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Predictors of the progression of diabetic nephropathy and the beneficial effect of angiotensin-converting enzyme inhibitors in NIDDM patients

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Summary A progressive decline in glomerular function occurs in diabetic nephropathy. The predictive effects of progression promoters were examined in 182 non-insulin-dependent diabetic patients from a baseline serum creatinine concentration of 133 μml/l. During a total of 605 person-years follow-up, 107 patients developed end-stage renal failure requiring dialysis. The rate of decline of renal function was highly variable. Urinary protein excretion was the strongest predictor correlated to the rate of decline, followed by diastolic and systolic blood pressure, total cholesterol and platelet count, while the protective effects were seen in serum albumin and haematocrit. Ajustment for urinary protein excretion revealed that diastolic blood pressure, familial predisposition to hypertension, serum albumin, and smoking were independent significant predictors. Angiotensin converting enzyme inhibitors (ACE-I) significantly retarded the development of end-stage renal failure compared to antihypertensives other than ACE-I (mostly nifedipine), and the effect was evident particularly in patients with proteinuria below the median (2.5 g/24 h) (presumably those who responded to ACE-I). A complex effect of proteinuria in association with blood pressure elevation, familial predisposition to hypertension, hypoalbuminaemia, and smoking may play an important role in the progression of nephropathy. [Diabetologia (1997) 40: 405–411]

Keywords Diabetic nephropathy, blood pressure, familial hypertension, angiotensin-converting enzyme inhibitor, smoking, proteinuria.

Diabetic nephropathy is a clinical syndrome accompanied by severe diabetic retinopathy, hypertension, and excess mortality. The number of diabetic patients suffering from end-stage renal failure (ESRF), mostly caused by non-insulin-dependent diabetes mellitus (NIDDM), is increasing worldwide [1]. Japan has the highest number in the world of patients on regular dialysis [1], and in 1994 more than 30 % of patients who were newly accepted for regular dialysis treatment had diabetic ESRF, with an average age of 61 years (n = 7376) [2]. The cost for dialysis amounts to approximately $ 50 000–100 000 per person per year. Therefore, prevention of diabetic nephropathy and therapeutic intervention to slow its progression are of prime importance not only for life-saving purposes but also for socioeconomic reasons.

Patients with diabetic nephropathy exhibit a progressive decline in glomerular function. Putative progression promoters in chronic renal disease have been suggested to be systemic hypertension [3–7], proteinuria [8–10], hyperlipidaemia [11, 12], hyperglycaemia [10, 13, 14] and dietary protein [15]. Not only biochemical but also genetic factors and/or habits may affect the progression [16]. These factors may interact with each other; however, their impact

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Abbreviations: ESRF, End-stage renal failure; ACE-I, angiotensin-converting enzyme inhibitors; NIDDM, non-insulin-dependent diabetes mellitus; CVD, cerebrovascular disease; CHD, coronary heart disease; CI, confidence interval.

and the additive effect of genetic and environmental factors have not been elucidated.

The aim of our study was to evaluate the impact of putative progression promoters on kidney function from a baseline serum creatinine concentration of 133 μmol/l until the development of ESRF in NIDDM patients with nephropathy. The effects of genetic factors and smoking, and the therapeutic effect of angiotensin-converting enzyme inhibitors (ACE-I) were also assessed.

Subjects and methods

Patients. A clinic-based epidemiological study was performed prospectively in order to evaluate risk factors for progression of diabetic nephropathy leading to ESRF. All NIDDM patients attending the Diabetes Center whose serum creatinine concentrations were within the normal range (62–115 μmol/l) on admission and increased to 133 μmol/l or higher during their regular visits between 1985 and 1993, were enrolled in the study (Fig. 1). To ensure that diabetic nephropathy was a major cause of their renal dysfunction, we only included patients who had proliferative diabetic retinopathy before their serum creatinine concentrations exceeded 133 μmol/l (n = 182). Diabetic patients whose serum creatinine concentrations were 133 μmol/l or greater but had no diabetic retinopathy or no persistent proteinuria were excluded. Patients with non-diabetic kidney disease were also excluded.

Baseline measurements. Baseline measurements for the study were established when the serum creatinine concentration, measured every 3–6 months as one of the routine laboratory investigations, was 133 μmol/l or more but was less than 177 μmol/l. Blood pressure was measured using a standard sphygmomanometer and an appropriately sized cuff with the patient in a seated position during their regular visits. Patients attended the Diabetes Center every 1–2 months. Blood pressure measurements were taken on more than four visits in a year at baseline and during the follow-up period the average was calculated. Hypertension was defined as a systolic blood pressure 160 mmHg or greater or a diastolic blood pressure 95 mmHg or greater (World Health Organization criteria). Patients with hypertension were treated intensively with antihypertensive drugs during their regular visits with the aim of controlling blood pressure below 160/95 mmHg. Antihypertensive drugs were selected without taking urinary protein excretion into account. ACE-I have been used as antihypertensive drugs since 1983 in Japan. Ninety-eight patients were treated with antihypertensive drugs other than ACE-I at baseline (Group 1). The antihypertensive agents included calcium antagonists and diuretics such as nifedipine (n = 79), nicardipine (n = 12) and furosemide (n = 7), in combination with beta blockers (n = 5) and methyldopa (n = 5). Two patients were treated with ACE-I after their serum creatinine concentrations exceeded 133 μmol/l, but were included in Group 1. A total of 28 patients were treated with ACE-I for at least 3 months (a median of 12 months up to the baseline) (Group 2) alone (n = 10) or together with nifedipine (n = 15) or other agents (n = 3) at baseline. Fifty-six patients did not have hypertension at baseline, and thus received no antihypertensive agents (Group 3). Data on family history of diabetes, hypertension, cerebrovascular disease (CVD) and coronary heart disease (CHD) in first-degree relatives was obtained from patients by interview. A dietary intake of 0.8–1.0 g protein and 35 kcal per kg of ideal body weight per day was recommended. Body mass index was calculated as weight (kg)/height (m^2). Urinary protein excretion was obtained from two or three 24-h sterile urine samples and the median value was used. The average of glycated haemoglobin (HbA_{1c}) measurements obtained on more than four visits in a year at baseline and during the follow-up was calculated. Proliferative retinopathy was determined as retinal neovascularization, corresponding to grade 60 or more in the modified Airlie House System. Serum creatinine was measured using Jaffe's method. Serum concentrations of total cholesterol, HDL-cholesterol, triglyceride, and albumin were measured by enzymatic colorimetric methods using an automated multi-analyzer (7450; Hitachi Tokyo, Japan). Urinary protein concentration was measured using the pyrogallol red-molybdate method [17]. HbA_{1c} was measured by liquid chromatography (HPLC, AUTOA1c HA8110; Kyoto Daiichi Kagaku, Kyoto, Japan). The interassay variation coefficients were 5–8 % for all assays.

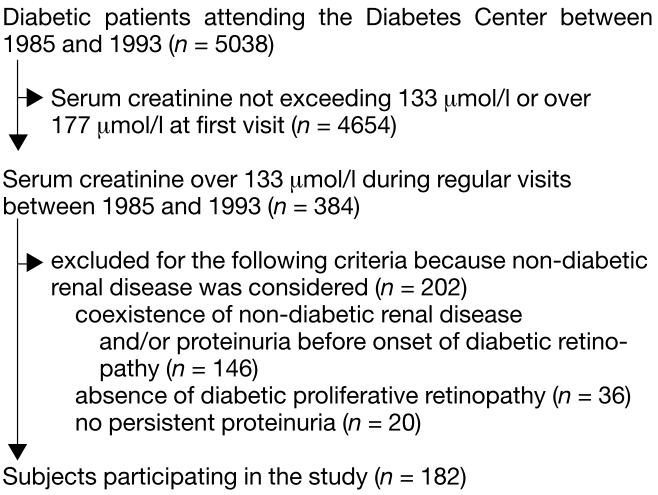

Fig. 1. Patient selection for the study

End point. Patients were followed until the start of regular dialysis treatment, death, or the end of the follow-up period during which they did not undergo dialysis. Dialysis was indicated when serum creatinine concentration exceeded 707 μmol/l (or creatinine clearance decreased to less than 10 ml/min) or uraemic symptoms occurred which were refractory to conservative therapy.

Statistical analysis

The predictive effect of baseline variables on development of ESRF requiring dialysis was explored using the Cox proportional hazard regression analysis. Univariate and multivariate analyses with conditional forward elimination of the independent variables were performed, and Hazard risk ratios with 95 % confidence intervals (CI) are given. The time was calculated from the study entry (baseline) until the development of ESRF, i.e. being accepted for regular dialysis therapy, or the end of the follow-up and not undergoing dialysis (up to March 1996). The cumulative incidence of dialysis treatment was plotted using the Kaplan-Meier method with the log-rank test statistic. A comparison of the incidence density with the rate ratio was performed using probability models with likelihood risk ratio to provide an estimate and a CI. The rate of decline of renal function was expressed as changes in the reciprocal of the

Table 1. Baseline clinical and biochemical characteristics of the 182 patients

n	Total 182	Group 1 98	Group 2 28	Group 3 56
Male/female	124/58	60/37	21/7	43/14
Age (years)	57 ± 11	56 ± 10	60 ± 10	57 ± 12
BMI (kg/m^2)	22.5 ± 3.3	22.5 ± 3.5	23.0 ± 3.0	22.4 ± 3.1
Current smoking (yes/no)	67/115	35/63	11/17	21/35
Family history (yes/no) of:				
diabetes	89/93	53/45	12/16	24/32
hypertension	55/127	33/65	10/18	12/44
CVD or CHD	71/111	43/55	10/18	18/38
HbA_{1c} (%)	8.3 ± 1.6	8.4 ± 1.5	7.8 ± 1.5	8.4 ± 1.8
Systolic blood pressure (mmHg)	145 ± 15	150 ± 13	145 ± 12	135 ± 14[a]
Diastolic blood pressure (mmHg)	82 ± 9	83 ± 9	82 ± 6	79 ± 9[a]
24 h urinary protein excretion (g)	2.5 (0.9–4.7)	3.4 (1.4–6.0)	1.9 (0.6–4.0)[b]	1.8 (0.5–3.3)[a]
Serum creatinine (μmol/l)	139 ± 9	138 ± 8	141 ± 10	140 ± 10
Creatinine clearance (ml/min)[c]	41.3 ± 10.3	40.8 ± 10.0	41.5 ± 11.4	42.2 ± 10.4
Total cholesterol (mmol/l)	6.31 ± 1.71	6.57 ± 1.68	6.05 ± 1.71	6.00 ± 1.71
HDL cholesterol (mmol/l)	1.24 ± 0.47	1.27 ± 0.54	1.14 ± 0.36	1.22 ± 0.39
Triglyceride (mmol/l)	1.99 (1.43–2.83)	2.15 (1.51–2.82)	1.87 (1.12–3.35)	1.81 (1.40–2.81)
Serum albumin (g/l)	34 ± 6	33 ± 6	35 ± 5	35 ± 6
Haematocrit (%)	36.8 ± 5.5	36.7 ± 6.7	37.1 ± 6.1	36.1 ± 4.9
Platelet (10^4/mm^3)	24.1 ± 7.0	23.8 ± 7.7	25.5 ± 6.6	23.4 ± 6.6

Data are mean ± SD or ■ and (range)
CVD, Cerebrovascular disease; CHD, coronary heart disease.
[a] $p < 0.01$ vs Group 1; [b] $p < 0.05$ vs Group 1; [c] calculated by Cockcroft's formula

serum creatinine concentration per month ($l \cdot \mu mol^{-1} \cdot l^{-1} \cdot month^{-1}$) which was calculated by the least squares method using the data measured during the follow-up period. Pearson's coefficients were calculated for correlation analyses. Differences between relevant groups were tested using the Mann-Whitney test for continuous variables (with non-normally distributed variables first being logarithmically transformed) and the chi-squared test for dichotomized variables. *P*-values under 5% (two-tailed) were taken to indicate statistical significance. All analyses were run on the personal computer statistics package SPSS for Windows version 6.0.

Results

Table 1 shows the patients' clinical and biochemical characteristics. No differences were found between the groups except that blood pressure was lower in Group 3 and the 24-h urinary protein excretion rate was lower in Groups 2 and 3 than in Group 1. For a total of 605 person-years, end points were the start of dialysis for 107 patients (329 person-years), the end of follow-up and not on dialysis for 59 patients (232 person-years), death before development of ESRF for 6 (19 person-years), and discontinued regular visits for 10 (25 person-years). No differences were found in the proportion of ACE-I users or HbA_{1c} levels according to the calendar year of study entry. Blood pressure and HbA_{1c} were measured every 1–2 months during the follow-up. Blood pressure during the follow-up was comparable in the three groups (mean systolic ± SD/diastolic ± SD: Group 1, 151 ± 12/80 ± 9; Group 2, 150 ± 12/82 ± 9; Group 3, 144 ± 14/82 ± 9). Systolic and diastolic blood pressures at baseline significantly correlated

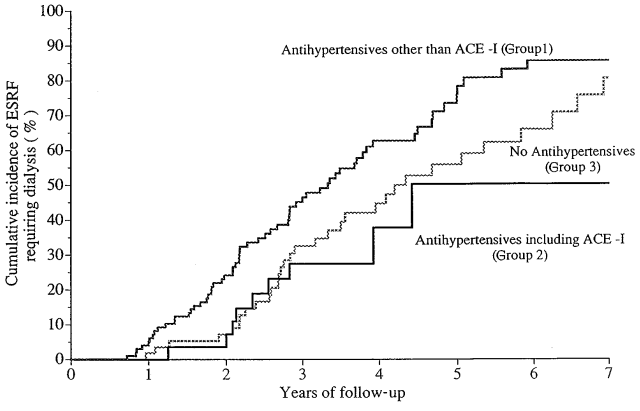

Fig. 2. Cumulative incidence of dialysis due to end-stage renal failure from a baseline serum creatinine concentration of 133 μmol/l in patients with diabetic nephropathy. Patients with hypertension at baseline were treated with antihypertensive agents without (Group 1) or with (Group 2) ACE-I. Patients without hypertension at baseline did not receive any antihypertensive agents (Group 3). Group 1 vs Group 2, $p = 0.02$ by log-rank test

Table 2. Coefficients of correlation of baseline variables to the rate of decline of renal function expressed as reciprocal change of serum creatinine concentration during the follow-up period

Baseline variables	Correlation coefficients			
	Total	Group 1	Group 2	Group 3
HbA_{1c}	0.03	0.01	0.05	0.05
Systolic blood pressure	0.32[a]	0.30[b]	0.23	0.16
Diastolic blood pressure	0.34[a]	0.32[b]	0.50[b]	0.25
Log urinary protein excretion	0.62[a]	0.54[a]	0.82[a]	0.63[a]
Total cholesterol	0.24[b]	0.17	0.29	0.27[c]
HDL cholesterol	0.10	0.06	−0.05	0.17
Log triglyceride	0.08	−0.02	0.41[c]	0.08
Serum albumin	−0.51[a]	−0.47[a]	−0.66[a]	−0.52[a]
Haematocrit	−0.20[b]	−0.24[c]	−0.17	−0.33[b]
Platelet	0.16[c]	0.12	0.38[c]	0.21

[a] $p < 0.0001$, [b] $p < 0.01$, [c] $p < 0.05$

Table 3. The predictive effect of baseline variables on development of end-stage renal failure requiring dialysis

Baseline variables	Hazard ratio	*p* value
Current smoking	1.58 (1.07–2.34)	0.02
Family history of diabetes	0.92 (0.62–1.35)	0.66
hypertension	1.85 (1.21–2.81)	0.004
CVD or CHD	1.17 (0.78–1.73)	0.45
HbA_{1c}	1.00 (0.91–1.13)	0.86
Systolic blood pressure	1.02 (1.01–1.04)	0.0008
Diastolic blood pressure	1.07 (1.04–1.10)	0.00001
Log urinary protein excretion	12.6 (6.9–23.0)	0.00001
Total cholesterol	1.01 (1.00–1.01)	0.0004
HDL cholesterol	1.00 (0.99–1.01)	0.96
Log triglyceride	2.88 (1.25–6.63)	0.01
Serum albumin	0.18 (0.13–0.27)	0.00001
Haematocrit	0.98 (0.94–1.01)	0.17
Platelet	1.04 (1.01–1.07)	0.008
ACE-I	0.55 (0.28–1.05)	0.07
Hypertension	1.32 (0.88–2.00)	0.18

Hazard ratio (95% CI) indicates alteration of risk per unit increase of baseline variables

to those during the follow-up ($r = 0.67$, $r = 0.59$, respectively, $p < 0.0001$). HbA_{1c} levels during the follow-up period were similar in the three groups: Group 1, 8.0 ± 1.5; Group 2, 7.5 ± 1.4; Group 3, 8.0 ± 1.4.

The rate of decline in renal function was 1.549 ± 1.244 (range: -0.791–6.447) ($\times 10^{-4}$ l · μmol^{-1} · month^{-1}) in all patients (10.7 ± 1.7 measurements of serum creatinine per person). This rate was highly variable especially between patients started on dialysis and those who were not (2.092 ± 1.266 vs 0.780 ± 0.720, $p < 0.0001$). The rate was significantly higher in Group 1 (1.866 ± 1.380) than in Group 2 (1.097 ± 0.938) and Group 3 (1.233 ± 0.995) ($p < 0.01$, respectively). The rate for the two patients assigned to Group 1 but who were administered ACE-I after serum creatinine concentrations exceeded 133 μmol/l was 0.271 and 1.357, respectively. The cumulative incidence of dialysis was higher in Group 1 than in Group 2 ($p = 0.02$) and Group 3 ($p = 0.05$) (Fig. 2).

Table 2 shows correlations of baseline variables to the rate of decline of renal function. Significant effects on the rate of decline were found in urinary protein excretion followed by diastolic, systolic blood pressure, total cholesterol and platelet count while the protective effects were seen in serum albumin and haematocrit. The correlation with blood pressure was high in Group 1 and Group 2 compared to Group 3, while in Group 3 the correlation with total cholesterol was high. Blood pressure during the follow-up correlated to the rate of decline to the same degree as correlations seen at baseline.

Table 3 shows the predictive effect of baseline variables on later events such as start of dialysis. Smoking, family history of hypertension, systolic and diastolic blood pressure, urinary protein excretion, total cholesterol, triglyceride, serum albumin and platelet count had significant predictive effects while treatment with ACE-I or the presence of hypertension as single independent variables did not reach statistical significance. If adjusted for urinary protein excretion, the predictive effects of systolic blood pressure, cholesterol, and triglyceride were abolished whereas family history of hypertension ($p = 0.01$), serum albumin ($p = 0.0001$), diastolic blood pressure ($p = 0.01$) and smoking ($p = 0.04$) still remained significant (Table 4). Multivariate analysis demonstrated that urinary protein excretion, family history of hypertension, serum albumin and diastolic blood pressure were significant independent predictors of the development of ESRF (Table 4).

Finally the impact of familial hypertension, smoking, and ACE-I treatment on the incidence density of developing ESRF was evaluated according to the 24-h urinary protein excretion rate (below or above the median value of 2.5 g/24 h) (Table 5). Family history of hypertension and smoking increased the incidence density, the rate ratio being four and six times higher in the highest-risk than in the lowest-risk patients, respectively. ACE-I treatment significantly reduced the incidence of ESRF in mildly proteinuric patients, while the incidence did not differ between severely proteinuric patients receiving or not receiving ACE-I.

Discussion

This study investigated the clinical course of diabetic nephropathy from a baseline serum creatinine concentration of 133 μmol/l in a cohort of Japanese NIDDM patients. The cohort appeared to have a

Table 4. Result of multivariate analysis using the Cox proportional hazard model concerning the effects of urinary protein excretion, family history of hypertension, serum albumin, diastolic blood pressure, and smoking on the development of end-stage renal failure requiring dialysis

Baseline variables	Hazard ratio	*p* value
After adjustment for urinary protein excretion		
Family history of hypertension	1.70 (1.12–2.58)	0.01
Serum albumin	0.31 (0.20–0.49)	0.0001
Diastolic blood pressure	1.03 (1.01–1.06)	0.01
Current smoking	1.53 (1.03–2.28)	0.04
Variables pooled in the analysis		
Urinary protein excretion	3.25 (1.55–6.78)	0.0001
Family history of hypertension	1.84 (1.19–2.82)	0.007
Serum albumin	0.31 (0.20–0.48)	0.0001
Diastolic blood pressure	1.05 (1.01–1.08)	0.0007
Current smoking		0.19

Hazard ratio (95 % CI) indicates alteration of risk per unit increase of baseline variables

Table 5. Interactive effect of proteinuria in association with family history of hypertension, smoking, and treatment with ACE-I on the development of end-stage renal failure

	Proteinuria (≤ 2.5 g/24 h)		Proteinuria (> 2.5 g/24 h)	
Family history of hypertension (FH)	No	Yes	No	Yes
Incidence density for developing ESRF (/100 person-years)	8.0	11.9	30.1	33.7
Rate ratio (95 % CI)	1.0[a]	1.5 (0.7–3.4)	3.8 (1.9–7.7)	4.2 (2.3–7.9)
Smoking	No	Yes	No	Yes
Incidence density for developing ESRF (/100 person-years)	5.2	14.8	29.3	34.4
Rate ratio (95 % CI)	1.0[a]	2.9 (1.3–6.5)	5.6 (2.9–11.0)	6.6 (3.3–13.4)
ACE-inhibitors	Yes	No	Yes	No
Incidence density for developing ESRF (/100 person-years)	1.7	10.7	28.9	31.5
Rate ratio (95 % CI)	1.0[a]	6.3 (1.4–18.0)	16.9 (2.1–37)	18.4 (2.5–43)

Patients were divided into those with proteinuria below (mild proteinuria, $n = 89$, 346 person-years) or above (severe proteinuria, $n = 93$, 259 person-years) the median value of 2.5 g/24 h

[a] Reference group

sufficient number of subjects who developed ESRF and of control subjects in order to evaluate the progression of nephropathy. Our study showed that the rate of decline of renal function is highly variable, as seen in other studies [15, 18, 19]. In addition to the effects of putative progression promoters such as proteinuria, systemic blood pressure, and hypercholesterolaemia, the results of the present study demonstrated the effects of hypoalbuminaemia, smoking, and familial predisposition to hypertension on the development of ESRF which were independent of the effect of urinary protein excretion. Furthermore, the results may indicate that patients with proteinuria below the median (2.5 g/24 h) presumably in response to ACE-I are likely to have a substantially low risk for the progression of nephropathy.

The effect of ACE-I on the progression of nephropathy has been studied mainly in insulin-dependent diabetic patients [20–22]. A few studies also indicated the potential antiproteinuric effect of ACE-I in NIDDM patients, but failed to show the effect of ACE-I on reducing the rate of decline due to the small numbers of subjects or the short follow-up period [23, 24]. The present study demonstrated the potent effect on reducing the risk of developing ESRF, in a large group of NIDDM patients. The design was not an intervention cohort aimed at studying the effect of ACE-I; however, the significantly lower urinary protein excretion at baseline in Group 2 than in Group 1 may be due to an anti-proteinuric effect of ACE-I [20–24]. It appears that there are patients who are responsive (i.e. show mild proteinuria) and not responsive to ACE-I (showing severe proteinuria), the latter being at 17 times higher risk of developing ESRF than the former. This may explain why a single independent variable of ACE-I treatment did not reach statistical significance (Table 3). The severity of proteinuria may reflect the effectiveness of ACE-I, and seems to predict the rate of progression of nephropathy. The effect was even evident in mildly proteinuric patients. Thus, patients treated with ACE-I exhibited an incidence of 1.7 per 100 person-years, the rate being significantly less than that for mildly proteinuric patients not treated with ACE-I (incidence of 10.7).

Systemic blood pressure did not differ between patients treated with ACE-I and patients in the other two groups at baseline or during the follow-up. Furthermore, the levels of systolic and diastolic blood pressure were similar between the mildly proteinuric patients either receiving or not receiving ACE-I (data not shown). These facts support the proposal that the beneficial effects of ACE-I on the progression of nephropathy may be independent of its antihypertensive properties [21, 25]. The mechanism may be due to the beneficial effect of ACE-I on the glomerular extracellular matrix by 1) improving glomerular haemodynamics [26–28] and/or 2) inhibiting trophic properties of angiotensin II to promote glomerular hypertrophy and accumulation of mesangial matrix [26, 29, 30].

Family history of hypertension was a potent predictor independent of the effect of proteinuria. Patients with a family history of hypertension exhibited a slightly higher prevalence of hypertension at baseline (78 vs 65 %, NS), i.e. while undergoing antihypertensive treatment; they nevertheless still had

significantly high systolic blood pressure compared to those without hypertensive relatives (149 ± 15 vs 142 ± 14 mmHg, $p < 0.01$). Genetic predisposition to hypertension has been proposed as a risk factor for diabetic nephropathy [16, 31]. Our results indicate that familial predisposition to hypertension may be a risk factor not only for systemic blood pressure elevation but also for promoting further glomerular damage leading to ESRF in NIDDM patients.

Smoking was another independent progression promoter and the combination of two risk factors, i.e. degree of proteinuria and smoking, had an additive effect on developing ESRF. Previous studies showed that smoking is an important risk factor for progression of established diabetic nephropathy [32, 33]. These findings suggest that the beneficial effect of not smoking is applicable to diabetic patients, especially those with nephropathy.

The present study indicated a strong predictive effect of hypoalbuminaemia and reduced haematocrit on the progression of nephropathy. The degree of hypoalbuminaemia and anaemia may reflect nutritional status, which is important in protecting individuals from progression to renal failure. Hypoalbuminaemia at the start of dialysis is a potent risk marker for excess mortality in patients receiving dialysis [34]. This suggests that the goal of therapy, including dietary protein/calorie intake and medications prior to developing ESRF, should aim to reduce proteinuria together with maintenance of serum albumin levels.

This study may serve as a measure of the expected clinical course of Japanese NIDDM patients with nephropathy. The rate of decline of renal function seen in this study appears to be considerably higher than the rate seen in other renal diseases [35, 36] and in diabetic nephropathy with a glomerular filtration rate of more than 50 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ [6, 7, 12, 18, 19]. The rate of decline and the incidence of developing ESRF appear to be comparable to those reported by Lewis et al. [21] who demonstrated that the yearly increases in serum creatinine concentration from a baseline concentration of 1.5 mg/dl were 0.6 ± 1.2 mg/dl in captopril-treated patients and 1.4 ± 1.2 mg/dl in control patients (corresponding to reciprocal changes of 1.798 and $3.031 \times 10^{-4}\ l \cdot \mu mol^{-1} \cdot month^{-1}$) respectively.

In conclusion, the degree of urinary protein excretion may serve as a useful prognostic index of diabetic nephropathy that may reflect the therapeutic effect of ACE-I in NIDDM patients. Familial predisposition to hypertension, systemic blood pressure elevation, hypoalbuminaemia, and smoking had significant predictive effects on the progression of nephropathy independent of the degree of proteinuria. Interaction of proteinuria in association with these variables may play an important role in the progression of diabetic nephropathy in NIDDM patients.

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