의학석사 학위논문

Baseline FGF23 is associated with cardiovascular outcome in incident PD patients

복막투석을 처음 시작하는 환자에서 초기 FGF23 값과 심혈관계 사건의 연관성

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ABSTRACT

Introduction: 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 baseline FGF23 with cardiovascular (CV) events, all-cause mortality, residual renal function (RRF), and CV parameters.

Methods: The present study is a single-center, retrospective study. Patients who started PD at Seoul National University Hospital between Jan, 2005 and July, 2011 and whose baseline serum samples were available were enrolled. C-terminal FGF23 was measured. Subjects were divided into two groups; lower 2 tertiles (FGF23 $\leq$ 119.0 RU/mL) and top tertile (FGF23 > 119.0 RU/mL). The primary outcome was time-to-the 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 $\pm$ 20.0 months. The baseline median FGF23 level was 78.6 RU/ml (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 to the age, DM,

pre-existing coronary artery disease, cerebrovascular disease, congestive heart failure, and left ventricular mass index, higher FGF23 group exhibited significantly higher risk of primary outcome, compared with the lower group (HR, 2.54; 95% CI, 1.05-6.12; P = 0.045). There were no significant differences in all-cause mortality and development of anuria between the two FGF23 groups. In the subgroup analysis, FGF23 groups were not associated with pulse wave velocity and abdominal aortic calcification score calculated by lateral lumbar radiograph.

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

Keywords: Peritoneal dialysis, Fibroblast growth factor 23, FGF23, Cardiovascular disease
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LIST OF ABBREVIATIONS

AAC: Abdominal aorta calcification

AoAC: Aortic arch calcification

BMI: Body mass index

Ca: Calcium

CAD: Coronary artery disease

CACS: Coronary artery calcification score

CHF: Congestive heart failure

CRP: C-reactive protein

CKD: Chronic kidney disease

CV: Cardiovascular

DM: Diabetes mellitus

ESRD: End stage renal disease

FGF23: Fibroblast growth factor 23

GFR: Glomerular filtration rate

HD: Hemodialysis

iPTH: Intact parathyroid hormone

LVEF: Left ventricular ejection fraction

LVH: Left ventricular hypertrophy

LVMI: Left ventricular mass index

P: Phosphorus

PD: Peritoneal dialysis

PWV: Pulse wave velocity

RRF: Residual renal function

25(OH)VitD: 25-hydroxyvitamin D

$1,25(OH)_2D$: 1,25-hydroxyvitamin D

INTRODUCTION

Fibroblast growth factor 23 (FGF23) is a phosphorus regulating protein secreted by bone cells, mainly osteoblast (1, 2). It regulates phosphorus homeostasis and the serum level of FGF23 increases progressively as kidney function declines, even before the rise of phosphorus level (3). FGF23 levels increase in chronic kidney disease (CKD) as an appropriate adaptation to maintain phosphate homeostasis. However, previous studies showed that elevated FGF23 level may exert its negative effects. Several studies demonstrated that elevated FGF23 is independently associated with mortality in early stage CKD (4), advanced CKD (5), incident hemodialysis (HD) patients (6, 7), and even in patients with normal kidney function (8). Furthermore, elevated FGF23 is associated with adverse cardiovascular (CV) outcomes in patients with normal kidney function (9) and advanced CKD patients (5). Several studies showed elevated FGF23 is related with left ventricular hypertrophy (LVH) in CKD (10) and HD patients (11, 12).

CV disease and mortality events are more common in end stage renal disease (ESRD) patients (13). CV mortality is associated with not only conventional risk factors as hypertension or diabetes mellitus (DM) but also with vascular calcification (14) and vascular stiffness (15, 16). Arterial stiffness can be assessed by pulse wave velocity (PWV) (17, 18). It depends on the arterial wall structure and function. Increased PWV is an independent factor of CV mortality for ESRD patients (16). In addition, ESRD patients with vascular calcification have higher risk for CV morbidity and mortality, compared to a population of similar age and gender (19). Coronary artery

calcification score (CACS) evaluated by computed tomography is gold standard assessing vascular calcification (20). However, it is expensive and is not readily available in routine clinical practice. There have been easy and simplified semiquantitative methods such as abdominal aorta calcification (AAC) score (21) and aortic arch calcification (AoAC) score (22) measured by simple radiography which well correlates with CACS (23) and whole aortic calcification (24). AAC score measured by lateral lumbar radiography (25) and AoAC score detected by chest radiography (26) are independent predictors of all-cause and CV mortality in ESRD patients.

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

1. 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 Jan, 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 three months after PD catheter insertion. Finally, 205 patients whose baseline serum samples were available were enrolled. They were followed till 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.

2. Clinical data collection

The 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 by using routine laboratory methods. Albumin-corrected calcium levels were calculated as follows; corrected Ca (mg/dL) = measured total Ca (mg/dL) + 0.8 x [4 - measured serum albumin (g/dL)] (27). Residual glomerular filtration rate (GFR) was measured as the average of renal urea and creatinine clearance (28). Adequacy of dialysis was estimated

by measuring total weekly Kt/V urea and creatinine clearance using standard methods (29). Left ventricular ejection fraction (LVEF) was measured by echocardiography. Cardiac mass was calculated as: left ventricular mass (LVM) (g) = 0.8 x [1.04 x {(left ventricular internal diameter in diastole + interventricular septal thickness in diastole + posterior wall thickness in diastole)^3− left ventricular internal diameter in diastole^3}] + 0.6 (30). LVM was adjusted for body surface area [Left ventricular mass index (LVMI) (g/m^2)]. Left ventricular hypertrophy (LVH) is defined as LVMI ≥ 131 g/m^2 in male, and ≥ 100 g/m^2 in female (31). Arterial stiffness was measured by heart−to−femoral pulse wave velocity (PWV). It is a central stiffness index and used as arterial stiffness markers due to ease of measurement, reproducibility and validity exhibited in previous studies (32). AAC was measured by simple lateral lumbar radiograph with a range of 0 to 24 (21) and AoAC was measured by simple chest radiography with a range of 0 to 3 for assessing vascular calcification (22) .

3. 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 ten−fold dilution of the serum with dilution reagent.

4. 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 the fatal or non-fatal CV events. CV 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 subgroup analysis. Censoring events for outcomes included kidney transplantation and transfer to other PD centers.

5. Statistical analysis

Categorical variables were analyzed by χ^2 test and presented as frequencies and percentage. Continuous variables were evaluated with independent samples *t*-tests and Mann-Whitney test. Results are presented as mean ± standard deviation (SD) for normally distributed variables and median [interquartile range (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-the anuric state, we used Cox proportional hazards models with adjustment. Adjusted PWV was derived and compared between two FGF23 groups using covariance analysis (ANCOVA). *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 m^2/ 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 two groups (P = 0.625).

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 (β = −0.30, P < 0.001) and with DM (β = −0.22, P = 0.002) (Table 2). Other factors, such as iPTH (β = 0.16, P = 0.037) and phosphorus level (β = 0.15, P = 0.039) were also associated with FGF23.

Table 1. The baseline clinical characteristics of patients of the FGF23 groups

	Total (N = 205)	FGF 23 Groups		*P*− value
		Lower group (FGF23 ≤ 119.0 RU/ml) (n = 137)	Higher group (FGF23 > 119.0 RU/ml) (n = 68)	
Age (years)	47.4 ± 14.3	49.1 ± 14.3	44.1 ± 13.9	0.018
Gender (male, n, %)	122 (59.5)	87 (63.5)	35 (51.5)	0.130
Comorbidity (n, %)				
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 (n, %)	175 (85.4)	113 (82.5)	62 (91.2)	0.141
Ca containing P−binder (n, %)	168 (82.0)	110 (80.3)	58 (85.3)	0.444
Calcitriol (n, %)	33 (16.1)	19 (13.9)	14 (20.6)	0.231
BMI (g/m^2)	22.7 ± 3.4	22.5 ± 3.4	23.1 ± 3.3	0.292
Residual GFR (L/1.73 m^2/wk)	53.4 ± 33.0	62.4 ± 31.8	36.1 ± 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 ± 1.4	9.7 ± 1.4	9.2 ± 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 ± 0.7	8.6 ± 0.7	8.6 ± 0.8	0.841
P (mg/dL)	4.9 ± 1.3	4.7 ± 1.2	5.3 ± 1.5	0.008
Ca x P (mg^2/dL^2)	42.0 ± 10.6	40.5 ± 9.8	44.9 ± 11.4	0.007
Total cholesterol (mg/dL)	157.9 ± 41.6	160.5 ± 43.5	152.9 ± 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 ± 4.6	14.9 ± 5.2	13.4 ± 2.7	0.005
$1,25(OH)_2$VitD (pg/mL)	3.6 ± 2.1	3.8 ± 2.3	3.1 ± 1.7	0.013
LVMI (g/m^2)	117.1 ± 37.5	113.3 ± 33.9	124.6 ± 43.1	0.076
LVH (n, %)*	76 (42.5)	43 (36.1)	33 (55.0)	0.017

LVEF (%)	59.3 ± 9.0	60.2 ± 9.2	57.4 ± 8.6	0.044
AoAC score ≥ 1 (n, %)	58 (28.9)	40 (30.1)	18 (26.5)	0.625

Lower group: lower 2 tertiles, patients with FGF23 ≤ 119.0 RU/m, Higher group: top tertile, patients with FGF23 > 119.0 RU/ml

* LVH is defined as ≥ 131 g/m^2 in male, ≥ 100 g/m^2 in female.

FGF23: fibroblast growth factor 23; DM: diabetes mellitus; CAD: coronary artery disease; CHF: congestive heart failure; BMI: body mass index; CRP: C-reactive protein; Ca: calcium; P: phosphorus; iPTH: intact parathyroid hormone; 25(OH)VitD: 25-hydroxyvitamin D; $1,25(OH)_2D$: 1,25-hydroxyvitamin D; LVMI: left ventricular mass index; LVH: left ventricular hypertrophy; LVEF: left ventricular ejection fraction; AoAC: aortic arch calcification.

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 to 0.00	< 0.001
DM (yes)	−0.22	−0.51 to −0.11	0.002
Log iPTH (pg/ml)	0.16	0.01 to 0.45	0.037
P (mg/dL)	0.15	0.00 to 0.14	0.039

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 $1,25(OH)_2D$.

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

CV events, all-cause mortality, and development of anuria according to FGF23 groups

During follow-up period of 41.6 ± 20.0 months, three patients were lost to follow-up. Finally, twenty two 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 two groups at baseline (Table 3). In model A, adjusted for the age, DM, hypertension, pre-existing CAD, cerebrovascular disease, CHF, LVMI, presence of AoAC (AoAC score 0 vs. ≥ 1), and FGF23 groups, higher FGF23 group exhibited significantly higher risk of fatal or non-fatal CV events compared with the lower group (HR, 2.45; 95% confidence interval [CI], 1.02-5.90; P = 0.045) (Table 3, Figure 1). In model B, adjusted for covariates in Model A plus measures of mineral metabolism, higher FGF23 group still was 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 residual renal function, 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).

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 two 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).

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†)	2.54 (1.02– 5.90)‡	2.90 (1.07–7.82)‡	2.87 (1.06–7.76)‡
Preexisting CAD (yes)	3.95 (1.45–10.77)‡	8.76 (3.13–24.54)‡	8.70 (3.10–24.38)‡
Preexisting CHF (yes)	2.85(1.12 –7.27)‡	4.12 (1.54–11.04)‡	4.09 (1.53–10.97)‡
Age (per 1yr)	1.05 (1.01–1.09)‡		
Log iPTH (pg/ml)		0.20 (0.07–0.53)‡	0.20 (0.07–0.54)‡
25(OH)VitD (ng/mL)		0.87 (0.77–1.00)‡	0.87 (0.77–1.00)‡

*Time–to–the 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.

†Lower group: lower 2 tertiles, patients with FGF23 ≤ 119.0 RU/m; higher group: top tertile, patients with FGF23 > 119.0 RU/ml

HR: hazard ratio; CI: confidence interval; FGF23: fibroblast growth factor 23; DM: diabetes mellitus; CAD: Coronary artery disease; CHF: congestive heart failure; iPTH: intact parathyroid hormone; 25(OH)VitD: 25–hydroxyvitamin D; AoAC: aortic arch calcification; LVMI: left ventricular mass index. ‡significant association with primary outcome ($P < 0.05$). $P < 0.05$ was considered significant.

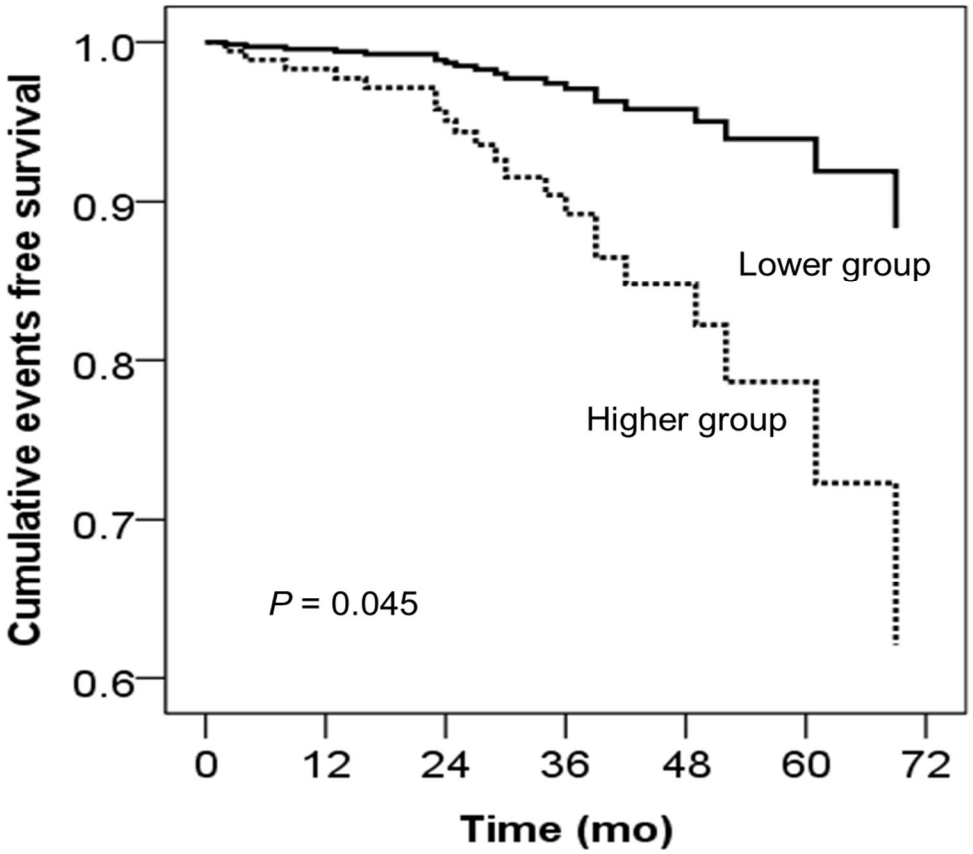

Figure 1. Cardiovascular events according to FGF23 groups. Analyzed by Cox proportional hazard models, cumulative event-free survival was lower in the higher FGF23 group (P = 0.045). Adjusted for age, DM, hypertension, CAD, cerebrovascular disease, CHF, LVMI, AoAC, and FGF23 groups. FGF23: fibroblast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

Pulse wave velocity and abdominal aorta calcification in association with FGF23 groups

Ninety seven patients (47.3%) were evaluated for PWV at baseline and their mean value was 1000.6 ± 281.3 (cm/s). After adjustment by ANCOVA, the PWV was not different between two FGF23 groups (lower vs. higher FGF23

group; 986.0 [95% CI, 986.9−1035.2] vs. 1046.6 [95% CI, 980.1−1113.1]; *P* = 0.161; Figure 2). At the baseline, 71 patients (34.6%) performed lateral lumbar radiograph for AAC score evaluation, among whom 48 (67.6%) exhibited no abdominal aortic calcification. AAC score was not significantly different between the two FGF23 groups.

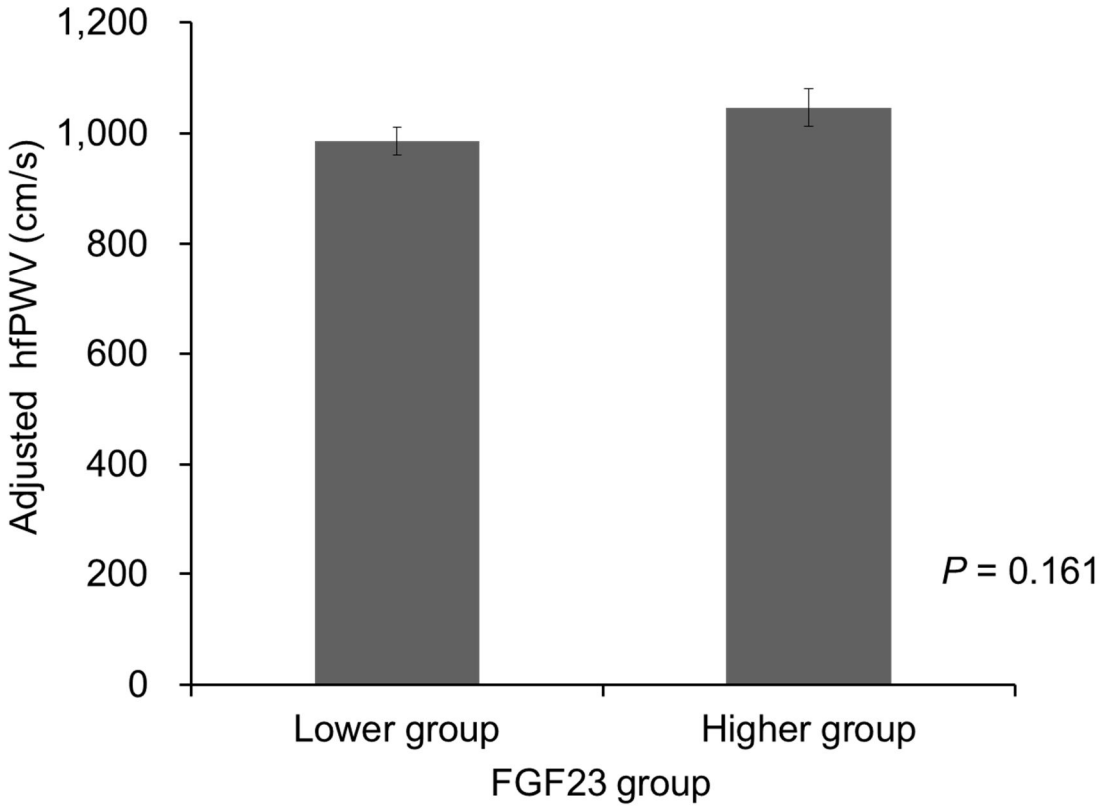

Figure 2. Adjusted mean pulse wave velocity (PWV). Adjusted PWV was derived and compared between the FGF23 groups using the covariance analysis (ANCOVA) that includes the parameters that were associated with PWV. Lower group: patients with FGF23 ≤ 119.0 RU/m, Higher group: patients with FGF23 > 119.0 RU/ml. Error bars denote standard error.

DISCUSSION

The present study showed that 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 phosphorous levels. However, elevated level of plasma FGF23 was shown to be associated with adverse outcomes. Baia et al.(33) 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.(34) 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 (5). 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 (35, 36). Several studies demonstrated that higher FGF23 levels are independently associated with impaired vasoreactivity in subjects with normal renal function (37) and with stage 3–4 CKD (38). Nakamura et al. (39) 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 an important CV risk factor for mortality in patients with CKD (40, 41). FGF receptors, particularly FGFR1, are expressed in myocardial cells and their activation could stimulate myocardial hypertrophy (42). Previous cross–sectional studies showed that association of FGF23 with LVMI and LVH (10, 11). However, definite mechanism between FGF23 and LVH remains, further prospective studies are needed to elucidate the causality between myocardial hypertrophy and FGF23 in PD patients.

Other parameters such as arterial stiffness and arterial calcification could influence CV events. Therefore, we conducted subgroup analysis to show the association between FGF23 and these parameters. In the general population with normal renal function, FGF23 was associated with increasing arterial stiffness (β = 0.26, P < 0.001) (37). However, Desjardins et al. (43) found no correlation between FGF23 and PWV in patients with various CKD stages.

In our PD patients, adjusted PWV tended to be higher in higher FGF23 group compared with lower FGF23 group. However, the difference was not significantly different (P = 0.161). In the present study, only a small number of patients performed PWV measurement at baseline, which might have weakened the statistical power. Further larger studies are required to better understand the relationship between FGF23 and arterial stiffness in PD patients. Furthermore, higher FGF23 was associated with more severe peripheral vascular calcification in HD patients (7). It was hard to show the association between FGF23 and vascular calcification in our PD patients. It might be that a small number of patients performed lateral lumbar radiograph at baseline and most of them exhibited little or no vascular calcification. Low level of vascular calcification score might be ascribed to the young age of our incident PD patients (47.4 ± 14.3 years of age). Further studies are needed to elucidate this association.

Previous studies showed the association between FGF23 and all-cause mortality. Jean et al. (7) demonstrated that the highest quartile FGF23 group had 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 (6) and in patients with normal kidney function (8). However, several studies presented different results. Westerberg et al. (34) showed FGF23 was not associated with all-cause mortality in community-based elderly population. Olauson et al. (44) demonstrated that FGF23 level was not associated with increased all-cause mortality in 229 incident dialysis patients (123 HD and 94 PD patients). However, in a subgroup analysis of men with previous CVD, FGF23 was a risk factor for all-cause mortality.

Sugimoto et al. (45) also showed that FGF23 level was not associated with increased all-cause mortality in 92 maintenance HD patients. They thought that the influence of FGF23 on all-cause mortality may be modified by comorbidities such as gender and previous CVD. 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 outcomes exclusively in PD patients. In addition, we measured vascular calcification easily using simple methods of chest and lateral lumbar radiograph. However, our study had several limitations. Due to 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, 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 dialysis population.

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국문 초록

서론: 섬유아세포 성장인자 23(FGF23)은 인(phosphorus) 조절 단백질이다. 이전 연구에서 상승된 FGF23 의 값은 초기 신부전 환자 및 혈액투석을 시작하는 환자의 사망률 증가와 독립적으로 연관관계가 있었다. 하지만 복막 투석환자에서 상승된 FGF23 값의 의미에 대해서는 연구가 부족한 실정이다. 이에 본 연구에서는 새롭게 복막 투석을 시작하는 환자에서 초기 FGF23 값과 심혈관계 사건의 발생, 사망률, 잔여 신기능 및 심혈관계 지표들과의 연관관계에 대해서 살펴보고자 한다.

방법: 본 연구는 단일 연구 기관의 후향적 연구로 2005 년 1 월부터 2011 년 7 월까지 서울대학교 병원에서 복막 투석을 시작한 환자 중 초기 혈액 샘플이 있는 환자들을 대상으로 하였다. 환자들의 C-terminal FGF 값을 측정하였다. 환자는 FGF23 의 값에 따라 두 그룹으로 분류 되었다(FGF23 ≤ 119.0 RU/mL vs. FGF23 > 119.0 RU/mL). 일차 결과는 치명적인 또는 비치명적인 심혈관계 사건의 발생으로 하였다. 하위집단 분석으로 FGF23 과 대동맥의 경직 또는 심혈관 석회화의 연관성에 대해서 분석하였다.

결과: 총 205 명의 환자를 대상으로 분석을 하였고 이들의 평균 추적기간은 41.6 ± 20.0 개월이었다. 초기 FGF23 의 중앙값은 78.6 RU/mL (IQR, 34.1-155.0) 이었다. 초기에 FGF23 값이 큰 그룹의 환자들이 더 젊고 당뇨 및 뇌혈관 질환의 유병율이 낮았으며 신기능은 더 낮았다. 추적 기간 동안 총 22 명(10.7%)의 환자에서 일차결과가 발생하였다. 나이, 당뇨, 기존의 관상 동맥 질환의 병력, 뇌혈관 질환, 울혈성 심부전 및 좌심실 비대 인자로 보정을 하였을 때, FGF23 값이 높은 그룹에서 낮은 그룹에 비해서 심혈관계 사건의 발생이 더 많은 것을 알 수 있었다 (HR, 2.54; 95% CI, 1.05-6.12; P = 0.045). FGF23 그룹간에 전체 사망률과 무

뇨의 발생은 차이가 없었다. 하위집단 분석에서 FGF23 그룹은 대동맥의 경직 또는 단순 방사선 사진으로 측정한 복부 대동맥 석회화와 유의한 연관성이 없었다.

결론: 상승된 초기 FGF23 값은 새롭게 복막 투석을 시작하는 환자에서 유해한 심혈관 사건과 연관성이 있다.

주요어 : 복막투석, 섬유아세포 성장인자 23, 심혈관질환
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