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Reduction of protein intake decreases glomerular filtration rate in young Type 1 (insulin-dependent) diabetic patients mainly in hyperfiltering patients

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Summary. The influence of different protein intake on renal function was studied in 16 Type 1 (insulin-dependent) diabetic patients, aged 15-23 years, with onset of diabetes before puberty and with a duration of diabetes between 5 and 20 years. The glomerular filtration rate, renal plasma flow, albumin excretion rate, and blood pressure were examined in a cross-over randomised order after 10 days on isocaloric diets with either 10% (i.e. 0.9 ± 0.06 g·kg^{-1}·day^{-1}) or 20% (1.9 ± 0.1 g·kg^{-1}·day^{-1}) of the calories as protein, the latter being equal to the recommended diet. Dietary compliance was evaluated using fractional phosphate excretion and overnight urea excretion. Glomerular filtration rate was lower after the low-protein diet compared to the usual protein diet ($p < 0.001$). Patients with glomerular filtration rate above +2 SD of the normal mean on the usual protein diet ($n = 6$) exhibited the steepest fall in glomerular filtration rate with a mean decrease of 20 ml/min compared to 7 ml/min in those with initially normal glomerular filtration ($p = 0.01$). Filtration fraction tended to decrease on low protein diet, more so in initially hyperfiltering patients ($p = 0.09$). Renal plasma flow remained unchanged. In patients with elevated glomerular filtration rate on usual protein diet, albumin excretion rate and systolic, but not diastolic blood pressure, were decreased on low protein diet ($p = 0.03$ and $p = 0.01$, respectively) but not in initially normal-filtering patients. Mean blood glucose and serum fructosamine were unchanged on both diets. In conclusion, low protein diet decreases glomerular filtration rate independently of glycaemic control in young Type 1 diabetic patients and more so in hyperfiltering patients. This decline in glomerular filtration rate is accompanied by a decrease in albumin excretion rate and systolic blood pressure in hyperfiltering patients.

Key words: Type 1 (insulin-dependent) diabetes, renal hyperfiltration, microalbuminuria, protein restriction.

It is well known that many patients with Type 1 (insulin-dependent) diabetes already early after onset have a sustained elevated glomerular filtration rate (GFR) [1-3]. It has been proposed that glomerular hyperfiltration plays a role in the development of the increased urinary albumin excretion and the structural glomerular changes that are associated with diabetic nephropathy in humans [4]. Several prospective studies suggest that microalbuminuria is an early predictor of the glomerular lesion [5-7]. Albuminuria might also be a secondary effect of the increase in ultrafiltration pressure [8-11] that is a feature of the hyperfiltration. Supportive evidence for a causative relationship between hyperfiltration and the renal damage in diabetes has been demonstrated in studies in animals with experimental diabetes mellitus [12].

In 1954, Pullman et al. had already shown that GFR could be influenced by different protein intake in normal man [13]. More recent studies in experimentally induced diabetes in the rat [14], as well as a few clinical studies in insulin-dependent diabetic patients [15, 16], have also demonstrated that hyperfiltration can be attenuated by low protein diet (LPD).

To further address the question whether an LPD affects renal function differently in hyperfiltering compared to normal-filtering diabetic patients, we have examined the effect of reduced protein intake on two groups of patients with Type 1 diabetes: one group with GFR more than +2 SD from normal mean, and a second group with normal GFR. In both groups the initial GFR used for this classification was determined when the patients were on the usual protein diet.

Subjects and methods

The study was approved by the local ethical committee and informed consent was given by patients and parents.

Study population

Seven female and 9 male patients, aged 15-23 years and with a duration of diabetes of 5-23 (mean 12) years were studied. All pa-

Table 1. Clinical characteristics of 16 Type 1 (insulin-dependent) diabetic patients before entry into the study

	Glomerular filtration rate	Renal plasma flow	Albumine excretion rate	Blood pressure	Insulin dose	Mean blood glucose[a]	Fructose-amine	Body weight	Protein intake	Energy intake[b]
	($ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$)		(μg/min)	(mm Hg)	(IU/kg)	(mmol/l)	(mmol/l)	(kg)	($g \cdot kg^{-1} \cdot day^{-1}$)	(kcal/day)
Mean	125	552	14	123/76	0.9	9.6	5.96	67	1.9	2400
Range	97-162	179-933	3-76	110-140/ 65-90	0.6-1.3	3.0-17.2	2.61-9.92	51-91	1.4-2.4	1800-3200

[a] Mean blood glucose during renal function test; [b] Estimated protein and energy intake based on 5 day dietary record

tients had an onset of diabetes before puberty. Selection criteria for participation in the study were age ≥ 15 and duration of diabetes ≥ 5 years. Clinical characteristics are given in Table 1.

The patients were divided into two groups according to their GFR values on the usual protein diet (UPD). 1) Group H included 6 patients with hyperfiltration, i.e. GFR above $127\ ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$. This value corresponds to the mean +2 SD as measured by the method used in age-matched healthy control patients [17]. The mean value of GFR measured twice within the last year in these patients was $141 \pm 5\ ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$ (mean ± SEM); 2) Group N included 19 patients with GFR below $127\ ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$. In this group the mean value of 2 preceding GFR examinations during the last year was $124 \pm 6\ ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$. The groups did not differ with respect to age, sex, or duration of diabetes (14 years in group H and 11 years in group N). Neither did age at onset (5 years in group H and 6.5 years in group N) differ between the two groups.

One male patient in group N (no. 8) was on a continuous subcutaneous insulin infusion, the others were conventionally treated using 3-4 subcutaneous injections daily. None of the patients were taking drugs other than insulin.

All patients had Albustix negative urine tests, but 6 patients had albumin excretion rate values exceeding 15 μg/min, 2 in group H and 4 in group N (nos. 4, 6, 8, 9, 10, 11). The highest albumin excretion rate values were found in group N.

Two patients in group N (nos. 8 and 9) had a diastolic blood pressure at the 90th percentile for age and sex (90 mm Hg), all other patients were normotensive.

All patients were examined for late complications from eyes (ophthalmoscopy) and nerves (nerve conduction velocity). Pathological findings were present only in group N. Three patients had background retinopathy (a few microaneurysms, patients nos. 8, 9, and 11) and 4 had diminution of nerve conduction velocity compatible with incipient neuropathy (patients nos. 8, 9, 10, and 11).

Metabolic control at the time of entrance into the study measured as fructosamine in serum was equal in both groups, 5.19 (2.61-9.92) mmol/l in group H and 6.43 (3.66-9.72) mmol/l in group N (normal value 1.9-2.7 mmol/l). No patient had been admitted to the hospital because of ketoacidosis within 6 months prior to the study.

Procedure

The day before entrance into the study, the patients were examined for GFR, renal plasma flow, albumin excretion rate, blood pressure, serum fructosamine, and mean blood glucose during the renal function test (Table 1). This examination was then repeated twice after the subjects had been on different diets as described below.

Diets. The mean energy and protein intake of the usual diet was calculated from a 5 day dietary record. The calculation was performed by a nutritionist. Estimated usual energy and protein intake is given in Table 1. The amount of dietary protein or calories did not differ between the two groups. In group H mean energy intake was 2400 (1800-3400) $kcal \cdot day^{-1}$ and mean protein intake was 1.9 (1.5-2.4) $g \cdot kg^{-1} \cdot day^{-1}$. Corresponding values for group N were 2080 (1800-2800) $kcal \cdot day^{-1}$ and 1.8 (1.4-2.4) $g \cdot kg^{-1} \cdot day^{-1}$, respectivly. Based on the dietary record diets containing either 10% (corresponding to $0.9 \pm 0.06\ g \cdot kg^{-1} \cdot day^{-1}$) or 20% ($1.9 \pm 0.1\ g \cdot kg^{-1} \cdot day^{-1}$) of the calories as protein were individually designed. The sources of protein were similar in the diets, i.e. both animal and vegetarian. The protein content of the different diets did not differ between groups H and N. The relative content of dietary fat was unchanged in the two diets and corresponded to 30% of the calories. The diets were based on prefabricated meals of known composition (Findus AB, Stockholm, Sweden) with individual recommendations of supplements of bred, butter, and milk. These isocaloric diets were taken in a randomised order during two 10-day periods with no interval between. Immediately before each renal function test, performed between 12.00 and 15.00 hours, the patients received a standard lunch at 11.30 hours with the same relative composition of protein, carbohydrates, and fat as that of the preceding 10 days.

Evaluation of dietary compliance

Overnight urea excretion (urea/creatinine ratio, enzymatic method, Boeringer Mannheim, Mannheim, FRG) was determined in urine collected at two separate occasions during the two study periods. In the same way, overnight phosphate excretion was measured in 12 patients, but fractional phosphate excretion calculated as clearance of phosphate/clearance of inulin was also determined on UPD and LPD during the renal function test in 4 portions of urine with 30 min intervals [18]. To be included in the analyses of the results, fractionatal phosphate excretion and overnight urea excretion should be higher on the UPD than on the LPD. Four patients were excluded from the study as one of these criteria was not fulfilled.

Kidney function

GFR, renal plasma flow, and filtration fraction (%, calculated from GFR/RPF) were measured using the continuous infusion technique of inulin (Inulin, Laevosan, Linz, Austria) [19] and p-aminohippuric acid (PAH, Merck Sharp and Dohme, Rahway, New Jersey, USA) [20]. The patients were examined in the recumbant position. They were orally hydrated with water corresponding to 1% of the body weight during 1 h preceding the start of the clearance study, thereafter, with 0.25% of the body weight, every 30 min. The clearance values were expressed per 1.73 m^2 surface area.

Albumin excretion rate (μg/min) was measured using a radioimmunological technique (Phadebas, Uppsala, Sweden) during each clearance investigation. It was estimated from 2 portions of urine voided at 120 and 150 min after the initial hydration to eliminate the wash-out effect on albumin excretion rate. Fractional albumin clearance was also estimated and calculated as the clearance of albumin/clearance of inulin.

Fractional sodium excretion was measured as clearance of sodium/clearance of inulin and the urine potassium/sodium ratio was also studied using a flamometer (Kontron, Stockholm, Sweden).

Table 2. Glomerular filtration rate, renal plasma flow, filtration fraction, serum fructosamine and mean blood glucose during clearance investigation in initially hyperfiltering, (Group H, GFR > +2 SD of normal mean) and initially normal-filtering (Group N) Type 1 diabetic patients. Results after usual (UPD) and low protein (LPD) diet. Mean ± SEM

	Glomerular filtration rate ($ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$)		Renal plasma flow ($ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$)		Filtration fraction (%)		Fructosamine (mmol/l)		Mean blood glucose (mmol/l)	
Group	H	N	H	N	H	N	H	N	H	N
UPD	144 ± 4	116 ± 3	572 ± 59 ($n=5$)	569 ± 26	26 ± 3 ($n=5$)	20 ± 1	4.3 ± 0.7	5.8 ± 1.1	7.7 ± 0.7	8.7 ± 0.5
LPD	124 ± 3	109 ± 3	573 ± 23	570 ± 28 ($n=9$)	23 ± 1	19 ± 1 ($n=9$)	4.2 ± 0.8	5.4 ± 0.8	5.5 ± 0.8	8.7 ± 0.7
p value	< 0.001	0.09	0.84	0.37	0.09	0.43	0.89	0.51	0.46	0.91

Blood pressure measurement

Systolic and diastolic blood pressure (mm Hg) were measured by the same observer at the start of each clearance investigation after a 15 min rest, left arm, sitting position, using a conventional sphygmometer technique. Diastolic blood pressure was read at phase 5.

Evaluation of metabolic control

During the study period, all subjects performed home blood glucose monitoring, and the insulin dose was adjusted according to the blood glucose values.

Blood glucose (enzymatic method, Glox, Pharmacia, Uppsala, Sweden) was also measured 10 times during a 22 h period in 12 patients and in all 16 patients before the intake of the standard lunch, thereafter, every half hour during the renal function test.

Serum fructosamine (Fructosamine test, Roche Diagnostica, Basel, Switzerland) [21] was determined in aliquots of blood samples obtained before each clearance investigation.

Statistical analysis

GFR, clearance of p-aminohippuric acid, and blood pressure were analysed using Student's t-test for paired observations and for comparisons between groups. Because of a skewed distribution of albumin excretion rate, this was analysed using the Wilcoxon's matched pairs sign test. Correlation studies were performed using either the the methods of Pearson or Speerman. A p value < 0.05 was considered statistically significant.

Results

Effect of low protein diet on renal function in all diabetic patients

Glomerular filtration rate. GFR was significantly lower after LPD, 114 ± 3 vs 127 ± 4 $ml \cdot min^{-1} \cdot 1.73\ m^{2-1}$ (mean ± SEM) after UPD ($p < 0.001$). A positive correlation between baseline GFR-values and delta GFR between UPD and LPD was seen ($r = 0.67$, $p < 0.001$). When excluding patients with signs of late diabetic complications (patients nos 8, 9, 10, 11) this correlation was still statistically significant ($r = 0.59$, $p = 0.04$).

Renal plasma flow and filtration fraction. Clearance of p-aminohippuric acid remained unchanged in the whole study population, 547 ± 34 vs 576 ± 38 $m \cdot min^{-1} \cdot 1.73^{-1}$ (mean ± SEM) after UPD and LPD, respectively. Filtration fraction tended to be higher on UPD than on LPD, 25 ± 3 vs 21 ± 1% (mean ± SEM), but the difference was not statistically significant ($p = 0.17$).

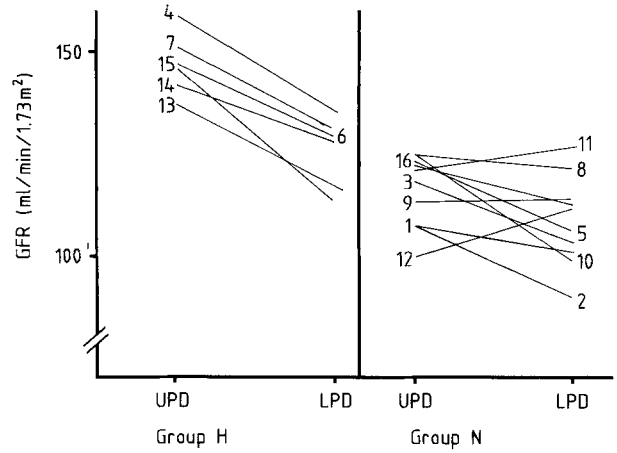

Fig. 1. GFR in young Type 1 (insulin-dependent) diabetic patients after usual (UPD) and low (LPD) protein diet. Groups H and N indicate hyperfiltering and normal-filtering groups respectively. The numbers in the figure refer to patient numbers in the text

Albumin excretion rate. Median albumin excretion rate was similar at the end of both 10 day study periods: after LPD 13 μg/min, range 4–61, after UPD 16 μg/min, range 6–79. Fractional clearance of albumin was also unchanged 56 ± 11 after LPD vs 76 ± 12 after UPD (mean ± SEM, $p = 0.27$).

Blood pressure. Systolic, but not diastolic blood pressure, was slightly decreased after LPD, 118 ± 2, as compared to 122 ± 2 mm Hg after UPD ($p = 0.02$). No correlation was seen between systolic or distolic blood pressure and GFR, but systolic blood pressure tended to be correlated to albumin excretion rate ($r = 0.31$, $p = 0.05$).

Comparisons of renal function tests in hyperfiltering versus normal-filtering diabetic patients

Glomerular filtration rate. Mean values of GFR in the two groups are given in Table 2. Individual GFR values are shown in Figure 1. The mean decrease of GFR was more pronounced in group H as compared

Table 3. Albumin excretion rate and blood pressure in initially hyperfiltering (Group H, i.e. > +2 SD of normal mean) and normal-filtering (Group N) Type 1 diabetic patients after usual (UPD) and low protein (LPD) diet

	Albumin excretion rate (μg/min) median (range)		Blood pressure systolic[a] (mm Hg)		Blood pressure diastolic[a] (mm Hg)	
	H	N	H	N	H	N
UPD	17 (9-20)	16 (6-79)	122±4	124±3	74±2	72±3
LPD	10 (7-14) ($n=5$)	16 (4-61) ($n=8$)	115±3	119±3	73±4	74±3
p value	0.03	0.88	0.01	0.16	0.17	0.30

[a] Mean ± SEM

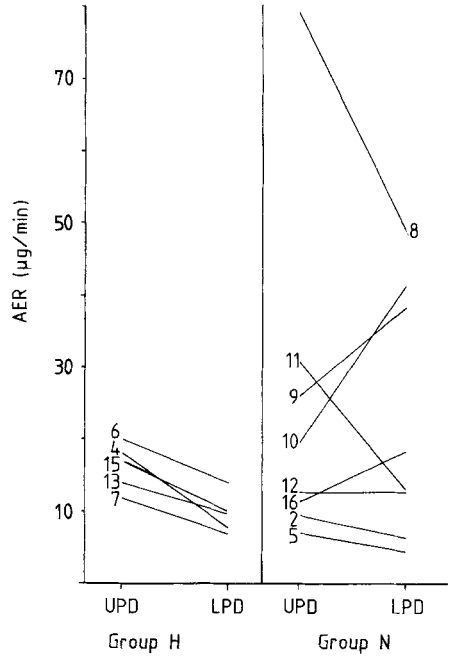

Fig. 2. AER in young Type 1 diabetic patients after usual (UPD) and low (LPD) protein diet. Groups H and N indicate hyperfiltering and normal-filtering groups respectively

to group N, 20±1.8 ml/min (mean±SEM) and 7±3 ml/min respectively. This difference was statistically significant ($p=0.01$).

Renal plasma flow and filtration fraction. No difference was noted in clearance of p-aminohippuric acid after LPD as compared to after UPD (Table 2) in any group. The mean value of filtration fraction tended to be higher on UPD than on LPD in the hyperfiltering group only, but this difference did not reach statistical significance ($p=0.09$) (Table 2). Two filtration fraction and clearance of p-aminohippuric acid values are missing due to technical error.

Albumin excretion rate. All hyperfiltering patients reduced their albumin excretion rate on the LPD, whereas no change was found in group N (Table 3). The individual values for both groups are found in Figure 2. Values from one patient in group H and two patients in group N are missing due to sampling error. In group H fractional albumin clearance was reduced in all patients from $48\pm7\times10^{-8}$ on UPD to $33\pm6\times10^{-8}$ on LPD (mean±SEM, $p=0.03$). In group N, corresponding values were $76\pm11\times10^{-8}$ on UPD and $56\pm11\times10^{-8}$ on LPD (mean±SEM, $p=1.27$).

Blood pressure. A significant decrease in systolic, but not diastolic pressure, was found only in the hyperfiltering group after the LPD (Table 3).

Metabolic control during low and usual protein diet

Insulin dose was unchanged during the study period and equal in groups H and N, 0.9±0.005 IU/kg body weight.

Serum fructosamine remained unchanged on the two diets in both groups (Table 2). No correlation between fructosamine and GFR was seen on any diet ($r=-0.33$, $p=0.21$ on UPD; $r=-0.19$, $p=0.48$ on LPD).

Mean blood glucose during the clearance investigation was not significantly different on LPD as compared to that recorded during UPD in any group. Neither was there any difference in blood glucose values between groups H and N (Table 2). Mean blood glucose during 22 h was also unchanged, 9.4±0.2 mmol/l on UPD vs 8.5±0.4 mmol/l on LPD (mean±SEM) (Fig. 3). The mean blood glucose levels did not differ significantly in group H as compared to group N.

Body weight was the same on the various diets, UPD 66.2±10.6 kg, LPD 66.4±10.1 kg (mean±SD).

Dietary control

Median overnight urea/creatinine excretion ratio was 28.7 (24.6-44.6) on UPD and 22.6 (14.3-27.8) after LPD ($p=0.001$). Fractional phosphate excretion decreased from 22 (10-32) on UPD to 17 (5-22) on LPD ($p<0.001$). Median overnight phosphate/creatinine excretion ratio was 3.4 (1.6-4.4) after UPD and 2.4 (1.5-3.3) after LPD ($p=0.01$). Fractional sodium excretion was 1.33±0.12 (mean±SEM) on LPD vs 1.44+0.15 on UPD ($p=0.60$). The potassium/sodium excretion ratio was also unchanged, 0.90±0.10 (mean±SEM) after LPD and 0.85±0.10 after UPD ($p=0.43$).

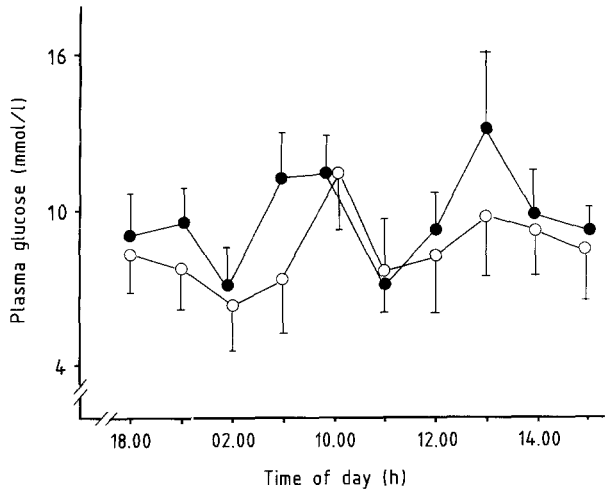

Fig. 3. Plasma glucose profiles in 12 Type 1 diabetic patients during usual (●) and low protein diet (○)

Discussion

This study clearly demonstrates that GFR decreases following a moderate reduction of protein intake also in patients with insulin-dependent diabetes. However, there is a considerable difference in the response of GFR to an LPD between initially hyperfiltering and normal-filtering patients. In the present study, we found that patients with supranormal elevation of GFR were more prone to reduce their GFR on an LPD than those with an initially normal glomerular filtration rate. It should be recalled, though, that this latter group was heterogenous as it included patients with and without signs of incipient nephropathy. One could therefore speculate that the different responses of GFR to LPD in hyperfiltering and normal-filtering patients might partly be due to the fact that some of the patients in group N had reached a stage of incipient renal damage as indicated by elevated albumin excretion rate values. Furthermore, the same patients in the normal-filtering group had, in addition, evidence of other late diabetic complications. One could therefore hypothesise that these patients might be less able to adapt their kidney function to a change in dietary protein intake; however, when excluding these patients, there was still a significant correlation between basal GFR and the magnitude of fall in GFR after LPD. This indicates a difference in the effect of LPD also between hyperfiltering and non-hyperfiltering patients without complications.

The present finding of a decline of GFR after LPD is in accordance with earlier findings in insulin-dependent diabetic patients [15, 16, 22]. However, these studies are not strictly comparable to our study, either with respect to experimental design - i.e. different amounts of protein in the diets, or regarding the clinical characteristics of the patients - i.e. chronological age, age at onset, or duration of diabetes, signs of microangiopathy. Furthermore, in our study a standard meal was given prior to the clearance investigation to enhance the "long-term" effect of different protein intake.

We chose not to supplement with phosphate for the lowering in phosphate intake on an LPD as we wanted to examine the usual situation of a decrease in dietary protein. The quantative reduction of protein content might not be the only contributor to the reduction of GFR. Thus, the lowering in phosphate intake on LPD may also influence renal function, as well as possible differences in amino acid composition of the two diets [23].

Glycaemic control is a well-known modulator of renal function in diabetes [24–26]. The present observations of unchanged levels of blood glucose and serum fructosamine on the various diets suggest that the influence of LPD on renal function occurs independently of glycaemic control. This confirms earlier findings [16].

The present findings of unchanged clearance of renal plasma flow and a tendency of decreased filtration fraction after LPD have been reported earlier in hyperfiltering diabetic patients [16]. In experimental diabetes, a reduction of single nephron GFR following an LPD has also been shown to be accompanied mainly be a decrease in the transcapillary pressure gradient [14]. In healthy subjects though, and in adolescent patients with short-term diabetes (mean 5 years) without signs of renal disease or other late diabetic complications, a parallel decrease in RPF and GFR was seen after LPD [13, 15]. These divergent results might be explained by the fact that the diabetic patients, as well as the healthy control patients in the latter of these studies, had a normal renal function but were made hyperfiltering by a very high protein diet. One could therefore hypothesise that normal subjects and diabetic patients with an intact renal function might react differently in renal haemodynamics than diabetic patients with more longstanding diabetes and with signs of early functional and/or structural renal changes.

It should be pointed out, however, that data on renal plasma flow and filtration fraction based on p-aminohippuric acid clearance studies should be interpreted with some caution in patients with diabetes. In the present study, as in others [15, 16], there was a wide variation in the clearance of p-aminohippuric acid values. A few patients showed a great variability in the clearance of p-aminohippuric acid with very low values that was not seen in the clearance of inulin which could partly be attributed to methodological problem but may also, for unknown reasons, be due to variabilities in tubular function. This might also explain the divergent results concerning renal plasma flow in diabetic patients that have been reported in earlier studies [15, 16, 27].

In order to standardise the investigation of albumin excretion rate and to eliminate the variability due to physical activity, we measured albumin excretion during the clearance investigation. The parallel decline in GFR and urinary albumin excretion on LPD, seen in

the hyperfiltering group only, is in agreement with the hypothesis that urinary albumin excretion is dependent on intraglomerular haemodynamic factors [8, 9] and also consistent with earlier findings [16, 23]. However, as fractional albumin clearance also was reduced in group H, this indicates that a decrease in albumin excretion rate is not only dependent on GFR but alternative explanations are also to be found [16].

Several studies in diabetic humans and in diabetic rats have failed to show an association between protein intake and blood pressure [14, 15, 23]. We have no apparent explanation for the slight decrease in systolic, but not diastolic blood pressure, seen in initially hyperfiltering patients after LPD. As the magnitude of fall in systolic blood pressure was small, it is reasonable to assume that this could only have had a marginal influence on the measured kidney function parameters.

In conclusion, this study has shown that an LPD will reduce GFR in diabetic patients. The effect is more pronounced in hyperfiltering patients and is accompanied by a decrease in albumin excretion rate and systolic blood pressure in these patients. Thus, if glomerular hyperfiltration initiates or accelerates the renal damage in diabetes as suggested by Brenner et al. [4], a moderate protein restriction could be recommended to hyperfiltering diabetic patients in addition to intensive metabolic regulation and early antihypertensive treatment. However, further studies have to ascertain the long-term renal functional effectivness of dietary protein restriction in diabetic patients.

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