Comparative Effectiveness of Dialysis Modality on Laboratory Parameters of Mineral Metabolism

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Keywords

Maintenance dialysis · Mineral and bone disorders · Marginal structural model · In-center hemodialysis · Peritoneal dialysis · Extended-hours hemodialysis · Nocturnal hemodialysis

Abstract

Introduction: Chronic kidney disease-mineral and bone disorders (CKD-MBD) are prevalent in patients undergoing maintenance dialysis. Yet, there are limited and mixed evidence on the effects of different dialysis modalities involving longer treatment times or higher frequencies on CKD-MBD markers. **Methods:** This cohort study used data from 132,523 incident dialysis patients treated with any of the following modalities: conventional thrice-weekly in-center hemodialysis, nocturnal in-center hemodialysis (NICHD), home hemodialysis (HHD), or peritoneal dialysis (PD) from 2007 to 2011.

We used marginal structural models fitted with inverse probability weights to adjust for fixed and time-varying confounding and informative censoring. We estimated the average effects of treatments with different dialysis modalities on time-varying serum concentrations of CKD-MBD markers: albumin-corrected calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase (ALP) using pooled linear regression. **Results:** Most of the cohort were exclusively treated with conventional in-center hemodialysis, while few were ever treated with NICHD or HHD. At the baseline, PD patients had the lowest mean and median values of PTH, while NICHD patients had the highest median values. During follow-up, compared to hemodialysis patients, patients treated with NICHD had lower mean serum PTH (19.8 pg/mL [95% confidence interval: 2.8, 36.8] lower), whereas PD and HHD patients had higher mean PTH (39.7 pg/mL [31.6, 47.8]

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and 51.2 pg/mL [33.0, 69.3] higher, respectively). Compared to hemodialysis patients, phosphate levels were lower for patients treated with NICHHD (0.44 mg/dL [0.37, 0.52] lower), PD (0.15 mg/dL [0.12, 0.19] lower), or HHD (0.33 mg/dL [0.27, 0.40] lower). There were no clinically meaningful associations between dialysis modalities and concentrations of calcium or ALP. **Conclusion:** In incident dialysis patients, compared to treatment with conventional in-center hemodialysis, treatments with other dialysis modalities with longer treatment times or higher frequency were associated with different patterns of serum phosphate and PTH. Given the recent growth in the use of dialysis modalities other than hemodialysis, the associations between the treatment and the CKD-MBD markers warrant additional study.

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Introduction

Derangements in mineral and bone disorder markers are commonly observed in advanced chronic kidney disease (CKD) patients, including those with chronic kidney failure requiring dialysis. Such markers include serum calcium, phosphate, alkaline phosphatase (ALP), and parathyroid hormone (PTH), and their associations with clinical outcomes (i.e., higher risks of cardiovascular events and mortality) have been well established [1–12]. Clinical guidelines for chronic kidney disease-mineral and bone disorder (CKD-MBD) treatment have stressed the importance of evaluating serial measurements and trends in CKD-MBD markers and targeting a range of respective goals rather than focusing on a single measurement [13, 14]. The majority of support for these recommendations comes from studies of conventional in-center hemodialysis populations, despite the recent growth of treatment with alternative dialysis modalities, including hemodialysis with longer treatment times or greater treatment frequency [15].

The pathophysiology underlying CKD-MBD is complex. Hyperphosphatemia remains a pervasive complication in patients with chronic kidney failure, partially explained by the imbalance of dietary intake and dialysis clearance of phosphate in the setting of little or no residual kidney function [16]. Clinical trials have shown that intensive modalities such as nocturnal in-center hemodialysis (NICHHD) and frequent home hemodialysis (HHD) can reduce hyperphosphatemia due to their longer duration or more frequent treatments, yet an effect on other CKD-MBD markers such as calcium and PTH was not clinically meaningful [17–19]. It remains unclear if this

relationship extends to other dialysis modalities. There are little data regarding the impact of alternative dialysis modalities on ALP, which has been identified as a strong survival predictor in hemodialysis patients [5, 7, 12].

Given the current trends showing substantial growth in the use of modalities other than conventional hemodialysis in the USA, this paucity of data represents a substantial gap in understanding [20, 21]. We hypothesized that differences in the clearance conferred across modalities may arise due to real-world practice patterns involving nutrition, phosphate dynamics, and medications thereby affecting CKD-MBD levels. Studies have been limited in addressing the biases inherent in observational studies, including time-varying confounding and informative censoring. Traditional regression methods are not well-suited to address such complex biases. Therefore, using a large cohort of incident dialysis patients, we sought to examine the effects of different dialysis modalities on time-varying levels of CKD-MBD markers, using inverse probability weighted marginal structural models (MSM) to address the biases that arise with longitudinal studies [22, 23].

Methods

Study Population and Data Source

The cohort comprised patients who initiated treatment within facilities operated by a large dialysis organization (LDO) in the USA from 2007 to 2011 [24–26]. Patients were excluded if treated for less than 60 days, ever received a frequent or less frequent hemodialysis treatment schedule (more or less than the conventional thrice-weekly in-center hemodialysis treatments per week for 6 consecutive weeks) during the follow-up, had missing data on race/ethnicity or sex, were not on a single modality for at least 45 consecutive days, or had missing treatment information in the first 91 days. The final cohort included 132,523 incident dialysis patients (Fig. 1). The Institutional Review Boards of the University of Washington and University of California, Irvine, approved this study and waived the need for informed consent.

Follow-up was divided into 20 consecutive quarters, representing 91-day intervals from the start of dialysis. Patients were censored at the time of death, transplantation, transfer to another facility outside of the LDO, discontinued dialysis, or at study conclusion (December 31, 2011).

Exposures, Outcomes, and Clinical Characteristics

The exposures of interest were the following time-updated modalities: conventional thrice-weekly in-center hemodialysis, NICHHD, peritoneal dialysis (PD), and HHD. Patients were assigned to a modality based on LDO treatment records. Assignment to an initial modality required that a patient was exclusively treated with the modality for at least 60 days from initiation. In all subsequent quarters until censorship, the patient needed exclusive treatment with the modality for at least 45 days in each quarter. In

Fig. 1. Cohort construction.

order to be considered as a switched modality, the patient had to be treated with the new modality for at least 60 consecutive days. If a patient were censored less than 45 days into the 91-day quarter, the longest modality was assigned.

The outcomes of interest were: (1) serum corrected calcium, (2) phosphate, (3) PTH, and (4) ALP. Blood samples were drawn at the dialysis facilities using standard techniques and uniformly analyzed at a central laboratory in Deland, FL, within 24 h. Most laboratory values were collected before treatment and measured monthly. The cumulative erythropoiesis-stimulating agent dose per quarter was divided by the number of dialysis treatments over each quarter and multiplied by the median number of treatments per week. Serum calcium was corrected when the serum albumin concentration was <4.0 g/dL [9]. Intravenous (IV) and oral medications were measured as the number of days of the medication over each quarter. Laboratory data were averaged during each quarter to minimize short-term variability effects. Measurements in the first 91-day interval of treatment were considered as baseline values.

Baseline covariates included age, sex, race/ethnicity, primary insurance, incidence year, diabetes, hypertension, dyslipidemia, congestive heart failure, atherosclerotic heart disease, and other cardiovascular diseases. In addition, the patient quarter of follow-up (time), previous modality, and following lagged (previous quar-

ter) time-varying covariates were included: serum albumin, hemoglobin, phosphate, PTH, median erythropoiesis-stimulating agent dose, vascular access type, and any hospitalization. Covariates were based on a priori knowledge as predictors of dialysis modality [24]. Information on time-varying (current quarter) days of medication use (0, 1– <31 , 31– <61 , 61–91 days) for the following medications were included in the model adjustment: calcium phosphate binders, non-calcium phosphate binders, cinacalcet, and combined oral and IV vitamin D.

Statistical Methods

Data were summarized using proportions, means ($\pm$ standard deviation, SD), and median (interquartile range, IQR), where appropriate. As conventional in-center hemodialysis was the predominant modality over follow-up, clinical characteristics were summarized for the following groups in Table 1: patients receiving only hemodialysis (HD only), NICHD and/or HD (ever NICHD), PD and/or HD (ever PD), and home HD and/or HD (ever HHD) during follow-up. The “other” category represents patients who received several modalities other than the aforementioned combinations (e.g., both NICHD and PD during follow-up).

MSM fitted using inverse probability weights were used to examine the average direct effects of dialysis modalities on individual CKD-MBD markers while controlling for time-varying

Table 1. Baseline patient characteristics of 132,523 patients, stratified by dialysis modality combination

Characteristics	Total	Dialysis modality combination				Other*
		HD only	ever NICH	ever PD	ever HHD	
Patients, <i>n</i>	132,523	114,168	1,018	15,398	1,711	228
Initial modality, % HD	91	100	64	32	69	40
Follow-up time, months	17 [8, 31]	16 [8, 30]	29 [17, 41]	20 [11, 33]	25 [14, 37]	35 [25, 47]
Age, years	62±15	63±15	51±13	56±16	53±14	49±15
Female, %	43	43	30	44	33	35
Race/ethnicity, %						
White	49	47	46	56	69	59
African American	30	31	38	23	20	32
Hispanic	14	15	11	13	6	6
Asian	3	3	3	4	3	1
Other	4	4	3	3	2	2
Primary insurance, %						
Medicare	52	53	35	45	35	33
Medicaid	7	7	8	5	4	3
Other	41	40	57	50	61	64
Comorbidities, %						
Diabetes	59	58	69	63	61	60
Hypertension	52	51	56	52	71	69
Congestive heart failure	35	37	56	19	49	52
Atherosclerotic heart disease	15	14	20	17	27	26
Other cardiovascular diseases	15	15	19	14	22	18
Dyslipidemia	28	25	30	46	44	59
Year of incidence, %						
2007	20	20	23	19	22	36
2008	20	20	24	19	25	27
2009	21	21	25	21	24	23
2010	21	21	18	23	16	11
2011	18	18	10	17	13	3
Access type in first 91 days, %						
CVC	74	80	76	28	61	44
AV fistula/AV graft	18	20	24	3	39	12
PD catheter	8	0	0	69	0	44
Treatment characteristics in first 91 days						
Treatment time per session, min	211±26	211±24	277±84	N/A	200±35	245±76
Treatments, <i>N</i>	31±9	31±8	33±8	N/A	34±13	27±11

Table 1 (continued)

Characteristics	Total	Dialysis modality combination				
		HD only	ever NICHd	ever PD	ever HHD	Other*
Laboratory measurements in first 91 days						
Serum albumin, g/dL	3.5±0.5	3.5±0.5	3.6±0.5	3.7±0.5	3.7±0.5	3.7±0.4
Blood hemoglobin, g/dL	11.1±1.2	11.1±1.2	11.1±1.2	11.3±1.2	11.2±1.2	11.3±1.2
Serum ferritin, ng/mL	274 [158, 473]	282 [164, 485]	235 [138, 372]	227 [125, 396]	234 [136, 402]	228 [132, 375]
Iron saturation, %	23.3±9.2	23.1±9.1	21.7±8.0	25.2±9.2	23.6±8.7	23.4±7.9
Serum calcium, mg/dL (corrected)	9.10±0.56	9.10±0.56	9.05±0.57	9.12±0.57	9.13±0.55	9.14±0.58
Serum phosphate, mg/dL	4.93±1.15	4.92±1.15	5.27±1.21	4.97±1.14	5.12±1.17	5.22±1.07
Median serum parathyroid hormone, pg/mL	312 [195, 486]	314 [197, 486]	377 [243, 567]	298 [185, 480]	317 [191, 490]	362 [224, 565]
Mean serum parathyroid hormone, pg/mL	393±331	393±329	464±359	388±343	390±308	489±416
Median serum alkaline phosphatase, U/L	86.2 [68.0, 113.3]	87.0 [68.8, 115.0]	86.8 [68.3, 111.0]	80.8 [64.0, 104.2]	78.3 [62.3, 102.0]	80.3 [63.3, 101.8]
Mean serum alkaline phosphatase, U/L	102.2±72.4	103.8±73.9	98.7±52.0	92.2±63.1	91.1±56.9	92.1±47.4
ESA dose, median U/week	4,713 [1,500, 11,931]	4,704 [1,496, 11,943]	4,820 [1,600, 12,789]	4,690 [1,496, 11,806]	5,028 [1,650, 12,571]	4,950 [1,586, 11,289]
Hospitalized in first 91 days, %	34	35	30	23	24	26
Medications in first 91 days, %						
Calcium-based phosphate binders, days						
0	67	67	60	64	59	60
1–<31	7	7	7	7	9	8
31–<61	8	9	10	8	9	7
61–91	18	17	22	21	23	25
Non-calcium phosphate binders, days						
0	64	64	58	59	58	59
1–<31	9	9	10	8	10	10
31–<61	10	10	12	10	10	13
61–91	17	16	20	23	22	19
Cinacalcet						
0	94	94	88	92	90	87
1–<31	2	2	4	3	4	5
31–<61	2	2	5	2	3	4
61–91	2	2	3	3	3	4
Oral and IV vitamin D						
0 days	29	28	20	31	26	17
1–<31	18	19	16	13	16	18
31–<61	18	18	20	17	18	24
61–91	35	35	44	39	40	42

Data presented as mean±standard deviation, median [interquartile range], or proportion as appropriate. HD, conventional in-center hemodialysis; NICHd, nocturnal in-center hemodialysis; PD, peritoneal dialysis; HHD, home hemodialysis; CVC, central venous catheter; AV, arteriovenous; ESA, erythropoiesis-stimulating agent; IV, intravenous. *The “other” category represents patients who received several modalities other than the HD only, ever NICHd, ever PD, or ever HHD, combinations.

confounding and informative censoring influenced by the prior history of modality and covariates. Inverse probability of treatment weights (IPTW) were calculated as the inverse of the predicted probability of a patient receiving the modality they were actually treated with in that patient quarter, given baseline and time-varying covariates [22, 23, 25]. Technical guides have further detailed these methods in the context of CKD [27–29]. Briefly, the IPTW numerator was calculated as the probability of the observed treatment, given the previous modality and baseline characteristics using multinomial logistic regression for each quarter of follow-up. The IPTW denominator was calculated as the probability of the observed treatment, given the previous modality and both baseline and previous (lagged) time-varying covariates or confounders for each quarter using multinomial logistic regression. Stabilized IPTW were calculated as the division of the estimated IPTW numerator and denominator for each quarter to reduce the potential impact of extreme values possibly due to the presence of atypical treatment assignments. Likewise, inverse probability of censoring weights (IPCW) were created using logistic regression models at each quarter to address informative censoring. The same covariates used to calculate the IPTW were used for the IPCW to model the probability of not having been censored at a prior quarter. Stabilized IPCW were similarly calculated.

The product of the stabilized IPTW and stabilized IPCW yielded stabilized weights (SW), which were used in our final analytical models. The final SW were expected to have a mean of 1.00. In observations with extreme weights likely due to a deterministic combination of variables, the final SW were trimmed at the 99.999th percentile of all observations. Distributions of SW are presented in online supplemental Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000521508). Summarized mean CKD-MBD marker levels across dialysis modalities and over 12 quarters of follow-up were weighted by the final SW (online suppl. Fig. 2).

After calculating the SW, we analyzed the associations between time-updated modalities and CKD-MBD markers using pooled generalized linear models, with conventional in-center hemodialysis as the referent group. The weighted MSM were adjusted for all baseline demographic characteristics, time, prior treatment, and ordinal groups of days of medications. To evaluate the robustness of the MSM in handling time-varying confounding and censoring, we also evaluated nonweighted models to show the combined impact of those biases. Finally, we tested for interaction through the use of an interaction term and stratification for baseline demographics in the weighted MSM. We additionally performed a series of sensitivity analyses to evaluate our results (online suppl. Text 1).

There were no missing data on baseline demographics or medications. Time-varying characteristics were missing in <4% of all patients at baseline and 40% of patients had at least one missing laboratory covariate during follow-up. Missing values for time-varying covariates were imputed using multiple imputations for 5 datasets under fully conditional specification [25]. Imputed time-varying covariates were used in SW estimation only. For each outcome, the unimputed value was used in the analyses given that <1% of the cohort was missing information on any CKD-MBD marker. Analyses were performed with SAS, version 9.4 (Cary, NC, USA).

Results

Study Cohort

The cohort of 132,523 incident dialysis patients included 43% females, 30% African Americans, and 59% diabetics (Table 1). Over a median [IQR] follow-up of 17 [8, 30] months, we observed 32,631 (25%) deaths and 5,733 (4%) transplants. A total of 114,168 (86%) patients were exclusively treated with conventional in-center hemodialysis during the follow-up, whereas the percentage of patients who were ever treated with NICHHD, PD, or HHD in addition to hemodialysis were 1,018 (0.8%), 15,398 (11.6%), and 1,711 (1.3%), respectively. There were 228 (<0.2%) patients who were treated with different combinations of multiple modalities over follow-up. Conventional in-center hemodialysis was the predominant modality in each patient quarter, although there was a rise in the proportion treated with PD, HHD, and NICHHD (online suppl. Fig. 3).

Patients exclusively treated with conventional in-center hemodialysis were older, primarily under Medicare insurance, and more likely to be hospitalized within the first 91 days of treatment as compared with those treated with other modalities. Patients treated with home modalities (HHD and PD) were more likely to be White, have a higher prevalence of dyslipidemia, and have higher serum albumin levels. Patients ever treated with NICHHD had longer treatment times and more treatments during the first 91 days of dialysis. Single-pool Kt/V for hemodialysis, ever NICHHD and ever HHD patients were 1.5 ± 0.3 , 1.6 ± 0.5 , and 1.4 ± 0.4 , respectively, while ever PD patients had a total weekly Kt/V of 2.6 ± 0.7 . Finally, HHD patients had more treatments during the first 91 days of dialysis and were treated for a median [IQR] of 5 [4, 6] times/week over follow-up.

The baseline mean $\pm$ SD of serum calcium and phosphate was 9.10 ± 0.56 and 4.93 ± 1.15 mg/dL, respectively; while the median [IQR] (mean $\pm$ SD) of PTH and ALP was 310 [195, 486] (393 ± 331) pg/mL and 86.2 [68.0, 113.3] (102.2 ± 72.4) U/L, respectively. The majority of patients were not taking phosphate binders or cinacalcet during the baseline period, although a majority of patients were prescribed oral and IV vitamin D.

Effect of Dialysis Modalities on Serum Calcium

At baseline, the mean $\pm$ SD serum calcium was lowest for those ever treated with NICHHD (9.05 ± 0.57 mg/dL), while the average serum calcium was similar for other groups. After weighting, mean serum calcium were similar across modalities early in follow-up, those on PD

Table 2. Estimates of the effect of dialysis modality on the difference in CKD-MBD markers among 132,523 patients in unweighted and weighted models

Modality	Unweighted		Weighted	
	estimate [95% CI]	<i>p</i>	estimate [95% CI]	<i>p</i>
Serum calcium				
HD	9.17 [9.15, 9.18]		9.15 [9.12, 9.18]	
NICHD	0.04 [0.01, 0.08]	0.008	0.04 [0.00, 0.08]	0.05
PD	−0.06 [−0.07, −0.05]	<0.0001	−0.06 [−0.08, −0.04]	<0.0001
HHD	−0.01 [−0.04, 0.01]	0.27	0.00 [−0.03, 0.04]	0.83
Serum phosphate				
HD	5.56 [5.52, 5.61]		5.63 [5.56, 5.69]	
NICHD	−0.48 [−0.56, −0.41]	<0.0001	−0.44 [−0.52, −0.37]	<0.0001
PD	−0.18 [−0.21, −0.15]	<0.0001	−0.15 [−0.19, −0.12]	<0.0001
HHD	−0.36 [−0.41, −0.30]	<0.0001	−0.33 [−0.40, −0.27]	<0.0001
Parathyroid hormone				
HD	347.8 [337.6, 358.1]		370.1 [349.8, 390.5]	
NICHD	−18.3 [−33.9, −2.7]	0.02	−19.8 [−36.8, −2.8]	0.02
PD	42.4 [36.1, 48.7]	<0.0001	39.7 [31.6, 47.8]	<0.0001
HHD	56.8 [42.5, 71.0]	<0.0001	51.2 [33.0, 69.3]	<0.0001
Alkaline phosphatase				
HD	117.1 [114.6, 119.5]		123.5 [120.0, 127.0]	
NICHD	−0.9 [−3.9, 2.1]	0.55	−0.9 [−4.3, 2.5]	0.61
PD	−6.2 [−7.9, −4.5]	<0.0001	−6.1 [−8.5, −3.7]	<0.0001
HHD	−9.2 [−12.0, −6.3]	<0.0001	−9.0 [−13.5, −4.5]	<0.0001

All models were adjusted for age, sex, race/ethnicity, primary insurance, incidence year, and the following comorbidities: diabetes, hypertension, dyslipidemia, congestive heart failure, atherosclerotic heart disease, and other cardiovascular disease, patient quarter, prior modality, and categories of medication use. Weighted models include the use of standardized weights as described in the text. CI, confidence interval; HD, conventional in-center hemodialysis; NICHD, nocturnal in-center hemodialysis; PD, peritoneal dialysis; HHD, home hemodialysis.

seemed to have slightly higher mean levels after 8 quarters of follow-up (2 years) (online suppl. Fig. 2). According to our weighted model, the adjusted population mean [95% confidence interval] of serum calcium per patient quarter for the conventional in-center hemodialysis reference group was 9.15 [9.12, 9.18] mg/dL (Table 2; Fig. 2a). Compared to conventional in-center hemodialysis patients, serum calcium levels for patients on NICHD for a given patient quarter was 0.04 [0.00, 0.08] mg/dL higher, whereas PD patients' serum calcium was lower (0.06 [0.04, 0.08] mg/dL lower). Notably, there was no difference in mean serum calcium per patient quarter for patients on HHD. Similar relationships were observed in unweighted models.

Effect of Dialysis Modalities on Serum Phosphate

At baseline, the mean $\pm$ SD serum phosphate was lowest for patients treated with conventional in-center hemodialysis or with PD. Weighted means of serum phosphate showed that those on home modalities experienced

a gradual increase over follow-up (online suppl. Fig. 2). The population mean of serum phosphate per patient quarter for the conventional in-center hemodialysis reference group in the weighted model was 5.63 [5.56, 5.69] mg/dL (Table 2; Fig. 2b). Mean serum phosphate levels for patients on NICHD, PD, or HHD for a given patient quarter were lower on average, compared to conventional in-center hemodialysis patients. NICHD patients had the lowest average serum phosphate per patient quarter (0.44 [0.37, 0.52] mg/dL lower). Unweighted models showed that mean serum phosphate levels for conventional in-center hemodialysis patients were slightly lower at 5.56 [5.52, 5.61] mg/dL after adjustment.

Effect of Dialysis Modalities on PTH

At baseline, the median [IQR] PTH was lowest for those ever treated with PD (298 [185, 480] pg/mL), while those ever treated with NICHD had the highest median PTH. After initiation, weighted mean PTH decreased and reach a nadir within the second patient quarter, while

weighted mean levels soon increased gradually over time (online suppl. Fig. 2). The adjusted population mean estimate of PTH per patient quarter for the conventional in-center hemodialysis reference in the weighted model was 370 [350, 391] pg/mL (Table 2; Fig. 2c). Only NICHHD patients had a lower PTH in comparison to conventional in-center hemodialysis patients (19.8 [2.8, 36.8] pg/mL lower). Conversely, both PD and HHD patients experienced a higher PTH (39.7 [31.6, 47.8] and 51.2 [33.0, 69.3] pg/mL). Unweighted models for PTH showed that the mean estimate of PTH for conventional in-center hemodialysis patients was lower than that of the weighted model. Similar patterns for each modality compared to conventional in-center hemodialysis were observed, where HHD patients also had the highest PTH.

Effect of Dialysis Modalities on ALP

At baseline, the mean $\pm$ SD and median [IQR] ALP were highest for conventional in-center hemodialysis and ever NICHHD patients. Weighted mean ALP showed a clear division between home modalities (PD and HHD) versus conventional in-center hemodialysis and NICHHD patients. During follow-up, home modality patients had lower mean ALP after weighting (online suppl. Fig. 2). The estimated population mean of ALP per patient quarter for the conventional in-center hemodialysis reference group in the weighted model was 123.5 [120.0, 127.0] U/L (Table 2; Fig. 2d). Compared to the reference group, both PD and HHD patients had a lower ALP. NICHHD patients also experienced on average a lower ALP. Moreover, the unweighted model also exhibited similar relationships, where HHD patients had the lowest ALP compared to conventional in-center hemodialysis patients.

Sensitivity and Subgroup Analyses

For all CKD-MBD outcomes, bias analysis with moderate and strong uncontrolled confounder strengths on the modality-CKD-MBD marker relationship yielded similar results to that of the main analyses (online suppl. Table 1). Inclusion of body mass index in our MSM was also comparable to our main analyses.

The modality and CKD-MBD marker relationships were modified by age ($p_{\text{interaction}} = 0.05$ for ALP and $p_{\text{interaction}} < 0.0001$ for all else) (Fig. 2). Moreover, the relationship of modality with serum calcium and PTH, respectively, were modified by race/ethnicity. Notably, among African American patients, observed differences in PTH levels for PD or HHD treatment were greater ($p_{\text{interaction}} < 0.0001$). African American patients treated with HHD had on average, a 107 [54, 161] pg/mL higher level com-

pared with African American conventional in-center hemodialysis patients; the difference in White HHD patients was a 32 [14, 51] pg/mL higher level compared with White conventional in-center hemodialysis patients. African American PD patients had larger negative differences in calcium compared with their conventional in-center hemodialysis treated counterparts ($p_{\text{interaction}} = 0.01$). Finally, only the association of modality and serum calcium was modified by sex ($p_{\text{interaction}} = 0.004$). In PD patients, men had a more negative difference in serum calcium compared to men treated with conventional in-center hemodialysis.

Discussion

In a cohort of incident dialysis patients, we observed that treatment with alternative dialysis modalities including hemodialysis modalities with longer treatment times or a greater frequency were associated with different patterns of CKD-MBD markers compared to treatment with conventional in-center hemodialysis. Although conventional thrice-weekly in-center hemodialysis is the predominant form of kidney replacement therapy in the USA, there has been a recent trend of increased use of other modalities [15]. The Advancing American Kidney Health Initiative includes increasing the number of patients on home dialysis modalities, and thus it is likely that more patients will initiate and/or switch to modalities other than in-center hemodialysis in the future [20, 21]. Given the prevalence of CKD-MBD in dialysis patients, this study adds to understanding the extent of how dialysis modalities influence changes in CKD-MBD markers.

A few studies have examined the effect of longer or frequent treatment modalities on CKD-MBD markers. The Frequent Hemodialysis Network Nocturnal Trial showed that frequent nocturnal HHD patients had a 1.24 mg/dL decrease in serum phosphate compared to conventional thrice-weekly HHD, respectively, over a year of follow-up [18]. Additionally, there was a trend toward lower PTH for frequent nocturnal home patients. Similar results were observed in other small clinical trials investigating CKD-MBD changes [17, 19]. These trials also showed that the intensive treatment group experienced

Fig. 2. Estimates of the effect of dialysis modality on the difference in serum calcium (a), serum phosphate (b), parathyroid hormone (c), and alkaline phosphatase (d) in weighted models.

(For figure see next page.)

the decrease in phosphate binder dose or even required phosphate supplement [17–19]. Comparatively, our study showed that NICHHD patients had similar associations with CKD-MBD markers with a lower magnitude of estimates, likely reflective of real-world practice patterns over a long period of follow-up where dialysis prescription (e.g., treatment time and frequency) and medications are often adjusted to meet the current goals of CKD-MBD parameters. Moreover, our source population comprised incident dialysis patients, many of whom had residual kidney function and hence can achieve current targets for dialysis adequacy with less intensified dialysis [30]. A slightly higher serum calcium level among NICHHD patients is likely due to the more frequent use of high dialysate calcium bath as shown in the Frequent Hemodialysis Network trial [18, 31].

Another important factor affecting the serum phosphate is dialysis frequency. Serum phosphate rapidly decreases during a hemodialysis session and then gradually increases, while PTH levels are not influenced by the day of measurement [32, 33]. Extended treatment times, such as with NICHHD, have shown to increase serum phosphate removal [17, 34]. Among patients on hemodialysis, the predialysis serum phosphate level is 30% higher than the corresponding time-averaged serum phosphate level [35]. This dynamic change is mitigated with frequent dialysis modalities such as HHD and more so with PD, leading to lower serum phosphate even with the same phosphate clearance [36]. It may partly explain our findings of lower serum phosphate levels and paradoxically higher PTH levels in HHD and PD than in conventional in-center hemodialysis; time-averaged serum phosphate levels may be actually higher in HHD and PD within our cohort. This does raise an important clinical question about the appropriateness of identical serum phosphate targets across dialysis modalities as suggested by current clinical practice guidelines [14].

While prior studies have investigated associations of modality with serum phosphate, PTH, and calcium, the association of modality with ALP has been understudied. Several studies have shown the linear association between ALP and mortality among hemodialysis and PD patients, and high ALP levels in this population are attributed to the high bone turnover in response to secondary hyperparathyroidism [5, 7, 37, 38]. Rhee et al. [7] reported a similar mortality risk between patients on hemodialysis and those on PD across baseline ALP strata, and our study found that compared to conventional in-center hemodialysis, HHD, and PD, but not NICHHD, were associated with slightly lower ALP levels. Interestingly, this associa-

tion with ALP is in the opposite direction to that of PTH despite their well-known positive correlation. This paradoxical finding needs to be validated in other studies including clinical trials and further investigated for underlying mechanisms if confirmed.

There are several limitations to this study. Our study period was from 2007 to 2011, and there could have been secular changes since the release and update of clinical guidelines as well as several drugs that have become available since the last decade. Additional contemporary studies would be needed to evaluate more recent changes. This study was also unable to evaluate other modalities such as in-center frequent or less frequent hemodialysis given the small sample size of these groups within the overall population. We required that patients had a sustained and regular treatment schedule in our modality assignment but were limited in distinguishing patients who temporarily switched between modalities in the given quarter, and thus, these patients may be subject to misclassification. Most laboratory values were drawn mid-week, yet measurements were also drawn earlier in the week, thus possibly resulting in measurement error due to the longer interdialytic interval [39]. We controlled for known confounders and predictors of dialysis modality including laboratory markers. Yet, we infer that potential sources of uncontrolled confounding at baseline and over follow-up include patient-level factors including quality of life, behavior, beliefs, and predialysis care or management, residual kidney function, c-reactive protein, fibroblast growth factor-23, and detailed information of daily dosage on calcimimetics, phosphate binders, vitamin D agents as well as phosphate supplements, which are often prescribed for patients on NICHHD or HHD treatments [12, 24]. Given our administrative database, information on dietary intake was unavailable and we could only include markers of malnutrition and cachexia as proxy measurements. Finally, we did not have information on laboratory measurements, treatments, or medications used during a hospital stay, nor incident comorbidities or causes of hospitalizations related to CKD-MBD levels, such as hyperparathyroidism, parathyroidectomy, heart failure, or fracture. Future trials are needed to investigate real-world practice patterns including treatment switching with clinical outcomes.

Nevertheless, the large nationally representative cohort sample with a long duration of follow-up and the evaluation of several dialysis modalities with repeated biomarker measurements strengthen this study. We accounted for CKD-MBD medication use and used inverse probability weighted fitting of MSM to address both fixed and time-varying confounding and informative censor-

ing. These methods remain advantageous over conventional regression given the complex study design. Finally, our series of sensitivity analyses add to the robustness of the observed results.

In conclusion, we observed different levels of serum CKD-MBD markers across dialysis modalities after addressing the complex relationship with fixed and time-varying confounding and informative censoring. Given the expected growth in dialysis modalities other than conventional in-center hemodialysis, especially home modalities, it is imperative to understand the relationship between dialysis modalities and patterns of CKD-MBD markers. Future studies should investigate these relationships with a special focus on hard clinical outcomes and patient-centered outcomes.

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Statement of Ethics

The Institutional Review Boards of the University of Washington and the University of California, Irvine approved this study and waived the need for informed consent due to the non-intrusive nature of the research, patient anonymity, and large sample size.

Conflict of Interest Statement

K.K.Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition & Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor,

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Author Contributions

Research idea and study design: M.B.R., K.K.Z., O.A.A., R.M., and E.S.; data acquisition: R.M., K.K.Z., and E.S.; data analysis/interpretation: M.S., Y.O., S.V.A., O.A.A., and E.S.; statistical analysis: M.S., Y.O., S.V.A., O.A.A., and E.S.; supervision or mentorship: O.A.A., R.M., and E.S.; writing manuscript draft: M.S., Y.O., and M.B.R.; critical revision to the manuscript: W.L.L., C.M.R., C.P.K., K.K.Z., and R.M.

Data Availability Statement

Data presented in this current study were exclusively obtained and derived from electronic health records of the large dialysis organization. Data are proprietary and not publicly available.

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