Medicine®

OPEN

Glycemic Control Modifies Difference in Mortality Risk Between Hemodialysis and Peritoneal Dialysis in Incident Dialysis Patients With Diabetes

Results From a Nationwide Prospective Cohort in Korea

Mi Jung Lee, MD, Young Eun Kwon, MD, Kyoung Sook Park, MD, Youn Kyung Kee, MD, Chang-Yun Yoon, MD, In Mee Han, MD, Seung Gyu Han, MD, Hyung Jung Oh, MD, Jung Tak Park, MD, PhD, Seung Hyeok Han, MD, PhD, Tae-Hyun Yoo, MD, PhD, Yong-Lim Kim, MD, PhD, Yon Su Kim, MD, PhD, Chul Woo Yang, MD, PhD, Nam-Ho Kim, MD, PhD, and Shin-Wook Kang, MD, PhD

Abstract: Although numerous studies have tried to elucidate the best dialysis modality in end-stage renal disease patients with diabetes, results were inconsistent and varied with the baseline characteristics of patients. Furthermore, none of the previous studies on diabetic dialysis patients accounted for the impact of glycemic control. We explored whether glycemic control had modifying effect on mortality between hemodialysis (HD) and peritoneal dialysis (PD) in incident dialysis patients with diabetes.

A total of 902 diabetic patients who started dialysis between August 2008 and December 2013 were included from a nationwide prospective cohort in Korea. Based on the interaction analysis between hemoglobin A_{1c} (HbA_{1c}) and dialysis modalities for patient survival (P for interaction = 0.004), subjects were stratified into good and poor glycemic control groups (HbA_{1c}< or ≥8.0%). Differences in survival rates according to dialysis modalities were ascertained in each glycemic control group after propensity score matching.

During a median follow-up duration of 28 months, the relative risk of death was significantly lower in PD compared with HD in the whole cohort and unmatched patients (whole cohort, hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.47–0.90, $P = 0.01$; patients with available HbA_{1c} [n = 773], HR = 0.64, 95% CI = 0.46–0.91, $P = 0.01$). In the good glycemic control group, there was a significant survival advantage of PD (HbA_{1c} <8.0%, HR = 0.59, 95% CI = 0.37–0.94, $P = 0.03$). However, there was no significant difference in survival rates between PD and HD in the poor glycemic control group (HbA_{1c} ≥8.0%, HR = 1.21, 95% CI = 0.46–2.76, $P = 0.80$).

This study demonstrated that the degree of glycemic control modified the mortality risk between dialysis modalities, suggesting that glycemic control might partly contribute to better survival of PD in incident dialysis patients with diabetes.

(*Medicine* 95(11):e3118)

Abbreviations: ADA = American Diabetes Association, ESA = erythropoiesis-stimulating agent, ESRD = end-stage renal disease, HbA_{1c} = hemoglobin A1c, HD = hemodialysis, hs-CRP = high-sensitivity C-reactive protein, PD = peritoneal dialysis, PS = propensity score, RRF = residual renal function.

INTRODUCTION

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) worldwide,[1] and the number of diabetic patients who commence dialysis therapy is constantly increasing.[2,3] Therefore, nephrologists are confronted with the problem of deciding which dialysis modality should be recommended to these patients in clinical practice. Although dialysis modality is usually determined based on a number of factors, including the patient's clinical condition, socioeconomic status, patient's or physician's preference, and the practice pattern of the institution, several other problems, such as vascular access and peritoneal membrane permeability, should be considered before making a decision for ESRD patients with diabetes mellitus.[2] In addition, patient survival rates in hemodialysis (HD) and peritoneal dialysis (PD) are another issue to consider. To date, numerous previous studies have compared differences in the survival rates between diabetic HD and PD patients, but the results were not consistent.[4–18] Heterogeneity of the study population, diverse dialysis duration, and difference in statistical analysis methods might contribute to these discrepant

Editor: Joshua Barzilay.
Received: November 23, 2015; revised: February 6, 2016; accepted: February 25, 2016.
From the Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam-si (MJL); Department of Internal Medicine (MJL, YEK, KSP, YKK, C-YY, IMH, SGH, HJO, JTP, SHH, T-HY, S-WK); Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul (T-HY, S-WK); Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu (Y-LK); Department of Internal Medicine, Seoul National University College of Medicine (YSK); Department of Internal Medicine, Catholic University of Korea College of Medicine, Seoul (CWY); Department of Internal Medicine, Chonnam National University Medical School, Gwangju (N-HK); and Clinical Research Centre for End-Stage Renal Disease, Daegu, Korea (Y-LK, YSK, CWY, N-HK, S-WK).
Correspondence: Shin-Wook Kang, MD, PhD, Department of Internal Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University College of Medicine, Seoul, Korea 134 Shinchon-Dong, Seodaemun-Gu, Seoul 120-752, Korea (e-mail: kswkidney@yuhs.ac).
This work was supported by the Brain Korea PLUS 21 Project for Medical Science, Yonsei University, by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2011–0030711), and by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (H10C2020).
The authors have no conflict of interest to disclose.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003118

findings among previous studies.[2,5,13,18,19] Recently, in this point of view, the European Renal Best Practice Diabetes Guideline Development Group proposed that there was a lack of evidence in favor or against a particular dialysis modality as the first choice in ESRD patients with diabetes.[18]

The survival advantage of one dialysis modality over another has been found to vary according to the presence of diabetes.[4,7,10,12,13] However, none of the previous studies on diabetic dialysis patients accounted for the impact of glycemic control, which is known to be closely associated with clinical outcomes in diabetic patients.[20–22] In this study, we hypothesized that glycemic control might have an impact on better clinical outcomes of one dialysis modality over another in dialysis patients with diabetes. In contrast to most prior studies in which only baseline demographic characteristics and comorbid diseases were adjusted for,[4,6,7,14,17] various previously demonstrated independent prognostic factors in dialysis patients, such as high-sensitivity C-reactive protein (hs-CRP), residual renal function (RRF), and hemoglobin A_{1c} (HbA_{1c}), were included in the final analysis. In result, we attempted to clarify the impact of glycemic control on the association between dialysis modality and patient survival in incident dialysis patients with diabetes.

METHODS

Ethical Statements

This study was carried out in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board at each participating hospital's Clinical Trial Centre. All patients provided their written informed consent before entering the study.

Study Design and Subjects

All diabetic ESRD patients who started HD or PD between August 1, 2008 and September 30, 2013 at 36 centers of the Clinical Research Center for ESRD (CRC for ESRD) in Korea were initially screened for this study. This study was part of a nationwide multicenter joint network prospective cohort study on ESRD patients in Korea designed to improve survival rates and quality of life and to draw up effective treatment guidelines (clinicaltrial.gov NCT00931970). Patients younger than 18 years, with a history of kidney transplantation before dialysis therapy, with underlying active malignancy or acute infection, or who were expected to survive <3 months were excluded before the initial screening. Among 2035 incident dialysis patients, diabetes mellitus was diagnosed in 1163 patients based on diagnostic criteria of the American Diabetes Association (ADA).[23] After excluding 261 patients who failed to maintain dialysis for >3 months, 902 patients were included in the final analysis as the whole cohort. To evaluate the impact of glycemic control, 773 patients were included after excluding 129 patients whose mean HbA_{1c} levels during the first 6 months were not available (Figure 1).

Data Collection and Follow-up

Demographic, clinical and laboratory data were extracted from the electronic data management system. Demographic and clinical data including age, sex, height, weight, comorbidities, smoking history, and body mass index were collected at the time of study entry. The following laboratory data were measured from fasting blood samples at 3 and 6 months after initiation of dialysis, and every 6 months thereafter: white blood cell, hemoglobin, blood urea nitrogen, creatinine, albumin, glucose,

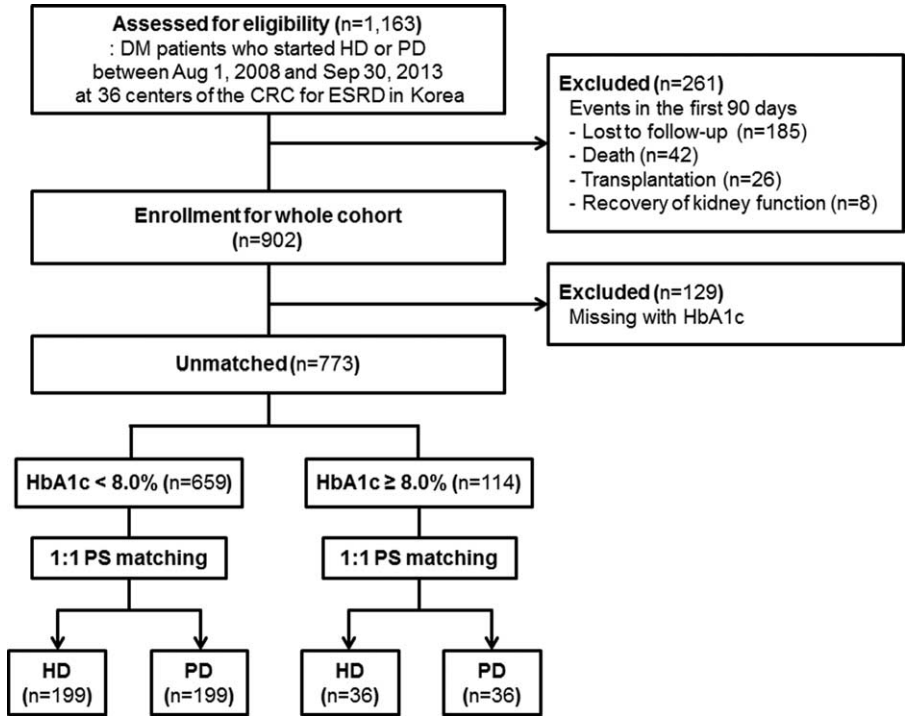

FIGURE 1. Flow diagram of patients. Among 1163 incident dialysis patients with diabetes, 902 patients were primarily analyzed as the whole cohort after excluding 261 patients who failed to maintain dialysis for the first 90 days. A total of 773 patients were categorized by HbA_{1c} <8.0% or ≥8.0%, then PS matching was performed in each glycemic control group. 1:1 Matching resulted in 199 matched pairs and 36 matched pairs, respectively. HbA_{1c} = hemoglobin A_{1c}, PS = propensity score.

HbA_{1c}, calcium, phosphorous, and hs-CRP. Blood glucose concentrations were determined by the hexokinase-UV method, and HbA_{1c} levels were measured by high-performance liquid chromatography. RRF was estimated by 24-hour urine collection. Participants were followed up until September 30, 2015. All death events were retrieved from the CRC for ESRD database and were carefully reviewed. Death events were also confirmed by the Korea National Statistics database. Loss to follow-up, renal transplantation, or recovery of renal function after the first 90 days of dialysis initiation was censored at the end of dialysis treatment.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS Inc, Chicago, IL) and R (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), and categorical variables were expressed as a number (percentage). To compare baseline characteristics according to dialysis modality, Student *t* test or Mann-Whitney *U* test and χ^2 test were used for continuous variables and categorical variables, respectively. Modality change was observed in 37 patients (4.1%; HD to PD in 8 patients and PD to HD in 29 patients), an intention-to-treat analysis was adopted rather than an as-treated analysis for survival analysis. The dialysis modality at day 90 was considered the initial dialysis modality. Cumulative survival curves were generated by the Kaplan–Meier method, and between-group survival was compared by a log-rank test. The relative hazard ratio (HR) for mortality of PD compared with HD was ascertained using Cox proportional hazard regression models. Violation of the proportional hazard assumption was tested by conducting a visual examination of the log-minus-log plots. To address our hypothesis whether glycemic control had a modifying impact on patient survival rates of one dialysis modality over the other, the interaction between HbA_{1c} and dialysis modalities were tested. Since HbA_{1c} levels had an interaction with dialysis modality on survival rates (P for interaction = 0.04), stratified analysis was performed based on the HbA_{1c} value of 8.0% (<8.0 or ≥8.0%). The mean value of HbA_{1c} was used at baseline, 3 months, and 6 months after dialysis initiation. Because HD and PD were not randomly assigned, we performed propensity score (PS) matching for mitigating the confounding effects of different baseline characteristics according to dialysis modalities. PS was calculated by multivariable logistic regression analysis in each HbA_{1c} group. All covariates were used for PS matching. Patients were matched 1:1 by PS using a nearest-neighbor matching algorithm. PS matching yielded 199 matched pairs in HbA_{1c} <8.0% and 36 pairs in HbA_{1c} ≥8.0%. Supplementary Figure 1, http://links.lww.com/MD/A804 shows the distribution of PS in the unmatched and matched groups. To compare baseline characteristics between two dialysis modalities in the matched group, the Wilcoxon signed rank test was used for continuous variables and McNemar test was used for categorical variables. Consecutive survival analysis was performed in each HbA_{1c} group. Two-sided P values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

The baseline data of 902 patients and 773 patients with available HbA_{1c} are shown in Table 1. In the whole cohort (n = 902), the mean age was 62.2 ± 11.9 years and 573 patients (63.5%) were male. HD was the initial modality in 637 patients (70.6%) and PD was the initial modality in 265 patients (29.4%). The median value of HbA_{1c} was 6.4% (IQR = 5.7–7.3). In 773 patients who had HbA_{1c} measurement, the initial modality was HD in 538 patients (69.6%) and PD in 235 patients (30.4%). There was no significant difference in the proportion of dialysis modality between patients with and without HbA_{1c}.

Survival Rates According to Dialysis Modality in the Whole Cohort and Patients With Available HbA_{1c}

During a median follow-up duration of 28 (IQR = 13–41) months, 191 patients among the whole cohort of 902 patients (21.2%) died. The crude death rates were 101.1/1000 patient-years in the HD group and 67.6/1000 patient-years in the PD group. Kaplan-Meier analysis showed that cumulative patient survival was significantly worse in HD patients compared with PD patients (log-rank test, $P = 0.009$) (Figure 2A). The 1-, 2-, and 5-year patient survival rates were 92.0%, 84.0%, and 59.0% for HD patients, whereas they were 97.0%, 90.0%, and 65.0% for PD patients, respectively. In 773 patients whose HbA_{1c} concentrations were available, Kaplan–Meier curves also revealed that cumulative survival rates were significantly lower in HD compared with PD patients (log-rank test, $P = 0.012$) (Figure 2B). Cox proportional hazard analysis found that PD was associated with a lower risk of death compared with HD in not only the whole cohort but also the available HbA_{1c} group (whole cohort, HR = 0.65, 95% confidence interval [CI] = 0.47–0.90, $P = 0.01$; patients with available HbA_{1c}, HR = 0.64, 95% CI = 0.46–0.91, $P = 0.01$) (Table 2).

Impact of Glycemic Control on Survival Advantage of PD Over HD

PS matching resulted in no differences in baseline characteristics between HD and PD in both HbA_{1c} <8.0% (Table 3) and ≥8.0% groups (Table 4). Difference in survival rates between HD and PD varied according to the degree of glycemic control (Figure 3). The cumulative survival rates were significantly lower in HD relative to PD in patients with HbA_{1c} <8.0% (log-rank test, $P = 0.021$) (Figure 3A). However, there was no significant difference in the cumulative survival rates between HD and PD in patients with HbA_{1c} ≥8.0% (log-rank test, $P = 0.770$) (Figure 3B). Furthermore, the survival advantage of PD over HD remained consistent in the good glycemic control group even after PS was adjusted in the multivariate model (HbA_{1c} <8.0%, HR = 0.59, 95% CI = 0.37–0.94, $P = 0.03$) (Table 2). However, patient survival rates were comparable between 2 dialysis modalities in the poor glycemic control group in PS-adjusted model (HbA_{1c} ≥8.0%, HR = 1.21, 95% CI = 0.46–2.76, $P = 0.80$) as well as in the crude model (Table 2).

DISCUSSION

Innumerable studies have demonstrated the survival advantage of one dialysis modality over another in diabetic dialysis patients, but the results have been conflicting. In this study, we demonstrate that PD was significantly associated with decreased risk of all-cause mortality compared with HD in Korean incident dialysis patients with diabetes. Moreover, we found that better patient survival in PD was associated with the

TABLE 1. Baseline Characteristics of Patients With and Without HbA_{1c}

	All (n = 902)	Patients With HbA_{1c} (n = 773)	Patients Without HbA_{1c} (n = 129)	*P*
Age, y	62.2 ± 11.9	62.2 ± 11.9	61.9 ± 11.9	0.78
Male, n (%)	573 (63.5%)	492 (63.6%)	81 (62.8%)	0.84
Hemodialysis, n (%)	637 (70.6%)	538 (69.6%)	99 (76.7%)	0.12
Modified CCI	6.2 ± 2.2	6.1 ± 2.1	6.4 ± 2.3	0.24
Comorbid disease, n (%)				
CAD	151 (16.7%)	130 (16.8%)	21 (16.3%)	0.9
PAD	92 (10.2%)	81 (10.5%)	11 (8.5%)	0.64
CVA	95 (10.5%)	80 (10.3%)	15 (11.6%)	0.64
CHF	119 (13.2%)	109 (14.1%)	10 (7.8%)	0.05
Smoker, n (%)	431 (47.8%)	379 (49.0%)	52 (40.3%)	0.07
Systolic blood pressure, mmHg	142.6 ± 22.3	142.5 ± 22.5	143.1 ± 21.5	0.80
Diastolic blood pressure, mmHg	76.4 ± 13.1	76.5 ± 13.0	75.9 ± 13.2	0.66
BMI, kg/m^2	23.4 ± 3.3	23.4 ± 3.4	23.5 ± 2.9	0.76
HbA_{1c} (%)	—	6.4 (5.7–7.3)	—	—
White blood cell, $\times 10^3/\mu L$	7.4 ± 3.3	7.4 ± 3.3	7.1 ± 3.2	0.32
Hemoglobin, g/L	90 ± 15	90 ± 16	91 ± 15	0.41
Blood urea nitrogen, mmol/L	27.7 ± 12.5	28.2 ± 12.4	25.0 ± 13.2	0.01
Creatinine, μmol/L	689.5 ± 291.7	689.5 ± 282.9	680.7 ± 300.6	0.76
Albumin, g/L	32 ± 6	32 ± 6	31 ± 5	0.09
Calcium, mmol/L	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	0.56
Phosphorous, mmol/L	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	0.49
hs-CRP, mg/L*	0.39 (0.12–1.43)	0.39 (0.12–1.33)	0.72 (0.20–2.48)	0.01
ESA use, n (%)	615 (68.2%)	552 (71.4%)	63 (50.0%)	<0.001
RRF, $mL/min/1.73\,m^2$	8.2 ± 4.4	8.2 ± 4.4	8.3 ± 4.7	0.9

Data are expressed as mean ± standard deviation, median (interquartile range), or number of patients (%). BMI = body mass index, CAD = coronary artery disease, CCI = Charlson comorbidity index, CHF = congestive heart failure, CVA = cerebrovascular accident, ESA = erythropoiesis-stimulating agent, HbA_{1c} = hemoglobin A1c, hs-CRP = high-sensitivity C-reactive protein, PAD = peripheral artery disease, RRF = residual renal function.

* hs-CRP values were available in 70 patients of patients without HbA_{1c}.

degree of glycemic control. PD patients had a survival advantage in the good glycemic control group, but not in the poor glycemic control group.

Even though the choice of dialysis modality is a critical issue, it remains an unsettled question in diabetic dialysis patients. Among a number of factors, patient survival is one important concern to consider before determining the dialysis modality. Several previous studies showed that PD patients had a lower risk of death in the first 1 to 2 years after starting dialysis therapy,[2,4,6,9,15,16,19,24] which was attributed to preserved RRF in these patients.[11,25] However, this issue was not fully evaluated because of lack of RRF data in previous studies.[4,6,16,24] In

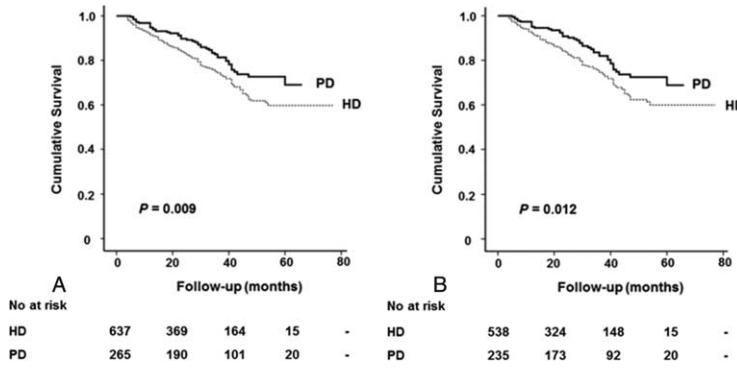

FIGURE 2. Kaplan–Meier analysis of all-cause mortality according to dialysis modality in the (A) whole cohort of 902 patients and (B) 773 patients who had available HbA_{1c}. Patients treated with HD showed significantly higher all-cause mortality than those with PD in the whole cohort (log-rank test, $P = 0.009$) and in 773 patients (log-rank test, $P = 0.012$). HbA_{1c} = hemoglobin A_{1c}, HD = hemodialysis, PD = peritoneal dialysis.

TABLE 2. HRs of Mortality for Peritoneal Dialysis Compared With Hemodialysis in the Whole Cohort, Unmatched Available HbA_{1c} Group, and PS-matched Group

		HR (95% CI)	*P*
Whole cohort (n = 902)	Crude	0.65 (0.47–0.90)	0.01
Unmatched group (n = 773)	Crude	0.64 (0.46–0.91)	0.01
PS matched group			
HbA_{1c} <8.0% (n = 398)	Crude	0.59 (0.37–0.93)	0.02
	Adjusted for PS	0.59 (0.37–0.94)	0.03
HbA_{1c} ≥8.0% (n = 72)	Crude	1.43 (0.47–2.81)	0.77
	Adjusted for PS	1.21 (0.46–2.76)	0.80

CI = confidence interval, HbA_{1c} = hemoglobin A_{1c}, HR = hazard ratio, PS = propensity score.

our study, RRF was not significantly associated with dialysis modality in terms of patient survival (*P* for interaction = 0.24). Moreover, there were no significant differences in mortality between HD and PD patients in both the lower and higher RRF group (data not shown). Therefore, we surmised that the survival advantage of our PD patients was not linked to RRF. Instead, these findings were more likely attributed to overall improvement of PD outcomes, which was recently observed in many cohort studies.[2,7,14,19,26,27] Mehrotra et al[26] demonstrated that a progressive decline in mortality risk was observed in PD patients between the earlier (1996–1998) and more recent (2002–2004) cohorts. Similarly, a study from the Taiwan showed that diabetic PD patients had worse survival than diabetic HD patients in the 1997 to 2001 cohort. However, the survival difference did not exist in the 2002 to 2006 cohort.[14] Although the exact mechanism for this salutary change in PD patient survival is not clear, application of quality-improvement programs in PD, individualization of PD prescription, and reduced risk of PD-related infectious complications have been proposed as reasonable candidates.[19]

TABLE 3. Baseline Characteristics for Unmatched and Propensity Score-Matched Groups in Patients With HbA_{1c} <8.0%

	Unmatched			PS-Matched		
	HD (n = 460)	PD (n = 199)	*P*	HD (n = 199)	PD (n = 199)	*P*
Age, y	64.1 ± 11.7	59.0 ± 11.6	<0.001	59.5 ± 12.3	59.0 ± 11.6	0.71
Male, n (%)	287 (62.4%)	137 (68.8%)	0.07	136 (68.3%)	137 (68.8%)	0.91
Modified CCI	6.2 ± 2.1	5.9 ± 2.3	0.24	6.0 ± 2.3	5.9 ± 2.3	0.86
Comorbid disease, n (%)						
CAD	77 (16.7%)	39 (19.6%)	0.22	43 (21.6%)	39 (19.6%)	0.62
PAD	44 (9.6%)	22 (11.1%)	0.32	22 (11.1%)	22 (11.1%)	1.0
CVA	52 (11.3%)	19 (9.5%)	0.30	17 (8.5%)	19 (9.5%)	0.73
CHF	54 (11.7%)	34 (17.1%)	0.04	32 (16.1%)	34 (17.1%)	0.79
Smoker, n (%)	221 (45.9%)	116 (58.3%)	0.002	102 (51.3%)	116 (58.3%)	0.16
SBP, mmHg	144.4 ± 22.9	139.7 ± 21.7	0.01	139.2 ± 22.4	139.7 ± 21.7	0.83
DBP, mmHg	75.5 ± 13.5	78.6 ± 12.8	0.01	76.8 ± 14.4	78.6 ± 12.8	0.20
BMI, kg/m^2	23.4 ± 3.5	23.5 ± 3.3	0.81	23.5 ± 3.6	23.5 ± 3.3	0.92
HbA_{1c} (%)	6.2 (5.6–6.8)	6.3 (5.6–6.9)	0.34	6.2 (5.6–6.9)	6.3 (5.6–6.9)	0.45
White blood cell, $\times 10^3/\mu L$	7.4 ± 3.7	7.3 ± 2.5	0.55	7.7 ± 3.6	7.3 ± 2.5	0.12
Hemoglobin, g/L	28.8 ± 5.4	32.8 ± 5.4	<0.001	32.8 ± 5.4	32.8 ± 5.4	0.92
BUN, mmol/L	80.7 ± 35.7	77.0 ± 34.3	0.22	77.2 ± 35.4	77.0 ± 34.3	0.95
Creatinine, μmol/L	698 ± 3.4	707 ± 292	0.73	698 ± 292	707 ± 292	0.79
Albumin, g/L	33 ± 6	33 ± 6	0.94	33 ± 6	33 ± 6	0.71
Calcium, mmol/L	2.0 ± 0.2	2.0 ± 0.2	0.50	2.0 ± 0.2	2.0 ± 0.2	0.79
Phosphorous, mmol/L	1.7 ± 0.6	1.8 ± 0.6	0.51	5.4 ± 0.6	5.5 ± 0.6	0.69
hs-CRP, mg/L	0.39 (0.14–1.50)	0.39 (0.11–1.24)	0.04	0.39 (0.10–1.33)	0.39 (0.11–1.24)	0.80
ESA use, n (%)	348 (75.7%)	131 (65.8%)	0.007	137 (68.8%)	131 (65.8%)	0.52
RRF, $mL/min/1.73m^2$	8.0 ± 4.3	8.1 ± 3.9	0.79	8.1 ± 3.9	8.1 ± 3.9	0.92

Data are expressed as mean ± standard deviation, median (interquartile range), or number of patients (%). BMI = body mass index, BUN = blood urea nitrogen, CAD = coronary artery disease, CCI = Charlson comorbidity index, CHF = congestive heart failure, CVA = cerebrovascular accident, DBP = diastolic blood pressure, ESA = erythropoiesis-stimulating agent, HbA_{1c} = hemoglobin A_{1c}, HD = hemodialysis, hs-CRP = high-sensitivity C-reactive protein, PAD = peripheral artery disease, PD = peritoneal dialysis, PS = propensity score, RRF = residual renal function, SBP = systolic blood pressure.

TABLE 4. Baseline Characteristics for Unmatched and PS-Matched Groups in Patients With $HbA_{1c} \geq 8.0\%$

	Unmatched			PS-Matched		
	HD (n = 78)	PD (n = 36)	*P*	HD (n = 36)	PD (n = 36)	*P*
Age, y	61.8 ± 11.9	57.2 ± 11.3	0.04	58.5 ± 12.1	57.2 ± 11.3	0.56
Male, n (%)	47 (60.3%)	21 (58.3%)	0.84	23 (63.9%)	21 (58.3%)	0.63
Modified CCI	6.4 ± 2.2	6.3 ± 1.7	0.42	6.4 ± 2.5	6.3 ± 1.7	0.72
Comorbid disease, n (%)						
CAD	10 (12.8%)	4 (11.1%)	0.79	3 (8.3%)	4 (11.1%)	0.69
PAD	11 (14.1%)	4 (11.1%)	0.66	5 (13.9%)	4 (11.1%)	0.72
CVA	6 (7.7%)	3 (8.3%)	0.91	4 (11.1%)	3 (8.3%)	0.69
CHF	14 (17.9%)	7 (19.4%)	0.85	5 (13.9%)	7 (19.4%)	0.53
Smoker, n (%)	37 (47.4%)	15 (41.7%)	0.69	18 (50.0%)	15 (41.7%)	0.48
SBP, mmHg	142.4 ± 21.8	134.9 ± 20.1	0.15	135.6 ± 18.5	134.9 ± 20.1	0.93
DBP, mmHg	77.1 ± 11.2	76.1 ± 10.6	0.47	77.1 ± 11.6	76.1 ± 10.6	0.68
BMI, kg/m^2	23.0 ± 3.3	23.2 ± 3.6	0.93	23.3 ± 3.5	23.2 ± 3.6	0.78
HbA_{1c} (%)	9.0 (8.4–9.8)	9.1 (8.2–9.9)	0.79	9.0 (8.3–9.8)	9.1 (8.2–9.9)	0.72
White blood cell, $\times 10^3/\mu L$	7.9 ± 2.9	7.6 ± 2.5	0.74	7.5 ± 2.6	7.6 ± 2.5	0.67
Hemoglobin, g/L	94 ± 14	97 ± 19	0.42	97 ± 15	97 ± 19	0.97
BUN, mmol/L	26.7 ± 10.9	27.1 ± 10.5	0.84	27.2 ± 11.7	27.1 ± 10.5	0.81
Creatinine, μmol/L	610 ± 221	566 ± 159	0.34	575 ± 194	566 ± 159	0.82
Albumin, g/L	31 ± 6	31 ± 6	0.67	32 ± 6	31 ± 6	0.89
Calcium, mmol/L	2.0 ± 0.2	2.0 ± 0.2	0.65	2.0 ± 0.2	2.0 ± 0.2	0.45
Phosphorous, mmol/L	1.7 ± 0.5	1.7 ± 0.5	0.25	1.7 ± 0.4	1.7 ± 0.5	0.72
hs-CRP, mg/L	0.39 (0.10–0.68)	0.24 (0.05–0.65)	0.29	0.39 (0.15–0.70)	0.24 (0.05–0.65)	0.20
ESA use, n (%)	53 (67.9%)	20 (55.6%)	0.14	19 (52.8%)	20 (55.6%)	0.81
RRF, $mL/min/1.73m^2$	8.9 ± 3.8	10.3 ± 7.7	0.23	9.2 ± 4.8	10.3 ± 7.7	0.31

Data are expressed as mean ± standard deviation, median (interquartile range), or number of patients (%). BMI = body mass index, BUN = blood urea nitrogen, CAD = coronary artery disease, CCI = Charlson comorbidity index, CHF = congestive heart failure, CVA = cerebrovascular accident, DBP = diastolic blood pressure, ESA = erythropoiesis-stimulating agent, HbA_{1c} = hemoglobin A_{1c}, HD = hemodialysis, hs-CRP = high-sensitivity C-reactive protein, PAD = peripheral artery disease, PD = peritoneal dialysis, PS = propensity score, RRF = residual renal function, SBP = systolic blood pressure.

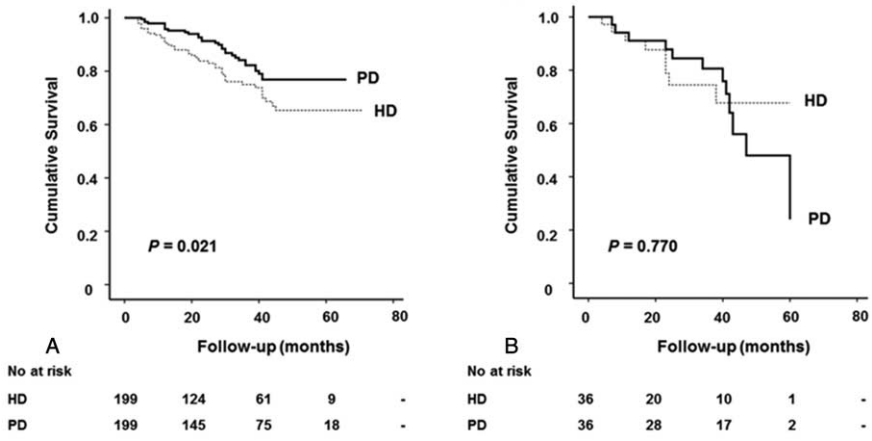

FIGURE 3. Kaplan–Meier analysis of all-cause mortality according to dialysis modality in the (A) PS-matched good glycemic control group (HbA_{1c} <8.0%) and (B) PS-matched poor glycemic control group (HbA_{1c} ≥8.0%). Cumulative survival rates were significantly lower in patients on HD compared with PD in good glycemic control group (n = 398, log-rank test, $P = 0.021$). However, there was no significant difference in survival rates between HD an PD in poor glycemic control group (n = 72, log-rank test, $P = 0.770$). HbA_{1c} = hemoglobin A_{1c}, HD = hemodialysis, PD = peritoneal dialysis, PS = propensity score.

It is noteworthy that the survival advantage of PD was altered by the degree of glycemic control in diabetic patients starting dialysis therapy. The survival advantage of one dialysis modality over the other varied according to the presence of diabetes.[4,7,10,12,13] However, so far, no study has explored the impact of glycemic control, which is closely related with clinical outcomes in diabetic patients,[20–22] on the difference in patient survival between the two dialysis modalities in diabetic dialysis patients. In our study, the better survival of PD patients was observed only in patients with HbA_{1c} <8.0%, suggesting that the survival benefit of PD was robust in the good glycemic control group. The mechanism by which glycemic control exerts an impact on the mortality of PD relative to HD in diabetic ESRD patients can somewhat be explained by peritoneal damage from hyperglycemia and adherence to treatment. Since PD patients are exposed to a large amount of glucose absorbed from the dialysate,[28] continuous exposure to dialysate might worsen glycemic control and induce peritoneal damage in diabetic patients. Indeed, high peritoneal membrane transport characteristic along with increased protein permeability is more commonly accompanied in diabetic PD patients than nondiabetic PD patients.[29] Although an objective assessment of peritoneal damage according to the degree of glycemic control was not performed, we inferred that the detrimental effect of poor glycemic control may accelerate peritoneal damage and late diabetic complications. This, in turn, lessened the survival benefit of PD in patients with HbA_{1c} ≥8.0%. Meanwhile, since PD is a home-based modality, a patient's adherence to treatment and their ability to follow instructions are crucial to maintaining therapy. Adherence to therapy was revealed to be associated with the risk of hospitalization and mortality in dialysis patients;[29] in other words, compliant patients had a lower mortality risk. Moreover, a recent study showed that patients starting PD had increased risks of hospitalization and peritonitis, especially in the early period.[30] These findings suggest that adaptation of self-care education is important to reduce mortality risk.[30] Taken together, we suggest that patients in the good glycemic control groups were more compliant, and thus were able to achieve self-care, which may partly contribute to the survival advantage of PD.

The present study has several limitations. First, even though the PS matching method was used to overcome limitations of nonrandom allocation to dialysis modality, residual confounding effect cannot be totally excluded. It was difficult to examine whether the indication bias of dialysis modality selection exerted any influence on clinical outcomes. However, to date, most studies included only demographics and comorbidities.[4,6,7,14,17] In contrast, various dialysis-related prognostic factors, including biochemical variables such as hemoglobin, albumin, calcium, phosphorous, and hs-CRP, as well as RRF were used in this study for PS matching to mitigate confounding effect. Second, as HbA_{1c} values at baseline, 3 months, and 6 months after dialysis initiation were not available in 129 patients, these patients were excluded from the final analysis of PS matching. But there were no significant differences between patients with and without mean HbA_{1c} levels except the use of erythropoiesis-stimulating agent (ESA). Third, shortened erythrocyte survival and ESA use can discredit HbA_{1c} as a marker of glycemic control in dialysis patients. To overcome this limitation, hemoglobin concentrations and ESA use were included in PS calculation and it was revealed that there were no significant differences in hemoglobin levels and ESA use between HD and PD after PS matching. Recent evidence indicated that HbA_{1c} had modest-to-strong correlations with serum glucose, glycated albumin, and serum fructosamine, and these correlations were similar between HD and PD patients.[31] Glycated albumin and fructosamine have been known to be impervious to anemia than HbA_{1c},[31] but unfortunately, these surrogates were not available in our cohort. Fourth, the HbA_{1c} cutoff value of 8.0% used to stratify patients into good and poor glycemic control groups was relatively arbitrary. However, as our subjects were incident dialysis patients and the mean value of HbA_{1c} at dialysis initiation and during the first 6 months was used, HbA_{1c} <8.0% was defined as the good glycemic control group according to the ADA guideline for patients with advanced micro or macrovascular complications (stage 3 or worse chronic kidney disease).[32] Fifth, as this study included only Korean incident dialysis patients, results may not be generalized to other populations. Primary outcome in the present study was relatively small compared with those in Western

ESRD patients. We surmised that the difference may be attributed to disparate ethnicities, as the mortality rates of our patients were comparable with those of Japanese patients.[33] Lastly, the follow-up duration was relatively short. Notwithstanding these limitations, the present study has distinct strengths. The heterogeneity of the study population has been indicated as a possible reason for discrepant findings among previous studies. According to a recent systematic review of 25 eligible studies by the European Renal Best Practice Diabetes Guideline Development Group, no study included only diabetic patients[18]; the proportion of diabetic patients ranged from 9%[12] to 61%.[16] On the contrary, we included only incident dialysis patients with diabetes to focus the impact of glycemic control in these patients and to preserve sufficient statistical power. Finally, the present study enrolled nationally distributed subjects from private clinics to tertiary hospitals between 2008 and 2013, suggesting that the results of this study on our nationwide contemporary cohort could be more helpful to provide evidence for deciding optimal dialysis modality for Korean diabetic dialysis patients in the present era.

In conclusion, the overall patient survival of PD was significantly higher compared with that of HD in incident dialysis patients with diabetes. In addition, better patient survival with PD was influenced by the degree of glycemic control. Survival advantage of PD patients was consistent only in the good glycemic control group. These findings suggest that glycemic control may partly contribute to better survival of PD in Korean incident dialysis patients with diabetes. Nevertheless, further well-designed randomized controlled studies are required to delineate the causal relationship between glycemic control and dialysis modality-related mortality in these patients.

ACKNOWLEDGMENTS

The authors would like to extend sincere appreciation to all participants and investigators of the cohort study (CRC for ESRD) in Korea.

REFERENCES

1. Collins AJ, Foley RN, Herzog C, et al. United States Renal Data System 2008 Annual Data Report. *Am J Kidney Dis.* 2009;53(1 suppl):S1–S374.
2. Locatelli F, Pozzoni P, Del Vecchio L. Renal replacement therapy in patients with diabetes and end-stage renal disease. *J Am Soc Nephrol.* 2004;15(suppl 1):S25–S29.
3. Collins AJ, Foley RN, Chavers B, et al. US Renal Data System 2013 Annual Data Report. *Am J Kidney Dis.* 2014;63(1 suppl):A7.
4. Fenton SS, Schaubel DE, Desmeules M, et al. Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. *Am J Kidney Dis.* 1997;30:334–342.
5. Vonesh EF, Moran J. Mortality in end-stage renal disease: a reassessment of differences between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol.* 1999;10: 354–365.
6. Choi SR, Lee SC, Kim BS, et al. Comparative study of renal replacement therapy in Korean diabetic end-stage renal disease patients: a single center study. *Yonsei Med J.* 2003;44:454–462.
7. Couchoud C, Bolignano D, Nistor I, et al. Dialysis modality choice in diabetic patients with end-stage kidney disease: a systematic review of the available evidence. *Nephrol Dial Transplant.* 2015;30:310–320.
8. van Diepen AT, Hoekstra T, Rotmans JI, et al. The association between dialysis modality and the risk for dialysis technique and non-dialysis technique-related infections. *Nephrol Dial Transplant.* 2014;29:2244–2250.
9. Yoo DE, Park JT, Oh HJ, et al. Good glycemic control is associated with better survival in diabetic patients on peritoneal dialysis: a prospective observational study. *PLoS One.* 2012;7:e30072.
10. Schaubel DE, Morrison HI, Fenton SS. Comparing mortality rates on CAPD/CCPD and hemodialysis. The Canadian experience: fact or fiction? *Perit Dial Int.* 1998;18:478–484.
11. Heaf JG, Lokkegaard H, Madsen M. Initial survival advantage of peritoneal dialysis relative to haemodialysis. *Nephrol Dial Transplant.* 2002;17:112–117.
12. Termorshuizen F, Korevaar JC, Dekker FW, et al. Hemodialysis and peritoneal dialysis: comparison of adjusted mortality rates according to the duration of dialysis: analysis of The Netherlands Cooperative Study on the Adequacy of Dialysis 2. *J Am Soc Nephrol.* 2003;14:2851–2860.
13. Vonesh EF, Snyder JJ, Foley RN, et al. Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? *Kidney Int Suppl.* 2006;70:S3–S11.
14. Collins AJ, Hao W, Xia H, et al. Mortality risks of peritoneal dialysis and hemodialysis. *Am J Kidney Dis.* 1999;34:1065–1074.
15. Jaar BG, Coresh J, Plantinga LC, et al. Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med.* 2005;143:174–183.
16. Liem YS, Wong JB, Hunink MG, et al. Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. *Kidney Int.* 2007;71:153–158.
17. Mehrotra R, Chiu YW, Kalantar-Zadeh K, et al. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med.* 2011;171:110–118.
18. Rhee CM, Leung AM, Kovesdy CP, et al. Updates on the management of diabetes in dialysis patients. *Semin Dial.* 2014;27:135–145.
19. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care.* 2015;38(suppl 1):S8–S16.
20. Kim H, Kim KH, Park K, et al. A population-based approach indicates an overall higher patient mortality with peritoneal dialysis compared to hemodialysis in Korea. *Kidney Int.* 2014;86:991–1000.
21. Mircescu G, Garneata L, Florea L, et al. The success story of peritoneal dialysis in Romania: analysis of differences in mortality by dialysis modality and influence of risk factors in a national cohort. *Perit Dial Int.* 2006;26:266–275.
22. Lukowsky LR, Mehrotra R, Kheifets L, et al. Comparing mortality of peritoneal and hemodialysis patients in the first 2 years of dialysis therapy: a marginal structural model analysis. *Clin J Am Soc Nephrol.* 2013;8:619–628.
23. Wu MS, Yu CC, Wu CH, et al. Pre-dialysis glycemic control is an independent predictor of mortality in type II diabetic patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int.* 1999;19(suppl 2):S179–S183.
24. Chen JL, Mehrotra R, Kalantar-Zadeh K. Surviving the first year of peritoneal dialysis: enduring hard times. *Am J Kidney Dis.* 2014;64:673–676.
25. Moist LM, Port FK, Orzol SM, et al. Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol.* 2000;11:556–564.
26. Kumar VA, Sidell MA, Jones JP, et al. Survival of propensity matched incident peritoneal and hemodialysis patients in a United States health care system. *Kidney Int.* 2014;86:1016–1022.
27. Huckvale K, Car M, Morrison C, et al. Apps for asthma self-management: a systematic assessment of content and tools. *BMC Med.* 2012;10:144.

28. Mehrotra R, Kermah D, Fried L, et al. Chronic peritoneal dialysis in the United States: declining utilization despite improving outcomes. *J Am Soc Nephrol.* 2007;18:2781–2788.
29. Saran R, Bragg-Gresham JL, Rayner HC, et al. Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. *Kidney Int.* 2003;64:254–262.
30. Pulliam J, Li NC, Maddux F, et al. First-year outcomes of incident peritoneal dialysis patients in the United States. *Am J Kidney Dis.* 2014;64:761–769.
31. Williams M, Mittman N, et MAL, et al. The glycemic indices in dialysis evaluation (GIDE) study: Comparative measures of glycemic control in diabetic dialysis patients. *Hem Int.* 2015;19: 562–571.
32. American Diabetes A. Glycemic targets. *Diabetes Care.* 2015;38(suppl):S33–S40.
33. Robinson BM, Port FK. International hemodialysis patient outcomes comparisons revisited: the role of practice patterns and other factors. *Clin J Am Soc Nephrol.* 2009;4(suppl 1):S12–S17.