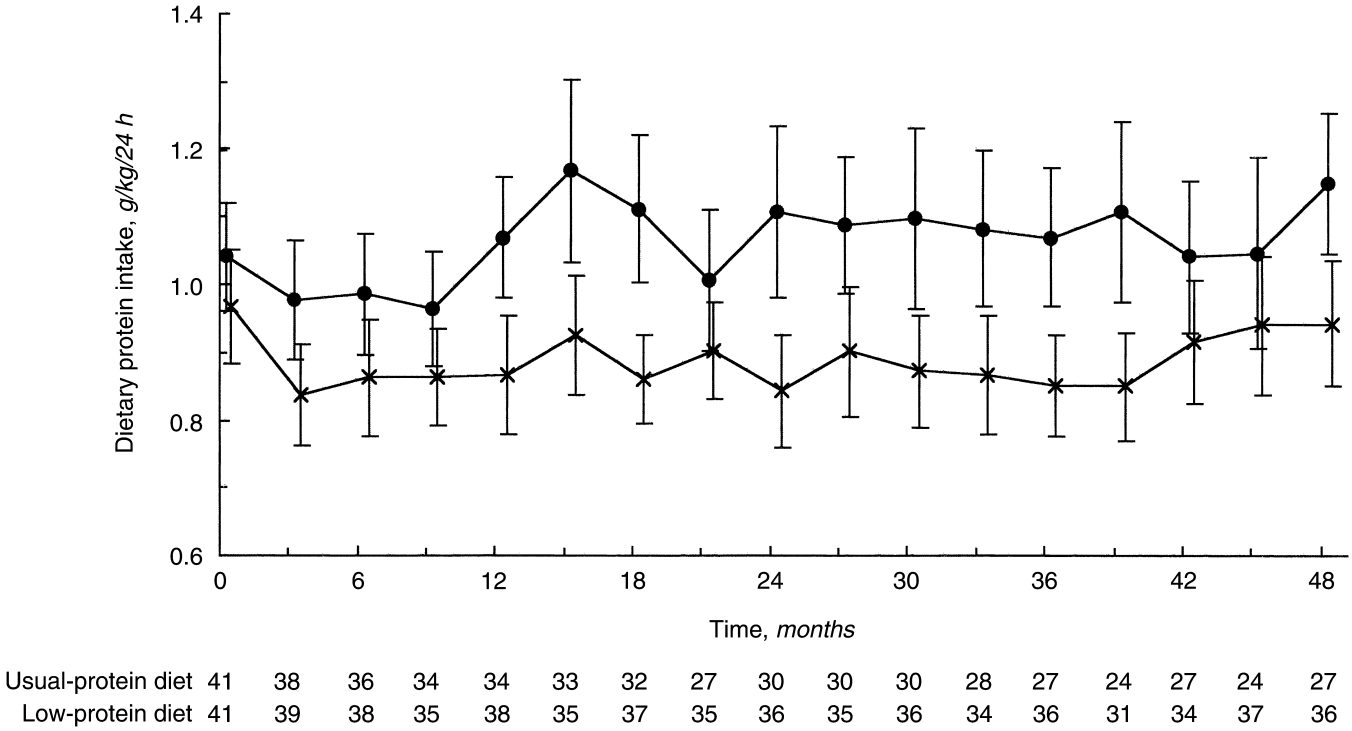

Fig. 2. Estimated dietary protein intake in type 1 diabetic patients with progressive nephropathy. Symbols are: (●) usual-protein diet; (×) low-protein diet. Values for the estimated dietary protein intake are mean and the 95% CI is indicated by the whiskers. The numbers of patients with an estimated dietary protein intake at each visit are shown below the panel.

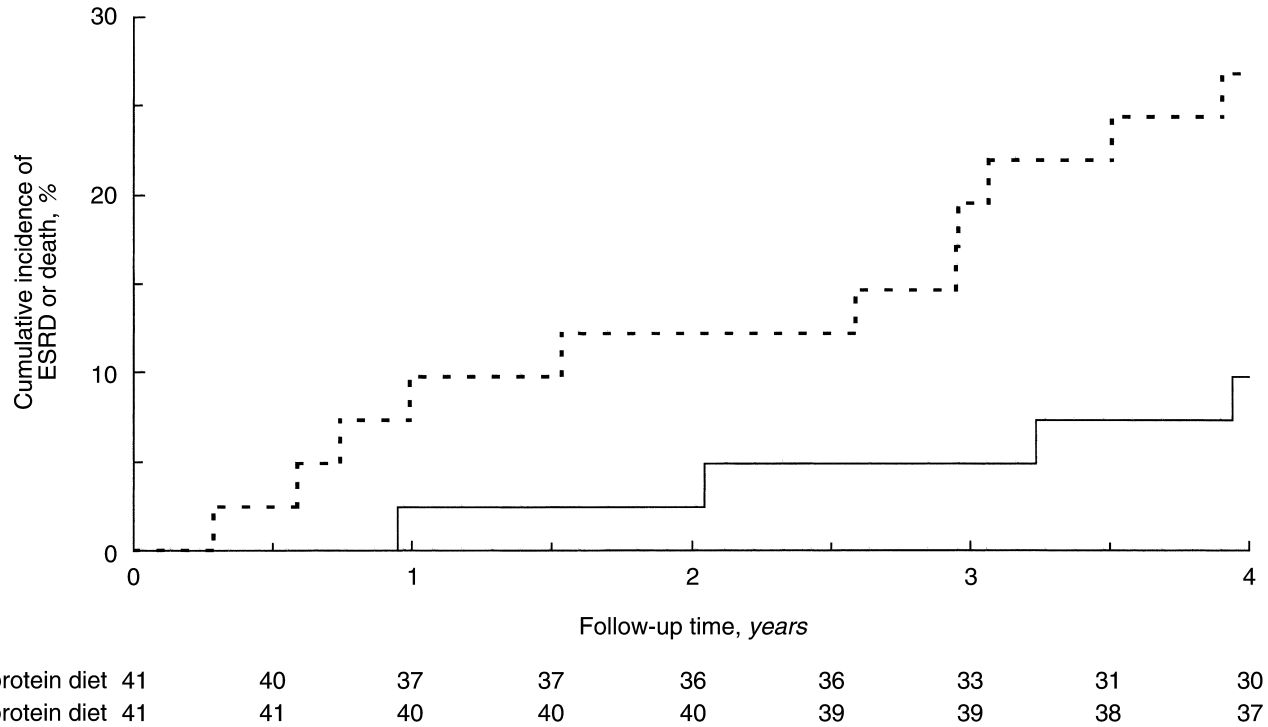

Fig. 3. Cumulative incidence of end-stage renal disease (ESRD) or death in type 1 diabetic patients with progressive diabetic nephropathy in the usual-protein group (dashed lines) and the low-protein diet group (solid line). Log rank text, $P = 0.042$. The numbers at the bottom denote the number of patients in each group at risk for the event at baseline and after each six month period.

in the usual-protein diet group consumed a mean of 1.02 (0.95 to 1.10) g/kg/day, as compared with 0.89 (0.83 to 0.95) g/kg/day in the low-protein diet group ($P = 0.005$, Fig. 2). From baseline during follow-up the mid-arm circumference, serum albumin and body weight were comparable in the two diet groups (data not shown).

Dialysis, transplantation and death

At the end of the study six patients had required dialysis or renal transplantation and nine patients had died. Causes of death were heart failure ($N = 4$) and myocardial infarction ($N = 5$). Dialysis, transplantation or death occurred in 27% of patients (dialysis, $N = 3$; transplantation, $N = 1$; death, $N = 7$) on the usual-protein diet, as compared with 10% in patients (dialysis, $N = 2$; death, $N = 2$) on the low-protein diet (log-rank test, $P = 0.042$; Fig. 3). The curves reflecting the cumulative incidence of ESRD or death continued the separation during the whole study period. A Cox regression analysis revealed a relative risk of ESRD or death of 0.23 (0.07 to 0.72; $P = 0.01$) for the patients assigned to the low-protein diet group, compared with those assigned to the usual-protein diet group, after adjustment for the presence at baseline of cardiovascular disease.

Renal function

Before randomization the rate of decline in GFR in the whole group of patients was 7.1 (CI, 5.8 to 8.5) mL/min/year during a median follow-up of 4.9 (range, 1.0 to 11.2) years. Within the first six months of follow-up there was a comparable significant decline in GFR of 4.1 mL/min ($P < 0.01$) in the usual-protein diet group and 4.4 mL/min ($P < 0.01$) in the low-protein diet group ($P = 0.87$ between groups). From randomization the rate of decline in GFR slowed significantly in both diet groups during the four years of follow-up (3.9 mL/min/year in the usual-protein diet group vs. 3.8 in the low-protein diet group), while urinary albumin excretion rate remained unchanged (Table 2). The average improvement of the rate of decline in GFR, comparing slopes before and after randomization, were comparable in the two diet groups; 2.7 (1.1 to 4.3) mL/min/year in the usual-protein diet group and 3.7 (1.6 to 5.9) mL/min/year in the low-protein diet group ($P = 0.44$). Geometric mean of albuminuria was comparable between diet groups during the follow-up (Table 2).

Glycemic control, blood pressure, serum lipids and urea

Hemoglobin A_{1c} and blood pressure values were comparable during follow-up in the two diet groups (Table 2). Blood pressure was equally significantly reduced during the study compared to the pre-study period in both diet groups, while hemoglobin A_{1c} was significantly reduced in the low-protein diet group (Table 2). During follow-

Table 2. Rate of decline in GFR, albuminuria, blood pressure and hemoglobin A_{1c} before and during the study in type 1 diabetic patients with diabetic nephropathy

	Usual-protein diet $N = 34$	Low-protein diet $N = 38$
Follow-up *years*		
Before the study	5.1 (1.0 to 10.1)	5.0 (1.0 to 11.2)
During the study	4.0 (1.5 to 4.2)	4.0 (2.1 to 4.3)
Rate of decline in GFR *mL/min/year*		
Before the study	6.6 (5.2 to 8.1)	7.6 (4.9 to 10.2)
During the study	3.9 (2.7 to 5.2)[a]	3.8 (2.8 to 4.8)[a]
Albuminuria *mg/24 h*		
Before the study	721 (502 to 1036)	690 (547 to 871)
During the study	614 (389 to 969)	542 (382 to 769)
Blood pressure *mm Hg*		
Before the study		
Systolic	138 (133 to 144)	140 (136 to 144)
Diastolic	85 (82 to 87)	85 (83 to 88)
Mean	102 (100 to 105)	104 (101 to 106)
During the study		
Systolic	140 (135 to 146)	142 (138 to 146)
Diastolic	79 (76 to 81)[b]	80 (78 to 83)[b]
Mean	99 (97 to 102)[c]	101 (99 to 103)[c]
Hemoglobin A_{1c} *%*		
Before the study	9.6 (9.2 to 9.9)	9.8 (9.4 to 10.1)
During the study	9.6 (9.3 to 10.0)	9.5 (9.1 to 9.9)[c]

Data are mean (95% CI). Except follow-up (median and range) and albuminuria (geometric mean and 95% CI), no significant differences were found between diet groups. A minimum of 1 year of follow-up during the study with at least 3 measurements of GFR was required for a patient to be included in this analysis ($N = 72$).

[a] $P < 0.005$, [b] $P < 0.001$, [c] $P < 0.05$ compared to the period before the study

up, serum total-cholesterol [5.8 (5.5 to 6.1) mmol/L and 5.5 (5.2 to 5.8), respectively], high density lipoprotein (HDL)-cholesterol [1.44 (1.31 to 1.58) mmol/L and 1.42 (1.26 to 1.58), respectively], triglycerides [1.47 (1.29 to 1.65) mmol/L and 1.59 (1.25 to 1.92), respectively] and serum urea [11.8 (9.9 to 13.7) mmol/L and 10.9 (8.9 to 12.8), respectively] were comparable in the usual-protein diet group and the low-protein diet group.

Medication and smoking

At baseline and during follow-up, a comparable number of patients in both diet groups received antihypertensive treatment, angiotensin-converting-enzyme inhibitors, diuretics, α and β blockers, calcium channel blockers, low-dose acetylsalicylic acid and lipid lowering agents, respectively (Table 3). At baseline and at follow-up numbers of smokers were comparable in the two diet groups. Numbers of smokers was reduced to 13 in the usual-protein diet group, and to 14 in the low-protein diet group during follow-up.

Regression analyses for pooled data

For all patients with cardiovascular disease at baseline (regardless of randomization) the relative risk of ESRD or death were 14.2 (4.4 to 45.6; $P < 0.0001$). Age and sex were excluded from the model. Univariate regression analyses revealed significant or borderline significant associations between the rate of decline in GFR and mean values during follow-up of blood pressure ($P < 0.001$), albuminuria ($P < 0.001$), hemoglobin A_{1c} ($P < 0.03$), serum cholesterol ($P < 0.04$) and dietary protein intake ($P = 0.07$). A multiple linear regression analysis using these parameters as independent variables and the rate of decline in GFR as the dependent variable, showed that an increase in mean blood pressure (of 10 mm Hg), hemoglobin A_{1c} (of 1%) and albuminuria (10-fold) were associated with a significant worsening in the rate of decline in GFR of 1.2 (0.2 to 2.3), 0.71 (0.08 to 1.35) and 1.94 (0.40 to 3.48) mL/min/year, respectively.

DISCUSSION

The main finding from our prospective, randomized controlled trial is that patients with type 1 diabetes suffering from progressive diabetic nephropathy experience a beneficial effect of moderate restriction in dietary protein on the development of ESRD or death. The beneficial effect of protein restriction appeared within the first year, and persisted with continued treatment, as also has been demonstrated in non-diabetic nephropathies [21], suggesting that type 1 diabetic patients with progressive diabetic nephropathy are highly sensitive to dietary protein restriction. Despite the differences in event rates, the decline in GFR in the two treatment groups did not differ significantly, while both diet groups demonstrated a progressive time-dependent reduction in the rate of decline in GFR as compared to the period before randomization. Blood pressure, albuminuria, and glycemic control were independent risk factors for the deterioration in GFR [15]. Statistical analyses were by intention-to-treat, that is, patients were included in their assigned diet group, regardless of the achieved dietary protein intake. A lack of adherence to the prescribed low-protein diet by some patients would result in an underestimation of the true beneficial effect of the diet. The achieved level of long-term dietary protein restriction reflects real life in an outpatient clinic set-up. Since diabetic patients have other restrictions to the diet, this may reduce compliance to an additional low-protein diet. Although better compliance can be obtained by applying much more intensive dietary counseling [4, 5, 22], it is not easy to lower dietary protein intake to less than 0.8 g/kg/day over extended periods of time [23], and patients with advanced non-diabetic renal disease are only able to lower their protein intake by 0.1 to 0.2 g/kg/day despite intensive nutritional counseling [24]. Our study did not reveal the mechanisms of the beneficial effect of moderate protein restriction, since neither the measured cardiovascular risk factors, nor the pharmacological treatment, or progression promoters in relation to kidney disease showed any significant differences between the two diet groups.

Table 3. Medication at baseline and follow-up in 82 type 1 diabetic patients with diabetic nephropathy randomized to either a usual-protein diet or a low-protein diet

Variable	At baseline *N* (%)		At follow-up *N* (%)	
	Usual-protein	Low-protein	Usual-protein	Low-protein
Antihypertensive treatment	34 (83)	33 (80)	38 (93)	37 (90)
Angiotensin-converting enzyme inhibitors	29 (85)	29 (88)	33 (87)	33 (89)
Diuretics	26 (76)	28 (85)	33 (87)	33 (89)
α- and β-blockers	7 (21)	9 (27)	9 (24)	9 (24)
Calcium channel blockers	8 (24)	10 (30)	10 (26)	9 (24)
Low-dose acetylsalicylic acid	7 (17)	5 (12)	13 (32)	9 (22)
Lipid lowering agents (statins)	4 (10)	3 (7)	12 (29)	14 (34)

There were no significant differences in medication between diet groups at baseline or at follow-up.

The natural history of diabetic nephropathy is characterized by an early progressive rise in systemic blood pressure associated with a relentless decline in GFR of approximately 10 to 15 mL/min/year [25–27]. Blood pressure elevation has proved to accelerate the progression of diabetic nephropathy [28]. Conversely, effective long-term antihypertensive treatment reduces the rate of decline in GFR to approximately 5 mL/min/year [29], in agreement with our present finding. The inverse correlation between duration of antihypertensive treatment and rate of decline in GFR demonstrated in the present study is in agreement with results previously obtained in diabetic and non-diabetic glomerulopathies, where a progressive time-dependent reduction in the rate of decline was obtained during long-term aggressive antihypertensive treatment [14, 30, 31]. The mechanisms of this time dependent reduction in the rate of decline in GFR in diabetic and non-diabetic nephropathies are unknown. However, animal models of different kidney diseases suggest a shift in the balance between synthesis and degradation of extracellular mesangial matrix, preservation of functioning (normal or only slightly damage) glomeruli, and even the possibility of new growth of glomerular capillaries, as recently reviewed by Fogo [32]. It should be recalled that the beneficial effect of improved glycemic control in The Diabetes Control and Complications Trial on the initiation and progression diabetic micro-angiopathy [33], or reversal of structural lesions in diabetic glomerulopathy during normalization of glycemic control with pancreas transplantation [34], are delayed for several years. Importantly, the improvement in rate of decline in the present study will reduce the power to detect a difference between the two diet groups.

In the present study, control of blood pressure rather than dietary protein restriction was of major importance for the preservation of GFR during follow-up. Previous experimental data have suggested that a low protein diet, similar to treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, acts through a blockade of the renal renin-angiotensin system [35]. However, the combination of a low protein diet and maximal effective doses of either enalapril or losartan have proved to reduce renal fibrosis slightly more effectively than treatment with a low protein diet or angiotensin II blockade alone [36], suggesting that dietary protein restriction also acts on pathways independent of the renin-angiotensin system. Nevertheless, since the majority of the renal protective effect of dietary protein restriction seems to be mediated through the renin-angiotensin system, simultaneous treatment with an angiotensin-converting enzyme inhibitor, widely used in the MDRD (Modification of Diet in Renal Disease) study [22] and the present study, may have blunted the additive beneficial effect of dietary protein restriction on the decline in GFR in these two studies and albuminuria in the present study. When rate of decline in GFR is slow, a time-to-event analysis has greater statistical power to detect a beneficial effect of an intervention than an analysis based on the slope of GFR [37]. The REIN (Ramipril Efficacy in Nephropathy) and MDRD studies support the validity of this analysis in non-diabetic nephropathies [21, 38].

It should be emphasized, however, that a valid determination of the rate of decline in GFR in patients with chronic renal disease requires a reliable method for the determination of GFR, repeated measurements of the GFR, and a follow-up of at least two years [39]. These requirements were fulfilled in our prospective study, except for one patient with a follow-up period of only 18 months. We have previously documented the validity of the formula of Cockroft and Gault for the determination of the rate of decline in GFR [40].

We performed a prospective, randomized controlled trial as compared to the previous trials examining the effect of low-protein diet in type 1 diabetic patients, which were carried out as non-randomized, or partly randomized, and/or self-controlled studies [4–8]. Type 1 diabetic patients with normo- and microalbuminuria were enrolled in one study [8], while only type 1 diabetic patients with macroalbuminuria were enrolled in the remaining studies. None of the previous studies required that patients also should have progressive diabetic nephropathy.

All previous studies examined small numbers of patients; the largest study examined 35 subjects [5]. The main outcome measures in our trial were time-to-event analysis and rate of decline in GFR. Several of the previous studies evaluated changes in urinary albumin excretion rate or short-term changes in creatinine clearance [6, 7], the latter confounded by dietary protein intake [41]. Only Walker et al [4] and Zeller et al [5] performed valid determinations of the rate of decline in GFR. The reduction in rate of decline observed by Walker et al [4] can partly be explained by the previously mentioned phenomenon of a progressive time-dependent reduction in the rate of decline in GFR as observed in the present study and previous studies during antihypertensive treatment [14, 30]. Zeller et al found a rate of decline in GFR of 3.1 mL/min/year during the low-protein diet (0.72 g/kg/day) [5], similar to what was found in both diet groups in our study and previously reported during long-term aggressive antihypertensive treatment [13, 30], while the rate of decline was 12.1 mL/min/year in the control diet group (1.08 g/kg/day), comparable to what has been demonstrated during the natural course of diabetic nephropathy (10 to 14 mL/min/year) in patients not receiving antihypertensive treatment [25–27]. However, baseline proteinuria and mean blood pressure during follow-up were higher in the control group (4.3 g/day and 105.5 mm Hg, respectively) compared to the low-protein diet group (3.1 g/day and 102.3 mm Hg, respectively), which may well have contributed to the accelerated decline in GFR in the control group.

In conclusion, moderate dietary protein restriction improves prognosis in type 1 diabetic patients with progressive diabetic nephropathy in addition to the beneficial effect of antihypertensive treatment. Our study suggests that a wider use of dietary protein restriction is indicated in these patients.

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