Determinant Effects of Average Fasting Plasma Glucose on Mortality in Diabetic End-Stage Renal Disease Patients on Maintenance Hemodialysis

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Introduction: Diabetic kidney disease is an increasingly frequent cause of end-stage renal disease. However, mixed results were shown between glycated hemoglobin and mortality.

Methods: We used the average fasting plasma glucose (FPG) levels to predict mortality rates in long-term hemodialysis patients. We enrolled 46,332 hemodialysis patients with diabetes mellitus, who were registered in the Taiwan Renal Registry Data System between January 2005 and December 2012. The patients were stratified based on the quartiles of average FPG levels measured for the first (1-year FPG) and third years (3-year FPG) of hemodialysis. Survival analysis was conducted via multivariable Cox regression.

Results: After the first year of hemodialysis, the mean FPG levels were 103.5 ± 14.5, 144.7 ± 11.5, 189.6 ± 15.2, and 280.8 ± 1.2 mg/dl for the first, second, third, and fourth quartile, respectively. The Kaplan-Meier curve showed an incremental reduction in the survival as FPG levels increased ($P < 0.0001$). In the Cox regression model, the adjusted hazard ratios were 1.15 (95% CI: 1.10–1.20), 1.30 (95% CI: 1.25–1.36), and 1.45 (95% CI: 1.39–1.51) for the pairwise comparisons between the first quartile and the second, third, and fourth quartile, respectively. Similar trends were observed by 3-year FPG. Patients whose FPG levels increased had a 22% increased risk (95% CI: 1.16–1.29) for all-cause mortality compared with patients whose FPG levels decreased.

Discussion: Our results suggest that the average FPG levels are useful predictors of all-cause mortality in dialysis patients. In addition, an increasing trend in average FPG levels indicates poor survival.

T he incidence of diabetic kidney disease is rapidly increasing across the world.[1] Furthermore, diabetic kidney disease accounts for nearly one-half of the incident end-stage renal disease (ESRD) cases.[2,3] Several landmark trials such as the Diabetes Control and Complication Trial[4] with the Epidemiology of Diabetes Interventions and Complications follow-up study,[5] and the United Kingdom Prospective Diabetes Study[6] have

shown that sustained, long-term, intensive glycemic control can reduce microvascular complications. However, numerous observational studies examining the association between glycemic control and outcome in dialysis patients have reported mixed conclusions. In a cohort of 24,875 diabetic patients undergoing hemodialysis at Fresenius Medical Care facilities, no association between glycated hemoglobin (HbA1c) and survival was observed during short-term follow-up;[7] however, during a follow-up of 3 years, increased risk of mortality was found for patients with HbA1c levels of <48 mmol/mol or >97 mmol/mol (International Federation of Clinical Chemistry [IFCC] units).[8] Similar results were reported in a larger cohort of 54,757 diabetic patients undergoing hemodialysis at

DaVita facilities; specifically, HbA1c levels of <42 mmol/mol or >64 mmol/mol (IFCC units) were associated with an increased risk of mortality.[9] At present, clinical practice guidelines published by the Kidney Disease Outcomes Quality Initiative and the Kidney Disease: Improving Global Outcomes foundation recommend that HbA1c levels be maintained over 53 mmol/mol (IFCC units) even in patients with advanced chronic kidney disease and dialysis patients.[10] In Taiwan, blood tests are performed every month for dialysis patients, and the reports are uploaded to the Taiwan Renal Registry Data System (TWRDS) quarterly. However, multiple factors associated with ESRD such as erythrocyte fragility and anemia may cause divergent HbA1c levels. On the other hand, fasting plasma glucose (FPG) levels are not affected by variations in hematocrit or uremic toxin levels. Hence, we propose that short-term (1-year) or long-term (3-year) FPG-based indicators may serve as predictors for mortality rates in hemodialysis patients. In this study, we used data recorded between 2005 and 2012 in the TWRDS to determine whether glycemic levels can be used to predict all-cause mortality in diabetic patients undergoing maintenance hemodialysis.

RESEARCH DESIGN AND METHODS

This study was approved by the ethics committee of Taipei Medical University's institutional review board (number: N201507028), and was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for written informed consent was waived, as the data analysis was blinded to the patients' identification information.

The Taiwan Renal Registry Data System

The TWRDS was founded in 1987 for the accreditation of dialysis therapy at medical facilities in Taiwan. To receive reimbursements within the national health insurance plan, all dialysis units were asked to provide the relevant laboratory data for the patients who underwent dialysis at any of their facilities. In 1996, a self-developed software program, HOPE, was used for computerized data collection. Additional data were gathered in 1997, and included information regarding comorbidities such as hypertension, congestive heart failure, left ventricular hypertrophy (defined as a chest-to-thoracic ratio of >0.5 on plain film of the chest), cerebral artery disease, and myocardial infarction; rehabilitation status; Kt/V as residual renal function plus hemodialysis dose; laboratory data with levels of hematocrit, albumin, alkaline phosphatase, calcium (Ca), phosphate (P), total cholesterol (TC), triglyceride (TG), and intact parathyroid hormone; hepatitis serological results; and the use of medication for the

management of hypertension and anemia.[11] Therefore, the data available in the TWRDS provide a robust foundation for ongoing quality control of dialysis practice at the national level.[12–15]

Patient Enrollment

At the end of 2012, a total of 569 hemodialysis units were registered in Taiwan, which submitted seasonal and annual reports to the TWRDS. A total of 115,565 patients were registered in the TWRDS between 2005 and 2012. Only those patients who had received hemodialysis for more than 1 month were considered. After excluding 4661 patients who had changed their dialysis modality, the sample population consisted of 110,904 hemodialysis patients. Of these, 9232 patients opted for peritoneal dialysis and 101,672 patients (91.7%) opted for hemodialysis as their initial renal replacement therapy modality. The following hemodialysis patients were excluded from our study: 52,370 (51.5%) nondiabetic patients, 1972 (1.9%) patients whose records did not include glucose level measurements, and 998 (1%) patients who were either young (<20 years) or extremely elderly (>90 years). Therefore, a total of 46,332 (45.6%) patients with diabetes mellitus were included in this study (Figure 1).

The data from the Union Clinical Laboratory were reported to the TWRDS via the Internet by special nurses at the participating dialysis units. The biochemical data, including FPG levels, were collected every 3 months. In the context of our study, the 1-year average FPG levels (1-year FPG) represent the mean levels of FPG in the first year after the initiation of hemodialysis, computed based on a maximum of 4 quarterly measurements. Similarly, the 3-year average FPG levels (3-year FPG) represent the mean levels of FPG in the first 3 years after the initiation of hemodialysis, computed based on a maximum of 12 quarterly measurements. The patients were stratified based on quartile limits of the distribution of 1- and 3-year FPG values. Subsequently, the evolution of each patient was evaluated as the change of status between the 1-year average and the 3-year average with respect to the patient's assignment to a specific FPG quartile. After this analysis, each patient was further assigned to either the "decrease group" (when their corresponding 3-year FPG quartile was inferior to their 1-year quartile) or the "increase group" (when their 3-year FPG quartile was superior to their 1-year quartile).

The primary outcome measured in this study was the 3-year mortality rate in different quartiles of 1-year and 3-year FPG. Three-year mortality rate was also compared between the FPG increase and decrease group. Patients were identified as dead or lost to follow-up based on their records of the national health insurance policy, which
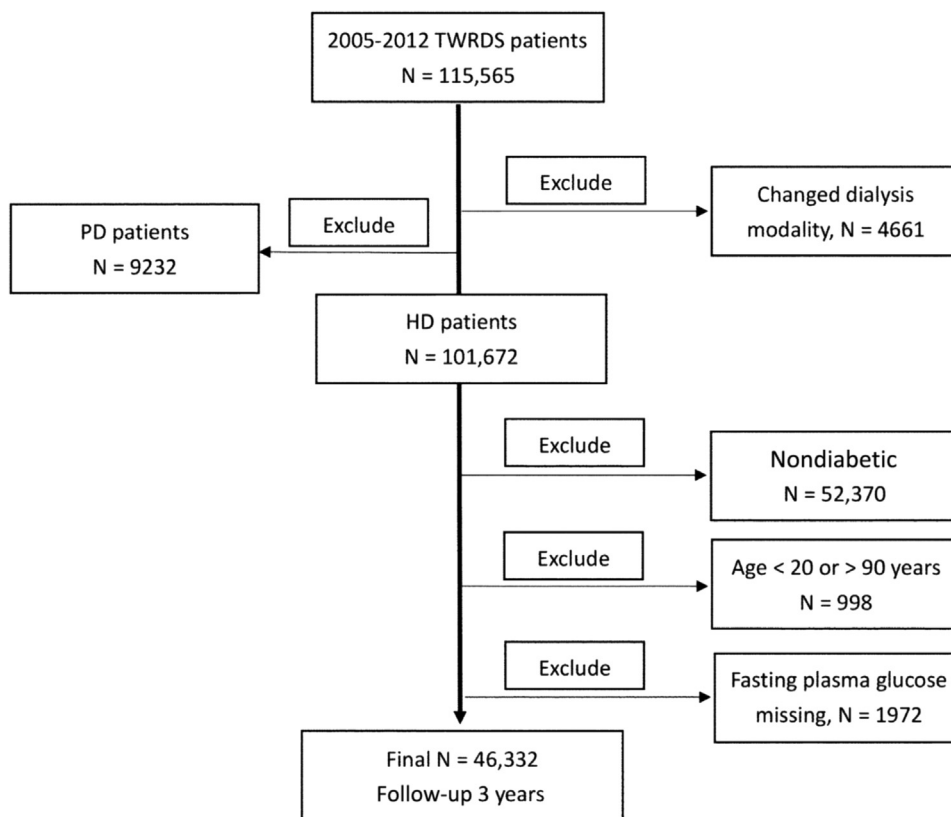
Figure 1. Flowchart of enrollment of the study cohort: from 1 January 2005 to 31 December 2012, a total of 46,332 patients with diabetes on maintenance hemodialysis were identified from the Taiwan Renal Registry Data System (TWRDS). HD, hemodialysis; PD, peritoneal dialysis.

provides complete national coverage for all renal replacement therapy expenditure in Taiwan.

Statistical Analysis

Descriptive statistics were expressed as mean ± SD, median (range), or frequency (percentage) for continuous variables and proportions for categorical variables. The 1-way analysis of variance test or the Kruskal-Wallis test was used for the analysis of continuous variables as appropriate, and the differences between nominal variables were compared by the χ^2 test. The log-rank test was used for the Kaplan-Meier analysis. The level of significance was set at 0.05, 2 tailed for all tests. We performed a Cox regression analysis to estimate the hazard ratios with 95% confidence intervals for mortality, stratified by quartiles of the distributions of 1- and 3-year FPG values. Independent variables were selected for multivariable analysis if they had a *P* value < 0.05 in the univariable analysis and were also clinically important confounders in the study. The case-mix adjusted model included the following confounding factors: age, sex, hypertension, congestive heart failure, left ventricular hypertrophy, cerebral artery disease, use of antihypertensive agents, laboratory data (levels of hematocrit, albumin, alkaline phosphatase, Ca, P, and intact parathyroid hormone), and Kt/V. All

descriptive and multivariable regression analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL) and SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 46,332 patients with diabetes mellitus undergoing hemodialysis were included in this study. Table 1 shows the demographic and clinical characteristics of patients in the different groups defined in this study. The mean age of the patients was 63.2 ± 11.7 years, and 51% of the patients were male. The average FPG levels were 103.5 ± 14.5 (51.0–125.0) mg/dl, 144.7 ± 11.5 (125.3–165.0) mg/dl, 189.6 ± 15.2 (165.1–217.8) mg/dl, and 280.8 ± 61.2 (218.0–903.0) mg/dl for the first, second, third, and fourth quartile of the distribution of 1-year FPG values, respectively. With respect to the distribution of 3-year FPG values, the average FPG levels were 107.6 ± 14.6 (51.0–129.0) mg/dl, 147.7 ± 10.8 (129.1–166.7) mg/dl, 188.3 ± 13.3 (166.7–213.0) mg/dl, and 268.1 ± 54.4 (213.1–901.0) mg/dl for the first, second, third, and fourth quartile, respectively. There was a slight predominance of male patients in the groups defined by the first 3 quartiles of the distribution of FPG values. The patients in all quartiles exhibited similar incidence of comorbidities (hypertension, congestive heart failure, left ventricular

Table 1. Baseline characteristics of 46,332 diabetic patients on maintenance hemodialysis by quartile of 1-yr FPG and 3-yr FPG in the TWRDS database, 2005–2012

Variable	Total (N = 46,332)	First quartile (N = 11,652)	Second quartile (N =11,552)	Third quartile (N = 11,557)	Fourth quartile (N = 11,571)	P
1-yr FPG (mg/dl, min–max)		103.5 ± 14.5 (51.0–125.0)	144.7 ± 11.5 (125.3–165.0)	189.6 ± 15.2 (165.1–217.8)	280.8 ± 61.2 (218.0–903.0)	
Measurement times, median (interquartile)	4 (3, 4)					
3-yr FPG (mg/dl, min–max)		107.6 ± 14.6 (51.0–129.0)	147.7 ± 10.8 (129.1–166.7)	188.3 ± 13.3 (166.7–213.0)	268.1 ± 54.4 (213.1–901.0)	
Measurement times, median (interquartile)	6 (3, 10)					
Age (yr)	63.2 ± 11.7	62.9 ± 12.1	63.5 ± 11.8	63.5 ± 11.4	62.9 ± 11.3	<0.01
Male (%)	23,787 (51%)	6364 (55%)	6158 (53%)	5839 (51%)	5426 (47%)	<0.0001
HTN (%)	23,313 (50%)	5979 (51%)	5870 (51%)	5792 (50%)	5672 (49%)	0.0033
CHF (%)	7447 (16%)	1832 (16%)	1820 (16%)	1861 (16%)	1934 (17%)	0.1410
LVH (%)	6516 (14%)	1694 (15%)	1638 (14%)	1602 (14%)	1582 (14%)	0.2450
CVA (%)	4779 (10%)	1133 (10%)	1214 (11%)	1205 (10%)	1227 (11%)	0.1080
CAD (%)	7658 (17%)	1871 (16%)	1904 (16%)	1954 (17%)	1929 (17%)	0.3523
MI (%)	1896 (4%)	466 (4%)	466 (4%)	489 (4%)	475 (4%)	0.8182
HTN drugs (%)	27,719 (60%)	6987 (60%)	7001 (61%)	6977 (60%)	6754 (58%)	0.0022
Laboratory data						
TC (mg/dl)	171.4 ± 38.3	169.6 ± 36.5	168.7 ± 37.3	171.9 ± 38.4	175.3 ± 40.7	<0.0001
TG (mg/dl)	181.2 ± 116.2	152.4 ± 92.8	170.3 ± 105.0	189.2 ± 115.7	213.0 ± 138.0	<0.0001
Alb (g/dl)	3.7 ± 0.4	3.8 ± 0.4	3.7 ± 0.4	3.7 ± 0.4	3.7 ± 0.4	<0.0001
Hct (%)	30.5 ± 3.2	30.7 ± 3.2	30.6 ± 3.2	30.5 ± 3.1	30.3 ± 3.1	<0.0001
Ca (mg/dl)	9.1 ± 0.7	9.1 ± 0.7	9.1 ± 0.7	9.1 ± 0.7	9.0 ± 0.7	<0.0001
P (mg/dl)	4.8 ± 1.2	4.9 ± 1.2	4.8 ± 1.2	4.8 ± 1.2	4.7 ± 1.2	<0.0001
Alk-P (u/l)	119.0 ± 92.8	111.7 ± 88.7	113.4 ± 84.9	119.1 ± 91.8	131.9 ± 103.4	<0.0001
i-PTH (pg/ml)	169.4 ± 157.9	183.8 ± 170.4	167.0 ± 157.7	162.7 ± 150.1	163.8 ± 151.5	<0.0001
Ca*P	43.5 ± 11.7	44.8 ± 12.1	43.6 ± 11.8	43.1 ± 11.5	42.5 ± 11.4	<0.0001
Kt/V	1.52 ± 0.21	1.52 ± 0.22	1.52 ± 0.21	1.52 ± 0.21	1.53 ± 0.21	<0.0001

Alb, albumin; Alk-P, alkaline phosphatase; Ca, calcium; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebral vascular accident; FPG, fasting plasma glucose; Hct, hematocrit; HTN, hypertension; i-PTH, intact parathyroid hormone; LVH, left ventricular hypertrophy; MI, myocardial infarction; P, phosphorus; TC, total cholesterol; TG, triglyceride; TWRDS, Taiwan Renal Disease Registry System.

hypertrophy, cerebral vascular accident, cerebral artery disease, and myocardial infarction) and use of hypertensive drugs. However, there were significant differences with respect to TC and TG levels. Specifically, with respect to the distribution of 1-year FPG values, the TC and TG levels were increasing from the first to the fourth quartile. The same trend of TC and TG was noted in quartiles of 3-year FPG values.

The 3-year mortality rates were 27.3%, 31.8%, 33.8%, and 38.5% for the first, second, third, and fourth quartile of the distribution of 1-year FPG values, respectively. The slope of the Kaplan-Meier survival curves based on the 1-year FPG values (Figure 2) decreased by 16.5%, 23.7%, and 41.1% for the pairwise comparisons between the first quartile and the second, third, and fourth quartile ($P < 0.0001$), respectively. Figure 3 shows a similar phenomenon for the survival curves based on the 3-year FPG values (3-year mortality rates: 26.7%, 31.3%, 33.0%, and 40.1% from the first to the fourth quartile; slope decreased by 17.2%, 23.6%, and 50.3% for comparisons between the first quartile and the second, third, and fourth quartile, respectively; $P < 0.0001$).
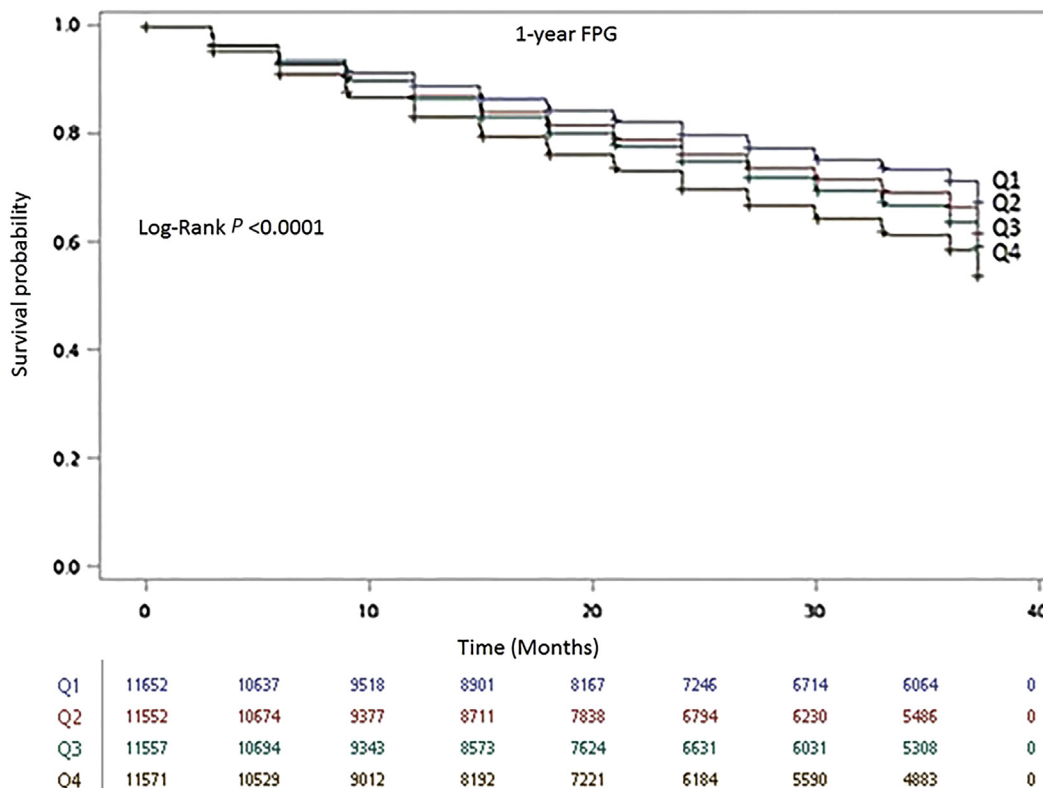
In the Cox regression analysis (Table 2), after adjusting for age, gender, comorbidities (hypertension, congestive heart failure, left ventricular hypertrophy,

cerebral vascular accident, cerebral artery disease, and myocardial infarction), use of medication for hypertension, relevant laboratory results (albumin, hematocrit, Ca, P, intact parathyroid hormone, and alkaline phosphatase), and Kt/V, the mortality hazard ratios were, respectively, 1.15 (95% CI: 1.10–1.20), 1.30 (95% CI: 1.25–1.36), and 1.45 (95% CI: 1.39–1.51) for the second, third, and fourth quartile compared with the first quartile of the distribution of 1-year FPG values. Similarly, the mortality hazard ratios were 1.17 (95% CI: 1.12–1.22), 1.26 (95% CI: 1.21–1.311), and 1.57 (95% CI: 1.51–1.64) when comparing the second, third, and fourth quartile with the first quartile of 3-year FPG values.

After 3 years of hemodialysis, 32,424 (70%) patients remained in the same quartile, whereas 13,908 patients were assigned to a different quartile: 6745 patients (48%) were thus included in the "increase group" and 7163 patients (52%) were included in the "decrease group." The adjusted hazard ratio of mortality was 1.22 (95% CI: 1.16–1.29, $P < 0.01$) in the "increase group" compared with the "decrease group" (Table 3).

DISCUSSION

Our study showed that higher 1- and 3-year FPG levels after hemodialysis are significantly associated with a higher mortality in the 3-year follow-up.

Q1	11652	10637	9518	8901	8167	7246	6714	6064	0
Q2	11552	10674	9377	8711	7838	6794	6230	5486	0
Q3	11557	10694	9343	8573	7624	6631	6031	5308	0
Q4	11571	10529	9012	8192	7221	6184	5590	4883	0

Figure 2. The Kaplan-Meier survival curves on the 1-year fasting plasma glucose (FPG): 3-year mortality rates were 27.3%, 31.8%, 33.8%, and 38.5% in the first, second, third, and fourth quartiles of 1-year average FPG (1-year FPG), respectively. Rates of reduction were 16.5%, 23.7%, and 41.1% for the pairwise comparisons between the first quartile and the second, third, and fourth quartile, respectively ($P < 0.0001$). Q1, first quartile; Q2, second quartile; Q3, third quartile; and Q4, fourth quartile by the distribution of 1-year FPG values.
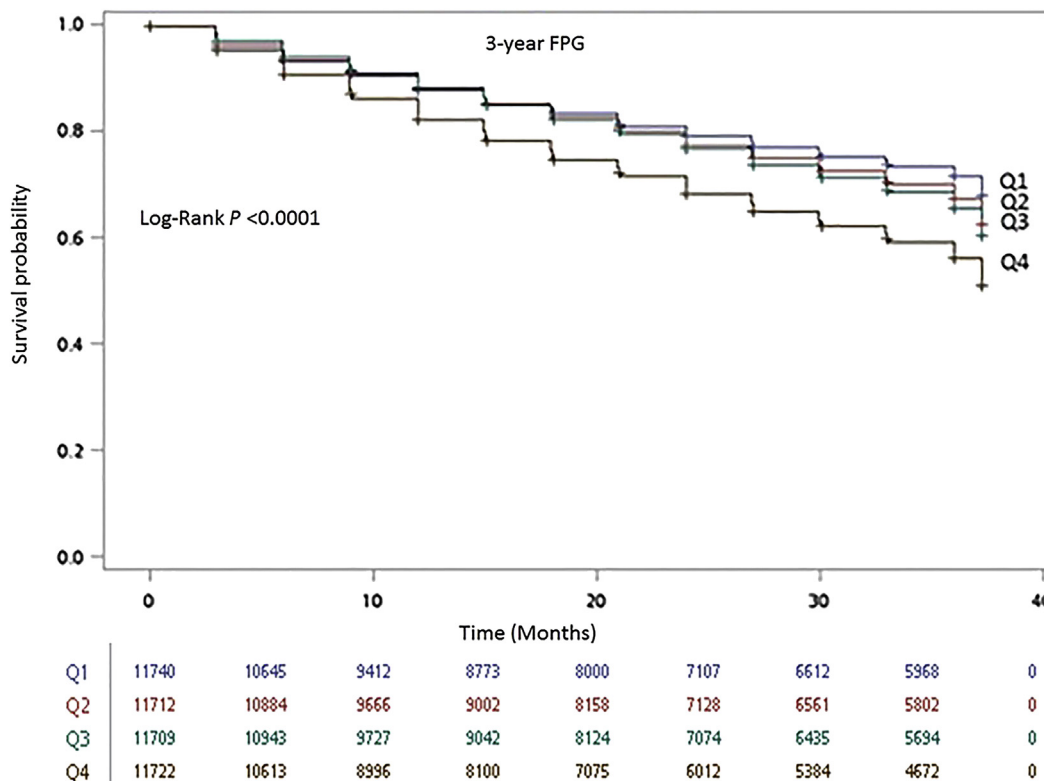
Figure 3. The Kaplan-Meier survival curves on the 3-year fasting plasma glucose (FPG): 3-year mortality rates were 26.7%, 31.3%, 33.0%, and 40.1% in the first, second, third, and fourth quartiles of 3-year averge FPG (3-year FPG), respectively. Rates of reduction were 17.2%, 23.6%, and 50.3% for the pairwise comparisons between the first quartile and the second, third, and fourth quartile, respectively ($P < 0.0001$). Q1, first quartile; Q2, second quartile; Q3, third quartile; and Q4, fourth quartile by the distribution of 3-year FPG values.

Furthermore, an increase in FPG levels between the first and third year after the initiation of hemodialysis was associated with a 22% increase in mortality. To the best of our knowledge, this is the first study that demonstrated that higher average FPG levels indicate increased mortality among diabetic patients receiving hemodialysis. Thus, FPG levels may also be considered as a useful surrogate marker in predicting mortality in patients with diabetic uremia.

Diabetes mellitus is the major cause of ESRD in Taiwan, accounting for one-half of the patients receiving maintenance hemodialysis. In clinical practice, glycemic control is a difficult task in this type of population. HbA1c, which is formed by a nonenzymatic reaction between glucose and the hemoglobin in red blood cells, reflects the concentration of glucose over a 120-day period. HbA1c is the gold standard of assessing glycemic control in the majority of diabetic patients. However, previous studies showed inconsistent results with respect to dialysis patients. This may be attributed to the fact that, in dialysis patients, factors such as high blood pH, high levels of hemoglobin, hemoglobinopathy, recent blood transfusion, use of erythropoietin-stimulating agents, and recent blood

Table 2. Crude and adjusted hazard ratio (HR) for all-cause mortality of 46,332 diabetes patients on maintenance hemodialysis by quartile of 1-yr FPG and 3-yr FPG in the Cox regression model

Groups of FPG	Crude HR	Adjusted HR
1-yr FPG		
First quartile	Reference	Reference
Second quartile	1.21 (1.17–1.26)*	1.15 (1.10–1.20)*
Third quartile	1.34 (1.29–1.39)*	1.30 (1.25–1.36)*
Fourth quartile	1.55 (1.49–1.61)*	1.45 (1.39–1.51)*
3-yr FPG		
First quartile	Reference	Reference
Second quartile	1.21 (1.16–1.26)*	1.17 (1.12–1.22)*
Third quartile	1.30 (1.25–1.35)*	1.26 (1.21–1.31)*
Fourth quartile	1.72 (1.66–1.79)*	1.57 (1.51–1.64)*

FPG, fasting plasma glucose.
*$P < 0.01$, adjusted for age, gender, hypertension, congestive heart failure, left ventricular hypertrophy, cerebral vascular disease, coronary artery disease, myocardial infarction, antihypertensive agents, albumin, hematocrit, calcium, phosphate, parathyroid hormone, alkaline phosphatase, and Kt/V.

Table 3. Crude and adjusted hazard ratio (HR) for all-cause mortality of diabetes patients on maintenance hemodialysis by trend of fasting plasma glucose (FPG) in the Cox regression model

Trend of group	Number	Crude HR	Adjust HR
	13,908		
Decrease FPG group	7163	Reference	Reference
Increase FPG group	6745	1.22 (1.16–1.28)*	1.22 (1.16–1.29)*

*$P < 0.01$, adjusted for age, gender, hypertension, congestive heart failure, left ventricular hypertrophy, cerebral vascular disease, coronary artery disease, myocardial infarction, antihypertensive agents, albumin, hematocrit, calcium, phosphate, parathyroid hormone, alkaline phosphatase, and Kt/V.

loss can falsely decrease HbA1c. On the other hand, uremic toxins such as elevated levels of blood urea nitrogen and low blood pH will spuriously elevate HbA1c levels.[16] It was shown that mortality rates in dialysis patients were higher for HbA1c levels below 42–53 mmol/mol, that is, estimated average glucose levels of approximately 130–160 mg/dl. There are several other tools for monitoring intermediate-term glucose levels other than HbA1c. Fructosamine and glycated albumin represent promising alternatives for glycemic control assessment, as they provide surrogates of glycemic control during periods of 2 weeks. Laboratory abnormalities and comorbidities associated with the uremic state may still impact the accuracy of these methods for assessing intermediate glycemic control. Furthermore, the target ranges for fructosamine and glycated albumin levels are unknown in the chronic kidney disease population, and such measurements are not routinely available in clinical laboratories. Most important of all, there are limited data on the relevance of such measurements.[17,18] Chen *et al.* demonstrated that, in patients with stage 3 and 4 chronic kidney disease, the average glucose levels calculated based on HbA1c or fructosamine levels may have underestimation compared with the mean glucose levels measured using self-monitoring blood glucose devices.[19] In contrast, direct plasma glucose measurements such as FPG represent the most reliable assessment of glucose levels. FPG also has several advantages, such as follows: it is easy to measure and shows less variability than postprandial glucose, which is significantly affected by different food intake.

In this study, higher 1- and 3-year FPG levels were significantly associated with higher mortality at 3 years after the initiation of hemodialysis. These 2 FPG-based indicators may have different clinical implications. In the first year of hemodialysis, the average FPG levels reflect the initial degree of glycemic control achieved at this stage of hemodialysis therapy. If a patient had worse glycemic control when initiating hemodialysis, he or she likely had a poorer survival outlook. The possible explanations include disease complexity, usage of multiple drugs, unfavorable general condition, or immunocompromised state during hyperglycemia at the onset of hemodialysis. On the other hand, the 3-year FPG levels reflect the long-term glycemic control of hemodialysis therapy and the general condition of the hemodialysis patient at this stage. In a Japanese cohort of dialysis patients, poor glycemic control was found to be a predictor of infection-related hospitalization.[20] In this case, higher glucose levels are likely the result of multiple acute or chronic illnesses or comorbidities that need further medical attention during this period and can result in poor prognosis.

In dialysis patients, glucose control is often a matter of debate, because clinical trials of glucose-lowering agents do not include such patients. The Kidney Disease Outcomes Quality Initiative guideline advising to maintain HbA1c levels between 53 and 75 mmol/mol (IFCC units) is based on observational studies with inconsistent conclusions. Data from a UK renal registry suggested that higher HbA1c levels are associated with increased mortality only in dialysis patients younger than 60 years, but not in older patients.[21] Glycemic control data from Asian populations of dialysis patients are scarce, and typically limited to a small study population.[22,23] These data showed no association between mean mortality rates and HbA1c levels after the initiation of hemodialysis. However, for hemodialysis patients (n = 245) with type 1 and type 2 diabetes mellitus, the hazard ratio for mortality was higher in patients with postprandial glucose levels > 180 mg/dl than in those with levels < 160 mg/dl.[22]

In this study, patients whose FPG levels decreased by the third year of hemodialysis had a more favorable outcome than patients whose FPG levels increased. It is interesting to note, however, that most patients (70%) remained in the same group defined by the quartiles of the distribution of FPG levels, suggesting no significant evolution in any direction. A previous study showed that lower HbA1c levels (<48 or <42 mmol/mol, IFCC units) were associated with higher mortality in dialysis patients.[24] The term ''burnt-out diabetes'' refers to spontaneous normalization of hyperglycemia in dialysis patients, and is associated with hypoglycemia episodes. The phenomenon can be a consequence of multiple factors such as malnutrition, anemia, and impaired excretion of oral antidiabetic drugs. This often leads to down-titration or even cessation of diabetes treatment in patients with ESRD, including insulin and oral medication. However, when excluding anemia and nutritional status, lower HbA1c levels seemed to be associated with better survival in patients undergoing maintenance dialysis.[25] The results of our study also showed that patients whose FPG levels decreased by the third year of hemodialysis had better outcome than those whose FPG levels increased, suggesting that, despite the development of ESRD in diabetic patients, glucose control still has a role in improving survival.

The cholesterol and TG values appeared to increase progressively from the first to the fourth quartile for both the 1- and 3-year FPG distributions. However, the correlation between cholesterol or TG levels and major outcomes in hemodialysis patients are controversial. In the guidelines published by the Kidney Disease: Improving Global Outcomes foundation, the initiation of statin is no longer suggested in dialysis patients.[26] There are several reasons for this, the first being the

lack of solid evidence as to the beneficial effect regarding cardiovascular outcomes in dialysis patients.[27,28] Second, as the concept of reverse epidemiology suggests, lower cholesterol levels may be associated with worse cardiovascular disease outcome, independently or confounded by malnutrition or inflammation when the patient undergoes maintenance dialysis therapy.[29,30] In this population, the role of lipid levels is inconclusive. Therefore, we did not adjust for the TC or TG levels in the Cox regression model; instead, the adjusted factors included in our Cox regression were those that are relevant to mortality, such as age, underlying disease, Ca/P, albumin levels, and Kt/V.

There are some limitations in this study. First, the specific cause of mortality such as infection or cardiovascular death is not available in this dataset. Therefore, the specific effect of hyperglycemia on mortality is hard to explore. Other residual confounding factors included the lack of information about patients receiving renal transplant and HbA1c level. However, the number of patients with renal transplant is small, that is, 200 subjects per year, which had a mild effect on the cohort. Although HbA1c data were not assessable in the TWRDS, the accuracy of HbA1c in HD population had not come to an agreement. The strength of our study is that the data were collected based on a long follow-up of a large study population, covering all dialysis patients in Taiwan, with results from complete and regular laboratory tests.

In conclusion, for the studied Taiwanese population of diabetic patients undergoing hemodialysis, increased mortality rates are associated with higher average FPG levels at 1 and 3 years after the initiation of dialysis. Patients whose FPG levels decrease between the first and the third year of hemodialysis have a more favorable outlook than patients whose FPG levels increase. Further prospective, randomized trials are warranted to confirm our findings.

DISCLOSURE

ACKNOWLEDGMENTS

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