Glycemic Control Is a Predictor of Survival for Diabetic Patients on Hemodialysis

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OBJECTIVE — To investigate the impact of glycemic control on the survival of diabetic subjects with end-stage renal disease (ESRD) starting hemodialysis treatment.

RESEARCH DESIGN AND METHODS — This single-center prospective observational study enrolled 150 diabetic ESRD subjects (109 men and 41 women; age at hemodialysis initiation, 60.5 ± 10.2 years) at start of hemodialysis between January 1989 and December 1997. The subjects were divided into groups according to their glycemic control level at inclusion as follows: good HbA_{1c} <7.5%, $n = 93$ (group G), and poor HbA_{1c} ≥7.5%, $n = 57$ (group P); and survival was followed until December 1999, with a mean follow-up period of 2.7 years.

RESULTS — Group G had better survival than group P (the control group) ($P = 0.008$). At inclusion, there was no significant difference in age, sex, systolic blood pressure (SBP), BMI, cardio-to-thoracic ratio (CTR) on chest X-ray, and serum creatinine (Cre) or hemoglobin (Hb) levels between the two groups. After adjustment for age and sex, HbA_{1c} was a significant predictor of survival (hazard ratio 1.133 per 1.0% increment of HbA_{1c}, 95% CI 1.028–1.249, $P = 0.012$), as were Cre and CTR.

CONCLUSIONS — Good glycemic control (HbA_{1c} <7.5%) predicts better survival of diabetic ESRD patients starting hemodialysis treatment.

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Intensive glycemic control prevents the development and progression of diabetic microangiopathy including retinopathy, nephropathy, and neuropathy, as shown by the Diabetes Control and Complications Trial (DCCT) (1), the Kumamoto Study (2), and the U.K. Prospective Diabetes Study (UKPDS) (3). However, intensive glycemic control did not significantly improve the outcome of cardiovascular disease (the main cause of death of diabetic subjects) in these randomized intervention studies (1,3,4). In other prospective observational studies, it has remained unclear whether glycemic control is associated with the risk of development of cardiovascular disease and mortality in diabetic populations (5–10).

Several studies identified clinical predictors of survival of diabetic end-stage renal disease (ESRD) patients on hemodialysis, including age at hemodialysis initiation (11–15), nutritional status (14,16), dyslipidemia (17,18), and existence of cardiovascular complications (11,12,14,15). However, it is still unknown whether glycemic control has beneficial effects in diabetic patients with advanced nephropathy. Only a few studies have investigated the long-term impact of glycemic control at the initiation of hemodialysis treatment on the survival of diabetic patients with ESRD (11,19).

The aim of the present observational study in a single dialysis center was to determine whether predialysis glycemic control affects the mortality of diabetic patients with ESRD who start hemodialysis treatment. We also examined whether the predialysis state of glycemic control was preferentially associated with cardiovascular or noncardiovascular mortality in the diabetic ESRD cohort. We found that good glycemic control at hemodialysis initiation reduced the risk of death for diabetic patients on maintenance hemodialysis.

RESEARCH DESIGN AND METHODS

— A total of 150 diabetic patients with ESRD (109 men and 41 women) were enrolled to undergo maintenance hemodialysis between January 1989 and December 1997 in our dialysis center at Inoue Hospital, Suita, Japan. All diabetic subjects were enrolled in the present observational study (Osaka Diabetes and Dialysis Study). The survival or death of subjects was investigated until December of 1999, 24 months after the final month of entry. During the survey period, 114 (76%) subjects died, and 36 (24%) subjects were alive at the end of the survey period. None of the patients underwent renal transplantation during the survey period. We analyzed 114 subjects as noncensored cases and 36 subjects as censored cases for life analyses; 7 subjects had type 1 diabetes and 143 had type 2 diabetes according to the classification of the American Diabetes Association (20). The median survey period was 2.69 years, with a range of 0–9.0 years. The mean age

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Abbreviations: Cre, creatinine; CTR, cardio-to-thoracic ratio; DCCT, Diabetes Control and Complications Trial; ESRD, end-stage renal disease; HR, hazard ratio; OHA, oral hypoglycemic agents; SBP, systolic blood pressure; T-chol, total cholesterol; TP, total protein; UKPDS, U.K. Prospective Diabetes Study.

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

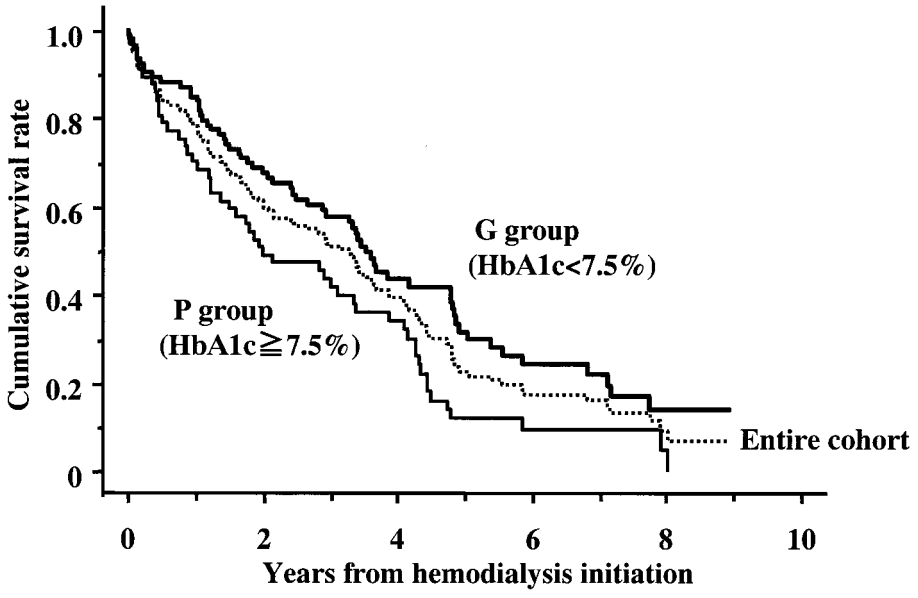

Figure 1—*Cumulative survival curves for diabetic ESRD subjects on hemodialysis with good (G group) and poor (P group) glycemic control. All diabetic ESRD subjects were divided into two groups by HbA_{1c} level before the initiation of hemodialysis: G group, good glycemic control group (HbA_{1c} <7.5%), and P group, poor glycemic control (HbA_{1c} ≥7.5%). The cumulative survival curve for all diabetic ESRD subjects is represented as a dotted line, that of the G group as a thick solid line, and that of the P group as a thin solid line. The cumulative survival curve of the G group was significantly better than that of the P group (P = 0.005, log-rank test).*

at hemodialysis initiation was 60.5 ± 10.2 years (range 29–85) and that of known duration of diabetes was 17.8 ± 8.8 years (range 0.1–44.6). A total of 71 subjects were treated with insulin therapy, 39 subjects with oral hypoglycemic agents (OHA), 13 with the combination of insulin and OHA, and 27 with medical nutritional therapy alone. To certify the cause of death as precisely as possible, we categorized the cause of death according to the medical records for 72 diabetic ESRD subjects who died in our dialysis center. Cardiac, cerebrovascular, and peripheral vascular diseases were categorized as cardiovascular disease, whereas sepsis and pneumonia caused by bacteria or fungi were categorized as infectious disease. Informed consent was obtained from all participants, and the present study was approved by the local Ethics Committee (no. 102).

Clinical status and laboratory data for all diabetic subjects enrolled in the study were evaluated by routine clinical examinations before the first hemodialysis session. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine position after a 10- to 15-min rest, and the cardio-to-thoracic ratio (CTR) on chest X-ray was measured. Laboratory data included fasting plasma glucose, HbA_{1c}, hemoglobin (Hb), serum creatinine (Cre), blood urea nitrogen, serum sodium (Na), potassium (K), total protein (TP), and total cholesterol (T-chol). The blood for laboratory examination was drawn before initiation of the hemodialysis session, and assays were performed by a routinely used autoanalyzer (Hitachi 7150; Hitachi, Tokyo). HbA_{1c} was measured by high-performance liquid chromatography method, and its reference range was 3.8–5.5%. The mean and median HbA_{1c} levels for all diabetic subjects were 7.3 ± 2.2 and 7.1%, respectively (range 4.2–15.8%). To determine the impact of glycemic control on survival, all diabetic subjects were divided into two groups according to glycemic control. The G group consisted of 93 subjects with good glycemic control, HbA_{1c} <7.5%, and the P group included 57 subjects with poor glycemic control, HbA_{1c} ≥7.5%. The mean HbA_{1c} level in the G group was 6.2 ± 0.9% and that in the P group 9.2 ± 1.7%.

Analytical methods

All values are expressed as mean ± SD, unless otherwise indicated. Statistical analyses were performed with the StatView V system (Abacus Concepts, Berkeley, CA). Student's unpaired *t* test, Mann-Whitney *U* test, and χ^2 tests were used as appropriate. Survival curves were obtained using the Kaplan-Meier estimation method and compared by log-rank test. Predictive variables for survival were analyzed by Cox proportional hazards models. The proportional hazard assumption of the model was assessed by inspection of the log time–log hazard plot for all covariates. $P < 0.05$ was considered significant.

RESULTS

Characteristics and survival of diabetic subjects on hemodialysis

The cumulative survival curve for all diabetic subjects after hemodialysis initiation is shown in Fig. 1. The 1-, 3-, and 5-year cumulative survival rates for all diabetic subjects were 79.3, 52.5, and 23.3%, respectively. Predialysis clinical characteristics of survivors and nonsurvivors are shown in Table 1. The median survey period in the survivor group, 3.58 years (range 1.8–9.0), was significantly longer than that in the nonsurvivor group, 1.98 years (range 0–8.0) ($P < 0.0001$). Age at hemodialysis initiation and HbA_{1c} level were significantly lower in the survivor group than in the nonsurvivor group, and serum Cre level was significantly higher in the survivor group than in the nonsurvivor group. There was no significant difference in sex, SBP, DBP, BMI, CTR, Hb, or serum levels of TP, Na, K, and T-chol between the two groups.

Characteristics and survival of subjects with good and poor glycemic control

Table 2 compares predialysis clinical characteristics of the G and P groups. The mean serum sodium in the P group was significantly lower than that in the G group. At hemodialysis initiation, there was no significant difference in age, sex, SBP, DBP, CTR, BMI, K, Cre, TP, Hb, or T-chol levels between the two groups. Cumulative survival in the G group was significantly better than that in the P group (Fig. 1) ($P = 0.005$, log-rank test). The 1-, 3-, and 5-year cumulative survival rates of the G group (84.9, 57.8, and 31.7%, respectively) were significantly higher than those for the P group (70.2, 43.7, and 12.1%, respectively).

Table 1—*Predialysis clinical characteristics of surviving and nonsurviving diabetic subjects on hemodialysis*

	Survivors	Nonsurvivors	*P*
n (% Male)	36 (72.2)	114 (72.8)	0.999
Age at hemodialysis initiation (years)	56.9 ± 10.5	61.7 ± 9.9	0.013*
SBP (mmHg)	167 ± 19	159 ± 22	0.052
DBP (mmHg)	83 ± 10	82 ± 14	0.580
BMI (kg/m^2)	23.4 ± 3.2	22.0 ± 3.6	0.086
CTR (%)	51.7 ± 5.3	53.9 ± 6.6	0.061
HbA_{1c} (%)	6.7 ± 1.3	7.5 ± 2.1	0.031*
Cre (mg/dl)	9.9 ± 3.3	8.5 ± 3.0	0.015*
Na (mEq/l)	138 ± 5	136 ± 7	0.149
K (mEq/l)	4.5 ± 0.8	4.4 ± 0.9	0.721
TP (g/dl)	6.4 ± 0.7	6.3 ± 0.8	0.494
Hb (g/dl)	7.9 ± 1.5	7.9 ± 1.5	0.981
T-chol (mg/dl)	203 ± 80	185 ± 62	0.149

Data are *n* (%) or means ± SD. *$P < 0.05$.

Predictors of survival

Table 3 shows hazard ratios (HRs) of possible predictive variables for survival for all of the participating diabetic subjects. With unadjusted HRs, age at hemodialysis initiation, CTR, Cre, HbA_{1c}, and T-chol were significant predictive variables for survival. After adjustment at hemodialysis initiation for age and sex, HbA_{1c} was a significant predictor of survival, as were Cre and CTR.

Causes of death

Table 4 shows causes of death for 72 diabetic ESRD subjects with certification of the causes of death determined by medical records. Cardiovascular diseases accounted for 43.1%, infectious diseases for 19.4%, malignant disease for 12.5%, bleeding for 9.7%, and liver disease for 2.8% of the deaths. The incidence of cardiovascular death in the G group was comparable to that in the P group. Although the causes of death between the G and P groups did not reach statistical significance ($\chi^2 = 4.66$, $P = 0.097$), the incidence of death from infectious disease in the G group was 56% of that in the P group.

CONCLUSIONS — This prospective observational study revealed that better glycemic control was associated with longer survival in 150 diabetic patients with ESRD who began hemodialysis, and that poor glycemic control increased the risk for death from infectious diseases but not from cardiovascular complications.

It is well documented that diabetic ESRD patients on hemodialysis have higher mortality and morbidity than ESRD patients without diabetes in the U.S., Europe, and Japan (21–23). In previous studies, older age, malnutrition (14,16), dyslipidemia (17,18), and coexistence of cardiovascular disease (11,12,14,15) were reported to affect the survival rate of diabetic ESRD patients after the initiation of hemodialysis. The most common cause of death of diabetic patients with ESRD as well as of diabetic patients without ESRD is cardiovascular disease.

The DCCT study of type 1 diabetes (1), the Kumamoto study (2), and the UKPDS (3) of type 2 diabetes clearly demonstrated that intensive glycemic control prevented the development and progression of diabetic microangiopathy in diabetic patients without ESRD. In contrast, it remains unclear whether intensive glycemic control improves the outcome of macroangiopathy. Some prospective observational studies found that glycemic control was associated with cardiovascular mortality (5–9), whereas other studies did not (10). Although intensive glycemic control reduced the risk of cardiovascular events by 41% in the DCCT study and that of myocardial infarction by 16% in the UKPDS, neither result was statistically significant. In the Veterans Affairs Cooperative Study (4), intensive glycemic control reduced neither the onset nor the mortality of cardiovascular disease.

Until the present study, the clinical significance of glycemic control in diabetic ESRD patients had not been clearly determined. To the best of our knowledge, only a few studies have examined whether good glycemic control during chronic renal failure has beneficial effects on the outcome for diabetic ESRD patients after the initiation of hemodialysis. Wu et al. (19) reported that poor glycemic control, defined as $HbA_{1c} \geq 10\%$, before initiation of hemodialysis was a predictor of cardiovascular morbidity and long-term survival for 137 type 2 diabetic patients on hemodialysis. Medina et al. (12) found that the average blood glucose level before the initiation of hemodialysis was a predictor of survival along with age, physical disability, and macrovascular disease in 638 patients with ESRD. Suzuki et al. (11) found that the survival period was

Table 2—*Predialysis clinical characteristics of diabetic subjects on hemodialysis with good glycemic control (G group) and poor glycemic control (P group)*

	G group	P group	*P*
n (% Male)	93 (73.1)	57 (71.9)	0.999
Age at hemodialysis initiation (years)	60.6 ± 10.4	60.5 ± 10.0	0.964
SBP (mmHg)	161 ± 22	160 ± 21	0.841
DBP (mmHg)	81 ± 13	83 ± 13	0.444
BMI (kg/m^2)	22.5 ± 3.5	22.0 ± 3.5	0.502
CTR (%)	53.1 ± 6.6	54.0 ± 6.2	0.378
Cre (mg/dl)	9.1 ± 3.2	8.4 ± 2.9	0.161
Na (mEq/l)	138 ± 6	134 ± 7	0.0005*
K (mEq/l)	4.4 ± 0.9	4.4 ± 0.8	0.794
TP (g/dl)	6.4 ± 0.9	6.3 ± 0.8	0.222
Hb (g/dl)	7.8 ± 1.5	8.1 ± 1.5	0.195
T-chol (mg/dl)	187 ± 68	193 ± 66	0.601

Data are *n* (%) or means ± SD. The G group consists of subjects with $HbA_{1c} < 7.5\%$, and the P group consists of subjects with $HbA_{1c} \geq 7.5\%$ at hemodialysis initiation. *$P < 0.05$.

Table 3—*HRs of possible predictive variables for survival of diabetic subjects on hemodialysis (n = 150)*

	Unadjusted			Adjusted for age and sex		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age (year)	1.028	1.009–1.048	0.004*	—	—	—
Sex (female)	0.913	0.604–1.381	0.667	—	—	—
SBP (mmHg)	0.996	0.987–1.005	0.360	0.993	0.984–1.002	0.126
DBP (mmHg)	0.999	0.984–1.013	0.844	1.000	0.986–1.015	0.977
BMI (kg/m^2)	0.950	0.881–1.025	0.186	0.952	0.882–1.027	0.199
CTR (%)	1.033	1.004–1.062	0.025*	1.038	1.003–1.074	0.031*
Cre (mg/dl)	0.920	0.859–0.986	0.018*	0.930	0.867–0.997	0.042*
HbA_{1c} (%)	1.116	1.011–1.232	0.029*	1.133	1.028–1.249	0.012*
Na (mEq/l)	0.981	0.955–1.008	0.162	0.975	0.949–1.001	0.060
K (mEq/l)	0.813	0.642–1.030	0.086	0.840	0.663–1.164	0.148
TP (g/dl)	0.857	0.680–1.080	0.190	0.855	0.675–1.083	0.194
Hb (g/dl)	1.066	0.947–1.199	0.289	1.103	0.973–1.251	0.126
T-chol (mg/dl)	0.997	0.994–1.000	0.040*	0.997	0.994–1.000	0.099

The HR for each variable is expressed per increment of 1 unit of each variable; the HR for sex refers to females. *$P < 0.05$.

longer for patients with HbA_{1c} levels <7.5% than for patients with HbA_{1c} levels >7.5% among diabetic ESRD patients. The report from the National Kidney Foundation (24) recommended a target HbA_{1c} value of 8% to provide reasonable protection against metabolic disorders and infections due to hyperglycemia with a lower risk of hypoglycemia, if intensive glycemic control was not recommended.

The present study clearly demonstrated that good glycemic control, HbA_{1c} levels <7.5%, in diabetic ESRD patients at initiation of chronic hemodialysis predicted better long-term survival and that the HR of HbA_{1c} was a significant predictor for survival. Furthermore, the HR of HbA_{1c} per 1.0% (1.116) was approximately four times that of age at hemodialysis initiation per 1 year in the unadjusted Cox proportional hazards model, thus comparable with data on age at hemodialysis initiation obtained in previous studies (15,25). The HR in HbA_{1c} was also found to be statistically significant, even after the adjustment at the hemodialysis initiation for age and sex. Our adjusted Cox proportional hazards model findings indicate that a 1.0% increment of HbA_{1c} increased the risk of death by 13.3%. This impact of glycemic control on the prognosis of survival in diabetic ESRD patients is approximately twice that of average blood glucose per 30 mg/dl, as calculated from the data presented by Medina et al. (12). The HR of HbA_{1c} was not clearly documented in previous studies of the survival of diabetic ESRD patients on hemodialysis.

Cardiovascular causes accounted for ~43% of deaths for our subjects, a percentage comparable with that in a study in Japan (16) and lower than that in a study in the U.S. (21). Contrary to our expectation before data analyses, we failed to find significant differences in the frequency of cardiovascular disease as cause of death between the good and poor glycemic control groups. Infectious diseases accounted for 20% of all the deaths of our subjects, a percentage comparable with that in previous reports (11,13,16). The frequency of infectious diseases in the G group was one-third that in the P group. Hyperglycemia in patients with diabetes is well known to decrease protection against various microorganisms because of defects in defense mechanisms that subsequently result in lethal infections, such as severe pneumonia, and sepsis (26). Furthermore, diabetic ESRD patients are exposed to increased opportunities for infection, such as vascular access, severe diabetic neuropathy, and hemodialysis maneuvers. Taken together with results of previous studies, our findings suggest that hyperglycemia per se is not directly associated with cardiovascular death but significantly affects prognosis by increasing the risk of infection.

Table 4—*Causes of death of diabetic subjects on hemodialysis*

Cause of death	G group	P group	Both groups
Cardiovascular disease	19	12	31
Infectious disease	5	9	14
Pneumonia	3	5	8
Sepsis	2	4	6
Malignant disease	7	2	9
Bleeding	4	3	7
Liver disease	1	1	2
Other	7	2	9
Total	43	29	72

Values are *n*. The G group consists of subjects with $HbA_{1c} < 7.5\%$, and the P group consists of subjects with $HbA_{1c} \geq 7.5\%$ at hemodialysis initiation.

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