BASELINE FGF23 IS ASSOCIATED WITH CARDIOVASCULAR OUTCOME IN INCIDENT PD PATIENTS

Hyo Jin Kim,¹ Miseon Park,² Hayne Cho Park,^{1,3} Jong Cheol Jeong,^{1,3} Dong Ki Kim,¹ Kwon Wook Joo,¹
Young-Hwan Hwang,⁴ Jaeseok Yang,⁵ Curie Ahn,^{1,3} and Kook-Hwan Oh^{1,2}

*Department of Internal Medicine,¹ Seoul National University Hospital, Seoul, Korea; Clinical Research
Institute,² Seoul National University Hospital, Seoul, Korea; Transplantation Research Institute,³
Seoul National University Hospital, Seoul, Korea; Department of Internal Medicine,⁴ Eulji
General Hospital, Eulji University, Seoul, Korea; and Transplantation Center,⁵
Seoul National University Hospital, Seoul, Korea*

◆ **Background:** Fibroblast growth factor 23 (FGF23) is a phosphate regulating protein. Several studies demonstrated that elevated FGF23 is independently associated with mortality for early-stage chronic kidney disease and incident hemodialysis (HD) patients. However, little is known about the significance of elevated FGF23 in peritoneal dialysis (PD) patients. Here, we analyzed the association of FGF23 with cardiovascular (CV) events, all-cause mortality, residual renal function (RRF), and CV parameters in PD patients.

◆ **Methods:** The present study is a single-center, retrospective study. Patients who started PD at Seoul National University Hospital between January 2005 and July 2011 and whose baseline serum samples were available were enrolled. C-terminal FGF23 was measured. Subjects were divided into 2 groups; lower 2 tertiles (FGF23 ≤ 119.0 RU/mL) and top tertile (FGF23 > 119.0 RU/mL). The primary outcome was time to fatal or non-fatal CV events. In the subgroup analysis, the associations of FGF23 with aortic stiffness or with vascular calcification were analyzed.

◆ **Results:** A total of 205 incident PD patients were analyzed. Mean duration of follow-up was 41.6 ± 20.0 months. The baseline median FGF23 level was 78.6 RU/mL (interquartile range [IQR], 34.1 – 155.0). At baseline, subjects in the higher FGF23 group were younger, and had a lower RRF, lower prevalence of diabetes mellitus (DM), and cerebrovascular disease. During follow-up, 22 of the 205 patients (10.7%) reached primary outcome. After adjustment for age, DM, pre-existing coronary artery disease, cerebrovascular disease, congestive heart failure, and left ventricular mass index, the higher FGF23 group exhibited significantly higher risk of primary outcome, compared with the lower

group (hazard ratio [HR], 2.54; 95% confidence interval [CI], 1.05 – 6.12; $p = 0.045$). There were no significant differences in all-cause mortality and development of anuria between the 2 FGF23 groups. In the subgroup analysis, FGF23 groups were not associated with pulse wave velocity and abdominal aortic calcification score.

◆ **Conclusion:** Elevated FGF23 is associated with higher risk of adverse CV outcome for incident PD patients.

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Fibroblast growth factor 23 (FGF23) is a phosphorus regulating protein secreted by bone cells, mainly osteoblast (1). It regulates phosphorus homeostasis, and the serum level of FGF23 increases progressively as kidney function declines, even before the rise of the phosphorus level (2). FGF23 levels increase in chronic kidney disease (CKD) as an appropriate adaptation to maintain phosphate homeostasis. However, previous studies showed that elevated FGF23 levels may exert negative effects. Several studies demonstrated that elevated FGF23 is independently associated with mortality in early stage CKD (3), advanced CKD (4), incident hemodialysis (HD) patients (5,6), and even in patients with normal kidney function (7). Furthermore, elevated FGF23 is associated with adverse cardiovascular (CV) outcomes in patients with normal kidney function (8) and advanced CKD patients (4). Several studies have shown elevated FGF23 is related to left ventricular hypertrophy (LVH) in CKD (9) and HD patients (10).

Cardiovascular disease and mortality events are more common in end-stage renal disease (ESRD) patients

Correspondence to: Kook-Hwan Oh, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-Ro, Jongno-Gu, 110-744, Seoul, Republic of Korea.
khoh@snu.ac.kr

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(11,12). Cardiovascular mortality is associated not only with conventional risk factors such as hypertension or diabetes mellitus (DM), but also with vascular calcification (13) and vascular stiffness (14,15).

Since the majority of patients included in most previous studies were ESRD patients on HD, little is known about the significance of elevated FGF23 in peritoneal dialysis (PD) patients and its association with CV parameters. Here, we analyzed the association of baseline FGF23 with CV events, all-cause mortality, and residual renal function (RRF). Moreover, we investigated the correlation between FGF23 and CV parameters.

MATERIALS AND METHODS

STUDY SUBJECTS

The present study is a single-center, retrospective study. Three hundred ninety five patients over 18 years of age started PD at Seoul National University Hospital between January 2005 and July 2011. Among them, 174 patients were excluded due to preceding history of kidney transplantation, HD over 3 months before starting PD, or transfer to another PD center within 3 months after PD catheter insertion. Finally, 205 patients whose baseline serum samples were available were enrolled. They were followed until May 2013. This study was approved by the Seoul National University Hospital Institutional Review Boards. All clinical investigations were conducted in accordance with the guidelines of the 2008 Declaration of Helsinki.

CLINICAL DATA COLLECTION

Baseline demographic data such as age, gender, comorbidities, body mass index (BMI), and history of medication such as phosphate binder and calcitriol were investigated. Serum levels of hemoglobin, calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH), total cholesterol, C-reactive protein (CRP), 25-hydroxyvitamin D (25[OH]D), and 1,25-hydroxyvitamin D (1,25[OH]₂D) were measured using routine laboratory methods. Albumin-corrected calcium levels were calculated as follows; corrected Ca (mg/dL) = measured total Ca (mg/dL) + 0.8 × (4 – measured serum albumin [g/dL]). Residual glomerular filtration rate (GFR) was measured as the average of renal urea and creatinine clearance. Adequacy of dialysis was estimated by measuring total weekly Kt/V urea and creatinine clearance using standard methods. Left ventricular mass index (LVMI) was calculated as described elsewhere (16). Left ventricular hypertrophy (LVH) is defined as LVMI ≥ 131 g/m² in males, and

≥ 100 g/m² in females (17). Arterial stiffness was measured by heart-to-femoral pulse wave velocity (PWV). Abdominal aorta calcification (AAC) was measured by simple lateral lumbar radiograph with a range of 0 – 24 (18) and aortic arch calcification (AoAC) was measured by simple chest radiography with a range of 0 – 3 for assessing vascular calcification (19).

BIOCHEMICAL ANALYSIS OF FGF23

C-terminal FGF23 was measured using second generation human FGF23 ELISA kit (Immutopics, San Clemente, California, USA). The lowest measurable concentration of human FGF23 is 1.5 RU/mL and the highest measurable concentration without dilution is the value of the highest standard. Samples with C-terminal FGF23 concentration over the highest standard value were detected by 10-fold dilution of the serum with dilution reagent.

OUTCOME MEASUREMENT

Patients were categorized into 2 groups: lower 2 tertiles (FGF23 ≤ 119.0 RU/mL, hereafter referred to as the lower FGF23 group) and top tertile (FGF23 > 119.0 RU/mL, hereafter referred to as the higher FGF23 group). Primary outcome was time to fatal or non-fatal CV events. Cardiovascular events were defined as acute coronary syndrome, arrhythmia, congestive heart failure (CHF), cerebrovascular disease, and symptomatic peripheral artery disease. Secondary outcomes were time-to-death from all-cause or time-to-anuric state. In addition, we evaluated the association between FGF23 and PWV or FGF23 and AAC as a subgroup analysis. Censoring events for outcomes included kidney transplantation and transfer to other PD centers.

STATISTICAL ANALYSIS

Categorical variables were analyzed by chi square test and presented as frequencies and percentage. Continuous variables were evaluated with independent sample *t*-tests and the Mann-Whitney test. Results are presented as mean ± standard deviation (SD) for normally distributed variables and median (IQR) for variables with skewed distributions. A log transformation was used to normalize variability of the FGF23, iPTH and CRP. After Pearson's correlation analysis, multivariate linear regression analysis was used to determine factors independently associated with FGF23. In order to explore the independent risk factors related to CV events, all-cause mortality, and time to anuric state, we used Cox proportional hazards models with adjustment. *P* values < 0.05

were considered statistically significant. SPSS Statistics software (SPSS version 18.0, Chicago, IL, USA) was used for statistical analysis.

RESULTS

CLINICAL CHARACTERISTICS AND INDEPENDENT FACTORS ASSOCIATED WITH FGF23

A total of 205 incident PD patients were analyzed. Mean age was 47.4 ± 14.3 years, and 64 (31.2%) patients had DM (Table 1). The residual GFR was 53.4 ± 33.0

(L/1.73 m²/wk). The baseline median FGF23 level was 78.6 RU/mL (IQR, 34.1 – 155.0). The subjects in the higher FGF23 group ($n = 68$) were significantly younger ($p = 0.018$) and had lower prevalence of DM ($p = 0.010$) and cerebrovascular disease ($p = 0.038$) than the lower FGF23 group ($n = 137$) (Table 1). The subjects in the higher FGF23 group had a lower RRF ($p < 0.001$), higher phosphorus ($p = 0.008$), higher iPTH levels ($p = 0.015$), and higher prevalence of LVH ($p = 0.017$). However, there was no significant difference in AoAC (proportion of subjects with AoAC score ≥ 1) between the 2 groups ($p = 0.625$).

TABLE 1
Baseline Clinical Characteristics of Patients of the FGF23 Groups

	Total ($n=205$)	Lower group (FGF23 ≤ 119.0 RU/mL) ($n=137$)	FGF 23 Groups Higher group (FGF23 >119.0 RU/mL) ($n=68$)	<i>p</i> -value
Age (years)	47.4 $\pm$ 14.3	49.1 $\pm$ 14.3	44.1 $\pm$ 13.9	0.018
Gender (male, <i>n</i> , %)	122 (59.5)	87 (63.5)	35 (51.5)	0.130
Comorbidity (<i>n</i> , %)				
DM	64 (31.2)	51 (37.2)	13 (19.1)	0.010
Hypertension	147 (71.7)	100 (73.4)	47 (69.1)	0.622
CAD	14 (6.8)	11 (8.0)	3 (4.4)	0.395
CHF	16 (7.8)	9 (6.6)	7 (10.3)	0.409
Cerebrovascular disease	19 (9.3)	17 (12.4)	2 (2.9)	0.038
Phosphate binder (<i>n</i> , %)	175 (85.4)	113 (82.5)	62 (91.2)	0.141
Ca containing P-binder (<i>n</i> , %)	168 (82.0)	110 (80.3)	58 (85.3)	0.444
Calcitriol (<i>n</i> , %)	33 (16.1)	19 (13.9)	14 (20.6)	0.231
BMI (g/m ²)	22.7 $\pm$ 3.4	22.5 $\pm$ 3.4	23.1 $\pm$ 3.3	0.292
Residual GFR (L/1.73 m ² /wk)	53.4 $\pm$ 33.0	62.4 $\pm$ 31.8	36.1 $\pm$ 27.9	<0.001
FGF23, median (Q1, Q3) (RU/mL)	78.6 (34.1, 155.0)	52.5 (25.0, 79.5)	222.0 (155.0, 378.3)	<0.001
Hemoglobin (g/dL)	9.5 $\pm$ 1.4	9.7 $\pm$ 1.4	9.2 $\pm$ 1.5	0.018
CRP, median (Q1, Q3) (mg/dL)	0.01 (0.14, 0.64)	0.01 (0.11, 0.65)	0.21 (0.02, 0.66)	0.192
Ca (mg/dL)	8.6 $\pm$ 0.7	8.6 $\pm$ 0.7	8.6 $\pm$ 0.8	0.841
P (mg/dL)	4.9 $\pm$ 1.3	4.7 $\pm$ 1.2	5.3 $\pm$ 1.5	0.008
Ca $\times$ P (mg ² /dL ²)	42.0 $\pm$ 10.6	40.5 $\pm$ 9.8	44.9 $\pm$ 11.4	0.007
Total cholesterol (mg/dL)	157.9 $\pm$ 41.6	160.5 $\pm$ 43.5	152.9 $\pm$ 37.2	0.194
iPTH, median (Q1, Q3) (pg/mL)	167.0 (91.0, 293.0)	150.5 (86.5, 251.8)	194.0 (97.5, 375.0)	0.015
25(OH)VitD (ng/mL)	14.4 $\pm$ 4.6	14.9 $\pm$ 5.2	13.4 $\pm$ 2.7	0.005
1,25(OH) ₂ VitD (pg/mL)	3.6 $\pm$ 2.1	3.8 $\pm$ 2.3	3.1 $\pm$ 1.7	0.013
LVM (g/m ^{2.7})	117.1 $\pm$ 37.5	113.3 $\pm$ 33.9	124.6 $\pm$ 43.1	0.076
LVH (<i>n</i> , %)*	76 (42.5)	43 (36.1)	33 (55.0)	0.017
LVEF (%)	59.3 $\pm$ 9.0	60.2 $\pm$ 9.2	57.4 $\pm$ 8.6	0.044
AoAC score ≥ 1 (<i>n</i> , %)	58 (28.9)	40 (30.1)	18 (26.5)	0.625

FGF23 = fibroblast growth factor 23; DM = diabetes mellitus; CAD = coronary artery disease; CHF = congestive heart failure; Ca = calcium; P = phosphorus; BMI = body mass index; GFR = glomerular filtration rate; CRP = C-reactive protein; iPTH = intact parathyroid hormone; 25(OH)VitD = 25-hydroxyvitamin D; 1,25(OH)₂D = 1,25-hydroxyvitamin D; LVM = left ventricular mass index; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; AoAC = aortic arch calcification.

Lower group: lower 2 tertiles, patients with FGF23 ≤ 119.0 RU/mL; higher group: top tertile, patients with FGF23 >119.0 RU/mL.

* LVH is defined as ≥ 131 g/m^{2.7} in males, ≥ 100 g/m^{2.7} in females.

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We performed linear regression analysis including age, DM, coronary artery disease (CAD), cerebrovascular disease, residual GFR, hemoglobin, iPTH, phosphorus, FGF23, and 1,25(OH)₂D, which showed a negative correlation of FGF23 with residual GFR ($\beta = -0.30, p < 0.001$) and with DM ($\beta = -0.22, p = 0.002$) (Table 2). Other factors, such as iPTH ($\beta = 0.16, p = 0.037$) and phosphorus level ($\beta = 0.15, p = 0.039$) were also associated with FGF23.

PRIMARY OUTCOME: RISK OF CV EVENT

During the follow-up period of 41.6 ± 20.0 months, 3 patients were lost to follow-up. Finally, 22 of the 205 patients (10.7%) reached the primary outcome.

In the univariate analysis, there were no significant differences in the development of fatal or non-fatal CV events between both FGF23 groups. However, subjects in the higher FGF23 group were significantly younger and had lower comorbidities at baseline. We performed Cox proportional hazard model analysis including variables that were significantly different between the 2 groups at baseline (Table 3). In model A, adjusted for age, DM, hypertension, pre-existing CAD, cerebrovascular disease, CHF, LVMI, presence of AoAC (AoAC score 0 vs ≥ 1), and FGF23 groups, the higher FGF23 group exhibited significantly higher risk of fatal or non-fatal CV events compared with the lower group (HR, 2.45; 95% CI, 1.02 – 5.90; $p = 0.045$) (Table 3, Figure 1). In model B, adjusted for covariates in Model A plus measures of

TABLE 2
Factors Associated with Baseline FGF23 Level

Variable	β coefficient	95% CI Coefficient	p value
Residual GFR (L/1.73 m ² /wk)	-0.30	-0.01– 0.00	<0.001
DM (yes)	-0.22	-0.51– -0.11	0.002
Log iPTH (pg/mL)	0.16	0.01– 0.45	0.037
P (mg/dL)	0.15	0.00– 0.14	0.039

FGF23 = fibroblast growth factor 23; CI = confidence interval; GFR = glomerular filtration rate; DM = diabetes mellitus; CAD = coronary artery disease; iPTH = intact parathyroid hormone; P = phosphorus; 1,25(OH)₂D = 1,25-hydroxyvitamin D. The following variables at baseline were included in a multiple linear regression model as covariates: age, DM, preexisting CAD, cerebrovascular disease, residual renal function, hemoglobin, iPTH, phosphorus, FGF23, and 1,25(OH)₂D.

TABLE 3
Variables Independently Associated with the Primary Outcome* Estimated by Various Cox Proportional Hazard Models

Variable	Model A ^a HR (95% CI)	Model B ^b HR (95% CI)	Model C ^c HR (95% CI)
FGF23 (higher vs lower group ^d)	2.54 (1.02–5.90) ^e	2.90 (1.07–7.82) ^e	2.87 (1.06–7.76) ^e
Preexisting CAD (yes)	3.95 (1.45–10.77) ^e	8.76 (3.13–24.54) ^e	8.70 (3.10–24.38) ^e
Preexisting CHF (yes)	2.85 (1.12–7.27) ^e	4.12 (1.54–11.04) ^e	4.09 (1.53–10.97) ^e
Age (per 1 yr)	1.05 (1.01–1.09) ^e		
Log iPTH (pg/mL)		0.20 (0.07–0.53) ^e	0.20 (0.07–0.54) ^e
25(OH)VitD (ng/mL)		0.87 (0.77–1.00) ^e	0.87 (0.77–1.00) ^e

HR = hazard ratio; CI = confidence interval; FGF23 = fibroblast growth factor 23; CAD = coronary artery disease; CHF = congestive heart failure; iPTH = intact parathyroid hormone; 25(OH)VitD = 25-hydroxyvitamin D; DM = diabetes mellitus; LVMI = left ventricular mass index; AoAC = aortic arch calcification.

* Time to fatal or non-fatal CV events.

^a Model A adjusted for age, DM, hypertension, CAD, cerebrovascular disease, CHF, LVMI, AoAC, and FGF23 groups.

^b Model B adjusted for covariates in Model A plus phosphorus, iPTH, 25(OH)VitD.

^c Model C adjusted for covariates in Model B plus residual renal function.

^d Lower group: lower 2 tertiles, patients with FGF23 ≤ 119.0 RU/mL; higher group: top tertile, patients with FGF23 > 119.0 RU/mL.

^e Significant association with primary outcome ($p < 0.05$). $p < 0.05$ was considered significant.

Figure 1 — Cardiovascular events according to FGF23 groups. Analyzed by Cox proportional hazard models, cumulative event-free survival was lower in the higher FGF23 group ($p=0.045$). Adjusted for age, DM, hypertension, CAD, cerebrovascular disease, CHF, LVMI, AoAC, and FGF23 groups. FGF23 = fibroblast growth factor 23; DM = diabetes mellitus; CAD = coronary artery disease; CHF = congestive heart failure; LVMI = left ventricular mass index; AoAC = aortic arch calcification.

mineral metabolism, the higher FGF23 group was still associated with significantly higher CV events (higher vs lower group; HR, 2.90; 95% CI, 1.07 – 7.82; $p=0.036$; Table 3). In addition, adjusted for covariates in Model B plus RRF, the higher FGF23 group exhibited significantly higher risk of CV events (higher vs lower group; HR, 2.87; 95% CI, 1.06 – 7.76; $p=0.037$; Table 3).

SECONDARY OUTCOMES

There were 14 (6.8%) cases of death and 58 (28.3%) cases of developing anuric state. There were no significant differences in all-cause mortality and development of anuria between the 2 FGF23 groups. In a Cox proportional hazard model adjusted for age, DM, preexisting CAD, cerebrovascular disease, CHF, FGF23 groups, phosphorus, CRP, and LVEF, the parameters independently related with all-cause mortality were preexisting CAD (HR, 5.73; 95% CI, 1.72 – 19.16; $p=0.005$) and CRP (HR, 2.34; 95% CI, 1.05 – 5.19; $p=0.037$). Development of anuric state, when adjusted for age, DM, preexisting CAD, cerebrovascular disease, CHF, FGF23 groups, residual GFR, total cholesterol, and LVMI, was associated with residual GFR (HR, 0.986; 95% CI, 0.98 – 1.00; $p=0.018$) and total cholesterol level (HR, 1.010; 95% CI, 1.00 – 5.19; $p=0.006$).

In a subgroup of randomly selected subjects ($n=32$ from the lower and $n=16$ from the higher group), both PWV and AAC were measured at baseline. The PWV was not different between the lower vs higher FGF23 groups (1094.4 ± 289.9 vs 951.2 ± 220.8 ; $p=0.100$). The AAC score was not significantly different between the 2 FGF23 groups ($p=0.219$).

DISCUSSION

The present study showed that the higher (top tertile) FGF23 group exhibited higher risk of fatal or non-fatal CV events than the lower FGF23 group (lower 2 tertiles), after adjustment for the established risk factors, including age, DM, hypertension, RRF and parameters of mineral metabolism in PD patients.

The baseline parameters at the start of PD were different between the higher and lower FGF23 groups in the present study. Subjects in the higher FGF23 group were younger and had lower prevalence of DM and preexisting cerebrovascular disease, compared to the lower FGF23 group. On the other hand, they exhibited lower residual GFR and poorer profiles of mineral metabolic parameters. The association between the FGF23 groups and the primary outcome remained statistically significant in various models including age, DM, other comorbid conditions, LVMI, and mineral metabolic parameters as covariates.

FGF23 concentration increases in CKD as a compensatory mechanism to maintain appropriate serum phosphorus levels. However, elevated level of plasma FGF23 was shown to be associated with adverse outcomes. Baia *et al.* (20) showed higher FGF23 was independently associated with CV mortality and all-cause mortality after kidney transplantation, adjusted for the measures of mineral metabolism and CV risk factors. In a community-based elderly cohort, Westerberg *et al.* (21) found that FGF23 correlated with CV mortality only in the sub-cohort with preserved renal function. Not only in the general population with normal kidney function but also in advanced CKD patients, FGF23 is associated with CV events (4). Our findings for incident PD patients showed that baseline FGF23 concentration is associated with adverse CV outcomes after adjustment.

The mechanisms that underlie the association between elevated FGF23 concentration and adverse CV outcomes are unknown. It is possible that FGF23 has direct vascular toxicity. Endothelial dysfunction is related to CV outcomes in patients with CKD (22). Several studies demonstrated that higher FGF23 levels are independently associated with impaired vasoreactivity in subjects with normal renal function (23) and with stage 3 – 4 CKD (24). Nakamura *et al.* (25) showed that FGF23 is an important

factor for endothelial cell biology. In his experiments with heterozygous *klotho* knockout mice, a model which mirrors the effects of elevated FGF23, decrease of *klotho* induced a counter-regulatory increase in FGF23. Further studies are necessary to determine the endothelial dysfunction effect of FGF23 in PD patients. In addition, LVH is associated with CV morbidity and mortality in PD patients (26). Fibroblast growth factor receptors, particularly FGFR1, are expressed in myocardial cells and their activation could stimulate myocardial hypertrophy (27). Previous cross-sectional studies have shown that association of FGF23 with LVMI and LVH (9,10). However, a definite mechanism between FGF23 and LVH remains unknown, and further prospective studies are needed to elucidate the causality between myocardial hypertrophy and FGF23 in PD patients.

Previous studies have shown the association between FGF23 and all-cause mortality. Jean *et al.* (6) demonstrated that the highest quartile FGF23 group had a 2.5-fold increased risk of all-cause mortality in long-term HD patients. Elevated FGF23 is also independently associated with all-cause mortality in incident HD patients (5) and in patients with normal kidney function (7). In the present study, all-cause mortality was not different between higher and lower FGF23 groups. Mortality rates were only 6.8% during the follow-up period (41.6 ± 20.0 months), which is remarkably lower than reported in other studies. Therefore, the statistical power was not strong enough to verify the influence of FGF23 on all cause mortality rates.

The present study showed the influence of higher FGF23 for the 'incident PD' patients. To our knowledge, this is the first study that thoroughly examined the association between FGF23 and CV outcome exclusively in PD patients. However, our study had several limitations. Due to the low mortality rate of our subjects on PD, it was not possible to demonstrate the effect of FGF23 on mortality. Aortic stiffness and vascular calcification was not evaluated in all patients. Therefore, the mechanistic link between FGF23 and CV outcome was not elucidated.

In conclusion, elevated FGF23 was associated with higher risk of adverse CV outcome for incident PD patients. Further studies are needed to elucidate the mechanisms by which higher FGF23 concentrations are associated with CV outcomes and whether therapeutic interventions to counter FGF23 are clinically beneficial in the dialysis population.

DISCLOSURES

KHO serves as a consultant and received honoraria for lectures from Fresenius, Korea, and Baxter, Korea. All

the other authors have no financial conflicts of interest to declare.

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