Factors Affecting Progression of Renal Failure in Patients With Type 2 Diabetes

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OBJECTIVE — Hyperglycemia and hypertension are known to be risk factors for the development of proteinuria in patients with diabetes. Little is known, however, about predictors of progression of renal failure in diabetic patients.

RESEARCH DESIGN AND METHODS — We investigated factors affecting progression of renal failure by measuring the doubling of serum creatinine (s-Cr) as an end point in a cohort of 85 type 2 diabetic patients with chronic renal insufficiency/failure (s-Cr >1.5 and <3.7 mg/dl, 61 ± 11 years old, 51 men and 34 women, mean s-Cr 2.3 ± 0.6 mg/dl).

RESULTS — The survey period (mean ± SD) was 14.2 ± 10.8 months. The cumulative incidence of the end point in patients with insulin therapy ($n = 41$) was significantly lower than that in patients without it ($n = 44$) ($P = 0.0022$, P values by log-rank test). Multivariate Cox analysis revealed insulin therapy (hazard ratio [HR] 0.435, 95% CI 0.252–0.750, $P = 0.0027$), serum albumin (0.484, 284–0.823, $P = 0.0074$), mean blood pressure (1.023, 1.004–1.043, $P = 0.017$), and hemoglobin (0.841, 0.728–0.972, $P = 0.0194$) to be independent and significant predictors of progression to renal failure, whereas HbA_{1c} or serum cholesterol were not.

CONCLUSION — In type 2 diabetic patients with renal failure, hypoalbuminemia, anemia, higher mean blood pressure, and lack of use of insulin predict rapid progression of renal failure, but HbA_{1c} does not, and insulin therapy may be possibly an indicator of the delay in progression of renal failure.

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There have been several studies in which factors affecting the development of diabetic nephropathy were examined in a relatively large number of patients with both type 1 and type 2 diabetes (1–7). In these studies, hypertension, hyperglycemia, aging, cholesterol, and smoking have been revealed to be significant risk factors for development of diabetic nephropathy. The Diabetes Control and Complication Trial (DCCT) Research Group clearly demonstrated that better glycemic control delays the development of microalbuminuria and overt proteinuria in type 1 diabetic patients (1). The U.K. Prospective Diabetes Study (UKPDS) Group showed that hyperglycemia and hypertension are significant factors for the development of diabetic nephropathy in type 2 diabetic patients (2). Although these studies examined the risk factors for the development of proteinuria in patients without nephropathy or in the early stage of nephropathy (microalbuminuria), few studies have examined which factors are associated with the progression of diabetic nephropathy at the stage of renal insufficiency or renal failure (8,9). It is unknown whether the risk factors for progression of diabetic nephropathy, such as poor glycemic control, are similar to those for development of diabetic nephropathy. We examined factors affecting the progression of renal failure in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Between March 1995 and January 2001, a total of 202 type 2 diabetic patients with renal insufficiency/failure (serum creatinine [s-Cr] >1.5 mg/dl) were admitted to Osaka City University Hospital. The diagnosis of type 2 diabetes was established according to the Report of the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (10). All of the patients were admitted for the evaluation and treatment of diabetes and its complications. A total of 12 patients died before doubling of s-Cr, and 27 patients were lost to follow-up, mostly due to moving to other hospitals. In 65 patients with s-Cr >5.2 mg/dl, hemodialysis was initiated before doubling of s-Cr. Of 13 patients with s-Cr between 3.8 and 5.0 mg/dl, hemodialysis was initiated before doubling of s-Cr in 5 patients for various reasons, such as massive edema and uremic symptoms, and hemodialysis was initiated after doubling of s-Cr in 8 patients. In the remaining 85 patients with s-Cr <3.7 mg/dl, hemodialysis was initiated after doubling of s-Cr and examined in the present observational study. All 85 patients had diabetic retinopathy (simple, preproliferative, or proliferative). Informed consent to participate in this study was obtained from all subjects, and the present study was approved by the local ethics committee.

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Abbreviations: GFR, glomerular filtration rate; HR, hazard ratio; s-Cr, serum creatinine; TNF-α, tumor necrosis factor-α.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics of the patients*

Age (years)	61.1 ± 11.1
M/F	51/34
Duration of diabetes (years)	16.3 ± 10.5
BMI (kg/m^2)	23.3 ± 3.3
Mean blood pressure (mmHg)	105 ± 15
Blood urea nitrogen (mg/dl)	35.6 ± 11.0
s-Cr (mg/dl)	2.3 ± 0.6
Serum albumin (g/dl)	3.1 ± 0.6
Total cholesterol (mg/dl)	234 ± 78
Triglycerides (mg/dl)	192 ± 165
Fasting plasma glucose (mg/dl)	152 ± 65
HbA_{1c} (%)	7.7 ± 1.9
Hemoglobin (g/dl)	10.8 ± 1.9
Antihypertensives therapy (yes/no)	72/13
Insulin therapy (yes/no)	41/44

Data are means ± SD, unless otherwise indicated.

Table 2—*HRs of possible predictive variables for progression of renal failure*

Variables	HR	95% CI	*P*
Age (per 1 year)	0.989	0.969–1.010	0.3075
Sex (male: 0; female: 1)	0.609	0.381–0.973	0.0378
BMI (kg/m^2)	1.029	0.967–1.096	0.3680
Mean blood pressure (mmHg)	1.007	0.991–1.023	0.4086
Serum creatinine (mg/dl)	1.316	0.890–1.945	0.1689
Serum albumin (g/dl)	0.427	0.291–0.627	<0.0001
Total cholesterol (mg/dl)	1.002	0.999–1.005	0.2405
Triglycerides (mg/dl)	1.000	0.998–1.001	0.8138
Fasting plasma glucose (mg/dl)	0.999	0.995–1.002	0.5426
HbA_{1c} (%)	0.922	0.820–1.037	0.1759
Hemoglobin (g/dl)	0.869	0.776–0.973	0.0152
Insulin therapy (versus no insulin therapy)	0.496	0.308–0.781	0.0027
Antihypertensives therapy (versus no antihypertensives)	1.320	0.711–2.450	0.3700

Table 1 shows the clinical characteristics of the patients. The age (mean ± SD) was 61.1 ± 11.1 years. The mean known duration of diabetes was 16.3 ± 10.5 years. The mean s-Cr concentration was 2.3 ± 0.6 mg/dl. Mean HbA_{1c} was 7.7 ± 1.9%. A total of 72 patients (85%) were treated with antihypertensives, including 16 patients with ACE inhibitors. A total of 41 patients (48%) were treated with insulin (37 subjects with insulin alone and 4 with combinations of insulin and oral hypoglycemic agents), 15 subjects with oral hypoglycemic agents, and 29 with medical nutritional therapy alone. All the patients examined in the present study had overt proteinuria.

Blood pressure and biochemical assays

Blood pressure was measured after the subject had been in a supine position for at least 10 min, using a standard mercury sphygmomanometer. Blood was obtained after an overnight fast for analysis of serum concentrations of creatinine, total cholesterol, triglycerides, and HDL cholesterol. These concentrations were measured using an autoanalyzer. HbA_{1c} levels were determined by high-performance liquid chromatography (HI-AUTO A1C; Sekisui, Osaka, Japan).

Definition of end point and statistical analysis

Progression of diabetic nephropathy was estimated by doubling of baseline s-Cr concentration. The subjects were examined until March of 2002. During the survey period, the s-Cr concentration of 79 patients increased more than twofold, whereas those of six patients did not reach a twofold increase. The 79 patients were analyzed as noncensored case subjects, and the 6 patients as censored case subjects. The mean survey period was 14.3 ± 10.8 months, with a range of 3.0–59.1 months.

Continuous variables were expressed as the means ± SD. Student's unpaired *t* test and the χ^2 test were performed to evaluate differences in mean values and prevalence, respectively. Prognostic curves were obtained using the Kaplan-Meier estimation method and compared by log-rank test. Predictive variables for the end point were analyzed by Cox proportional hazards models. $P < 0.05$ was considered statistically significant. All of these analyses were performed using statistical software (StatView 5; SAS Institute, Cary, NC) designed for the Macintosh computer.

RESULTS

Hazard ratios of possible predictive variables for progression of renal failure

Table 2 shows hazard ratios (HRs) of possible predictive variables for progression of renal failure for the group of all diabetic subjects. Lower serum albumin was a significant predictor for progression of renal failure (HR 0.427, 95% CI 0.291–0.627, $P < 0.0001$), as were hemoglobin (0.869, 0.776–0.973, $P = 0.152$) and male sex (0.609, 0.381–0.973, $P = 0.0378$). Insulin therapy was found to be a significant predictor for slow progression of renal failure (0.496, 0.308–0.781, $P = 0.0027$).

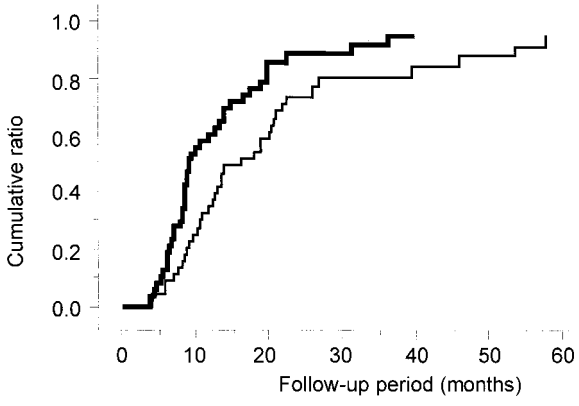

Figure 1—*Cumulative incidence ratio for end point determined by Kaplan-Meier curves in the study cohort, for patients with (thin line, n = 41) and without (thick line, n = 44) insulin therapy. The cumulative incidence curve for patients with insulin therapy was significantly lower than that for patients without it (P = 0.0022, log-rank test).*

Table 3—*Clinical characteristics of patients with and without insulin therapy*

Variables	Patients		*P*
	With insulin therapy	Without insulin therapy	
n	41	44	
Age (years)	60.4 ± 10.9	61.7 ± 11.3	0.5773
M/F	23/18	28/16	0.4784
BMI (kg/m^2)	23.1 ± 3.2	23.5 ± 3.5	0.5754
Mean blood pressure (mmHg)	108 ± 15	102 ± 14	0.0809
Blood urea nitrogen (mg/dl)	34.5 ± 9.5	36.5 ± 12.3	0.3909
s-Cr (mg/dl)	2.1 ± 0.5	2.4 ± 0.7	0.0440
Serum albumin (g/dl)	3.1 ± 0.7	3.1 ± 0.5	0.7251
Total cholesterol (mg/dl)	251 ± 79	219 ± 74	0.0591
Triglycerides (mg/dl)	219 ± 221	166 ± 82	0.1462
Fasting plasma glucose (mg/dl)	161 ± 67	144 ± 63	0.2539
HbA_{1c} (%)	8.2 ± 2.0	7.3 ± 1.7	0.0302
Hemoglobin (g/dl)	10.9 ± 1.9	10.7 ± 2.0	0.5612
Antihypertensives therapy (yes/no)	33/8	39/5	0.1885
Duration of follow-up (months)	17.6 ± 12.9	11.2 ± 7.3	0.0054

Values are means ± SD. *P* values are by Student's unpaired *t* test and χ^2 test.

Cumulative incidence of doubling of baseline s-Cr concentrations according to use or disuse of insulin

Curves of cumulative incidence of the end point are shown in Fig. 1, for patients with insulin therapy and those without it. The 1-, 2-, and 3-year cumulative incidences in patients with insulin therapy were 39, 77, and 89%, respectively, while those of patients without it were 66, 93, and 100%, respectively. Progression of renal failure in patients with insulin therapy was significantly slower than that in patients without it ($P = 0.0022$, *P* values by log-rank test).

Clinical characteristics of patients with and without insulin therapy

Table 3 compares baseline clinical characteristics between patients with and without insulin therapy. S-Cr concentrations were significantly lower in patients with insulin therapy than in those without it (2.1 ± 0.5 and 2.4 ± 0.7, respectively; $P = 0.0440$). HbA_{1c} levels were also significantly higher in the former than in the latter group (8.2 ± 2.0 and 7.3 ± 1.7, respectively; $P = 0.0302$). Total cholesterol concentrations were higher in the former than in the latter group, with borderline significance ($P = 0.0591$). The mean blood pressures were higher in the former than in latter group, with borderline significance ($P = 0.0809$). Other baseline clinical parameters were not significantly different between the patients with and without insulin therapy, including age, sex, BMI, serum albumin concentrations, triglycerides, hemoglobin levels, and use of antihypertensives.

Independent predictors of progression of renal failure

Independent predictors of progression of renal failure were identified by a multivariate Cox model (Table 4). Sex, mean blood pressure, baseline s-Cr, serum albumin, total cholesterol, HbA_{1c}, hemoglobin, and insulin therapy were chosen as independent variables in the model. These variables were significant predictors of progression of renal failure (Table 2) and/or exhibited significant or borderline differences between patients with and without insulin therapy (Table 3). The multivariate Cox model demonstrated that insulin therapy (HR 0.435, 95% CI 0.252–0.750, $P = 0.0027$) as well as serum albumin (0.484, 0.284–0.823, $P = 0.0074$), mean blood pressure (1.023, 1.004–1.043, $P = 0.017$), and hemoglobin (0.841, 0.728–0.972, $P = 0.0194$) were significant and independent predictors of the rate of progression of renal failure in patients with type 2 diabetes.

CONCLUSIONS — In the present observational study, we examined predictors of progression of renal failure in patients with type 2 diabetes who had had advanced nephropathy in the range of renal insufficiency/failure. In Cox proportional hazards analyses, lower serum albumin, lower hemoglobin, male sex, and lack of insulin therapy were significant factors for the progression of renal failure. Kaplan-Meier analysis showed that patients without insulin therapy had significantly faster progression of renal failure. In multivariate Cox proportional hazards analysis, lower serum albumin concentration, lower hemoglobin value, higher mean blood pressure, and lack of use of insulin were significant factors favoring progression of renal failure.

Several studies have examined factors favoring development of diabetic nephropathy. Although hypertension, poor glycemic control, advanced age, and smoking were reported to be significant risk factors for the development of diabetic nephropathy (1–3,5,6), it is unknown whether these risk factors also predict loss of renal function. In examining factors associated with the progression of diabetic nephropathy with overt proteinuria in type 1 diabetic subjects, Alaveras et al. (11) found that poor glycemic control and higher mean diastolic blood pressure were significantly associated with more rapid decline of glomerular filtration rate (GFR). Recently, Hovind et al. (12) also reported similar results for

Table 4—*Multivariate Cox proportional HR of variables for progression of renal failure*

Variables	HR	95% CI	*P*
Insulin therapy (versus no insulin therapy)	0.435	0.252–0.750	0.0027
Serum albumin (per 1 g/dl)	0.484	0.284–0.823	0.0074
Mean blood pressure (per 1 mmHg)	1.023	1.004–1.043	0.0170
Hemoglobin (per 1 g/dl)	0.841	0.728–0.972	0.0194
Sex (male: 0; female: 1)	0.652	0.379–1.055	0.1240
HbA_{1c} (per 1 %)	0.924	0.804–1.063	0.2679
Serum creatinine (per 1 mg/dl)	1.213	0.775–1.898	0.3978
Total cholesterol (per 1 mg/dl)	1.000	0.996–1.003	0.9060

Global model significance is $P < 0.0001$.

type 1 diabetic subjects, with a significant independent association found between decline in GFR and mean arterial blood pressure, albuminuria, and HbA_{1c}. In our study, Cox hazards analyses did not reveal a significant association of HbA_{1c} with progression of renal failure, whereas mean blood pressure was a significant factor. This difference may be attributable to the fact that the patients of their studies were without renal insufficiency, in contrast to the present study, in which all patients had renal insufficiency/failure.

Breyer et al. (9) examined the risk factors for progression of established nephropathy in type 1 diabetic patients, as defined by urinary protein excretion >500 mg/day and s-Cr concentration <2.5 mg/dl. For progression of nephropathy as judged by doubling of s-Cr concentration (the same method as the present study), they found that significant independent predictors were lower hematocrit, higher blood glucose, higher urinary protein excretion, and higher creatinine (9). In examining type 2 diabetic patients with overt nephropathy, in whom the baseline average s-Cr level was 1.5 mg/dl, Yokoyama et al. (8) found that proteinuria, blood pressure elevation, family predisposition to hypertension, hypoalbuminemia, and smoking were significant independent predictors for progression of nephropathy. They also found that lower hematocrit was a significant predictor for progression of renal failure, and that poor glycemic control as judged by lower HbA_{1c} levels did not affect renal outcome. In the present study, lower hemoglobin and hypoalbuminemia were significant independent predictors, consistent with the previous two studies. Not only in diabetic patients, but also in nondiabetic patients with renal failure, anemia and hypoalbuminemia have been reported to be risk factors for progression of renal failure (13–16). It seems conceivable that anemia decreases oxygen delivery to kidney tissue, thereby causing hypoxia, which is detrimental to this tissue. The results of Yokoyama's study (8) and our own did not demonstrate a beneficial effect of better glycemic control on progression of renal failure, unlike the study by Breyer et al. This may be because our group and Yokoyama et al. examined type 2 diabetic subjects, whereas Breyer et al. examined type 1 diabetic subjects, because the importance of glycemic control for the progression of nephropathy is reported to differ somewhat between type 1 and type 2 diabetic patients with established nephropathy (17,18).

It has been reported that intensive insulin treatment inhibited the development of diabetic nephropathy, and the mechanism of this inhibition has been reported to be better glycemic control (1–3). However, there have been no reports in which insulin therapy in itself has been shown to have an effect on the progression of diabetic nephropathy in patients with renal insufficiency/failure. In multivariate Cox proportional hazards analysis in the present study, we found that use of insulin therapy was a significant independent predictor for better renal survival. The reason why insulin therapy was a significant predictor of better renal survival in our study is unknown. In patients with renal failure, insulin clearance by the kidney decreases and insulin requirement for blood glucose control is reduced (19,20). Our results suggest that renal clearance of insulin may be reduced in patients without insulin therapy, resulting in a decreased requirement for insulin therapy, i.e., patients without insulin therapy had a greater decrease in capacity of insulin clearance caused by more advanced deterioration of renal function, making this a significant predictor of poor renal prognosis. Several clinical and experimental studies have demonstrated that insulin mediates vasodilation in various vascular beds, including the renal vasculature (21–24). In patients receiving insulin therapy in the present study, insulin may have had a vasodilatory effect and therefore a renoprotective effect. In patients with renal failure, serum tumor necrosis factor-α (TNF-α) concentration is reported to be increased and related to insulin resistance, malnutrition, and inflammation (25,26). Insulin resistance caused by TNF-α may be alleviated or partly overcome by exogenous insulin administration and may improve tissue metabolism, such as in the kidneys, possibly resulting in a renoprotective effect. Further studies are needed to clarify the significance of the effect of insulin therapy on renal prognosis. Considering our observational study, insulin therapy may be recommended to patients with renal failure whenever possible.

In summary, in type 2 diabetic patients with renal insufficiency/failure, hypoalbuminemia, anemia, hypertension, and disuse of insulin therapy are significant independent predictors for rapid progression of renal failure, and the use of insulin therapy may be an indicator of delay in the progression of renal failure.

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