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Original Article

ORIGINAL ARTICLE

Associations of calcium, phosphate and intact parathyroid hormone levels with mortality, residual kidney function and technical failure among patients on peritoneal dialysis

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ABSTRACT

Background. Associations of calcium, phosphate and intact parathyroid hormone (iPTH) levels with outcomes may be different between patients on peritoneal dialysis (PD) and hemodialysis (HD). The aim of the study is to evaluate these associations among PD patients.

Methods. In this prospective cohort study on the Japan Renal Data Registry, adults on PD at the end of 2009 were included. The observation period was until the end of 2018 and the data were censored at the time of transplantation or transition to HD. Exposures were time-averaged or time-dependent albumin-corrected calcium (cCa), phosphate and iPTH levels. Outcomes were all-cause and cardiovascular mortality, transition to HD and urine output. Data were analyzed using Cox regression models or linear mixed-effects models and the results were shown as cubic spline curves.

Results. Among 7393 patients, 590 deaths and 211 cardiovascular deaths were observed during a median follow-up of 3.0 years. Higher cCa and phosphate levels were associated with higher mortality. Lower cCa levels were associated with a faster decline, whereas lower phosphate was associated with a slower decline in urine output. Lower phosphate and iPTH levels were associated with a lower incidence of transition to HD.

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Conclusions. Among PD patients, the observed associations of cCa, phosphate and iPTH with mortality, residual kidney function and technical failure suggest that avoiding high cCa, phosphate and iPTH levels might improve outcomes.

Keywords: calcium, mortality, parathyroid hormone, peritoneal dialysis, phosphate

INTRODUCTION

Associations of calcium (Ca), phosphate and intact parathyroid hormone (iPTH) levels with mortality have been extensively studied among hemodialysis (HD) patients [1–9]. Higher phosphate, calcium, lower phosphate and calcium levels, and high iPTH levels in some studies, were shown to be associated with higher mortality among HD patients [1–9]. However, studies limited to peritoneal dialysis (PD) patients are scarce (one study limited to incident PD patients [10] and one study lacking information on important confounders [11]). Among PD patients, adynamic bone disease is more prevalent [12]. Ca, phosphate, iPTH and bone turnover seem to play a lesser role in vascular calcification among PD patients compared with HD patients [13]. In addition, rapid shifts of Ca during HD [14], which might be one of the causes of cardiovascular (CV) events among HD patients [15], do not happen in PD. As a result, associations of Ca, phosphate and iPTH levels with mortality may be different between patients on PD and HD.

Studies on the associations of Ca, phosphate and iPTH levels with residual kidney function are scarce among HD patients [16], and there have been no studies among PD patients. Among PD patients, preservation of residual kidney function is especially important to prevent technical failure (transition to HD).

In this study, we examined the associations of Ca, phosphate and iPTH levels with mortality, residual kidney function represented by daily urine output, and transition to HD among patients on PD based on the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR).

MATERIALS AND METHODS

Study design

This is a prospective cohort study on the database from JRDR.

JRDR is a nationwide cohort of dialysis patients in Japan. Details about JRDR have been published previously [17]. The Japanese Society for Dialysis Therapy (JSDT) conducts a survey of all dialysis units in Japan at the end of every year. The response rates were above 95% throughout the study period. The study protocol was approved by the Medicine Ethics Committee of JSDT (Approval No. 62), and the study was conducted in accordance with the Helsinki Declaration. The waiver of consent for JRDR was also approved by the Ethics Committee. Complete de-identification has secured the privacy of human subjects in our database, and its secondary or unofficial use (i.e. any distribution to a third party, unauthorized replication or manipulation of the database, and deviation from the proposal accepted by the Committee of Renal Data Registry) is strictly prohibited by the provision of agreements between the principal investigators and JSDT, by which all rights regarding the database are reserved.

Setting and participants

The inclusion criterion was subjects undergoing PD at the end of 2009. The observation period terminated at the end of 2018. The exclusion criteria were age <18 years, withdrawal from dialysis or apparent errors in the data (the date of death before 2009 or date of death not available).

Exposure of interest and outcomes

Exposures of interest were time-averaged and time-dependent albumin-corrected calcium (cCa), phosphate and iPTH levels. Corrected Ca was calculated by Payne's formula [18]. To convert whole PTH to iPTH values, whole PTH values were multiplied by 1.7 [19–21], as PTH levels were reported as iPTH in some and as whole PTH in others in JRDR database. Outcomes were all-cause and CV mortality, transition to HD (including the transition to a combination of PD and HD [22]), and residual kidney function represented by daily urine output. CV mortality was defined as one of the following: death due to myocardial infarction, valvular heart disease, cardiomyopathy, arrhythmia, pulmonary edema, sudden cardiac death, endocarditis, pericarditis or stroke.

Statistical analyses

Data are shown as number (%), mean [standard deviation (SD)] or median [interquartile range (IQR)] as appropriate. Descriptive statistics were performed by analysis of variance, Kruskal–Wallis test, Chi-square test or Fisher's exact test, as appropriate. Time-averaged cCa, phosphate and iPTH values were calculated as the average of values up to the end of the preceding year (for example, time-averaged cCa values in 2012 were calculated as the average of cCa values from 2009 to 2011). In this study, we employed time-averaged models as primary analyses as a previous study demonstrated that the association between higher phosphate levels and mortality was stronger in a time-averaged model than in a baseline model [23]. Time-dependent cCa, phosphate and iPTH values were defined as values at the end of the preceding year (for example, time-dependent cCa values in 2012 were cCa values at the end of 2011). Associations of cCa, phosphate and iPTH levels with all-cause mortality, CV mortality and transition to HD were examined by Cox regression analyses. The end of the observation period was at the end of 2018 and the data were censored at the time of transition to HD or transplantation. In the JRDR database, dates of modality changes were not available. Those on HD or a combination of PD and HD at the end of the given year and on PD alone at the end of the preceding year were assumed to have started HD in the middle of the given year. For the associations of cCa, phosphate and iPTH with mortality, the observation period started at the end of 2009 as the data at the end of 2009 included the use of phosphate binders, vitamin D receptor activators and cinacalcet (only available calcimimetic in 2009 in Japan). However, the data for daily urine output and peritonitis were available after 2010. For the association of cCa, phosphate and iPTH with the transition to HD, the observation period started at the end of 2010 as the data for residual kidney function and peritonitis is essential for the analyses. Data were adjusted for age, sex, body mass index, PD vintage and causes of end-stage kidney disease; history of myocardial infarction, stroke, amputation, hip fracture, parathyroidectomy and parathyroid ethanol injection therapy; pre-dialysis creatinine,

albumin, C-reactive protein (log-transformed), hemoglobin and performance status; the use of calcium carbonate, lanthanum, sevelamer, other phosphate binders, vitamin D receptor activators and cinacalcet at the end of 2009; and time-averaged or time-dependent albumin-corrected calcium, phosphate and iPTH levels at baseline. All missing values were imputed by multiple imputations by chained equation (five imputed datasets were created). For the association of cCa, phosphate and iPTH with the transition to HD, the data for phosphate binder use, vitamin D receptor activators use and cinacalcet use at the end of 2009 were used (the last observation carried forward), and the data were further adjusted for baseline daily urine output and an annual number of events of peritonitis (time-dependent). The results were shown as restricted cubic spline curves. To exclude the inaccurate estimation at the extreme values of cCa, phosphate and iPTH, values approximately less than 1 percentile and values more than 99 percentile (the closest integers were selected as cutoffs) were excluded from the figures.

For the analysis of the annual decline in daily urine output, the data at the end of 2010 were considered to be the baseline. The annual decline in daily urine output was predicted by linear mixed effects models adjusted for age, sex, causes of end-stage kidney disease and PD vintage; history of myocardial infarction, hemorrhagic stroke, ischemic stroke and limb amputation; and time-dependent annual events of peritonitis and baseline daily urine output. The association of time-averaged cCa, phosphate and iPTH with annual decline in daily urine output was examined by restricted cubic spline analyses adjusted for time-averaged cCa, phosphate and iPTH. Statistical analyses were performed using Stata MP version 17.0 (Stata Corp., College Station, TX, USA).

RESULTS

Patient characteristics

Among patients in the JRDR database, 7393 patients on PD at the end of 2009 met the criteria for this study (Supplementary data, Fig. S1). The demographics are shown in Table 1. The mean (SD) age was 61.4 (13.5) years, 61.3% were male and the median (IQR) PD vintage was 2.4 (1.0–4.6) years. Among 7393 patients, 36.0%, 36.0% and 48.6% had missing values for cCa, phosphate and iPTH, respectively. The proportion of patients with values outside of the current Japanese guideline [24] were as follows: cCa <8.4 mg/dL 8.6%, cCa >10 mg/dL 21.8%, phosphate <3.5 mg/dL 10.9% and phosphate >6.0 mg/dL 21.0%. The demographics of the patients stratified by tertiles of cCa, phosphate and iPTH levels are shown in Supplementary data, Tables S1–S3. Among patients in the highest tertile of cCa levels, PD vintage was longer, the proportion of diabetes was lower and the proportion of patients with poor performance status was higher compared with those in the lower tertiles of cCa. Patients in the highest tertile of phosphate levels were significantly younger, and had longer PD vintage, better performance status, and higher creatinine and albumin levels. Patients in the highest tertile of iPTH levels were significantly younger, and had shorter PD vintage and better performance status.

Association of cCa, phosphate and iPTH with all-cause mortality

Higher cCa and phosphate levels were associated with higher all-cause mortality both in time-averaged and time-dependent models. Higher iPTH levels were associated with higher all-cause mortality in a time-averaged model (Fig. 1). Adjustment for daily urine output at the end of 2010 and annual events of peritonitis after 2010 did not change the results substantially (Supplementary data, Fig. S2). There were no effect modifications by the use of Ca-containing phosphate binders, non-Ca-containing phosphate binders or active vitamin D for any of the associations presented in Fig. 1 except for an effect modification by the use of calcium-containing phosphate binders for the association between time-averaged cCa levels and all-cause mortality. Higher Ca levels were associated with higher mortality among users of calcium-containing phosphate binders but not among non-users (*P* for interaction .03, Supplementary data, Fig. S3).

Table 1: Demographics

	$n = 7393$
Age (years)	61.4 (13.5)
Male sex	4532 (61.3)
PD vintage (years)	2.4 (1.0–4.6) ($n = 7384$)
Primary causes of end-stage kidney disease	
Glomerulonephritis	3140 (42.5)
Diabetes	2108 (28.5)
Hypertension	812 (11.0)
Others	1333 (18.0)
Performance status[a]	
0	2751 (61.9)
1	1072 (24.1)
2	323 (7.3)
3	156 (3.5)
4	143 (3.2)
	($n = 4445$)
History of myocardial infarction	252 (5.6) ($n = 4495$)
History of hemorrhagic stroke	132 (2.9) ($n = 4488$)
History of ischemic stroke	481 (10.7) ($n = 4496$)
History of limb amputation	47 (1.1) ($n = 4480$)
History of hip fracture	52 (1.2) ($n = 4460$)
History of parathyroidectomy	86 (1.9) ($n = 4532$)
History of parathyroid ethanol injection therapy	19 (0.4) ($n = 4515$)
Body mass index (kg/m^2)	22.4 (3.9) ($n = 3425$)
Creatinine (mg/dL)	9.6 (3.5) ($n = 4767$)
Albumin (g/dL)	3.4 (0.5) ($n = 4633$)
C-reactive protein (mg/dL)	0.1 (0.05–0.5) ($n = 3964$)
Hemoglobin (g/dL)	10.3 (1.5) ($n = 4727$)
Albumin-corrected calcium (mg/dL)	9.5 (0.9) ($n = 4734$)
Phosphate (mg/dL)	5.0 (1.3) ($n = 4729$)
iPTH (pg/mL)	163 (90–280) ($n = 3799$)
Calcium carbonate	2494 (52.0) ($n = 4800$)
Lanthanum	416 (8.8) ($n = 4745$)
Sevelamer	1184 (24.9) ($n = 4749$)
Other phosphate binders	145 (3.1) ($n = 4758$)
Vitamin D receptor activators	2585 (54.0) ($n = 4785$)
Cinacalcet	453 (10.1) ($n = 4507$)
Urine output (mL/day)[b]	500 (100–1000) ($n = 2327$)
Peritonitis (events/year)[b]	
0	2304 (81.1)
1	402 (14.1)
≥2	137 (4.8)
	($n = 2843$)

Data are shown as *n* (%), mean (SD) or median (IQR). When the data contain missing values, the numbers of available data are shown in parenthesis.
[a]Performance status: 0, fully active; 1, restricted in physically strenuous activity; 2, ambulatory and capable of self-care but unable to carry out any work activities; 3, limited self-care, confined to bed or chair more than 50% of waking hours; 4, completely disabled.
[b]Data at the end of 2010.

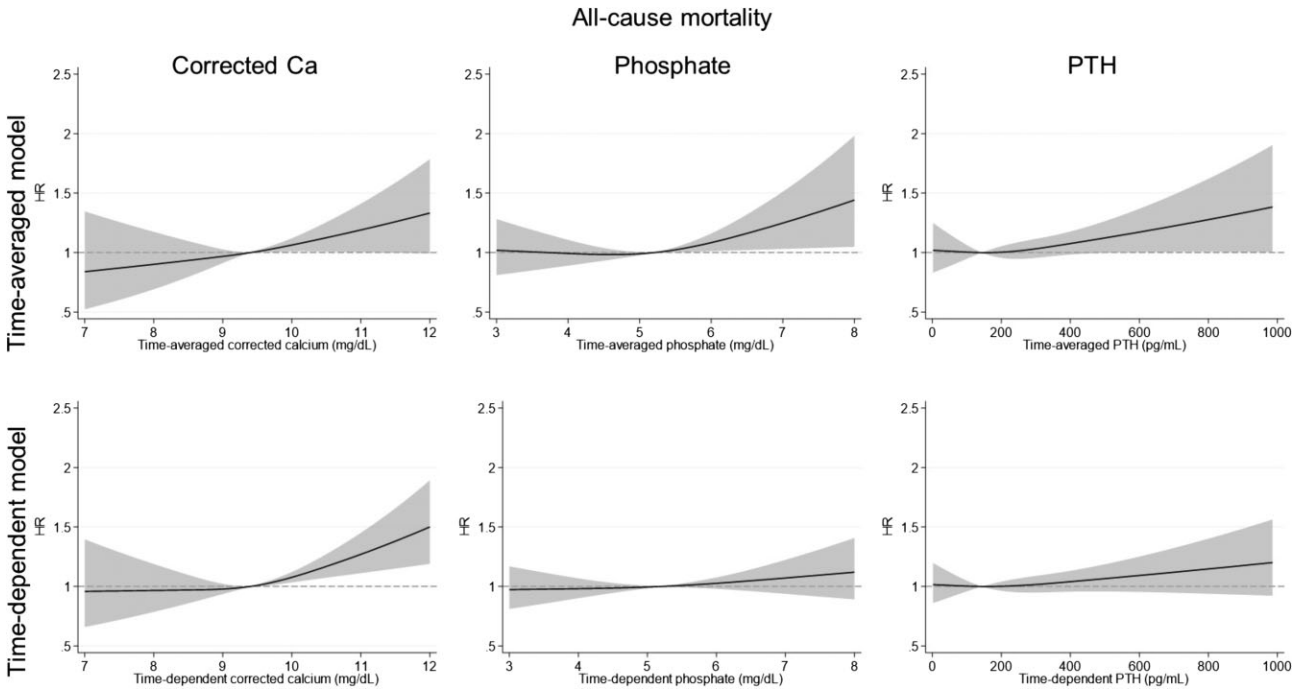

Figure 1: Associations of cCa, phosphate and iPTH levels with all-cause mortality. Data were adjusted for age, sex, body mass index, PD vintage, causes of end-stage kidney disease, history of myocardial infarction, stroke, amputation, hip fracture, parathyroidectomy, parathyroid ethanol injection therapy, pre-dialysis creatinine, albumin, C-reactive protein (log-transformed), hemoglobin, performance status, the use of calcium carbonate, lanthanum, sevelamer, other phosphate binders, oral vitamin D, intravenous vitamin D, cinacalcet, time-averaged or time-dependent albumin-corrected calcium, phosphate and iPTH levels. All missing values were multiply imputed before analysis.

Association of cCa, phosphate and iPTH levels with CV mortality

Higher cCa levels were significantly associated with CV mortality both in time-averaged and time-dependent models. Higher phosphate levels were associated with higher CV mortality. iPTH levels were not associated with CV mortality (Fig. 2). Adjustment for daily urine output at the end of 2010 and annual events of peritonitis after 2010 did not change the results substantially (Supplementary data, Fig. S4). There were no effect modifications by the use of Ca-containing phosphate binders, non-Ca-containing phosphate binders or active vitamin D for any of the associations presented in Fig. 2.

Association of cCa, phosphate and iPTH with annual decline in urine output

Lower cCa levels were associated with faster decline in urine output, whereas lower phosphate levels were associated with a slower decline in urine output. iPTH levels were not associated with a decline in urine output (Fig. 3). There were no effect modifications by the use of Ca-containing phosphate binders, non-Ca-containing phosphate binders or active vitamin D for any of the associations presented in Fig. 3.

Association of cCa, phosphate and iPTH with the transition to HD

Lower phosphate and iPTH levels were significantly associated with a lower incidence of the transition to HD in both time-averaged and time-dependent models. The association between cCa and the transition to HD was not significant (Fig. 4). There were no effect modifications by the use of Ca-containing phosphate binders, non-Ca-containing phosphate binders or active vitamin D for any of the associations presented in Fig. 4.

DISCUSSION

In this study, we demonstrated that higher cCa, phosphate and iPTH levels were associated with all-cause mortality, higher cCa was associated with CV mortality, lower phosphate levels were associated with a slower decline in urine output, and lower phosphate and iPTH levels were associated with lower incidence of transition to HD among patients on PD.

Associations of cCa, phosphate and iPTH levels with mortality among PD patients were somewhat different from those among HD patients. Among HD patients, hypocalcemia (calcium levels lower than reference range) was associated with higher mortality in a few studies [6, 9]. However, in this study, lower cCa levels even in the range of hypocalcemia were associated with lower mortality among PD patients. Among HD patients, lower cCa levels were associated with a rapid shift of Ca from dialysate to serum and a rapid increase in serum Ca levels [14, 15]. This rapid shift of Ca might be a mediator of the association between lower serum Ca levels and higher mortality [15]. However, in PD, such a rapid shift in Ca does not happen, which may explain the different associations of hypocalcemia and mortality among PD and HD patients. Hypocalcemia might predispose arrhythmia and sudden cardiac death, which might explain the association between hypocalcemia and mortality among HD patients. Among Japanese PD patients, the prevalence of CV comorbidities was low compared with HD patients and thus

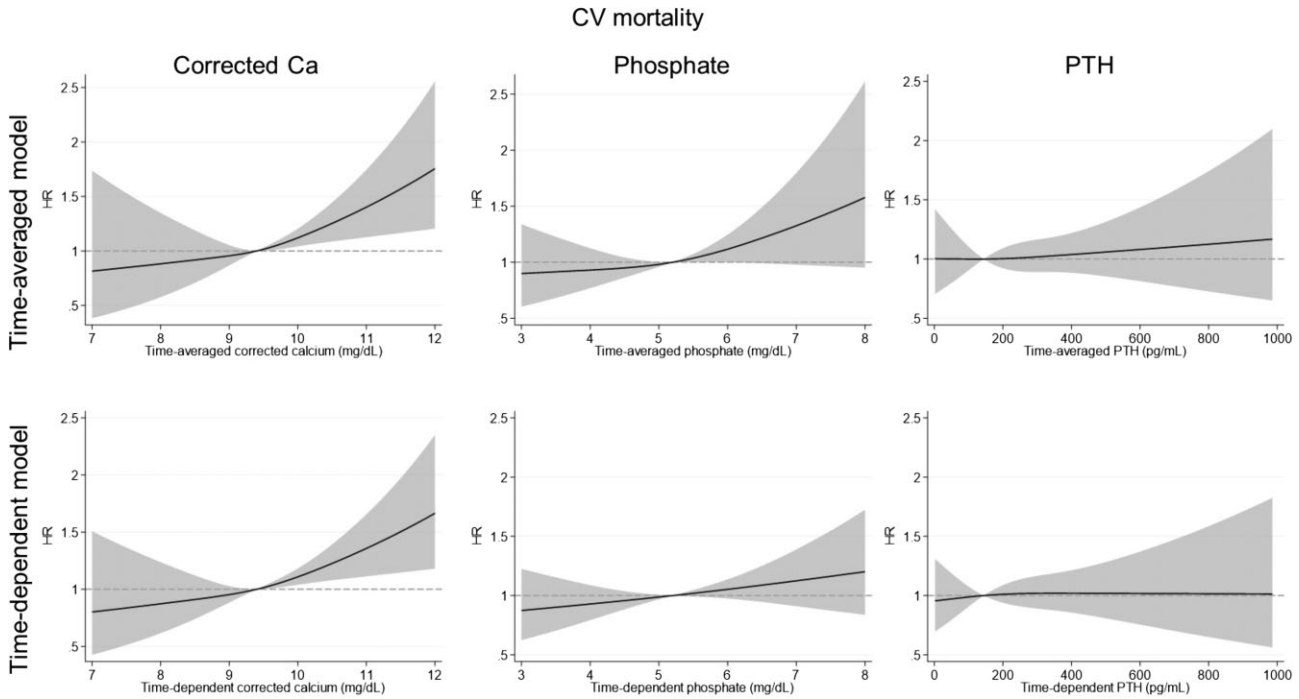

Figure 2: Associations of cCa, phosphate and iPTH levels with CV mortality. The data were adjusted for the same covariates as in Fig. 1.

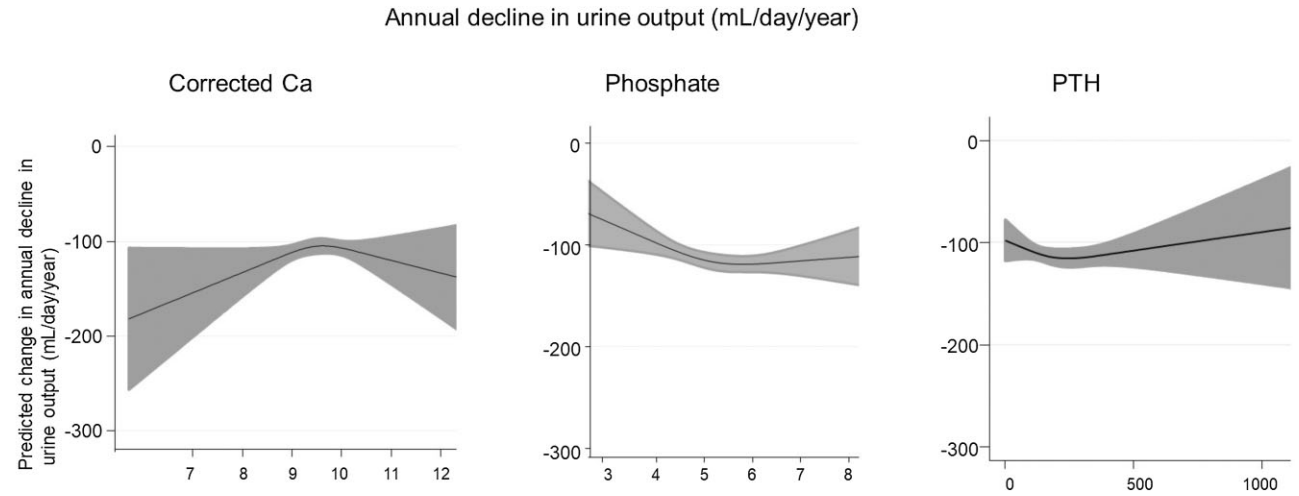

Figure 3: Association of cCa, phosphate and iPTH levels with annual decline in urine output. The annual decline in urine output was estimated by a mixed-effects model. Data were adjusted for age, sex, causes of end-stage kidney disease, PD vintage, history of myocardial infarction, stroke, limb amputation, baseline urine output, annual events of peritonitis, time-averaged albumin-corrected calcium, phosphate and iPTH levels.

the association between hypocalcemia and mortality may not be apparent. Also, among HD patients, hypophosphatemia is consistently associated with higher mortality [3, 6, 7, 9], which has been considered to be due to malnutrition. However, in this study, lower phosphate levels were associated with lower mortality among PD patients. Among PD patients, low phosphate levels might reflect higher residual kidney function. However, adjustment for daily urine output did not change the results, although the data for urine output was the data 1 year after the baseline. As many patients on PD are younger, have good performance status and are well-nourished, low phosphate levels might reflect better adherence to dietary restriction and phosphate binders. Associations of higher Ca, phosphate and iPTH levels with mortality were similar between PD and HD patients [1–9]. These associations might be due to the progression of vascular calcification both in PD and HD patients. A recent study showed that achieving the target for Ca, phosphate and iPTH among maintenance dialysis patients was associated with slower progression of vascular calcification and that progression of vascular calcification was associated with higher mortality [25]. The association of higher iPTH with all-cause mortality, but not with CV mortality suggests that higher iPTH levels are associated with non-CV mortality. Higher iPTH might be a marker of more

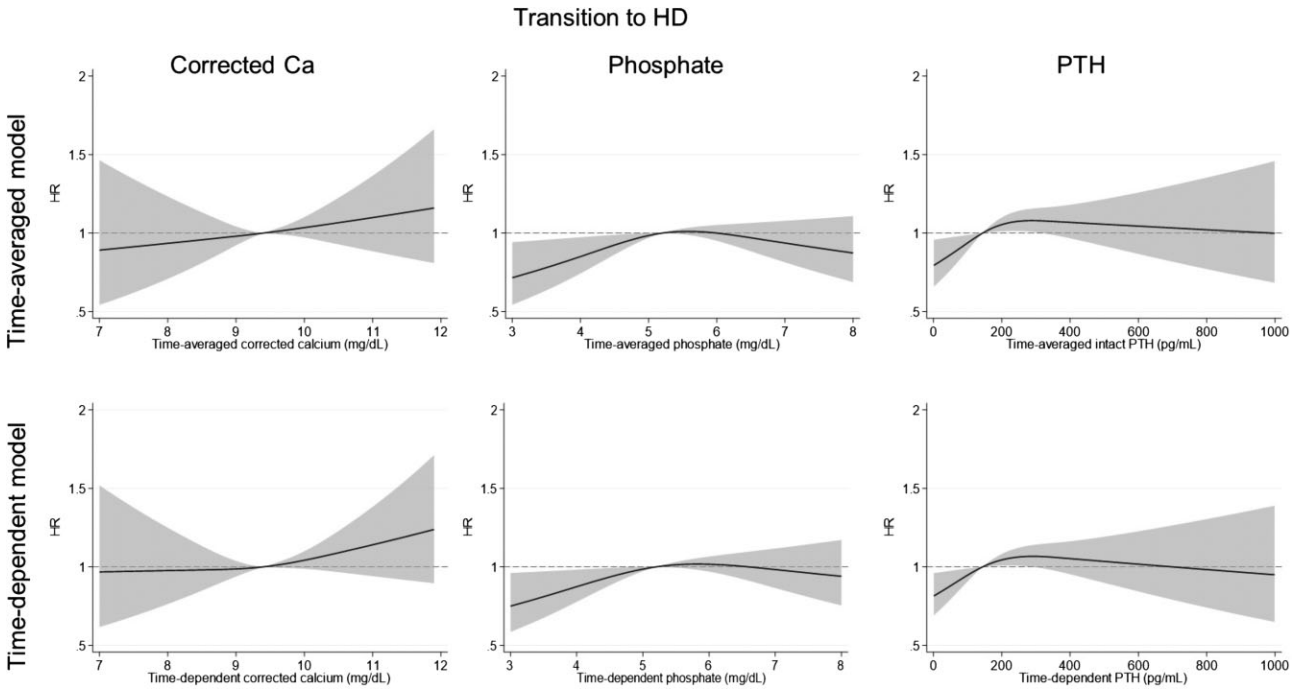

Figure 4: Associations of cCa, phosphate and iPTH levels with the transition to HD. The data were adjusted for the same covariates as in Fig. 1, baseline urine output and time-dependent annual events of peritonitis.

profound vitamin D deficiency, which is associated with a higher risk of infection [26].

Only a few previous studies examined the association of Ca, phosphate and iPTH levels with outcomes among PD patients. One study from China [10] showed that higher phosphate levels were associated with higher all-cause and CV mortality and that lower Ca levels were associated with higher all-cause mortality among PD patients. Their study differs from ours in that they only included incident PD patients and used a baseline model, which might explain the different results. Another study from Taiwan including about 12 000 prevalent PD patients [11] showed that hypercalcemia (Ca ≥9.5 mg/dL), hypophosphatemia (phosphate <3.5 mg/dL) and hyperphosphatemia (phosphate ≥7.5 mg/dL) were associated with higher mortality in time-dependent models. They did not adjust for previous histories of CV diseases, which might explain why hypophosphatemia was associated with higher mortality in their study but not in ours. Recently, another study showed that higher phosphate levels were associated with higher mortality among PD patients [23].

Associations of Ca, phosphate and iPTH levels with a decline in residual kidney function have not been studied among the PD population. One study examined associations of Ca, phosphate and iPTH levels with a slope of residual urea clearance among HD patients [16]. They demonstrated that higher phosphate, lower calcium and higher iPTH levels were associated with a faster decline in residual urea clearance. In our study, lower phosphate levels were associated with a slower decline in daily urine output, although the association of higher phosphate levels (phosphate >6.5 mg/dL) with a decline in daily urine output was less clear, with a wide confidence interval. These findings were in line with findings in animal models of chronic kidney disease in which a high phosphate diet exacerbates kidney damage such as tubular injuries, interstitial fibrosis and inflammation [27, 28]. The association between lower Ca levels and faster decline in residual urine output was similar between their study and our study. Hypocalcemia may be a manifestation of severe tubular damage leading to lower 1,25-dihydroxy vitamin D production. Lower 1,25-dihydroxy vitamin D was reported to be associated with a faster decline in kidney function among patients with non-dialysis-dependent chronic kidney disease [29]. iPTH levels were not associated with a decline in residual kidney function, though lower iPTH levels were associated with a lower incidence of transition to HD. The reasons for these associations were not clear. Higher phosphate, lower Ca and higher iPTH levels may be a manifestation of more severe kidney damage, which leads to faster decline in residual kidney function.

The strength of the study is a large sample size with a long follow-up (maximum 9 years). The association of cCa, phosphate and iPTH levels with residual kidney function has not been studied among PD patients and the findings were novel. Limitations of the study are that this is a study based on registry data that only included Japanese patients, so the generalizability to PD patients in other countries is unclear. The data were only collected annually. Residual kidney function was evaluated by urine output, not by creatinine or urea clearance. The data for daily urine output were not available at the end of 2009 and the data for phosphate binders use and vitamin D receptor activator use were only available at the end of 2009. Among 7393 patients, 36.0%, 36.0% and 48.6% had missing values for cCa, phosphate and iPTH, respectively, which were imputed. Bone alkaline phosphate levels were not available in JRDR. Data for calcium concentration of peritoneal dialysate, which is a potentially important confounder, were not available in JRDR. Transient hypo- or hypercalcemia may contribute to mortality, which might be missed by time-averaged models. We also used time-dependent models to examine the association of cCa, phosphate and iPTH closest to the time of outcome events with outcomes. However, it

might not be enough to capture transient episodes of hypo or hypercalcemia as the data were available only once a year. No information was available on assays used for calcium and phosphate measurements. Also, the detailed information on iPTH assays is not available in JRDR, although about 80% of facilities in Japan used ELECSYS assay for iPTH measurements (Roche Diagnostics, Mannheim, Germany) [30].

In conclusion, our results suggest that higher Ca, higher phosphate and higher iPTH levels should be avoided in terms of mortality, residual kidney function and technical survival among PD patients. Hypocalcemia might be permissive in terms of mortality among PD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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FUNDING

None.

AUTHORS' CONTRIBUTIONS

M.M.: conception and design of the study, data analysis, interpretation of the data and drafting the manuscript. N.F.: data analysis and review and approval of the final manuscript. S.G.: conception and design of the study, interpretation of the data, and review and approval of the final manuscript. T.Hasegawa: conception and design of the study, interpretation of the data, and review and approval of the final manuscript. M.A.: review and approval of the final manuscript. N.H.: review and approval of the final manuscript. M.F.: review and approval of the final manuscript. T.Hamano: conception and design of the study, interpretation of the data, and review and approval of the final manuscript.

DATA AVAILABILITY STATEMENT

The dataset used in this study is not publicly available due to the restriction by JSDT.

CONFLICT OF INTEREST STATEMENT

M.M. receives honoraria from Kyowa Kirin Co., Ltd, and Torii Pharmaceutical Co., Ltd. N.F. receives honoraria from Astellas Pharm Inc., Bayer Yakuhin Ltd, Kissei Pharmaceutical Co., Ltd, Kyowa Kirin Co., Ltd, Ono Pharmaceutical Co., Ltd, Sanwa Kagaku Kenkyusho Co., Ltd, and Torii Pharmaceutical Co., Ltd. S.G. receives research funds from Kyowa Kirin Co., Ltd, Bayer Yakuhin, Ltd, and Chugai Pharmaceutical Co., Ltd, and honoraria from Kyowa Kirin Co., Ltd, Sanwa Kagaku Kenkyusho Co., Ltd, Kissei Pharmaceutical Co., Ltd, and Astellas Pharm Inc. T.Hasegawa receives honoraria from Kyowa Kirin Co., Ltd, Baxter and Termo. M.F. receives research funds from Kyowa Kirin Co., Ltd, and honoraria from Kyowa Kirin Co., Ltd, Kissei Pharmaceutical Co., Ltd, Bayer Yakuhin, Ltd, Ono Pharmaceutical Co., Ltd, and Sanwa Kagaku Kenkyusho Co., Ltd. M.A. receives research funds from Torii Pharmaceutical Co., Ltd, and Kyowa Kirin Co., Ltd, and honoraria from Kyowa Kirin Co., Ltd, Torii Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, and Bayer Yakuhin Ltd. T.Hamano receives research funds from Chugai Pharmaceutical Co., Ltd, Torii Pharmaceutical Co., Ltd, Kyowa Kirin Co., Ltd, Sanwa Kagaku Kenkyusho Co., Ltd, Kissei Pharmaceutical Co., Ltd, and Astellas Pharm Inc., and honoraria from Astellas Pharm Inc., Kissei Pharmaceutical Co., Ltd, Kyowa Kirin Co., Ltd, Torii Pharmaceutical Co., Ltd, Sanwa Kagaku Kenkyusho. Co., Ltd, Ono Pharmaceutical Co., Ltd, and Bayer Yakuhin Ltd.

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