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Glomerular hypertension as one cause of albuminuria in Type II diabetic patients

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Abstract

Aims/hypothesis. Results from animal models of glomerular hypertension have suggested that this disorder is one cause of albuminuria in diabetic nephropathy. We evaluated this hypothesis clinically.
Methods. The subjects were 20 patients with Type II (non-insulin-dependent) diabetes mellitus but without uraemia or hypertension: 8 had normoalbuminuria and 12 had albuminuria (≥ 20 μg/min). In the 2-week study, patients were on a diet with ordinary amounts of sodium for 1 week and on a sodium-restricted diet for 1 week. Urinary excretion of sodium and albumin and the systemic blood pressure were measured daily. Intrarenal haemodynamics, in terms of the glomerular pressure and resistance of afferent and efferent arterioles, were calculated from renal clearance, the plasma total protein concentration, and the pressure-natriuresis relation. In 8 of the 12 patients with albuminuria, an angiotensin-converting enzyme inhibitor, cilazapril, was given orally (2 mg/day) and the 2-week study was repeated.
Results. In patients with albuminuria, resistance of efferent arterioles and the glomerular pressure were higher than in patients with normoalbuminuria (glomerular pressure, 53 ± 5 vs 43 ± 5 mmHg, means ± SD, $p < 0.001$). Urinary excretion of albumin correlated ($n = 20, r = 0.675, p < 0.001$) with the glomerular pressure but not with systemic pressure. The increased glomerular pressure and the albuminuria were decreased by cilazapril but systemic pressure was not.
Conclusion/interpretation. These findings are consistent with the hypothesis that glomerular hypertension is present in Type II diabetic patients with early nephropathy and can cause albuminuria. [Diabetologia (1999) 42: 999–1005]

Keywords Diabetes mellitus, diabetic nephropathies, renal circulation, albuminuria, glomerular capillary hypertension.

Glomerular capillary hypertension may cause albuminuria and nephropathy in diabetes mellitus, according to animal studies [1–5]. This hypothesis has been supported by the results of many clinical studies showing that antihypertensive drugs, especially angiotensin-converting enzyme (ACE) inhibitors, can reduce albuminuria and slow the progression of diabetic nephropathy [6–8]. Direct measurement of glomerular capillary hydraulic pressure (PGC) by the micropuncture method in diabetic rats given an ACE inhibitor showed that in this animal model, glomerular hypertension is one cause of albuminuria and diabetic nephropathy [9,10]. In humans, PGC cannot, however, be measured directly, so changes in glomerular haemodynamics in diabetic patients have not been reported. Recently, a method for the clinical assessment of glomerular haemodynamics was published [11–13]. Here, using this method, we investi-

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Abbreviations: PGC, Glomerular capillary hydraulic pressure; ACE, angiotensin converting enzyme; MAP, mean arterial pressure; RPF, renal plasma flow; GFR, glomerular filtration rate; ΔPF, effective filtration pressure; PT, hydrostatic pressure in Bowman's space; ΠG, mean oncotic pressure; RA, resistance of afferent arterioles; RE, resistance of efferent arterioles; UNaV, urinary sodium excretion.

Table 1. Characteristics of diabetic patients at the start of the study

	Patients with normoalbuminuria ($n = 8$)	Patients with microalbuminuria ($n = 10$)	Patients with macroalbuminuria ($n = 2$)
Sex (male/female)	3/5	6/4	2/0
Age (years)	58 ± 12 (33–68)	63 ± 6 (47–68)	66, 70
Body mass index (kg/m^2)	21.8 ± 2.4	23.3 ± 4.5	26.0, 18.6
Duration of diabetes (years)	14.4 ± 7.0	16.0 ± 7.0	15, ≥ 14
FPG (mmol/l)	6.9 ± 0.9	6.7 ± 0.7	9.0, 7.3
HbA_{1c} (%)	8.6 ± 1.1	8.1 ± 1.9	6.8, 8.9
Serum creatinine (μmol/l)	53 ± 13	61 ± 14	88, 62
Systolic blood pressure (mmHg)	134 ± 13	136 ± 10	142, 128
Diastolic blood pressure (mmHg)	75 ± 6	79 ± 6	84, 66
Mean arterial pressure (mmHg)	94 ± 5	98 ± 6	103, 87

Values are expressed as means ± SD except those of patients with macroalbuminuria. The range of ages is given in parentheses. FPG, fasting plasma glucose. Differences between the two groups were not statistically significant (by Student's *t*-test for unpaired samples).

gated whether glomerular capillary hypertension exists and causes albuminuria in diabetic patients with early nephropathy.

Materials and methods

Patients. Our subjects were 20 inpatients with Type II (non-insulin-dependent) diabetes mellitus at Osaka City General Hospital; the 11 men and 9 women were aged 33 to 70 years. All patients met the criteria for Type II diabetes of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [14]. Patients with a history of non-diabetic renal disease, heart disease, or urinary tract infection or with serum creatinine of 97.4 mmol/l or more were excluded. In all 20 patients, urinary sediment was free from erythrocytes and other indications of non-diabetic renal disease. The systemic blood pressure of all subjects was less than 150/90 mmHg without antihypertensive medication. All patients were fully informed before their consent was obtained and the study was approved by an institutional ethics committee. The patients were divided into three groups by their degree of albuminuria when the study started (Table 1). When subjects were on the regular hospital diet (8–10 g of NaCl/day), urinary albumin excretion of less than 20 μg/min (< 28.8 mg/24 h), that of 20–200 μg/min (28.8–288 mg/24 h) and that of more than 200 μg/min (> 288 mg/24 h) were defined as normoalbuminuria ($n = 8$), microalbuminuria ($n = 10$) and macroalbuminuria ($n = 2$), respectively. The highest urinary excretion of albumin found among these patients was less than 650 mg/24 h. Table 1 shows characteristics of the patients at the start of the study. Differences in the mean values (age, etc.) of the groups were not statistically significant.

Study protocol. This study was done after plasma glucose concentrations were brought under control during at least 2 weeks in hospital. The patients were then put on a diet with a low salt content (about 5 g of NaCl/day) or an ordinary salt content (about 15 g of NaCl/day) for 1 week at each of these in random order, with no time intervening. This was done so that the pressure-natriuresis relation could be investigated. The calories and amount of protein provided to individual patients daily during the study were kept constant. Medication other than insulin or an oral antihyperglycaemic agent was not given. On each of the last 3 days of the diets, 24-h urine collection was done and the urine was assayed for its concentrations of sodium, creatinine and albumin. Sodium and albumin were assessed in terms of the means of these values. On the last day of each diet, a 24-h record of blood pressure was taken with a portable monitor by an oscillometric technique (Listmini, BP-8800, Colin, Aichi, Japan) with measurement once hourly. The mean arterial pressure (MAP) was calculated by addition of one-third of the pulse pressure to the diastolic pressure, both of which were calculated as the means of the values from the 24-h record. The renal plasma flow (RPF), glomerular filtration rate (GFR), renal clearance of creatinine, plasma total protein concentration and blood haematocrit were investigated simultaneously on the last day of the diet with an ordinary salt intake. Renal plasma flow was calculated by the usual clearance method with *p*-aminohippurate. One method for estimation of the GFR was from the fractional renal accumulation of ^{99m}Tc-diethylenetriaminepentaacetic acid, calculated from computed renograms with a gamma camera (GCA7200A/DI, Toshiba, Nasu, Japan) [15]. The filtration fraction was obtained as the ratio of GFR to RPF. Renal plasma flow, GFR, and creatinine clearance were measured simultaneously with the patient supine. The results for RPF, GFR, and creatinine clearance were standardized for a body surface area of 1.73 m^2.

After the 2-week study, in 8 of the 12 patients with albuminuria (7 of the 10 with microalbuminuria and 1 of the 2 with macroalbuminuria), another 2-week study was done with cilazapril (2 mg/day) given orally. Cilazapril is an inhibitor of ACE. Renal clearance tests were done under the same conditions as before.

Calculation of pressure-natriuresis curves and glomerular haemodynamics. Pressure-natriuresis curves [11,16] were constructed by plotting the urinary sodium excretion (UNaV) on the ordinate as a function of MAP on the abscissa. Assuming a linear relation between MAP and UNaV, a pressure-natriuresis curve for a patient can be drawn by linkage of two datum points obtained when the patient's sodium balance is in a steady state during the two diets with different amounts of sodium. We calculated one mean UNaV for the last 3 days of each diet.

The intercept, A (mmHg), extrapolated at the x-axis of the pressure-natriuresis curve and the slope, B (mEq/day per mmHg), were calculated as follows [11,12]:

$$A = \frac{\{U_{Na}V_{(O)} \times MAP_{(L)}\} - \{U_{Na}V_{(L)} \times MAP_{(O)}\}}{U_{Na}V_{(O)} - U_{Na}V_{(L)}} \quad (1)$$

$$B = \frac{U_{Na}V_{(O)} - U_{Na}V_{(L)}}{MAP_{(O)} - MAP_{(L)}} \quad (2)$$

where subscripts O and L denote results obtained in a steady state of sodium balance during a diet with an ordinary or low salt content, respectively. With A and B, UNaV can now be expressed as a function of MAP [11, 12]:

$$U_{Na}V = B \times (MAP - A) \quad (3)$$

Assuming that A indicates the critical level of blood pressure below which glomerular filtration ceases, as predicted from equation 3, and therefore corresponds to the sum of the pressure drop from heart to glomeruli plus the pressures opposing filtration at the glomeruli, the effective filtration pressure (ΔPF) across the glomerular capillary walls can be estimated as the difference between MAP and A [11, 12, 17].

$$\Delta PF = MAP - A \quad (4)$$

The effective filtration pressure (ΔPF) is the difference between the PGC and the sum of pressures against filtration, so in general, PGC can be represented as:

$$PGC = \Delta PF + PT + \Pi G \quad (5)$$

where PT is the hydrostatic pressure in Bowman's space, assumed to be 10 mmHg, and ΠG is the mean oncotic pressure within glomerular capillaries, estimated from the mass balance law of plasma protein during glomerular ultrafiltration [11, 18].

Glomerular haemodynamics are described here in terms of four values: the PGC, the whole-kidney ultrafiltration coefficient (GFR/ΔPF) and the preglomerular (afferent) and postglomerular (efferent) vascular resistances (RA and RE, respectively) [11, 12]. On the basis of Ohm's law, RA is calculated as the ratio of (MAP–PGC) divided by the renal blood flow rate [11]. RE is calculated as the difference between total renal vascular resistance and RA [11].

Glomerular capillary hydraulic pressure in our study is an estimation based on the pressure-natriuresis relation because it cannot be measured directly in humans. Where the MAP intercepts the x-axis of the pressure-natriuresis curve, the urinary excretion of sodium becomes zero because of the decrease to nearly zero of both the GFR and the effective filtration pressure (see equation 4) [11, 12, 19]. As mentioned, the difference between the MAP and the x-intercept extrapolated from the pressure-natriuresis relation can be assumed to be the ΔPF, the effective filtration pressure across glomerular capillary walls [11, 12]. The ΔPF plus the oncotic pressure within the capillaries equals the transcapillary difference in pressure. The transcapillary difference equals PGC minus the hydrostatic pressure in Bowman's space (see equation 5), a small and nearly constant pressure of about 10 mm Hg. We do not have to assume that the ultrafiltration coefficient (Kf = GFR/ΔPF) is constant, as must be done in Gómez's equation. This is one of the advantages of our approach, making possible estimation and comparison of the coefficient in our normoalbuminuric and albuminuric patients, and also comparison before and during treatment with an ACE inhibitor.

Statistical analysis. The values used for statistical analysis of glomerular haemodynamics, MAP and urinary excretion of albumin were those found during the diet with an ordinary salt content. Results were expressed as means ± SD except for the urinary excretion of albumin, the resistance of glomerular arterioles and the whole-kidney ultrafiltration coefficient, expressed as means with a range, because the values were not in a Normal distribution. With again these three exceptions, the significance of differences between patients with normoalbuminuria and those with microalbuminuria was evaluated by Student's *t*-test for unpaired samples and the significance of differences before and during the cilazapril treatment was evaluated by Student's *t*-test for paired samples. The significance of differences in the urinary excretion of albumin, the resistance of glomerular arterioles and the whole-kidney ultrafiltration coefficient between the two groups of patients was examined with the Mann-Whitney U test and that before and during cilazapril treatment was examined with the Wilcoxon signed-rank test. The correlation coefficients for urinary excretion of albumin with the PGC, GFR, filtration fraction and MAP were evaluated by the least-squares method. The correlation between the two PGC s incorporating different GFRs, calculated from accumulation of the radionuclide and from creatinine clearance, was evaluated for significance by the least-squares method. The same was done for the RA and RE and for the whole-kidney ultrafiltration coefficient. Statistical analysis was done with StatView J. ver. 4.5 (Abacus Concepts, Berkeley, Calif., USA). A difference with a *p*-value of less than 0.05 was considered to be significant.

Results

The differences in urinary excretion of albumin and in haemodynamics between the two groups of patients (with normoalbuminuria and with microalbuminuria) during the diet with an ordinary salt content are shown in Table 2. Renal haemodynamics in this table were calculated with, as the GFR, the renal clearance of ^{99m}Tc-diethylenetriaminepentaacetic acid, obtained from the renogram. The MAP of patients with normoalbuminuria and microalbuminuria was not significantly different. The PGC was, however, significantly higher in the patients with microalbuminuria. Compared with patients with normoalbuminuria, those with microalbuminuria had greater postglomerular resistance, RE, but not preglomerular resistance, RA. The whole-kidney ultrafiltration coefficient was lower in the patients with microalbuminuria than in the patients with normoalbuminuria. The differences between the two groups in the GFR, RPF, and filtration fraction were not statistically significant. In the two patients with macroalbuminuria, urinary excretion of albumin, MAP, PGC, RA, RE and the whole-kidney ultrafiltration coefficient during the diet with an ordinary salt content were 335 and 635 mg/day, 113 and 92 mmHg, 57 and 57 mmHg, 5100 and 4200 dynes · s · cm^{-5}, 5300 and

Table 2. Urinary excretion of albumin, systemic pressure and renal haemodynamics in diabetic patients on the diet with an ordinary salt content

	Patients with normoalbuminuria ($n = 8$)	Patients with microalbuminuria ($n = 10$)	*P* value
Urinary excretion of albumin (mg/day)	10.7 (5.1–21.0)	74.6 (29–251)	< 0.001
Mean arterial pressure (mmHg)	95 ± 10	101 ± 8	0.144
P_{GC} (mmHg)	43 ± 5	52 ± 5	0.001
R_A (dynes · s · cm^{-5})	4900 (2500–8900)	6100 (3600–11 100)	0.374
R_E (dynes · s · cm^{-5})	3900 (2400–7100)	6600 (3300–14 800)	0.013
Kf (ml/s per mmHg)	0.562 (0.107–1.589)	0.178 (0.084–0.328)	0.033
GFR (ml/min per 1.73 m^2)	117 ± 25	109 ± 26	0.551
RPF (ml/min per 1.73 m^2)	562 ± 138	470 ± 141	0.186
Filtration fraction (%)	22.3 ± 8.5	25.4 ± 11.8	0.549

Values are expressed as means ± SD, except for urinary excretion of albumin, resistance of glomerular arterioles and the ultrafiltration coefficient, given as means followed in parentheses by the range. Kf, whole-kidney filtration coefficient; GFR, glomerular filtration rate obtained from a renogram with ^{99m}Tc-diethylenetriaminepentaacetic acid

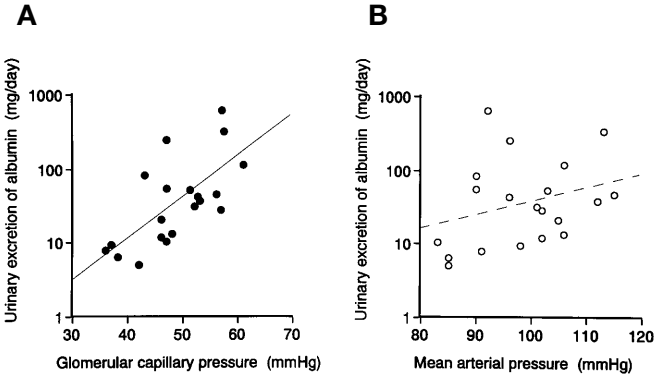

Fig. 1A, B. Relation between the urinary excretion of albumin and haemodynamics in diabetic patients ($n = 20$). **A**, Correlation between urinary excretion of albumin and glomerular capillary pressure, PGC; log y = 0.055 x – 1.137, $r = 0.675$ $p < 0.001$. **B**, Correlation between urinary excretion of albumin and mean arterial pressure; log y = 0.020 × –0.383, $r = 0.320$ $p = 0.191$

6800 dynes · s · cm^{-5}, and 0.050 and 0.064 ml/s per mmHg, respectively. The PGC in the 12 patients with albuminuria (micro- or macro-) was 53 ± 5 mmHg, significantly higher than that in patients with normoalbuminuria ($p < 0.001$).

The correlation of the urinary excretion of albumin with the PGC was significant ($n = 20$, $p < 0.001$; Fig. 1A), but its correlation with the MAP was not significant ($n = 20$, $p = 0.191$; Fig. 1B). The excretion of albumin was not correlated with the GFR or the filtration fraction ($r = –0.222$, $p = 0.351$, and $r = 0.207$, $p = 0.387$, respectively; both, $n = 20$).

Values for renal haemodynamics with the renal clearance of creatinine taken as the GFR for the two groups of patients (those with normoalbuminuria, $n = 8$, vs those with microalbuminuria, $n = 10$) were as follows: PGC, 42 ± 5 compared with 53 ± 6 mmHg (mean ± SD, $p < 0.001$); RA, 5000 (2600–9000) compared with 5900 (3600–10 000) dynes · s · cm^{-5} [mean (range), $p = 0.477$]; RE, 3900 (2600–7000) compared with 6800 (3400–15 800) dynes · s · cm^{-5} ($p = 0.013$). These values of PGC, RA, and RE were significantly correlated with those in Table 2 ($r = 0.981$, $r = 0.993$, and $r = 0.998$, respectively; all $p < 0.001$; $n = 18$).

Table 3 shows the effects of cilazapril on the urinary excretion of albumin and on haemodynamics in eight patients with albuminuria (seven of the ten with microalbuminuria and one of the two with macroalbuminuria) on the ordinary salt diet. The urinary excretion of albumin decreased but the MAP did not change significantly. The high PGC was lowered by cilazapril. Cilazapril did not decrease RA significantly but did decrease RE. Glomerular filtration rate was decreased but the difference was not significant statistically and the RPF was increased significantly by cilazapril. The whole-kidney ultrafiltration coefficient was not changed significantly.

Discussion

Among our patients, all with Type II diabetes without azotaemia or hypertension of 150/90 mmHg or more, the mean PGC of the patients with albuminuria was higher than that in the other patients. The urinary excretion rate of albumin was correlated significantly with PGC, but not with MAP. Cilazapril decreased glomerular hypertension in our patients with albuminuria, and albuminuria decreased as well.

The method we used here for clinical investigation of glomerular haemodynamics has been described elsewhere [11] and examined carefully [12, 13] as mentioned in the Materials and methods.

In our study, we mainly used the GFR obtained from renograms with ^{99m}Tc-diethylenetriaminepentaacetic acid. In diabetic patients when the GFR is 120 ml/min or more, the GFR obtained from renograms seems, however, to be an underestimate compared with that obtained from iothalamate clearance,

Table 3. Effects of cilazapril on urinary excretion of albumin and haemodynamics of diabetic patients with albuminuria on the diet with an ordinary salt content ($n = 8$)

	Before cilazapril	With cilazapril (2 mg/day)	*P* value
Urinary excretion of albumin (mg/day)	157 (31.3–635)	108 (25.1–437)	0.012
Mean arterial pressure (mmHg)	100 ± 10	96 ± 9	0.056
P_{GC} (mmHg)	52 ± 6	44 ± 8	0.019
R_A (dynes · s · cm^{-5})	6600 (3600–11100)	5600 (2800–9900)	0.161
R_E (dynes · s · cm^{-5})	7200 (3300–14700)	4900 (2700–10800)	0.012
Kf (ml/s per mmHg)	0.183 (0.064–0.328)	0.3456 (0.078–1.174)	0.327
GFR (ml/min)	107 ± 27	90 ± 16	0.051
RPF (ml/min)	430 ± 147	526 ± 150	0.005

Values are expressed as means ± SD, except for urinary excretion of albumin, resistance of glomerular arterioles and the ultrafiltration coefficient, given as means followed in parentheses by the range.

Kf, whole-kidney ultrafiltration coefficient; GFR, glomerular filtration rate obtained from a renogram with ^{99m}Tc-diethylenetriaminepentaacetic acid. Values of P_{GC}, R_A, R_E, and Kf were obtained from calculation of the renal haemodynamics with the renal clearance of ^{99m}Tc-diethylenetriaminepentaacetic acid taken to be the GFR

and the creatinine clearance has better correlation with the iothalamate clearance than the clearance of diethylenetriaminepentaacetic acid [20]. Therefore, we also assessed the renal haemodynamics with the creatinine clearance used as the GFR. The results were similar to those with the radionuclide clearance used as the GFR. Our results of renal haemodynamics, especially PGC, depend mostly on the pressure-natriuresis curve, and the GFR affects the oncotic pressure within the glomeruli.

In humans, there is no direct way to check our indirect estimates. A previous study [21] permits, however, plotting of the pressure-natriuresis relation and comparison of indirect estimates with directly measured results for glomerular haemodynamics. In rats with extensive renal ablation (five-sixths nephrectomy), direct micropuncture showed PGC to be 65 ± 2 mmHg (means ± SEM) [21]. This value for the PGC is virtually identical to a value estimated elsewhere from the pressure-natriuresis curve [13]. The values we estimated for glomerular haemodynamics in a clinical setting are likely to be consistent with the actual values.

We did not investigate the renal haemodynamics in aged-matched non-diabetic subjects. The same method as that in our study has, however, been used for calculation of PGC s in patients with essential hypertension [17]; the mean PGC was 47 ± 1 mmHg and the MAP was 120 ± 2 mmHg (± SEM, $n = 18$; these PGC values were obtained with the creatinine clearance used as the GFR). In our diabetic patients with albuminuria, the absolute value of the PGC seems to be high. In the patients with essential hypertension, RA and RE were 9600 ± 600 and 5000 ± 300 dynes · s · cm^{-5}, respectively (± SE, $n = 18$; these values also were obtained with the creatinine clearance used as the GFR) [17]. The afferent arterioles seem to be constricted against systemic high blood pressure in hypertensive patients. In rats with Type I (insulin-dependent) diabetes mellitus, the RA is usually lower than that in nondiabetic rats [9, 22]. Results from those hypertensive patients and our nonhypertensive patients with Type II diabetes suggest that the glomerular afferent arterioles were dilated in diabetes. In our patients with albuminuria (micro- or macro-), PGC was raised, as was the RE, without a significant change in the RA. This pattern of change may help to maintain the GFR, which declines gradually as nephropathy progresses. These seem not to contradict the results from the animal experiments.

An increased GFR (i.e. glomerular hyperfiltration) has long been recognized in Type I diabetes and has been found recently in patients with Type II diabetes, as well [22, 23]. In the Type II diabetic patients (mean age, 52.5 ± 10.1 years) without hypertension, haematuria or proteinuria, the mean GFR was 117 ± 22 ml/min (± SD) per 1.73 m^2, significantly higher than that in the aged-matched healthy subjects (95 ± 12 ml/min per 1.73 m^2) [23]. In our study, the GFR in the two groups of Type II diabetic patients without definite hypertension or haematuria and without or with albuminuria (mean ages, 58 ± 12 and 63 ± 6 years, respectively) was 117 ± 25 and 109 ± 26 ml/min (± SD) per 1.73 m^2, respectively. Glomerular filtration rate decreases with age. We did not investigate the GFR in aged-matched healthy subjects but the GFRs obtained in this study were consistent with those of the recent report [23]: patients with Type II diabetes had high GFRs.

Many researchers have believed that glomerular hyperfiltration is important in the development of diabetic nephropathy [2, 5, 8, 22]. Hyperfiltration in diabetes seems to involve changes in humoral factors (atrial natriuretic peptide, prostanoids, nitric oxide and so on [8,10]) and metabolic abnormalities (for example, activation of protein kinase C [24]). In addition, glomerular hypertension may be one haemodynamic cause of hyperfiltration; such hypertension causes sclerosis of the glomerulus [8, 22]. That there is glomerular hypertension in diabetic patients has

been only a hypothesis, based on the correlation between the urinary excretion of albumin and the filtration fraction and from the decrease in albumin excretion caused by ACE inhibitors [8, 22]. There is one report, however, that urinary albumin excretion rates are not correlated with the GFR or filtration fraction in patients with Type II diabetes [23]. In the Type II diabetic patients of our study, urinary excretion of albumin was not significantly correlated with the GFR or filtration fraction, but was with the PGC. The filtration fraction was not an index of PGC in Type II diabetes.

In rats with experimental diabetes and proteinuria, both glomerular hyperfiltration and glomerular capillary hypertension have been found [1, 2, 9]. Results with inhibitors of ACE have, however, suggested that glomerular hypertension rather than glomerular hyperfiltration in itself accounts for most of the increased proteinuria and the progress of nephropathy in such rats [9, 25]. It has been shown that inhibition of ACE prevents the progress of diabetic glomerulopathy in normotensive diabetic rats when such inhibition causes PGC to become normal and remain there without change in the raised GFR [9]. Results from our study are consistent with those in the studies of diabetic rats. In our previous study assessing how cilazapril decreases albuminuria by the same method we used here, PGC seemed to be important in early diabetic nephropathy [26]. Glomerular capillary hypertension could not, however, be proven in those diabetic patients with albuminuria [26]. Here, it could be done.

Systemic blood pressure is important in the PGC and the progression of diabetic nephropathy [8, 27]. The aim of our study was to find if glomerular hypertension exists and causes albuminuria in patients with early diabetic nephropathy before systemic blood pressure clearly increases. We chose subjects without definite systemic hypertension (less than 150/90 mmHg) to exclude the effect of high systemic blood pressure. Thus there was no significant difference in MAP between the groups with and without albuminuria. Another reason why the urinary excretion of albumin was correlated with the PGC but not with the MAP in our diabetic patients could be the exclusion of systemic hypertension.

Whether glomerular capillary hypertension is primary in the pathogenesis of diabetic nephropathy is not known. Results of previous studies and the findings reported here indicate, however, that glomerular hypertension is important in both the initiation and progression of diabetic nephropathy.

Many recent studies postulate that glomerular hypertension affects the growth and activity of glomerular cells and increases the synthesis of cytokines and other mediators that stimulate mesangial matrix formation and cause structural damage [22] but few details are known of the mechanisms in diabetic subjects. Our study could not assess how glomerular hypertension causes the damage but suggested the presence of such damage: the whole-kidney ultrafiltration coefficient (reflecting the area for filtration or number of glomeruli) in the patients with albuminuria was lower than in patients with normoalbuminuria.

In conclusion, the results of this clinical study support the hypothesis that in patients with diabetes and albuminuria, PGC is high and has a role in albuminuria even when the systemic blood pressure is not high.

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