Impact of Arterial Blood Pressure and Albuminuria on the Progression of Diabetic Nephropathy in IDDM Patients

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To evaluate the impact of systemic blood pressure and albuminuria on the progression of diabetic nephropathy, we followed 41 IDDM patients with persistent albuminuria (>300 mg/24 h) by measuring glomerular filtration rate (^{51}Cr-EDTA technique), blood pressure, and albuminuria. None of the patients were taking drugs other than insulin. Arterial blood pressure, albuminuria, and blood glucose were measured four to eight times/yr, whereas glomerular filtration rate was determined twice yearly. During the median investigation period of 36 (15–66) mo, glomerular filtration rate decreased from 102 ± 23 to 83 ± 27 ml · min^{-1} · 1.73 m^{-2} ($P < 0.001$), albuminuria increased from 633 to 1435 μg/min ($P < 0.001$), and blood pressure rose from 133/85 ± 10/9 to 149/93 ± 8/11 mmHg ($P < 0.001$). Univariate analysis revealed a significant correlation between the rates of decline in glomerular filtration rate and diastolic blood pressure ($r = 0.52$, $P < 0.01$) and glomerular filtration rate and albuminuria ($r = 0.34$, $P < 0.02$). But stepwise multiple linear regression analysis only showed a significant correlation between the rate of decline in glomerular filtration rate and diastolic blood pressure ($P < 0.01$). In patients with diastolic blood pressure below the mean value of 89 mmHg, stepwise multiple regression analysis showed that albuminuria and not blood pressure was correlated significantly with rate of decline in glomerular filtration rate. Patients were stratified by average value of diastolic blood pressure measured during the investigation period. Patients in the lowest tertile had a rate of decline in glomerular filtration rate of 4.3 ± 4 ml · min^{-1} · yr^{-1} compared with the middle and the highest tertiles of 7.7 ± 5 and 10.1 ± 5 ml · min^{-1} · yr^{-1}, respectively ($P < 0.01$). The average diastolic blood pressure in the three groups was 81, 89, and 98 mmHg, respectively. This study suggests that systemic blood pressure elevation and albuminuria accelerate the progression of diabetic nephropathy. The latter progression promoter seems only to play a role in patients with normotension (diastolic blood pressure <89 mmHg). *Diabetes* 42:715–19, 1993

The clinical syndrome of diabetic nephropathy is characterized by persistent albuminuria associated with a relentless decline in the GFR and raised systemic BP (1). Of all IDDM patients, ~35% suffer with this complication (2,3). Nephropathy is the main cause of increased morbidity and mortality in IDDM patients. Diabetic nephropathy is the leading cause of end stage renal disease in the U.S., and the cost of caring for these patients currently exceeds $1.8 billion/yr and is rising rapidly (4,5).

On average, death takes place 7 yr after the start of persistent proteinuria, but the range is wide (2–32 yr) (6). The factors responsible for this highly variable course of the natural history of diabetic nephropathy are not known. Watkins et al. (7) demonstrated that IDDM patients with heavy proteinuria (>3 g/24 h) and marked renal structural lesions have the worst prognosis. The impact of other putative progression promoters such as systemic BP elevation have yielded conflicting results in IDDM patients with diabetic nephropathy (8–10).

The aim of our longitudinal study was to evaluate the impact of systemic BP and albuminuria on kidney function in IDDM patients with diabetic nephropathy. The natural history of diabetic nephropathy is elucidated, because none of the IDDM patients were taking drugs other than insulin.

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IDDM, insulin-dependent diabetes mellitus; BP, blood pressure; dBP, diastolic blood pressure; sBP, systolic blood pressure; GFR, glomerular filtration rate; CV, coefficient of variation; RIA, radioimmunoassay; UAE, urinary albumin excretion; STZ, streptozocin.

TABLE 1
Clinical characteristics of 41 IDDM patients with diabetic nephropathy

Sex (F/M)	Age (yr)	Duration of diabetes (yr)	Retinopathy (nihil/background/ proliferative)	Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	Observation period (mo)
12/29	31 ± 7	19 ± 7	2/18/21	0.64 ± 0.2	36 (15–66)

Data are means ± SD or median (range).

RESEARCH DESIGN AND METHODS

The patients are part of a cohort of 45 patients with IDDM and persistent albuminuria attending Steno Memorial and Hvidöre Hospital. The patients participated in various prospective studies conducted between 1976 and 1991 (9,11,12). From these, the 41 who fulfilled the inclusion criteria and had been followed systematically for at least 15 mo were selected for this study. The inclusion criteria were persistent albuminuria >300 mg/24 h, serum creatinine <150 μmol/L, an average of three or more consecutive BP readings <160/100 mmHg, age <50 yr and onset of IDDM before age 41 yr, and not taking any drugs other than insulin. Finally, two GFR determinations per year were conducted during the observation period.

All patients had been insulin dependent from the time of diagnosis, and all were receiving at least two daily injections of purified porcine insulin. All patients took their usual diabetic diet containing 45–55% carbohydrate, 30–35% fat, and 15–20% protein, without sodium or protein restriction throughout. Diabetic nephropathy was diagnosed clinically according to established criteria (13). The 2 patients lacking retinopathy had a kidney biopsy performed and in both cases diffuse diabetic glomerulosclerosis was found. The study was approved by the local ethical committee, and the investigated patients gave fully informed consent (Table 1).

All investigations were made on the same day between 0900 and 1300. Patients had their normal breakfast and morning insulin before the procedures, which were conducted with the patients resting in the supine position. The patient drank 200 ml tap water/h during the study period. The procedure was performed 4 to 13 times (mean 7) in each patient during a period ranging from 15 to 66 mo (median 36 mo). The observation of the natural history of diabetic nephropathy was ended because of myocardial infarction in 1 patient and because of antihypertensive treatment in 27 other patients. The observation has continued in 13 patients. Antihypertensive treatment was started if repeated measurements showed a dBP ≥100 mmHg or if the patient had a sustained dBP ≥90 mmHg preceded by an increase in mean arterial BP ≥10 mmHg during the past 2 yr.

To measure GFR, we gave the patient a single intravenous injection of 3.7 MBq ^{51}Cr-EDTA at 0900 and determined the plasma radioactivity in venous blood samples taken from the other arm 180, 200, 220, and 240 min after the injection (14,15). The small underestimation (10%) of ^{51}Cr-EDTA clearance versus clearance of insulin was corrected for by multiplying the EDTA clearance by 1.10. The results were standardized for 1.73 m^2 body surface area, using the patients surface area at the start of the study throughout. The mean CV in GFR of each patient from day to day was 4%.

UAE was measured during the 4-h clearance period by radial immunodiffusion (16) between 1976 and 1984 and later by RIA (17). The assays had a sensitivity of 2 and 0.5 mg/L, respectively, and a CV between assays of 8 and 9%, respectively. Albumin concentration was measured simultaneously by both methods in urine collected from 27 IDDM patients. The UAE rate ranged from 19 to 4860 μg/min (median 599 μg/min), and the results of both methods showed a close relation ($y = 0.98x - 2$; $r = 0.98$, where y and x represent the albumin concentration determined with immunodiffusion and RIA, respectively).

BP was measured with a standard mercury sphygmomanometer (cuff size: 25 × 12 cm). Two readings were performed while the patient was in the supine position during each investigation and visit to the outpatient clinic. dBP was recorded at the disappearance of the Korotkoff sounds (phase 5).

All patients visited the clinic every 3–4 mo during the study. At each visit, the postprandial blood glucose concentration was measured along with glucosuria, BP, and body weight.

Statistical analysis. Data are means ± SD. All measurements made in each patient over the entire study period were used to calculate the mean values. Values for UAE rate were logarithmically transformed before analysis because of positively skewed distributions; the median and range are given. Linear regression analysis (least squares method) was used to determine the rate of decline in GFR for each patient. Wilcoxon's nonparametric test was used for paired comparison, and Mann-Whitney's nonparametric U test was used for unpaired comparison. The Kruskal-Wallis test of variance was used to test for differences between three groups (separated by tertiles), and if differences were found, the Mann-Whitney test was used for comparison between two groups. Linear regression analysis and forward stepwise multiple regression analysis were used to analyze data for correlations. In the linear regression analysis, the stochastic variation of rate of decline in GFR was calculated as the residual SD and expressed as a percentage of the mean rate of decline in GFR. All calculations were made by using Statgraphics (STSC, Rockville, MD). $P < 0.05$ was considered significant (two tailed).

RESULTS

During the median investigation period of 36 (15–66) mo, GFR decreased significantly, albuminuria and arterial BP

TABLE 2
GFR, arterial BP, albuminuria, and blood glucose in 41 IDDM patients with nephropathy

	At entry	At exit
GFR (ml · min^{-1} · 1.73 m^2)	102 ± 23	82 ± 27
sBP/dBP (mmHg)	133/85 ± 10/9	149/93 ± 18/11*
Albuminuria (μg/min)	633 (269–3912)	1435 (255–10229)*
Blood glucose (mM)	11 ± 5	9 ± 4

Data are means ± SD or median (range).
*P < 0.01 vs. at entry.

rose significantly, and postprandial blood glucose concentration remained about the same (Table 2). All patients, except 2 normotensive subjects, showed a decline in GFR during the observation period. The rate of decline in GFR was highly variable, ranging from −2.1 to 17 ml · min^{-1} · yr^{-1} (mean 7.1 ml · min^{-1} · yr^{-1}).

The rate of decline in GFR rose with increasing dBP levels during the observation period (Table 3). Univariate linear regression analysis with the rate of decline in GFR as the dependent variable showed a significant correlation with dBP (r = 0.52, P < 0.001) (Fig. 1). A weaker correlation was found with mean arterial BP (r = 0.40, P < 0.01), whereas the correlation with sBP did not reach significance.

Patients with albuminuria in the lowest tertiles had a rate of decline in GFR of only 3.8 ± 4 ml · min^{-1} · yr^{-1}, whereas the rate of decline was 9 ± 4 ml · min^{-1} · yr^{-1} in those patients with albuminuria in the highest tertiles (P < 0.01) (Table 4). This study also revealed a weak correlation between albuminuria and the rate of decline in GFR (r = 0.34, P < 0.05).

Table 5 shows that patients with a dBP and albuminuria below the median values have a rate of decline in GFR of only 2.9 ml · min^{-1} · yr^{-1} compared with 8.7–9.8 ml · min^{-1} · yr^{-1} (P < 0.01) in patients belonging to groups with a dBP or albuminuria or both above the median values. In patients with a dBP below the mean value (89 mmHg), a stepwise multiple linear regression analysis with rate of decline in GFR as the dependent variable and BP and albuminuria as independent variables showed a significant correlation between rate of decline in GFR and albuminuria (r = 0.51, P < 0.01).

A forward stepwise multiple linear regression analysis, including all patients, with the rate of decline in GFR as the dependent variable and dBP, sBP, albuminuria, insulin dose, age at onset, and duration of diabetes as independent variables revealed that only dBP was significantly correlated with the rate of decline in GFR (r = 0.35, P < 0.01).

TABLE 3
Impact of dBP on the progression of diabetic nephropathy in 41 IDDM patients

	Tertiles		
	Lowest	Middle	Highest
dBP (mmHg)	81	89	98
Rate of decline in GFR (ml · min^{-1} · yr^{-1})	4.3 ± 4	7.7 ± 5	10.1 ± 5*

Data are means ± SD.
P < 0.05 lowest vs. highest tertile.

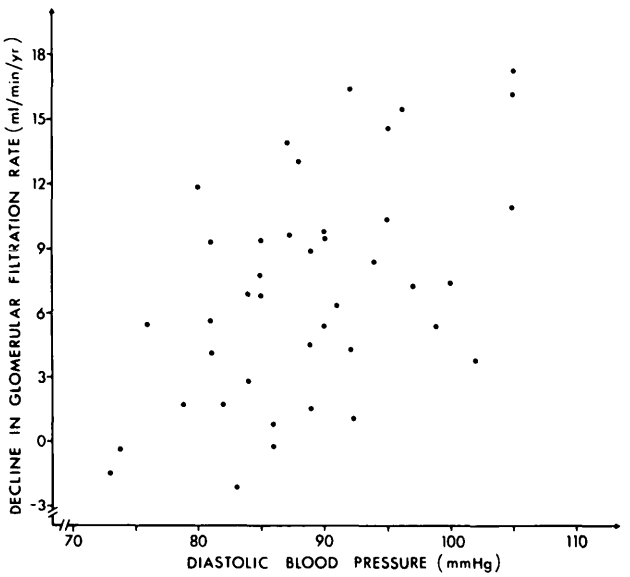

FIG. 1. Correlation between dBP and decline in GFR (r = 0.52, P < 0.001, residual SD of rate of decline in GRF was 62%) measured during a median observation period of 36 mo in 41 IDDM patients suffering with diabetic nephropathy. None of the patients received any drugs other than insulin.

DISCUSSION

This longitudinal study of the natural history of kidney function in IDDM patients suffering with diabetic nephropathy suggests that systemic BP and albuminuria accelerate the progression of diabetic nephropathy. The latter progression promoter seems only to play a role in patients with normotension. These progression promoters (18) can thus explain a part of the highly variable course of kidney function in the individual patients with diabetic nephropathy, rate of decline in GFR ranged from −2–17 ml · min^{-1} · yr^{-1}. The additional contribution from other progression promoters, e.g., metabolic control, hyperlipidemia, and dietary protein intake will be discussed below.

We have confirmed and extended Mogensen's observation (8) and have shown that the increase in systemic BP is an early feature of diabetic nephropathy. Originally, Mogensen (8) investigated 7 IDDM men with nephropathy and found a close correlation between the rate of decline in GFR and the dBP at the end of a 3-yr study period. Two other studies of the natural history of diabetic nephropathy in IDDM patients failed to confirm this relationship, but numbers were small (9,10). A recent observational study of 26 NIDDM patients with diabetic nephropathy, followed prospectively for 5 yr, has revealed a significant correlation between the rate of decline in GFR and arterial BP, and albuminuria and GFR at baseline (19). Furthermore, the modification of diet in a renal disease study (20) has found a substantial correlation between the rate of decline in GFR and the level of mean arterial BP in 100 patients with chronic nondiabetic

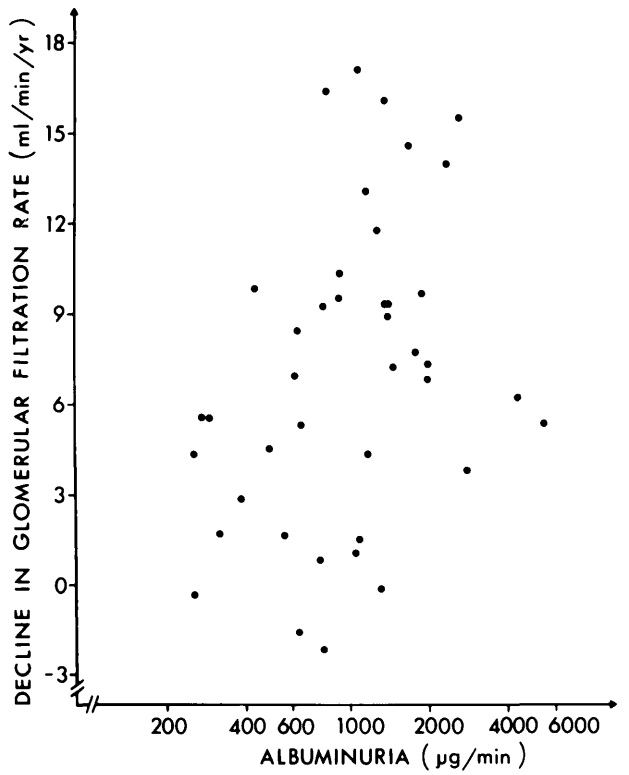

FIG. 2. Correlation between albuminuria and decline in GFR ($r = 0.34$, $P < 0.05$, residual SD of rate of decline in GFR was 69%) measured during a median observation period of 36 mo in 41 IDDM patients suffering with diabetic nephropathy. None of the patients received any drugs other than insulin.

renal disease. Feldt-Rasmussen et al. (7) have demonstrated that dBP and UAE rate enhanced the decline in GFR in 69 IDDM patients with persistent microalbuminuria followed for 5–8 yr. These findings suggest that systemic BP and albuminuria are important in the initiation and the progression of diabetic nephropathy. Furthermore, arterial BP seems to have a complex relationship with diabetic nephropathy—nephropathy raising BP and BP accelerating the course of nephropathy.

Until recently, the damaging effect of systemic hypertension on renal structure and function was thought to be mediated through vasocontriction and arteriolar nephrosclerosis. However, Brenner et al. (22,23) have presented evidence from experimental animal studies that shows that systemic hypertension is transmitted to the single glomerulus leading to hyperperfusion and increased glomerular hydraulic capillary pressure. Increased glomerular capillary hydraulic pressure has been shown even in normotensive STZ-induced diabetic rats treated with insulin (24,25). Other studies also have shown that hemodynamic factors accelerate the development of glomerulopathy in diabetic animals (26,27). Conversely, antihypertensive treatment reduces albuminuria and postpones renal insufficiency in diabetic nephropathy (13,28–33).

Proteinuria is generally regarded as a marker of the extent of glomerular damage, but recent studies in various experimental animal models suggest that proteinuria itself may contribute to glomerular damage, as reviewed by Remuzzi and Bertaini (34). Originally, Watkins et al. (7) demonstrated that IDDM patients with diabetic nephropathy and severe proteinuria >3 g/24 h) had the worst prognosis. The validity of proteinuria as a useful prognostic index recently has been supported by Williams et al. (35) in patients with mild to moderate renal failure (mean plasma creatinine 200 μmol/L) of different etiologies, including 14 patients with diabetic nephropathy. Our study of the early stages of diabetic nephropathy suggests that the magnitude of albuminuria was related to the rate of progression in kidney function in normotensive patients. Intervention that has ameliorated the progression of diabetic renal disease both experimentally (22,23,36) and in clinical trials (28,29,32,33) has always been associated with a reduction in proteinuria. Reduction of albuminuria is regarded as a surrogate end point in trials lasting more than a few years, because this phenomenon seems to be associated with preservation of GFR (principle end point) in diabetic nephropathy (5,37).

The possible impact of metabolic control on progression of diabetic nephropathy cannot be evaluated from this study, because HbA_{1c} was first introduced in our clinic in 1983. However, observations from other studies have yielded conflicting results. Nyberg et al. (38) found a significant correlation between HbA_{1c} and rate of decline in GFR, whereas two other studies failed to identify such a relationship (10,39). Finally, near normal blood glucose control obtained by subcutaneous insulin infusion for years has no significant effect on the rate of decline in GFR in diabetic nephropathy (40).

Studies in different animal models have demonstrated that hyperlipidemia play a role in initiation and progression of glomerular injury (41,42). Previously, Mulec et al. (43) have found a significant positive correlation between

TABLE 4
Impact of albuminuria on the progression of diabetic nephropathy in 41 IDDM patients

	Tertiles		
	Lowest	Middle	Highest
Albuminuria (μg/min)	423	988	2076
Rate of decline in GFR ($ml \cdot min^{-1} \cdot yr^{-1}$)	3.8 ± 4	7.4 ± 6	9.0 ± 4*

Data are means ± SD.
$P < 0.05$ lowest vs. highest tertile.

TABLE 5
Impact of dBP and albuminuria on progression of diabetic nephropathy in 41 IDDM patients

	dBP (mmHg)			
Albuminuria (μg/min)	*n*	Below mean (89)	*n*	Above mean (89)
Below median (1036)	14	2.9*	7	8.7*
Above median (1036)	9	9.0*†	11	9.8*

*Rate of decline in GFR ($ml \cdot min^{-1} \cdot yr^{-1}$).
†$P < 0.01$ above vs. below median albuminuria.

serum total cholesterol and rate of decline in GFR in IDDM patients with mild to moderately advanced diabetic nephropathy. In a double-blind randomized placebo-controlled simvastatin trial lasting 12 wk, this group found no effect on albuminuria or GFR in hyperlipidemic IDDM patients with diabetic nephropathy (44). In conclusion, the possible importance of hyperlipidemia in the initiation and progression of human renal disease still remains to be established.

All our patients received a normal diabetic diet containing 15–20% protein. Protein intake was not restricted, and we have demonstrated previously that the average protein intake in a subset of these same patients was 1.1 g protein $\cdot$ kg^{-1} $\cdot$ day^{-1} (12). Two intervention trials have suggested that a low-protein diet may have a beneficial onset on the progression of diabetic nephropathy (45,46).

In conclusion, this longitudinal study of the initial part of the natural history of diabetic nephropathy suggests that systemic BP and albuminuria act as progression promoters in IDDM patients with diabetic nephropathy. The latter progression promoter seems only to play a role in normotensive patients.

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