Impact of Glycemic Control on Survival of Diabetic Patients on Chronic Regular Hemodialysis

A 7-year observational study

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OBJECTIVE — To investigate the impact of glycemic control during regular hemodialysis on the survival of diabetic patients with chronic kidney disease (CKD) in a longitudinal observational study.

RESEARCH DESIGN AND METHODS — A total of 114 diabetic CKD patients on hemodialysis at Inoue Hospital (Suita, Japan) were surveyed from May 1995 to December 2002 (survey period 45.5 ± 29.3 [means ± SD] months). All subjects were categorized into three groups by mean HbA_{1c} (A1C) level during the 3-month period on hemodialysis preceding entry, as follows: good (A1C <6.5%, 5.7 ± 0.4%, $n = 34$), fair (6.5 ≤ A1C < 8.0%, 7.2 ± 0.4%, $n = 39$), and poor (A1C ≥8.0%, 9.2 ± 0.9%, $n = 41$) A1C groups.

RESULTS — There were no significant differences in age at entry, initiation of hemodialysis, duration of hemodialysis, blood pressure, cardiothoracic ratio, serum creatinine level, or hemoglobin level among the three groups. The cumulative survival of the poor A1C group during the survey was significantly lower than that of the fair and good A1C groups as determined by Kaplan-Meier estimation ($P = 0.041$, log-rank test). In a multivariate Cox proportional hazard model, both poor A1C group (hazard ratio 2.889, $P = 0.010$) and mean A1C (1.260 per 1.0%, $P = 0.003$) were significant predictors of survival.

CONCLUSIONS — In diabetic CKD patients on regular hemodialysis, poor glycemic control is an independent predictor of prognosis. This finding indicates the importance of careful management of glycemic control even after initiation of hemodialysis.

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Strict glycemic control in diabetic patients decreases diabetes complications, which determine the quality of life and prognosis of such patients. Since the Diabetes Control and Complications Trial in subjects with type 1 diabetes (1), intensive treatment with insulin or oral hypoglycemic agents has been established to prevent the development and progression of diabetic microangiopathy in the Kumamoto Study (2) and the U.K. Prospective Diabetes Study in subjects with type 2 diabetes (3). Recently, clinical evidence suggesting the favorable effects of strict glycemic control on cardiovascular disease, a main cause of death in diabetic patients, has also been obtained (4–6). However, it is unclear whether strict glycemic control has beneficial effects on the prognosis of diabetic patients with chronic kidney disease (CKD) undergoing regular hemodialysis (7).

There have been few well-designed studies of the impact of glycemic control on the prognosis of diabetic hemodialysis patients. Several cross-sectional studies have found a close association between glycemic control at initiation of hemodialysis and prognosis (8–10). In addition, a few observational studies, including our own, have successfully demonstrated that good glycemic control at initiation of hemodialysis is an independent predictor of prognosis (9,11,12). Subsequently, McMurray et al. (13) were the first to demonstrate improvements of outcome in diabetic hemodialysis patients undergoing intensive diabetes education and care management in a dialysis unit, despite only a short period of intervention. Clinical examination of the impact of glycemic control during hemodialysis, not just at initiation of hemodialysis, on prognosis is thus clearly needed to improve the clinical management of diabetic hemodialysis patients (14) who are now steadily increasing in number in the U.S., Japan, and Europe. In the present longitudinal observational study, we examined the clinical effects of glycemic control on prognosis during stable, regular hemodialysis in diabetic patients with CKD undergoing regular hemodialysis.

RESEARCH DESIGN AND METHODS

— A total of 114 diabetic patients with CKD on chronic regular hemodialysis as of 1 May 1995 in our dialysis center at Inoue Hospital, Suita, Japan, were enrolled in the present observational study (Osaka Diabetes and Dialysis Study [ODDS]-2). The enrolled subjects, who had undergone stable, regular hemodialysis for at least 3 months and who had no acute illnesses, were selected from 125 diabetic subjects on hemodialysis due to diabetic nephropathy at entry. Diabetic nephropathy was clinically diagnosed at initiation of hemodialysis by history of

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Abbreviations: CKD, chronic kidney disease; ODDS, Osaka Diabetes and Dialysis Study.

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

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Table 1—*Clinical characteristics of diabetic subjects on regular hemodialysis in good, fair, and poor glycemic control groups*

	Good	Fair	Poor	*P* value
n	34	39	41	
Age at entry (years)	61.5 ± 10.9	60.6 ± 10.4	60.4 ± 9.8	0.894
Age at hemodialysis initiation (years)	59.4 ± 11.7	57.6 ± 10.6	56.4 ± 12.0	0.743
Duration of hemodialysis (months)	42.0 ± 42.8	37.6 ± 28.2	53.8 ± 33.6	0.105
Existence of cardiac disease (*n*)	18	21	16	0.335
Systolic blood pressure (mmHg)	159.5 ± 25.5	164.7 ± 19.7	166.2 ± 22.6	0.593
Diastolic blood pressure (mmHg)	77.9 ± 10.9	79.4 ± 6.8	79.8 ± 9.1	0.768
Cardiothoracic ratio (%)	49.6 ± 4.0	50.2 ± 3.6	50.0 ± 3.9	0.875
Mean A1C (%)	5.7 ± 0.4	7.2 ± 0.4*	9.2 ± 0.9*	<0.0001
Creatinine (mg/dl)	11.4 ± 3.0	10.4 ± 2.2	10.9 ± 2.2	0.236
Sodium (mEq/l)	139 ± 3	138 ± 4	137 ± 4	0.083
Potassium (mEq/l)	5.2 ± 0.8	5.0 ± 0.6	4.8 ± 1.0	0.307
Total protein (g/dl)	6.5 ± 0.6	6.8 ± 0.5*	6.5 ± 0.4	0.020
Albumin (g/dl)	3.7 ± 0.3	3.8 ± 0.3	3.6 ± 0.4	0.068
Hemoglobin (g/dl)	9.5 ± 1.4	9.4 ± 1.1	9.5 ± 1.4	0.985
Total cholesterol (mg/dl)	150 ± 43	163 ± 36	167 ± 35	0.127
Uric acid (mg/dl)	6.8 ± 1.2	6.9 ± 1.0	6.6 ± 1.0	0.506

Data are means ± SD unless otherwise indicated. Existence of cardiac diseases, existence of coronary artery disease, and/or echocardiographic abnormalities. Diabetic subjects were divided into three groups by mean A1C level as follows: good A1C group <6.5%, fair A1C group ≥6.5 to <8.0%, and poor A1C group ≥8.0% A1C. *$P < 0.05$ vs. good A1C group.

long duration of diabetes, existence of diabetic retinopathy examined by ophthalmologists, lack of overt hematuria, and other clinical and laboratory data suggesting nondiabetic kidney diseases. The enrolled subjects consisted of 86 men and 28 women, including 10 type 1 and 104 type 2 diabetic patients, according to the classification of the American Diabetes Association (15). The mean age at study entry was 60.8 ± 10.2 years (range 33.0–80.0), and the duration of hemodialysis at entry was 44.7 ± 35.3 months (3.0–238.0). Ten type 1 diabetic patients were treated with intensive insulin therapy of regular insulin before meals and NPH insulin at bed time. Among 104 type 2 diabetic patients, 47 patients were treated with conventional insulin therapy of NPH or mixed-type insulin once or twice a day and 57 with diet therapy alone.

The observational study was performed from 1 May 1995 to 31 December 2002, and the survival or death of subjects was investigated until 31 December 2002, following our previous ODDS-1 study (12). Regular hemodialysis was performed at 4-h sessions three times a week. For all patients who missed a hemodialysis session, an alternative session on another day in the same week was arranged. The mean survey period was 45.5 ± 29.3 months, ranging from 1.5 to 84.0 months. A total of 72 (63.0%) subjects died during the survey period, and 28 (25.0%) were alive at the end of the survey period. At the end of the survey, the end point, survival or death, of 14 subjects (12%) could not be certified because of transfer to other hospitals or clinics, despite a follow-up survey with double referrals. Thus, 72 subjects were regarded as noncensored cases and 42 as censored cases for life analyses. To determine causes of death as precisely as possible, we categorized causes of death according to medical records for 72 diabetic hemodialysis subjects. Cardiac diseases, cerebrovascular diseases, and peripheral vascular disease were categorized as cardiovascular diseases and sepsis, pneumonia, enteritis, and other diseases caused by bacteria or fungi as infectious diseases.

The clinical status of all subjects enrolled in the study was evaluated by routine clinical examinations before the regular hemodialysis session. Systolic and diastolic blood pressures were measured in the supine position after 10–15 min rest, as was cardiothoracic ratio on chest X-ray. Echocardiography was routinely examined before entry. The subjects who had abnormal findings of left ventricular wall thickening, dilatation and/or ejection fraction, and/or received any drugs for coronary artery diseases were regarded as subjects with concurrent cardiac diseases (Tables 1 and 2). Laboratory data included A1C, hemoglobin level, and serum levels of creatinine, sodium, potassium, total protein, total cholesterol, and uric acid. The blood for laboratory examination was drawn before initiation of the hemodialysis session on Monday or Tuesday, and assays were performed with a routinely used autoanalyzer (Hitachi 7150; Hitachi, Tokyo, Japan).

To evaluate glycemic control during stable, regular hemodialysis, we used the mean A1C during the 3-month period preceding entry, that is, March, April, and May of 1995. A1C was measured by the high-performance liquid chromatography method with a reference range of 3.8 to 5.5%, which was standardized by the standard substance provided by the Japan Diabetes Association. The mean A1C level of all diabetic subjects was 7.5 ± 1.6% (range 4.7–11.6%). To determine the impact of glycemic control on survival, diabetic subjects were divided into three groups by mean A1C level, as follows: good A1C <6.5%, fair A1C ≥6.5% to <8.0%, and poor A1C ≥8.0%. The means of A1C in the fair (7.2 ± 0.4%) and poor (9.2 ± 0.9%) A1C groups were significantly higher than that in the good A1C group (5.7 ± 0.4%).

Statistical analysis

All values are expressed as means ± SD unless otherwise indicated. Statistical analyses were performed with the Statview V system (SAS Institute, Cary, NC). Student's unpaired *t* test and the χ^2 test were used as appropriate. Survival curves were obtained using the Kaplan-Meier estimation method and compared by log-rank test. Variables possibly predictive of survival were analyzed by Cox proportional hazards models. The proportional

Table 2—*HRs of variables possibly predictive of survival of diabetic subjects on regular hemodialysis determined by Cox proportional hazard model*

	Unadjusted			Adjusted for multivariates*		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age at entry (years)	1.045	1.018–1.072	0.0009	—	—	—
Sex (female = 1)	0.905	0.536–1.530	0.710	—	—	—
Duration of hemodialysis (years)	1.001	0.995–1.007	0.855	—	—	—
Existence of cardiac disease (no = 1)	1.767	1.110–2.814	0.017	—	—	—
Glycemic control (A1C) group (good group = 1)						
Fair group	1.030	0.557–1.904	0.925	1.317	0.695–2.495	0.399
Poor group	1.773	1.000–3.145	0.050	2.889	1.538–5.429	0.010
Mean A1C (%)	1.134	0.981–1.311	0.088	1.260	1.081–1.468	0.003
Systolic blood pressure (mmHg)	0.983	0.970–0.995	0.007	0.990	0.997–1.003	0.121
Diastolic blood pressure (mmHg)	0.963	0.935–0.992	0.014	0.984	0.952–1.017	0.338
Cardiothoracic ratio (%)	1.040	0.959–1.128	0.340	0.992	0.901–1.093	0.876
Creatinine (mg/dl)	0.947	0.866–1.036	0.231	0.921	0.825–1.029	0.148
Sodium (mEq/l)	0.992	0.940–1.048	0.777	0.961	0.912–1.014	0.144
Potassium (mEq/l)	0.849	0.643–1.123	0.251	0.867	0.643–1.169	0.349
Total protein (g/dl)	0.848	0.530–1.357	0.492	0.855	0.527–1.386	0.525
Albumin (g/dl)	0.229	0.086–0.606	0.003	0.373	0.130–1.069	0.066
Hemoglobin (g/dl)	1.006	0.840–1.205	0.946	1.034	0.853–1.253	0.732
Total cholesterol (mg/dl)	1.001	0.996–1.007	0.643	1.003	0.997–1.009	0.367
Uric acid (mg/dl)	1.004	0.827–1.317	0.720	1.027	0.805–1.311	0.829

Existence of cardiac diseases: existence of coronary artery disease and/or echocardiographic abnormalities. *Adjusted for age, sex, and duration of hemodialysis and existence of cardiac disease. The HR for each variable is expressed per increment of 1 unit of each variable. That for glycemic control group (A1C group) refers to good A1C group as 1, and that for sex refers to females as 1.

hazard assumption of the model was assessed by inspection of the log time-log hazard plot for all covariates. *P* values <0.05 were considered significant.

RESULTS

Clinical characteristics and survival of diabetic hemodialysis patients

The 1-, 3-, and 5-year cumulative survival rates during the survey period for the group of all diabetic hemodialysis subjects were 0.861, 0.636, and 0.439, respectively. The clinical characteristics of the good, fair, and poor A1C groups are shown in Table 1. There were no significant differences among the groups in age at entry, hemodialysis initiation, duration of hemodialysis, frequency of cardiac diseases, blood pressure, hemoglobin level, or serum levels of creatinine or total cholesterol. The cumulative survival of the poor A1C group was significantly lower than that of the fair and good A1C groups ($P = 0.041$, log-rank test) (Fig. 1). The 3- and 5-year cumulative survival rates of the poor A1C group were significantly lower than those of the good and fair A1C groups, although 1-year rates were comparable (1-year rates, 0.903, 0.863, and 0.825; 3-year rates, 0.739, 0.696, and 0.499; and 5-year rates, 0.529, 0.522, and 0.289 for good, fair, and poor A1C groups, respectively).

Predictors of survival of diabetic hemodialysis patients

Table 2 shows the hazard ratio (HR) with 95% CIs of variables possibly predictive of survival for the group of all diabetic hemodialysis subjects. In Cox proportional hazard models, female sex or good A1C control was entered as a reference. With unadjusted HRs, age at entry and blood pressure were significant predictors of survival. The HR for the poor A1C group was 1.773 (95% CI 1.000–3.145) and was borderline significant ($P =$

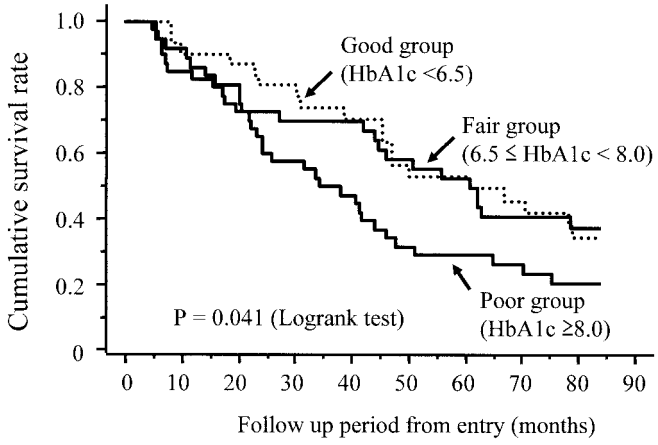

Figure 1—*Cumulative survival curves for diabetic CKD patients undergoing regular hemodialysis from entry in the study in May 1995. The patients were categorized into three groups, good, fair, or poor A1C, by mean A1C level during the 3-month period preceding entry as follows: good A1C group <6.5%, fair A1C group ≥6.5% to <8.0%, and poor A1C group ≥8.0% of A1C. The cumulative survival rate of the poor A1C (solid line) group was significantly lower than that of the fair (solid line) and good (dotted line) A1C groups (P = 0.041 by log-rank test of Kaplan-Meier estimation).*

Table 3—*Causes of death of diabetic subjects on regular hemodialysis during survey period*

Cause of death	Good	Fair	Poor	All groups
Cardiovascular diseases	7 (9.7)	7 (9.7)	10 (13.9)	24 (33.3)
Infectious diseases	4 (5.6)	4 (5.6)	10 (13.9)	18 (25.0)
Others	8 (11.1)	11 (15.3)	11 (15.3)	30 (41.7)
Total	19 (26.4)	22 (30.6)	31 (43.1)	72 (100)

Data are *n* (%). The glycemic control group is the same as in Table 1. $\chi^2 = 1.929$ ($P = 0.749$) by χ^2 test.

0.0502). However, after adjustment for age at entry, sex, duration of hemodialysis at entry, and existence of cardiac diseases, the poor A1C group was a significant predictor of survival (HR 2.889 [1.538–5.429], $P = 0.010$). Furthermore, mean A1C also showed a significant predictive HR of 1.260 per 1.0% (1.081–1.468, $P = 0.003$) after multivariate adjustment.

Causes of death of diabetic hemodialysis patients

The causes of death in the good, fair, and poor A1C groups are shown in Table 3. The poor group tended to have a higher frequency of cardiovascular or infectious diseases as causes of death than the fair and good A1C groups, compared with the frequency of other diseases, although not to a significant extent ($\chi^2 = 1.929$, $P = 0.747$).

CONCLUSIONS — The present study revealed better prognosis for diabetic patients undergoing regular hemodialysis with better glycemic control independent of other known risk factors. Furthermore, our findings suggest the usefulness of an A1C level of 8.0% during regular hemodialysis as a signpost for management of glycemic control and provide clinical evidence of the importance of glycemic control, even in patients with CKD, an end stage of diabetic microangiopathy, in whom management of glycemic control is often insufficient.

Most previous studies (8,9,11,12,16) examined the impact of glycemic control status at initiation of hemodialysis on prognosis following this initiation. Patients with better A1C values <7.0% had longer survival (8), and average blood glucose level before initiation of hemodialysis was reported to be a predictor of survival (9). Wu et al. (11) reported in a 10-year follow-up study of 137 type 2 diabetic patients on hemodialysis that poor glycemic control with A1C >10% before initiation of hemodialysis was a predictor of cardiovascular morbidity and long-term survival. We found in an initial 10-year observational study (ODDS-1) that 93 diabetic CKD patients with better glycemic control with A1C levels <7.5% at initiation of chronic hemodialysis had better long-term survival than 57 patients with worse glycemic control with A1C levels >7.5% (12). Furthermore, in that study, in a Cox-proportional analysis, the adjusted HR of A1C per 1.0% was 1.068, indicating significant increase of risk of death by 6.8% per increase of 1.0% A1C at initiation of hemodialysis. Okada et al. (16) reported in a study of 124 type 2 diabetic hemodialysis patients that A1C level at initiation of hemodialysis was a significant predictor of survival on univariate Cox proportional analysis but that this significance in prediction was lost on multivariate analysis. Although these studies were also not interventional but long-term observational, their findings suggest that better glycemic control during regular hemodialysis may improve prognosis.

Only one interventional study, by McMurray et al. (13), has revealed that intensive diabetes education and care management in a dialysis unit over a 12-month period improved glycemic control, leading to a decrease in diabetes-related hospitalization and better quality of life. In their study, the mean A1C level of the intensive intervention group was improved from 6.9 to 6.2%, whereas that of the control group remained unchanged at 7.0%. Although they failed to find a statistically significant difference in prognosis between the intensive intervention and control groups because of their relatively small number of subjects and short period of intervention, their findings provided the prospect of improvement of the prognosis of diabetic hemodialysis patients.

It is well established that, for diabetic patients without CKD, tight glycemic control prevents the development and progression of diabetic microangiopathy (1–3), and a target A1C level of 7.0% is recommended by the American Diabetes Association and a target of 6.5% by the Japan Diabetes Association. However, in treating diabetic hemodialysis patients, enthusiasm for achieving tight glycemic control occasionally must be tempered by the following, which are frequently encountered in diabetic hemodialysis patients on tight control (14,17): increased risk of hypoglycemia, asymptomatic hypoglycemic episodes due to coexisting autonomic neuropathy, loss of vision needed to maintain an intensive insulin regime and frequent self-monitoring of blood glucose, and refusal by patients to continue treatment due to various psychological problems. In fact, in the report from the National Kidney Foundation Task Force on Cardiovascular Disease, a target A1C value of 8% was recommended to provide reasonable protection against metabolic disorders and infections associated with hyperglycemia with a lower risk of hypoglycemia in patients for whom intensive glycemic control cannot be recommended (10).

The present study demonstrated that diabetic hemodialysis patients with poor glycemic control had a clearly poorer prognosis and that both poor glycemic control state and mean A1C during regular hemodialysis were significant predictors of prognosis independent of well-known factors such as age at study entry, sex, duration of hemodialysis, and concurrent cardiac diseases. Among the good, fair, and poor A1C groups, there were no significant differences in clinical factors affecting prognosis, as shown in Table 1. These findings differ considerably from those of previous observational studies that evaluated A1C levels at initiation of hemodialysis, not during regular hemodialysis, as an index of glycemic control. This strongly suggests the importance of achieving better glycemic control for improving prognosis even after induction of hemodialysis. Our findings may thus be applicable to the management of diabetic patients on regular hemodialysis.

There may be several reasons for the improvement of prognosis with better glycemic control, although our findings cannot discriminate among them. Hyperglycemia is associated with increased vulnerability to infection, poor neutrophil function, autonomic neuropathy leading to sudden death, and risk of cardiovascular disease. Although conflicting findings have been obtained concerning whether tight glycemic control has beneficial effects on risk of development of cardiovascular disease and/or death, the Epidemiology of Diabetes Interventions

and Complications study in type 1 diabetic patients (6), the Steno-2 study in type 2 diabetic patients (4), and the STOP-NIDDM trial in patients with impaired glucose tolerance (5) have obtained evidence for such effects. In our study, patients in the poor glycemic control group (A1C ≥8.0%) tended to have higher frequency of death due to cardiovascular and infectious diseases, though not to a significant extent, probably due to the relatively small number of subjects included (Table 3).

There are a few limitations of the present study. First, the number of our subjects was small, although all diabetic subjects who fulfilled the inclusion criteria at entry were included. Second, only cross-sectional data at entry were evaluated, and changes of confounding factors during the observational period were not considered for the analyses of prognosis, since the main purpose of our observational study was to examine the predictive value of glycemic control for prognosis. Third, a small number of comorbid factors were included and adjusted in our Cox proportional hazard model. Therefore, we cannot deny a possibility that an independent impact of glycemic control on prognosis may be overwhelmed by other strong confounding factor(s) such as anemia and nutrition state and their changes. To resolve these limitations, a multicenter interventional study with a larger number of subjects is needed.

In conclusion, our ODDS-2 study clarified that even in diabetic CKD patients undergoing regular hemodialysis, good glycemic control is an independent predictor of prognosis even after adjustment for known classical factors. This finding strongly suggests that intensive but careful management of glycemic control by diabeto-nephrologists will improve the prognosis even of diabetic CKD patients on regular hemodialysis.

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