Unique hemoglobin A1c level distribution and its relationship with mortality in diabetic hemodialysis patients

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Junichi Hoshino[1], Maria Larkina[2], Angelo Karaboyas[2], Brian A. Bieber[2], Yoshifumi Ubara[1], Kenmei Takaichi[1], Tadao Akizawa[3], Takashi Akiba[4], Shunichi Fukuhara[5], Ronald L. Pisoni[2], Akira Saito[6] and Bruce M. Robinson[2]

[1]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [3]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [4]Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan; [5]Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine and Public Health, Kyoto, Japan; and [6]Department of Nephrology and Endocrinology, Tokai University, Kanagawa, Japan

Diabetic hemodialysis patients with hemoglobin A1c (HbA1c) levels below 6.5% and over 8.0% face a higher mortality risk. To determine the optimal glycemic control in Japanese patients, we examined the association between HbA1c and mortality in 2,300 Japanese diabetic patients on maintenance hemodialysis with HbA1c levels determined at enrollment in the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS) phases 2-5, using Cox regression analysis with adjustment for baseline age, sex, dialysis vintage, 12 general comorbidities, hemoglobin, albumin and creatinine levels, and insulin use; stratification by JDOPPS phase; and facility clustering taken into account. Overall, 54% of patients had HbA1c levels under 6.0, including 14% with HbA1c levels under 5.0. Insulin or oral diabetes medications were used less frequently in patients with higher HbA1c levels. The dependence of mortality on HbA1c level was U shaped. When the group with the lowest mortality (HbA1c 6.0-7.0) was used as a reference, the hazard ratios for HbA1c categories under 5.0, 5.0-6.0, 7.0 to under 8.0, and 8.0 and greater were, respectively, 1.56 (95% confidence interval, 1.05-2.33), 1.26 (0.92-1.71), 1.23 (0.79-1.89), and 2.10 (1.32-3.33) in the adjusted model. The HbA1c level was not associated with self-reported hypoglycemic episodes in JDOPPS phase 5. The HbA1c levels in diabetic hemodialysis patients differ considerably between Japan and those reported from Western countries. Thus, our findings highlight the importance of domestic guidelines for glycemic control by race and country.

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Correspondence: *Junichi Hoshino, Nephrology Center, Toranomon Hospital, 2-2-2, Toranomon, Minato-ku, Tokyo 105-8470, Japan. E-mail: hoshino@toranomon.gr.jp*

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Hemoglobin A1c (HbA1c) is the most commonly used measure for monitoring glycemic control in diabetic patients. The 2012 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines highlight the complexities of deciding the most appropriate target range for glycemic control in diabetic dialysis patients, indicating that HbA1c levels of ~7.9% were associated with greater survival in some observational studies, with higher risks of death observed for HbA1c levels <6.5% and >8.0%.[1] Other glycemic measures, such as levels of fructosamine and glycated albumin, have been proposed as alternatives for assessing glycemic control in these patients. However, evidence that these indicators better predict outcomes of glycemic control and its relationship with subsequent morbidity or mortality in diabetic dialysis patients compared with HbA1c is still insufficient.[2]

Countries display large differences in hemodialysis (HD) patient characteristics and related practices, including patient case mix, methods and quality of dialysis therapy, dietary habits, exercise levels, and medication prescriptions.[3–7] For example, the target endotoxin level in ultrapure dialysate and measured C-reactive protein levels are lower in Japan than those in Europe,[4,8,9] and large differences exist in the dietary habits and nutritional measures of HD patients in Japan compared with those in the United States and Europe. Furthermore, a recent study demonstrated substantial differences by race in insulin resistance.[10] Therefore, the above differences among countries and by race may affect the association of HbA1c levels with outcomes in the HD patient population. There is a clear need to determine adequate HbA1c levels according to race and country. This is especially important for diabetic HD patients in Asia, where use of renal replacement therapy in this patient population is expected to rise sharply in the next decade.[11] Here, we investigated the relationship of HbA1c level with mortality in a large cohort of

diabetic Japanese HD patients using data from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS) of 2002 to 2015.[12]

RESULTS

Frequency of HbA1c measurement

During the first 4 months of JDOPPS phase 5, among diabetic patients in the study sample, 6%, 7%, 9%, and 67%, had HbA1c reported in 1, 2, 3, and all 4 of the 4 study months, respectively, with 10% having no reported HbA1c. The facility distribution in the frequency of measuring HbA1c for diabetic patients during the first 4 study months is shown Supplementary Figure S1 for JDOPPS phase 4 and 5 facilities. These results indicate that JDOPPS HD facilities routinely measure HbA1c in their diabetic patients (almost monthly for the majority of facilities).

Patient characteristics and glycemic control

A substantial shift in HbA1c control was observed in diabetic Japanese HD patients from 2002 to 2004 (phase 2) to 2012 to 2015 (phase 5) (Figure 1). The percentage of diabetic HD patients with intermediate HbA1c levels (5.0 to <7.0) gradually increased from 57% in phase 2 to 75% in phase 5. Furthermore, the percentage of patients in the highest HbA1c category (≥8.0) decreased from 9% in 2002 to 2004 (phase 2) to 4% by 2012 to 2015 (phase 5). The majority of study patients (97%) had type 2 diabetes as a cause of end-stage renal disease, and 86% of study patients had a prescription for erythropoietin-stimulating agents at DOPPS study enrollment.

Patient characteristics by HbA1c category for all patients in 2002 to 2015 are shown in Table 1. The group with HbA1c levels of 5.0 to <6.0 had the largest proportion of patients (40%), followed by the groups with HbA1c levels <5.0 (14%), 6.0 to <7.0 (27%), 7.0 to <8.0 (12%), and ≥8.0 (7%). Patients with lower HbA1c levels were more likely to be older and male and had lower dialysis vintage (years since dialysis initiation). In our cohort, 33% of diabetic HD patients were prescribed either oral diabetic pills or insulin, 23% of them were prescribed oral medication, and 12% were prescribed insulin (not exclusive). Patients with higher HbA1c levels were generally more likely to be prescribed a diabetes medication; the prevalence of prescription of insulin or oral medication was 18% among patients with an HbA1c level <5.0 and 41% among patients with an HbA1c level ≥8.0. Similarly, the incidence of insulin prescription was 5% and 21% in the groups with HbA1c levels <5.0 and ≥8.0, respectively. Interestingly, the prevalence of having an indicator of poor nutrition (body mass index <17.5 or serum albumin level <3.0 g/dl) showed a U-shaped relationship with HbA1c levels, with the highest prevalence of poor nutrition indicators seen at the highest and lowest HbA1c levels, whereas the lowest prevalence of poor nutrition was observed at HbA1c levels of 5.0 to <7.0.

Among patients with HbA1c levels <6.0, the prevalence of prescription of oral diabetes medications increased from 18% to 23%, respectively, between phases 2 and 5. In contrast, the corresponding prevalence for insulin varied between 8% and 11%, with no clear trend detected.

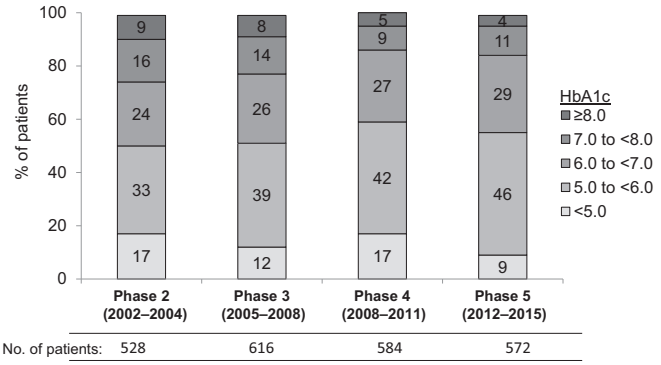

Figure 1 | Hemoglobin A1c (HbA1c) levels in diabetic patients for different phases of the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). Sample: diabetic patients with HbA1c levels as reported at enrollment in JDOPPS phases 2 to 5 (2002–2015), $N = 2300$.

Association between HbA1c level and mortality

A clear U-shaped relationship was observed between HbA1c levels and mortality in both unadjusted and adjusted models (Figure 2). When the group with HbA1c levels of 6.0 to <7.0 was used as a reference, the hazard ratios of mortality for HbA1c categories <5.0, 5.0 to <6.0, 7.0 to <8.0, and ≥8.0 were, respectively, 1.56 (95% confidence interval [CI] 1.05–2.33), 1.26 (95% CI 0.92–1.71), 1.23 (95% CI 0.79–1.89), and 2.10 (95% CI 1.32–3.33) in the adjusted model, with the lowest mortality seen for patients with HbA1c levels of 6.0 to <7.0. The overall P value (type 3) for HbA1c as a categorical variable was 0.02 in the adjusted model and 0.01 in the unadjusted model. Similar results were observed when the HbA1c level was averaged over 8 months instead of using a single baseline value (Supplementary Figure S2). In other analyses, no association was observed between the interaction of an HbA1c level <6.0 (vs. ≥6.0) with the use of any diabetic medication (vs. no use) and mortality ($P = 0.62$).

To check the association of the continuous HbA1c measure while capturing the proper functional form, spline regression was performed with 3 knots. The results (Supplementary Figure S3) from the spline model yielded a nadir of HbA1c 6.1%, with a pattern consistent with that seen in the main categorical HbA1c model. Additionally, we explored a model with smaller increments of HbA1c between 5.0% and 7.0% (Supplementary Figure S4), which was consistent with the main HbA1c and spline regression models in showing a lowest mortality risk between 6.0% and 6.5%. Converting HbA1c values from Japan Diabetes Society (JDS) standardized units into National Glycohemoglobin Standardization Program (NGSP) standardized units, using NGSP = (1.02*JDS) + 0.25 conversion, produced very similar results to those of the main model (Supplementary Figure S5). When