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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.

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The incidence of diabetic kidney disease is rapidly increasing across the world.[1] Furthermore, diabetic kidney disease accounts for nearly 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 (IFCC units).[8] Similar results were reported in a larger cohort of 54,757 diabetic patients undergoing hemodialysis at

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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

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