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Low-protein diet and kidney function in insulin-dependent diabetic patients with diabetic nephropathy

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Background. Initiation of a low-protein diet (LPD) in patients with various nephropathies induces a faster initial and slower subsequent decline in the glomerular filtration rate (GFR). Whether this initial phenomenon is reversible or irreversible remains to be elucidated.

Methods. We performed an eight-week prospective, randomized, controlled study comparing the effect of an LPD with a normal-protein diet (NPD) in 29 insulin-dependent diabetic patients with diabetic nephropathy. At baseline, the patients were randomized to either an LPD (0.6 g · kg^{-1} · 24 hr^{-1}, LPD group, $N = 14$) or their NPD (NPD group, $N = 15$) for four weeks (phase I). Between weeks 4 and 8, all patients received their NPD (phase II, recovery). Dietary protein intake (g · kg^{-1} · 24 hr^{-1}), GFR (^{51}Cr-EDTA, ml · min^{-1} · 1.73 m^{-2}), albuminuria (enzyme-linked immunoadsorbent assay, mg · 24 hr^{-1}), and arterial blood pressure (Hawksley random zero sphygmomanometer, mm Hg) were measured at baseline and after four- and eight-weeks of follow-up. During the investigation, all patients in the LPD group ($N = 12$) and in the NPD group ($N = 14$) received their usual antihypertensive treatment.

Results. At baseline, the LPD group and the NPD group were comparable regarding dietary protein intake, GFR, albuminuria, and arterial blood pressure. During phase I, a significant decline in dietary protein intake, GFR, and albuminuria (mean, 95% CI) was observed in the LPD group [0.4 (0.3 to 0.5) g · kg^{-1} · 24 hr^{-1}, 8.6 (3.2 to 13.9) ml · min^{-1} · 1.73 m^{-2}, and 28.7 (14.0 to 40.9)%, respectively] compared with the NPD group [0.0 (-0.1 to 0.2) g · kg^{-1} · 24 hr^{-1} ($P < 0.0001$ between diets), 2.5 (-1.8 to 6.8) ml · min^{-1} · 1.73 m^{-2} ($P = 0.07$ between diets), and 0.0 (-20.1 to 23.5)% ($P < 0.05$ between diets), respectively]. Conversely, during phase II, a significant increase in dietary protein intake, GFR, and albuminuria [mean, 95% CI; 0.3 (0.2 to 0.5) g · kg^{-1} · 24 hr^{-1}, 5.9 (0.8 to 11.1) ml · min^{-1} · 1.73 m^{-2}, and 25.0 (4.5 to 49.6)%, respectively] took place in the LPD group compared with the NPD group [0.0 (-0.2 to 0.1) g · kg^{-1} · 24 hr^{-1} ($P < 0.0001$ between diets), -2.9 (-6.4 to 0.6) ml · min^{-1} · 1.73 m^{-2} ($P < 0.01$ between diets), and 2.9 (-18.3 to 29.7)% ($P = 0.16$ between diets), respectively]. Arterial blood pressure was comparable in the two groups of patients during phase I and II.

Conclusions. Dietary protein restriction for four weeks induces a reversible decline in GFR and albuminuria in insulin-dependent diabetic patients with diabetic nephropathy, whereas systemic blood pressure remains unchanged.

Diabetic nephropathy, characterized by persistent albuminuria, a relentless decline in glomerular filtration rate (GFR), and raised arterial blood pressure, develops in nearly 40% of all insulin-dependent diabetic (IDDM) patients [1, 2]. Epidemiological studies of the natural cause of diabetic nephropathy have reported a median survival time after onset of persistent albuminuria of only 5 to 10 years [3–5]. Restriction of dietary protein intake has been proved to slow the progression of renal disease in many experimental animal models [6, 7]. Nevertheless, conflicting evidence of a beneficial effect of dietary protein restriction on the progression of nondiabetic and diabetic renal diseases has been presented in humans [8–13]. This discrepancy may in part be due to the phenomenon that initiation of dietary protein restriction induces a faster initial and slower subsequent decline in the GFR [14]. This short-term effect may confound the interpretation of clinical trials, especially if they are of short duration (less than two to three years) and are dealing with slow progressive renal diseases [14]. Whether this initial faster decline in GFR is caused by a functional (hemodynamic) effect, which will not attenuate over time, or whether it reflects an irreversible phenomenon (structural damage) is unknown. These mechanisms must be revealed in order to make a valid interpretation of the potential beneficial effect of dietary protein restriction on the progression of diabetic and nondiabetic nephropathies.

The aim of this study was to elucidate the mechanism(s) responsible for the faster initial decline in the GFR by recording GFR, albuminuria, and arterial blood pressure

Table 1. Clinical data in 29 insulin-dependent diabetic patients with diabetic nephropathy at baseline

	LPD group (N = 14)	NPD group (N = 15)	P
Females N	6	5	
Age *years*	47 (3)	44 (2)	0.45
Duration of diabetes *years*	29 (2)	29 (2)	0.91
Duration of diabetic nephropathy *years*	9 (2)	10 (2)	0.62
Insulin dosage $U \cdot kg^{-1} \cdot 24\ hr^{-1}$	0.56 (0.03)	0.55 (0.03)	0.70
Body mass index $kg \cdot m^{-2}$	25 (1)	25 (1)	0.95
Body weight *kg*	75.4 (3.0)	72.2 (3.9)	0.52
HbA$_{1c}$ %	8.4 (0.3)	8.6 (0.3)	0.55

Data are mean (SEM). Abbreviations are: LPD, low protein diet (recommended: 0.6 g·kg^{-1}·24 hr^{-1}); NPD, normal protein diet.

in IDDM patients with diabetic nephropathy before, during, and after short-term low-protein diet (LPD).

METHODS

Design and subjects

A prospective, randomized, controlled study for eight weeks that compared the effect of LPD and a normal-protein diet (NPD) on GFR, albuminuria, and blood pressure was carried out in IDDM patients with diabetic nephropathy (Table 1). At baseline, the patients were randomized to either LPD (LPD group) or NPD (NPD group) for four weeks (phase I). Between week 4 and week 8, all patients received NPD (phase II, recovery).

Thirty consecutive IDDM patients with diabetic nephropathy who fulfilled the following inclusion criteria were enrolled in this study: diabetic nephropathy (diagnosed clinically according to established criteria: albuminuria of more than 300 mg · 24 hr^{-1} in at least two out of three sterile urine samples, a duration of diabetes of 10 years or more, the presence of diabetic retinopathy, and no clinical or laboratory evidence of kidney or urinary tract disease) [15], GFR $\geq$ 25 ml · min^{-1} · 1.73 m^{-2}, and age between 18 and 60 years. Reduced urinary albumin excretion rate even into the normal range can be observed in IDDM patients with diabetic nephropathy during antihypertensive treatment [16]. All patients had been insulin-dependent from the time of diagnosis, and all were receiving at least two daily injections of insulin. Patients were excluded if they had malignant hypertension, a previous history of congestive heart failure and myocardial infarction, or coronary bypass surgery within the last three months. During the investigation, patients received their usual antihypertensive treatment [LPD group, N = 12; angiotensin-converting enzyme (ACE) inhibitors (N = 12), NPD group, N = 14; ACE inhibitors (N = 11) and non-ACE inhibitors (N = 3)]. Originally,

15 patients were allocated to each diet group, but one patient from the LPD group was unwilling to continue the study after randomization and was excluded from the calculation. All subjects included in the study were white, and all gave informed consent to participate in the study. The study was approved by the local ethics committee.

Protein intake

Dietary protein intake (g · 24 hr^{-1}) was estimated on the basis of three consecutive 24-hour urine collections completed immediately before the visit at baseline, week 4, and week 8 using the urinary excretion of urea nitrogen [17]. The variation in urinary creatinine excretion was 4.1% (between baseline and the visit at four weeks), 2.4% (between the visit at four and eight weeks), and 1.8% (between baseline and eight weeks). Protein intake was standardized for body weight (kg). To reduce protein intake, all food for lunch and dinner was prepared in the hospital kitchen, was deep-frozen, and was delivered at home to the patients in the LPD group. Advised by the dietitian, these patients prepared their own breakfast and snacks. At baseline, an isocaloric LPD of 0.6 g · kg body weight^{-1} · 24 hr^{-1} was prescribed to patients in the LPD group, whereas patients in the NPD group were told to continue their normal diet. In order to maintain an isocaloric diet, an increase in carbohydrates (bread, fruit, and vegetables) and fats (monounsaturated fatty acids) was recommended. Patients with albuminuria $\geq$ 2 g · 24 hr^{-1} were allowed an additional 1.0 g of dietary protein per extra gram of urinary albumin. Furthermore, energy intake (KJ) and other nutrients were assessed at each visit by a three-day dietary record performed by the patients at home. Nutritional data were calculated by a national nutritional data program (Danish Catering Center).

Apart from the urine collection, all of the investigations were carried out with the patients in the supine position between 8 a.m. and 1 p.m. The investigations were started in the morning after an overnight fast. Patients had breakfast and morning insulin approximately 30 minutes after the start of the GFR investigation. They drank 150 to 200 ml tap water per hour during the study period.

Glomerular filtration rate

GFR was measured after a single intravenous injection of 3.7 MBq ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) at 8 a.m. by determining the radioactivity in venous blood samples taken 180, 200, 220, and 240 minutes after the injection [18, 19]. Extra renal loss was corrected for by subtracting 3.7 ml · min^{-1} [20]. The small underestimation (10%) of ^{51}Cr-EDTA renal clearance versus renal clearance of inulin was corrected for by multiplying the EDTA clearance by 1.10 [20]. The results were standard-

ized for 1.73 m^2 body surface area. The mean day-to-day coefficient of variation in the GFR is 4% in our laboratory.

Blood pressure

Office blood pressure was measured on the right arm after at least 30 minutes of rest in the supine position with a Hawksley random zero sphygmomanometer and an appropriate cuff size [25 · 12 cm (upper arm circumference of less than 35 cm) and 30 · 15 cm (upper arm circumference of more than 35 cm)]. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase V). The individual blood pressure level was determined as the mean of at least two measurements performed during the GFR determination.

Albuminuria, fractional clearance of albumin and urinary sodium excretion

On the basis of the three consecutive 24-hour urine collections completed immediately before each visit, albuminuria and urinary sodium excretion were measured by an enzyme-linked immunoadsorbent assay (coefficient of variation was 2.1%) [21] and a flame photometric method, respectively. Fractional clearance of albumin (θ_{alb}) was obtained by dividing the clearance of albumin [calculated as (U · V)/P, where U is urine albumin concentration, V is urine flow, and P is plasma albumin concentration] with the measured GFR to correct albumin excretion for changes in plasma albumin concentration and in GFR.

Hemoglobin A$_{1c}$ and blood glucose

From venous blood samples, hemoglobin A$_{1c}$ (HbA$_{1c}$) was measured by high-performance liquid chromatography (Variant; Bio-Rad Laboratories, Hercules, CA, USA). The normal range of HbA$_{1c}$ in our laboratory is 4.1% to 6.4%. The venous blood glucose concentration was measured two to four times during the clearance period by a One Touch II (Lifescan, Milpitas, CA, USA).

Statistical analysis

Clinical characteristics at baseline are given as mean ± SEM or median (range). During follow-up urinary excretion of albumin, sodium and the fractional clearance of albumin were logarithmically transformed before statistical analysis because of their positively skewed distribution. A mean of nutritional data from the three-day dietary records and a mean of the venous blood glucose measurements taken at each visit were used for statistical analysis. Changes in variables between visits are expressed as means with 95% confidence intervals. An unpaired *t*-test was used to compare baseline data and changes in nutritional data, GFR, albuminuria, and blood pressure between the LPD group and the NPD group during phases I and II, except baseline data of

Table 2. Baseline dietary protein intake, energy intake, glomerular filtration rate, albuminuria and blood pressure in 29 insulin-dependent diabetic patients with diabetic nephropathy

	LPD group (N = 14)	NPD group (N = 15)	P
Dietary protein intake g·kg^{-1}·24 hr^{-1}	1.2 (0.1)	1.1 (0.1)	0.53
Energy intake KJ·kg^{-1}·24 hr^{-1}	124 (6)	129 (7)	0.63
Glomerular filtration rate ml·min^{-1}·1.73 m^{-2}	94 (6)	92 (6)	0.78
Albuminuria^a mg·24 hr^{-1}	397 (14 to 4091)	438 (94 to 2934)	0.37
Mean arterial blood pressure mm Hg	95 (2)	100 (3)	0.26

Data are mean (SEM).
^{a} Median (range); LPD, low protein diet (recommended: 0.6 g·kg^{-1}·24 hr^{-1}); NPD, normal protein diet

albuminuria, which was tested by the Mann–Whitney *U*-test. Spearman's rank correlation coefficient was used to analyze data for correlations.

All calculations were made using SPSS for Windows (SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered significant (two tailed).

RESULTS

At baseline

Dietary protein intake, energy (calorie) intake, GFR, albuminuria, and arterial blood pressure were comparable in the LPD group and the NPD group (Table 2). Furthermore, carbohydrate intake, fat intake, and alcohol intake were alike (data not shown).

Phase I

Nutritional data. Both dietary protein and energy intake significantly decreased in the LPD group during phase I, whereas they remained stable in the NPD group (Table 3). Carbohydrate intake, fat intake, and alcohol intake remained stable in both diet groups during phase I (data not shown).

GFR, albuminuria, fractional clearance of albumin, and urinary sodium excretion. Concomitantly with the decrease in dietary protein intake, a significant decline in GFR, albuminuria, and fractional clearance of albumin was observed in the LPD group during phase I, whereas GFR, albuminuria, and fractional clearance of albumin remained stable in the NPD group (Table 3). No significant changes in urinary sodium excretion was seen in either diet group (Table 3).

Blood pressure. Nonsignificant changes in mean arterial blood pressure were observed in both groups (Table 3).

Body mass index, HbA$_{1c}$, and serum albumin. Body mass index (BMI) and metabolic control (HbA$_{1c}$) were significantly reduced during LPD, but these changes

Table 3. Changes in dietary protein intake, energy intake, glomerular filtratioin rate, albumniuria, fractional clearance of albumin (θ_{alb}), mean arterial blood pressure, body mass index (BMI), hemoglobin A_{1c} (HbA_{1c}) and serum albumin, in 29 IDDM patients with diabetic nephropathy, during the study

Changes in	Phase I			Phase II		
	LPD group (N = 14)	NPD group (N = 15)	P Inter-group	LPD group (N = 14)	NPD group (N = 15)	P Inter-group
Dietary protein intake $g \cdot kg^{-1} \cdot 24\ hr^{-1}$	−0.4 (−0.5 to −0.3)[a]	0.0 (−0.2 to 0.1)	< 0.0001	0.3 (0.2 to 0.5)[I,a]	0.0 (−0.2 to 0.1)	< 0.0001
Energy intake $MJ \cdot 24\ hr^{-1}$	−0.9 (−1.7 to −0.1)	0.5 (−0.6 to 1.6)	< 0.05	0.1 (−1.5 to 1.7)	−0.3 (−1.3 to 0.6)	= 0.57
Glomerular filtration rate $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$	−8.6 (−13.9 to −3.2)[c]	−2.5 (−6.8 to 1.8)	= 0.07	5.9 (0.8 to 11.1)[II,b]	−2.9 (−6.4 to 0.6)	< 0.01
Albuminuria %	−28.7 (−40.9 to −14.0)[c]	0.0 (−23.5 to 20.1)	< 0.05	25.0 (4.5 to 49.6)[III,b]	2.9 (−18.3 to 29.7)	= 0.16
Urinary sodium excretion %	−1.8 (−16.6 to 15.7)	10.6 (−13.5 to 41.2)	= 0.40	11.4 (−9.4 to 37.2)	2.2 (−17.4 to 26.6)	= 0.54
θ_{alb} %	−22.6 (−37.6 to −3.9)[b]	5.4 (−19.4 to 37.8)	= 0.07	11.6 (−8.5 to 36.2)[IV]	10.4 (−10.2 to 35.6)	= 0.93
Mean arterial blood pressure $mm\ Hg$	−2.8 (−5.8 to 0.2)	−0.7 (−5.3 to 3.9)	= 0.43	−1.4 (−4.9 to 2.0)	−0.1 (−6.4 to 6.1)	= 0.70
BMI $kg \cdot m^{-2}$	−0.5 (−0.8 to −0.2)[c]	−0.2 (−0.4 to 0.1)	= 0.07	0.3 (0.1 to 0.5)[V,d]	0.2 (0.0 to 0.5)	= 0.55
HbA_{1c} %	−0.5 (−0.7 to −0.2)[d]	−0.2 (−0.5 to 0.2)	= 0.21	0.1 (−0.1 to 0.4)[VI]	−0.1 (−0.3 to 0.2)	= 0.27
Serum albumin $g/liter$	−0.2 (−1.3 to 0.8)	0.3 (−0.5 to 1.0)	= 0.41	−0.6 (−1.2 to 0.1)	−0.7 (±1.7 to 0.3)	= 0.87

Data are: mean (95% CI). Abbreviations are: LPD, low protein diet (recommended: 0.6 $g \cdot kg^{-1} \cdot 24\ hr^{-1}$) and NPD, normal protein diet. In Phase I, at baseline the patients were randomized to either the LPD (LPD group) or NPD (NPD group) for 4 weeks. Phase II, between week 4 and week 8 all patients received NPD.
[a] $P < 0.0001$, [b] $P < 0.05$, [c] $P < 0.005$, [d] $P < 0.01$ during Phase I or Phase II (intra-group comparison)
[I] $P < 0.0001$, [II] $P < 0.006$, [III] $P < 0.002$, [IV] $P < 0.05$, [V] $P < 0.001$ and [VI] $P < 0.002$ compared to the changes seen during Phase I in the LPD group

were not significantly different from the changes seen in the NPD group. Nonsignificant changes in serum albumin were observed in both diet groups (Table 3).

Phase II

Nutritional data. In the LPD group, dietary protein intake increased significantly during the last four weeks of investigation (phase II), whereas it remained constant in the NPD group (Table 3). Energy intake (Table 3), carbohydrate intake, fat intake, and alcohol intake were comparable in the two diet groups (data not shown).

GFR, albuminuria, fractional clearance of albumin, and urinary sodium excretion. Normalization in dietary protein intake was accompanied by a significant increase in GFR and albuminuria in the LPD group, whereas GFR and albuminuria remained stable in the NPD group (Table 3). In the LPD group, the level of GFR was identical at baseline and after eight weeks [median (range); 94 (81 to 108) ml · min^{-1} · 1.73 m^{-2} and 92 (79 to 105) ml · min^{-1} · 1.73 m^{-2}, NS]. The changes in the fractional clearance of albumin were alike in the two diet groups during phase II. The change in fractional clearance of albumin during phase I was significantly different from the change during phase II in the LPD group, but not the NPD group (Table 3). No significant changes in urinary sodium excretion were seen in either diet group (Table 3).

Blood pressure. Alterations in mean arterial blood pressure were comparable in the LPD group and the NPD group (Table 3).

BMI, HbA_{1c}, and serum albumin. Body mass index

was significantly increased in the LPD group, but this change was not significantly different from the change in BMI seen in the NPD group. Metabolic control (HbA_{1c}) was comparable in the two diet groups. Nonsignificant changes in serum albumin were observedin both diet groups (Table 3).

Blood glucose and insulin dosage. The blood glucose levels during the GFR measurements were comparable at baseline, week 4, and week 8 in both the LPD group (8.5 ± 0.8 vs. 9.8 ± 1.1 vs. 8.7 ± 0.9; mean ± SEM; NS) and the NPD group (10.9 ± 0.9 vs. 9.5 ± 0.9 vs. 8.6 ± 1.1; NS). Correspondingly, the daily dose of insulin (U·kd^{-1}·24 hr^{-1}) remained unchanged at baseline, week 4, and week 8 in both the LPD group (42 ± 3 vs. 42 ± 3 vs. 43 ± 3; NS) and the NPD group (39 ± 2 vs. 39 ± 2 vs. 40 ± 2; NS).

Correlations. In the whole group of patients, a significant correlation between the relative change in dietary protein intake and relative change in albuminuria during phase I ($\rho = 0.51$, $P < 0.01$) and phase II ($\rho = 0.38$, $P = 0.05$) was demonstrated (Fig. 1), whereas no significant association was found between the relative change in dietary protein intake and the relative change in GFR, either during phase I ($\rho = 0.25$, $P = 0.22$) or phase II ($\rho = 0.33$, $P = 0.10$). During phase I, a significant correlation between the initial decline (absolute) in GFR and baseline GFR (range 58 to 135 ml · min^{-1} · 1.73 m^{-2}) was found in the LPD group ($\rho = 0.53$, $P < 0.05$). Relative changes in mean arterial blood pressure (ΔMABP%) correlated significantly with relative changes in GFR (ΔGFR%) in the NPD group during phase I ($\rho = 0.71$,
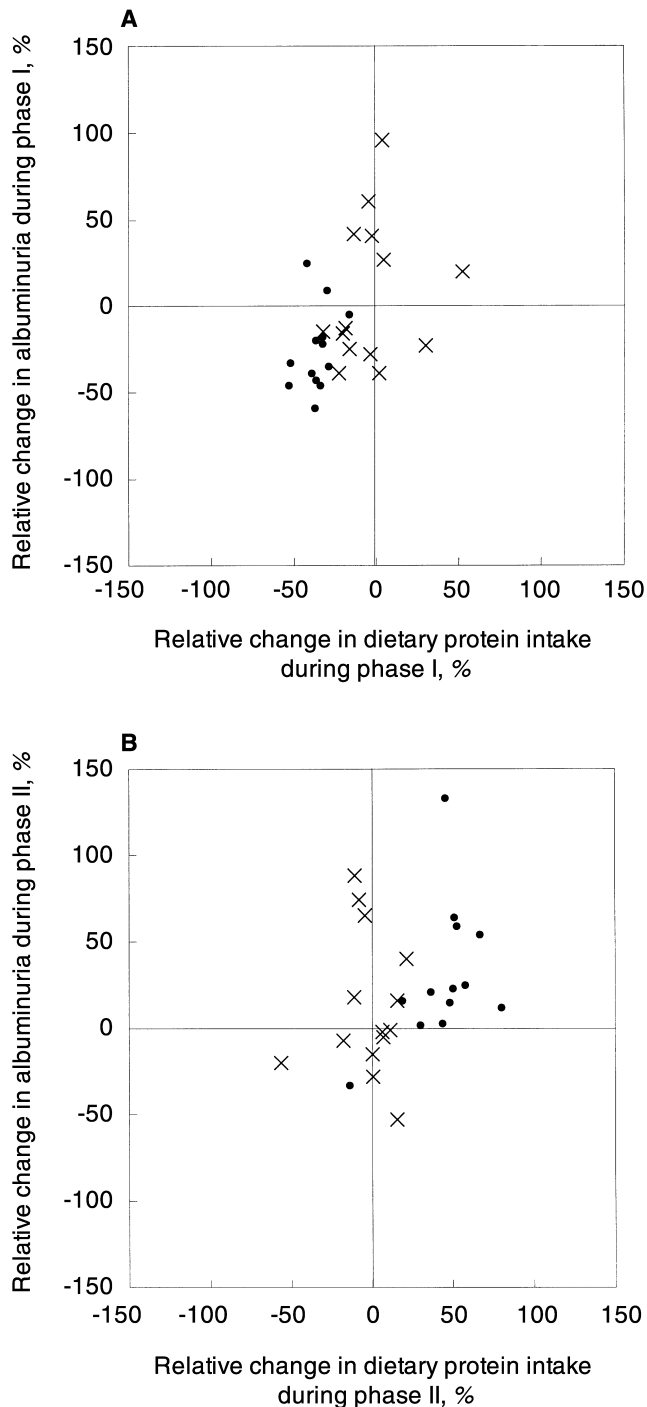
Fig. 1. Correlations between relative change in dietary protein intake and relative change in albuminuria in 29 insulin-dependent diabetic patients with diabetic nephropathy. (*A*) Phase I: At baseline, the patients were randomized to either LPD (•) or NPD (×) for four weeks (ρ = 0.51, *P* < 0.01). (*B*) Phase II: All patients received NPD from week 4 to week 8 (ρ = 0.38, *P* = 0.05). LPD, low-protein diet (0.6 g · kg^{-1} · 24 hr^{-1}); NPD, normal-protein diet.

P < 0.005), but not significantly during phase II (ρ = 0.40, *P* = 0.14; Fig. 2). Contrarily, no association between ΔMABP% and ΔGFR% was found in the LPD group either during phase I (ρ = −0.06, *P* = 0.84) or phase II (ρ = 0.09, *P* = 0.77). No significant correlations between relative changes in albuminuria and relative changes in mean arterial blood pressure or relative changes in GFR were found.

DISCUSSION

Our prospective study suggests a reversible decline in GFR and albuminuria during LPD for four weeks in insulin-dependent diabetic patients with diabetic nephropathy. The observed changes in GFR and albuminuria were not explained by changes in systemic blood pressure, which remained essentially unchanged during LPD. The initial decline in GFR during LPD was greater in patients with elevated baseline GFR, as also documented in the Modification of Diet in Renal Disease study [14].

Initiation of LPD (or pharmacological blood pressure lowering) in IDDM patients with elevated urinary albumin excretion and patients with nondiabetic glomerulopathies induces a faster initial (during the first four months) and a slower subsequent (four months to end of study) decline in GFR [8, 16, 22–24]. This short-term effect of protein restriction offsets the potential long-term beneficial effect of LPD on the progression of renal disease, as suggested in the Modification of Diet in Renal Disease study [8]. However, if the initial decline in GFR is reversible (hemodynamic) and does not attenuate over time, then only the sustained decline in GFR, reflecting progression in renal disease, should be analyzed. In contrast, if the initial decline in GFR during LPD reflects structural damage (irreversible), for example, closure of moderately/severely ischemic damaged glomeruli, it has to be accounted for when evaluating the long-term effects of intervention on progression in kidney disease.

We do not have any information on the physiological determinants of GFR, that is, the transcapillary hydraulic pressure difference (ΔP), the ultrafiltration coefficient (K_f), and the transcapillary oncotic pressure difference ($\Delta\pi$) in humans, but both hemodynamic and nonhemodynamic factors seem to be modified by dietary protein restriction in patients with renal disease [25–27]. Micropuncture studies have indicated that the abnormally elevated intraglomerular hydraulic pressure (P_{GC}) and the increased glomerular plasma flow rate [28] seen in experimental progressive glomerular diseases are reduced by dietary protein restriction [6, 29]. It has been suggested that these hemodynamic effects of LPD may be explained by alterations in preglomerular and/or postglomerular vascular resistance and changes in the tubuloglomerular feedback system [6, 30–32]. Recently, nonhemodynamic
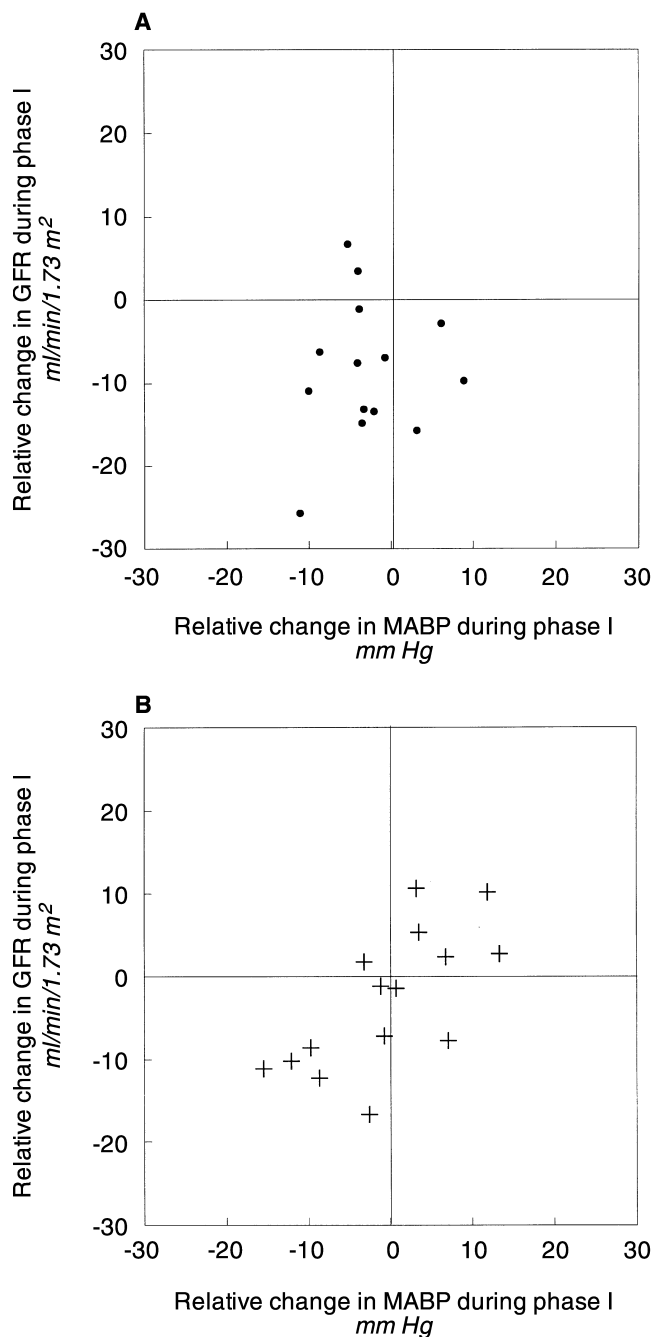
A

B

Fig. 2. Correlations between relative change in mean arterial blood pressure (MABP) and relative change in glomerular filtration rate (GFR) in 29 insulin-dependent diabetic patients with diabetic nephropathy receiving either (*A*) LPD (•; ρ = −0.06, *P* = 0.84) or (*B*) NPD (+; ρ = 0.71, *P* < 0.005) during the first four weeks of investigation (phase I). LPD, low-protein diet (0.6 g · kg^{-1} · 24 hr^{-1}); NPD, normal-protein diet.

effects, such as reduced uptake of plasma proteins in the mesangium and decreased renal expression of transforming growth factor and other growth factors [7], have been suggested to contribute to the diminished development and progression of glomerular sclerosis in experimental renal diseases during LPD [27].

Previous data suggest that the initial decline in GFR seen after the initiation of antihypertensive treatment in hypertensive IDDM patients suffering from diabetic nephropathy is reversible and does not attenuate over time [33]. The initial decrease in GFR seems to be explained by the pharmacologically induced reduction in systemic arterial blood pressure [33], as autoregulation of GFR, that is, the maintenance of relative constancy of GFR despite variations in mean arterial blood pressure, is abolished or impaired in patients with diabetic nephropathy [34]. Recently, Ruilope, Casal and Praga demonstrated a reversible decline in GFR during two weeks of LPD in patients with nondiabetic nephropathies [35]. Correspondingly, our short-term study suggests that the initial decline in GFR, seen after the initiation of LPD in IDDM patients with diabetic nephropathy, is completely reversible. Whether this reversibility in GFR is conserved during long-term treatment with LPD has to be elucidated. Interestingly, the initial reduction in GFR demonstrated during LPD was present during antihypertensive treatment (primarily with ACE inhibitors) and was not explained by changes in systemic blood pressure, because no effect of LPD on systemic arterial blood pressure was observed in our IDDM patients with diabetic nephropathy. Nevertheless, we found an association between ΔMABP% and ΔGFR% during phase I in the NPD group, but not in the LPD group. Because autoregulation of GFR is impaired/abolished in diabetic nephropathy [34], even during antihypertensive treatment, it is likely that changes in normal systemic blood pressure are transmitted, in part, downstream to the glomeruli affecting the GFR, as demonstrated in the NPD group. Because the association between ΔMABP% and ΔGFR% disappeared during LPD (LPD group), our findings provide some support for the concept that the reduction in GFR seen during LPD is due to a mechanism different from that induced by antihypertensive treatment (especially ACE inhibitors) [14, 35], probably by improving the abolished or impaired autoregulation of GFR seen in IDDM patients with diabetic nephropathy. This assumption is furthermore supported by previous findings by Bidani, Schwartz and Lewis, who found that LPD (8%) preserved renal autoregulation and protected the remnant kidney against the development of hypertensive injuries [36].

A few animal studies have suggested a beneficial effect of calorie restriction (40%) [37, 38] on the development of end-stage renal pathology in the 5/6 nephrectomized rat. Whether the significant, but small (9%), decrease in energy intake during phase I in the LPD group contributes to the decline in GFR during this phase is unknown, but seems, in this study, to be small or negligible, as GFR rose significantly during phase II, despite an unchanged energy intake. It appears in this study that the observed decline in calorie (energy) intake during LPD was due

to a failed increase in daily intake of carbohydrates and fat, despite a recommended isocaloric diet.

Because improved glycemic control does not have any short- or long-term effects on albuminuria or GFR in diabetic nephropathy [39, 40], it is unlikely that the slight but significant reduction in hemoglobin A_{1c} seen during protein restriction should affect the renal outcome in this study.

We have confirmed and extended the previously reported [9] reversible decrease in albuminuria during LPD in IDDM patients with diabetic nephropathy. Furthermore, we have demonstrated that this antiproteinuric effect of LPD is present during antihypertensive treatment. Studies in IDDM patients with diabetic nephropathy have suggested that albuminuria is pressure dependent to a large extent [34], but other studies in animals and humans with nondiabetic glomerulopathies have suggested a different, and probably additive, effect of dietary protein and enalapril on proteinuria, partly independent of the action on GFR [41, 42]. It has been suggested that LPD can improve the impaired size and charge-selective properties of the glomerular capillary filtration barrier [32, 43]. These nonhemodynamic effects of dietary protein restriction may also be active in humans and, thus, explain the presence of a correlation between changes in dietary protein intake and changes in albuminuria.

In conclusion, we have demonstrated that short-term LPD induces a reversible decline in GFR and albuminuria in insulin-dependent diabetic patients with diabetic nephropathy, in the absence of any significant alteration of systemic arterial blood pressure. Our data render some support of the hypothesis that the initial faster decline in GFR after initiating of LPD in these patients is due to a local intrarenal hemodynamic effect achieved by improved autoregulation of GFR.

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