Association between Markers of Glycemic Control, Cardiovascular Complications and Survival in Type 2 Diabetic Patients with End-Stage Renal Disease

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Abstract

Background and Objective The influence of glycemic control on cardiovascular (CV) complications or survival is not clear in diabetic patients with end-stage renal disease (ESRD). Although glycohemoglobin (HbA1c) is widely used as a marker of hyperglycemia in these patients, it may be unreliable because of shortened erythrocyte lifespan. Glycated albumin (GA) is an alternative marker. We investigated the relation between these markers and development of CV complications or survival in diabetic ESRD patients.

Patients and Methods We obtained three variables as markers of glycemic control: 1) mean HbA1c levels during 1-year after initiation of dialysis (HbA1c1), 2) mean HbA1c levels during 3 months from August to October 2002 (HbA1c2), 3) GA on October 2002 (GA2) from 78 type 2 diabetic patients on chronic hemodialysis. We examined the influence of these variables on survival or development of CV diseases using the multivariate Cox proportional-hazards models until September 2006.

Results The 3-year survival rate was 73%. A total of 27 patients died, 15 from CV diseases. A total of 23 CV diseases developed in 20 patients. Neither HbA1c1 nor HbA1c2 was associated with all-cause mortality, CV mortality or development of CV diseases. GA2 was also not associated with mortality. However, the higher GA2 group (GA $\geq$ 23.0%) had a significantly higher rate of development of CV diseases than the lower GA2 group (GA < 23.0%) (log-rank test $p=0.03$). The higher GA2 group was significantly associated with development of CV diseases relative to the lower GA2 group (hazard ratio 3.25, $p=0.04$).

Conclusion Neither HbA1c levels nor GA levels, at initiation of dialysis or on chronic dialysis, predicted mortality in diabetic ESRD patients. However, poor glycemic control as reflected by higher GA levels may be associated with the development of CV diseases. More studies are needed to clarify the beneficial effect of glycemic control in these patients.

Key words: glycemic control, survival, type 2 diabetes, end-stage renal disease, glycohemoglobin, glycated albumin

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Introduction

In diabetic patients, glycemic control has an essential role in preventing the development and progression of microvascular or cardiovascular (CV) complications (1-4). Glycohemoglobin (HbA1c) is the most representative marker of hyperglycemia for assessing glycemic control. In diabetic patients with end-stage renal disease (ESRD), there are two

unresolved and important problems. First, it is not clear whether glycemic control reduces the risk of cardiovascular complications or mortality. Second, it is not clear whether HbA1c is a reliable marker of hyperglycemia (5).

Only a few studies have shown beneficial impact of predialysis glycemic control on survival after initiation of dialysis (6, 7). In addition, limited studies showed an association of poor glycemic control with poor survival on chronic dialysis (8, 9). However, several studies showed no correlation

Table 1. Patient Characteristics

Age (years) (range)	63±10 (33-86)
Male/ Female (n)	60/ 18
Duration of dialysis (months)	49±32 (12-192)
Body weight (kg)	59.3±10.2 (39.0-94.5)
Body mass index (kg/m ²)	22.5±3.2 (16.6-32.5)
Systolic blood pressure (mmHg)	161±19 (119-217)
Diastolic blood pressure (mmHg)	79±13 (36-107)
Intradialytic weight gain (%)	4.5±2.0 (-0.6-8.5)
Hematocrit (%)	32.4±2.5 (25.9-40.1)
Serum albumin (g/dl)	3.83±0.26 (3.10-4.37)
Serum phosphorus (mg/dl)	5.75±1.11 (3.13-8.90)
Blood glucose (mg/dl)	163±43 (87-260)
Glycohemoglobin (%)	6.28±1.05 (4.17-8.67)
Glycated albumin (%)	23.6±5.1 (15.4-38.6)
KT/V	1.17±0.16 (0.78-1.61)
Therapy for diabetes (n)	Diet 33/ oral hypoglycemic agents 13/ Insulin 32
Erythropoietin doses (U/kg/week) (n)	4150±3480 (0-13500) No use, 17/ ≤3000U/week, 25/ 3000 to 6000U/week, 14 / 6000 to 9000U/week , 20/ >9000U/week; 2
History of CV diseases (n)	Ischemic heart disease 12/ Cerebrovascular disease 5/ Peripheral vascular disease 3

between glycemic control and survival (10, 11). Therefore, the significance of glycemic control is not established and appropriate targets of glycemic control have not yet been determined in diabetic ESRD patients.

HbA1c level is influenced by erythrocyte lifespan or erythropoietin therapy (12, 13). Shortened erythrocyte lifespan or erythropoietin therapy changes HbA1c levels independent of glycemic control. It is generally known that HbA1c levels tend to be lower in ESRD patients. Glycated albumin (GA) is an alternative marker of glycemic control and is not influenced by erythrocyte lifespan or erythropoietin therapy (14). GA levels may reflect blood glucose levels more correctly in ESRD patients (15). There have been no previous studies concerning the relation between GA levels and the prognosis in these patients.

To clarify the association between glycemic control and clinical outcome in diabetic ESRD patients, we obtained both HbA1c and GA levels simultaneously on chronic dialysis and examined the association with prognosis. In addition, we also obtained HbA1c levels at initiation of dialysis and examined the association with prognosis.

Subjects and Methods

A total of 78 type 2 diabetic ESRD patients receiving chronic hemodialysis in 4 outpatient dialysis centers in Tokyo were entered in the present study. Patients who had received hemodialysis for at least 12 months by October 2002 and who had no liver cirrhosis or unhealed malignancy, were selected. The diagnosis of diabetic nephropathy as the cause of renal disease was based on duration of diabetes,

existence of diabetic retinopathy or other clinical data. We obtained HbA1c values at initiation of dialysis, after 6 months, and after 12 months. In addition, we obtained HbA1c values on 3 occasions from August to October 2002 and a single GA value on October 2002. After that, we followed patients until September 2006. The duration of dialysis until October 2002 was 48±32 (12-128) months. The mean follow-up period from October 2002 was 35±16 (2-48) months. Clinical characteristics of patients are shown in Table 1. Clinical and laboratory data were collected on 3 occasions from August to October 2002 and the 3-month average values were used for each patient. Blood pressure was measured in the supine position before the regular hemodialysis session. Blood samples for laboratory data were obtained at the start of the hemodialysis session.

Non-fasting blood glucose was also obtained at the start of the hemodialysis session on 3 occasions during 3 months and the average values were used for each patient. Blood glucose was measured about 2 hours after breakfast in 66 patients receiving the morning hemodialysis session. It was measured about 4 hours after lunch in 12 patients receiving the evening hemodialysis session.

We adopted three variables as markers of glycemic control: 1) mean HbA1c levels during 1 year after initiation of dialysis (HbA1c1) (n=69), those were the mean value at initiation of dialysis, after 6 months and after 12 months, 2) mean HbA1c levels during 3 months from August to October 2002 (HbA1c2), and GA on October 2002 (GA2). We examined the influence of these variables on all-cause mortality, CV mortality, or development of CV diseases using the multivariate Cox proportional-hazards models. The co-

Table 2. Newly Diagnosed Cardiovascular Diseases and Causes of Death

Causes of death (n)		
Cardiovascular diseases	Myocardial infarction	5
	Sudden death	5
	Cerebral hemorrhage	4
	Congestive heart failure	1
	Unknown causes	3
Non-cardiovascular diseases	Infectious diseases	3
	Respiratory failure	3
	Malignancy	2
	Traffic accident	1
	Unknown causes	3
Development of cardiovascular diseases (n)		
	Myocardial infarction	2
	Ischemic heart disease	4
	Cerebral infarction	8
	Cerebral hemorrhage	3
	Peripheral vascular disease	5
	Complete AV block	1

variables included age, gender, duration of dialysis, body mass index, systolic blood pressure, intradialytic weight gain, hematocrit, serum albumin, serum phosphorus, KT/V and history of CV diseases in multivariate analysis. Hazard ratios (HR) were presented per unit (1%) increase in HbA1c or GA and 95% confidence intervals (CI) were calculated for the HR. Furthermore, we divided subjects into three sets of two groups according to the median values of HbA1c1, HbA1c2 and GA2, respectively. We examined the Kaplan-Meier survival curves of each set of two groups for each marker. We also examined HR of the group of the higher values relative to the lower values for each marker.

Development of CV diseases included ischemic heart disease, arrhythmia requiring treatment by permanent pacemaker, cerebral infarction, cerebral hemorrhage, and peripheral vascular disease. Ischemic heart disease included definite coronary artery disease diagnosed by coronary angiography, myocardial infarction or treatment by percutaneous coronary intervention or coronary artery bypass graft. Peripheral vascular disease included treatment by percutaneous transluminal angioplasty or other vascular surgery. Causes of death related to CV complications included sudden death, heart failure, myocardial infarction, cerebral infarction, and cerebral hemorrhage. Informed consent to use clinical data in this study was obtained from all patients.

Both HbA1c was measured by latex agglutination immunoassay (RAPIDIA AUTO; SRL, Tokyo, Japan) and the normal range was 4.3-5.8%. GA was measured by enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA; Asahi Kasei Pharma Co., Tokyo, Japan) and the normal range was 12.4-

16.3% (16).

Changes in the two groups were examined by Wilcoxon's signed-rank test. Correlation between two values was analyzed by Pearson's correlation coefficient. All values were expressed as means $\pm$ SD, and a P value of less than 0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed with a StatView computer program (Abacus Concepts, Berkeley, CA, USA).

Results

Survival and development of CV complications

The 1-, 3- and 4-year survival rates during the follow-up period were 90.8%, 73.1% and 60%, respectively. During follow-up, 27 patients died, 15 from CV diseases. A total of 23 cases of CV diseases developed in 20 patients. Causes of death and newly diagnosed CV diseases are shown in Table 2.

Glycemic control status and relationship between markers of glycemic control

Mean values (median values) of HbA1c1, HbA1c2 and GA2 were $6.53 \pm 1.16\%$ (6.43%), $6.28 \pm 1.05\%$ (6.20%) and $23.6 \pm 5.1\%$ (23.0%), respectively. Eight (11.6%) patients had HbA1c1 greater than 8.0% and 5 (6.4%) patients had HbA1c2 greater than 8.0%.

Relationship between HbA1c2 and GA2 levels are shown in Fig. 1. The correlation coefficients between HbA1c2 and GA2 levels, those between HbA1c2 and blood glucose levels, and those between GA2 and blood glucose levels were

0.53, 0.42 and 0.41, respectively (all $p < 0.001$).

Influence of markers of glycemic control on survival or development of CV complications using multivariate Cox proportional-hazards models and Kaplan-Meier survival curves

A 1% increase in HbA1c1, HbA1c2 or GA2 was not significantly associated with all-cause mortality, CV mortality or development of CV diseases in Cox models (Table 3).

In the model including GA2, a history of CV diseases remained a significant predictor of all-cause mortality (HR, 3.91; 95% CI, 1.54 to 9.90; $p=0.004$), CV mortality (HR, 3.81; 95% CI, 1.07 to 13.51; $p=0.04$) or development of CV diseases (HR, 4.83; 95% CI, 1.26 to 18.60; $p=0.02$) and systolic blood pressure remained a significant predictor of de-

velopment of CV diseases (HR, 1.03; 95% CI, 1.00 to 1.07; $p=0.04$).

In the model including HbA1c2, a history of CV diseases remained a significant predictor of all-cause mortality (HR, 3.89; 95% CI, 1.53 to 9.88; $p=0.004$) or development of CV diseases (HR, 5.35; 95% CI, 1.37 to 20.94; $p=0.02$) and systolic blood pressure remained a significant predictor of development of CV diseases (HR, 1.04; 95% CI, 1.01 to 1.07; $p=0.02$).

In the model including HbA1c1, a history of CV diseases remained a significant predictor of all-cause mortality (HR, 4.94; 95% CI, 1.68 to 14.52; $p=0.004$) or CV mortality (HR, 9.71; 95% CI, 1.49 to 63.11; $p=0.02$).

The Kaplan-Meier survival curves and Cox models using the groups according to the median values of each glycemic marker

The Kaplan-Meier survival curves showed no significant differences in mortality or development of CV diseases between the higher HbA1c2 (HbA1c $\geq 6.20\%$) group and the lower HbA1c2 (HbA1c $< 6.20\%$) group (Fig. 2). The cases of HbA1c1 were the same. There were also no significant differences in mortality between the higher GA2 (GA $\geq 23.0\%$) group and the lower GA2 (GA $< 23.0\%$) group (Figs. 3a, 3b). On the other hand, CV diseases developed in 15 patients in the higher GA2 group ($n=39$) and in 5 patients in the lower GA2 group ($n=39$). The higher GA2 group had a significant higher rate of development of CV diseases than the lower GA2 group (Fig. 3c) (log-rank test $p=0.03$).

HbA1c1 or HbA1c2 groups were not significantly associated with mortality or development of CV diseases according to the Cox models (Table 4). GA2 groups were also not significantly associated with mortality (Table 4). On the other hand, the higher GA2 group was significantly associated with development of CV diseases relative to the lower GA2 group (HR, 3.25; 95% CI, 1.04 to 10.19; $p=0.04$).

Figure 1. Correlation between HbA1c2 and GA2.

Table 3. Relationship of Glycemic Markers with All-cause Mortality, CV Mortality and Development of CV Diseases

	All-cause mortality		CV mortality		Development of CV diseases	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
HbA1c1 (per 1%)	1.11 (0.71 to 1.74)	0.66	1.04 (0.48 to 2.28)	0.92	1.34 (0.78 to 2.29)	0.29
HbA1c2 (per 1%)	0.99 (0.63 to 1.56)	0.98	0.78 (0.41 to 1.48)	0.45	1.38 (0.76 to 2.50)	0.29
GA2 (per 1%)	0.98 (0.89 to 1.08)	0.69	0.88 (0.75 to 1.03)	0.12	1.09 (0.96 to 1.24)	0.17

HR, hazard ratio; CI, confidence interval; CV, cardiovascular
Adjusted for age, gender, duration of dialysis, body mass index, systolic blood pressure, intradialytic weight gain, hematocrit, serum albumin, serum phosphorus, KT/V and history of CV diseases

Figure 2. The Kaplan-Meier survival curves of all-cause mortality (a), CV mortality (b) and development of CV diseases (c) in the higher HbA1c2 ($\text{HbA1c} \geq 6.20\%$) group and the lower HbA1c2 ($\text{HbA1c} < 6.20\%$) group.

Figure 3. The Kaplan-Meier survival curves of all-cause mortality (a), CV mortality (b) and development of CV diseases (c) in the higher GA2 ($\text{GA} \geq 23.0\%$) group and the lower GA2 ($\text{GA} < 23.0\%$) group.

Table 4. Relationship of the Groups According to Higher or Lower Values of Glycemic Markers with All-cause Mortality, CV Mortality and Development of CV Diseases

	All-cause mortality		CV mortality		Development of CV diseases	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
HbA1c1						
lower group ($< 6.43\%$)	1		1		1	
higher group ($\geq 6.43\%$)	0.93 (0.34 to 2.58)	0.90	1.06 (0.16 to 7.12)	0.95	0.81 (0.27 to 2.46)	0.72
HbA1c2						
lower group ($< 6.20\%$)	1		1		1	
higher group ($\geq 6.20\%$)	1.20 (0.48 to 2.99)	0.70	1.65 (0.47 to 5.76)	0.44	0.92 (0.30 to 2.86)	0.89
GA2						
lower group ($< 23.0\%$)	1		1		1	
higher group ($\geq 23.0\%$)	0.76 (0.31 to 1.84)	0.54	0.34 (0.12 to 1.46)	0.17	3.25 (1.04 to 10.19)	0.04

HR, hazard ratio; CI, confidence interval; CV, cardiovascular
Adjusted for age, gender, duration of dialysis, body mass index, systolic blood pressure, intradialytic weight gain, hematocrit, serum albumin, serum phosphorus, Kt/V and history of CV diseases

Effect of changes in HbA1c levels on prognosis

We divided subjects into two groups according to the changes between HbA1c1 and HbA1c2 levels. The group

with an increase of HbA1c levels (HbA1c2 levels $>$ HbA1c1 levels) consisted of 29 patients and the mean change value was $0.63 \pm 0.58\%$. The group with a decrease of HbA1c levels (HbA1c1 levels $>$ HbA1c2 levels) consisted of 40 patients

and the mean change value was $-0.87 \pm 0.75\%$. The Kaplan-Meier survival curves showed no significant differences in mortality or development of CV diseases between the increased group and the decreased group.

Discussion

Our results showed no significant associations between markers of glycemic control and survival in type 2 diabetic ESRD patients. The markers both at initiation of dialysis and on chronic dialysis did not predict mortality. A history of CV diseases and systolic blood pressure remained significant predictors of mortality in multivariate analysis.

We suggest several reasons for lack of associations between markers of glycemic control and survival. First, diabetic ESRD patients have already far advanced microvascular and macrovascular complications. Secondly, risk factors other than glycemic control may have more significant effects on CV complications and survival in these patients.

In the general population or in diabetic patients without renal dysfunction, the association between glucose levels and CV complications or survival was demonstrated in some previous studies (17-19). However, diabetic ESRD patients have already advanced atherosclerosis (20, 21). In addition to hyperglycemia, there are many risk factors associated with CV diseases, including traditional factors and uremia-related factors in diabetic ESRD patients (22). Some previous studies have demonstrated that increased all-cause mortality or CV mortality are associated with advanced atherosclerosis independent of diabetes in ESRD patients (23-25). Therefore, the direct influence of hyperglycemia on fatal CV diseases might be small in these patients.

Non-CV diseases such as infectious diseases or cancer may also influence the outcome in diabetic ESRD patients. Hyperglycemia impairs the host defense and increases the risk of infectious diseases (26). Diabetes increases the risk of cancer in some epidemiological studies (27). However, the influence of glycemic control on the development of infectious diseases or cancer is unclear in diabetic ESRD patients. Our results could not find these associations. The registry data of the Japanese Society for Dialysis Therapy also showed no significant differences of frequency of infectious diseases or cancer as causes of death between diabetic patients and non-diabetic patients (28).

The direct influence of hyperglycemia on the progression of atherosclerosis or development of CV diseases is not clear in diabetic ESRD patients. Our results showed an association between hyperglycemia, reflected by higher GA levels and development of CV diseases. Several mechanisms of toxic effects of hyperglycemia have been demonstrated, including endothelial dysfunction, oxidative stress, inflammation, formation of glycation products, and abnormal coagulation (29, 30). It is not clear whether these mechanisms influence the progression of atherosclerosis or development of CV diseases in ESRD patients as in general diabetic patients. There are few studies indicating the adverse effects of

hyperglycemia as an atherogenic factor in diabetic ESRD patients. Abnormal lipoprotein metabolism deteriorates in the presence of hyperglycemia and may influence atherosclerosis in diabetic ESRD patients (31). Studies are needed to clarify the atherogenic factors related to hyperglycemia in these patients.

Our results showed an association of hyperglycemia, reflected by higher GA levels, with development of CV diseases, but not with CV mortality. Hyperglycemia may have different effects on the development of CV disease and fatality. Risk factors for CV disease have two different characteristics: those related to CV events and those affecting fatality (32). To clarify this suggestion, further studies concerning an association between glycemic control and CV disease are needed.

One previous study showed a significant improvement of outcomes by intensive diabetes education and care management including glycemic control in diabetic dialysis patients (33). Multifactorial intervention aimed at many risk factors including hyperglycemia has been shown to reduce CV risk and microvascular events (34). Intervention of glycemic control alone may be insufficient and intervention for many other risk factors may be required for diabetic ESRD patients.

It has not been established that HbA1c is a reliable marker of hyperglycemia in ESRD patients (5, 13). Some previous studies showed a weak correlation between HbA1c levels and mean blood glucose levels in diabetic ESRD patients (11, 13, 15). HbA1c levels in ESRD patients do not always reflect the same blood glucose levels as those in general diabetic patients because of shortened erythrocyte lifespan, erythropoietin therapy or other factors (12, 13). Unreliability of HbA1c levels as a glycemic marker may have some influence on the results concerning associations between HbA1c levels and prognosis. Careful interpretation is therefore required for studies using HbA1c levels as a marker of glycemic control.

Previous studies have examined HbA1c levels as the sole marker of glycemic control, and some showed an association between poor survival and high HbA1c levels [$\geq 8\%$ (9), $\geq 9\%$ (35), $\geq 10\%$ (6), 12~14% (8)]. These values indicate extremely poor glycemic control because HbA1c levels tend to be lower in ESRD patients than in general diabetic patients. These results suggest that at least we should avoid such poor control.

The present study included few patients with poor glycemic control of HbA1c more than 8.0%. In contrast to previous studies, glycemic control was relatively good in our patients. In the study by Oomichi et al, mean HbA1c was 7.5% and patients with HbA1c of more than 8.0% consisted of 36% of all patients (9). These differences of glycemic control between the studies might have an influence on the different results concerning associations between HbA1c levels and prognosis.

The other marker of hyperglycemia, GA, is not influenced by erythrocyte lifespan or erythropoietin therapy (13, 14).

One previous study showed that GA levels might reflect blood glucose levels more correctly than HbA1c levels in ESRD patients (15). However changes in albumin turnover influence GA levels. Our patients had dialysis for a period of 12 months or longer and the influence of urinary protein excretion on albumin turnover may be small. Hypoalbuminemia induced by inflammation or malnutrition might influence GA levels in a small number of patients.

The correlation between HbA1c2 and GA2 was significant but weak. This indicates that factors other than blood glucose levels may influence on the levels of both markers. We suggest that the influence of the factors affecting HbA1c levels, such as shortened erythrocyte lifespan or erythropoietin therapy may be greater than those affecting GA levels. HbA1c reflects glycemic control during the preceding 1-2 months and GA reflects those during the preceding 2-4 weeks (36). These differences may influence the correlations between both markers.

The correlation between HbA1c2, GA2 and blood glucose levels were also significant but weak. The coefficients of correlation (r) were almost similar between HbA1c2 and blood glucose levels and between GA2 and blood glucose levels. Our results indicated no superiority of GA for reliability of blood glucose levels. However, we obtained only 3 samples of non-fasting blood glucose levels. More measurements of blood glucose levels with uniform condition may be needed to clarify the correlation between these markers and blood glucose levels.

Unfortunately we could obtain GA on only one occasion. GA reflects short-term glycemic control compared with

HbA1c levels. It is possible that GA levels change to some extent during the period of data collection. Therefore, more measurements of GA levels during a longer duration may be needed to clarify an association between GA levels and prognosis.

There are several limitations to the present study. First, the numbers of the patients were small. Secondly, the variables of glycemic control in this study do not always mean cumulative exposure of hyperglycemia. Long-term follow-up of the markers may be needed to examine the influence of hyperglycemic exposure. Third, other data concerning risk factors for CV complications, including smoking, dyslipidemia and inflammatory markers were not available in this study. However the main variables strongly affecting prognosis were included in this analysis.

In conclusion, markers of hyperglycemia at initiation of dialysis or on chronic dialysis did not predict mortality in diabetic ESRD patients. On the other hand, higher GA levels had an association with development of CV disease. Further studies are needed to clarify the beneficial effect of glycemic control and to establish more reliable methods for assessment of glycemic control in these patients.

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