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CLINICAL STUDY

Fibroblast Growth Factor 23 is a Predictor of Aortic Artery Calcification in Maintenance Hemodialysis Patients

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Abstract

Background: Our study aimed to investigate the factors associated with elevated plasma FGF23 (cFGF23) levels in maintenance hemodialysis (MHD) patients and to determine whether plasma FGF23 level is related to aortic artery calcification (AAC). *Methods*: This study included 120 MHD patients and 20 controls. The FGF23 level was measured using a C-terminal assay and AAC was detected by a lateral lumbar X-ray plain. *Results*: Plasma FGF23 levels were significantly higher among dialysis patients compared to controls: FGF23 level of 27691.42 ± 55646.41 RU/mL in MHD patients versus 49.89 ± 23.94 RU/mL in health people. Significant correlations were observed between FGF23 levels and vintage, intact parathyroid hormone (iPTH), serum phosphate, total calcium, 25(OH)D, urea nitrogen (BUN), and serum creatinine (SCR). Stepwise multiple regression analysis showed that the independent parameters associated with FGF23 level were serum phosphate, total calcium, parathyroid hormone (PTH), SCR, and prealbumin. There were 73 patients (60.83%) with visible calcification in the abdominal aorta. Bivariate analysis showed that AAC score correlated with FGF23, phosphate, total calcium, vintage, age, and diastolic blood pressure. Forward logistic analysis showed that the independent parameters associated with AAC were age, total protein, and Lg FGF23. *Conclusion*: Plasma FGF23 level is significant increased in hemodialysis patients and is independently associated with AAC.

Keywords: FGF23, hemodialysis, cardiovascular disease, vascular calcification, lateral lumbar radiography

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death in maintenance hemodialysis (MHD) patients. Vascular calcification is an important predictor of mortality in end-stage renal disease. Recently, several novel regulators of arterial calcification, including fibroblast growth factor 23 (FGF23), have been identified. Several studies reported that increased FGF23 was associated with higher rate of CVD.

Different vascular calcification scores have now been evaluated in the dialysis patient. The diagnosis of vascular calcification is usually based on very expensive and highly technical devices like electron beam computed tomography (EBCT) or multislice spiral computed tomography (MSCT). However, lateral lumbar X-ray is a useful approach to detect aortic artery calcification (AAC) with cheap price and low radiation. Additionally, the use of plain radiographic films of bone has already been suggested in kidney disease: improving global outcomes (KDIGO) chronic kidney disease mineral and bone disorder (CKD-MBD) clinic practice guideline.[1]

Our study aimed to survey the prevalence of AAC and investigate the factors associated with elevated plasma C-terminal FGF23 (cFGF23) levels and to determine whether plasma FGF23 level is related with AAC in Chinese MHD patients.

METHOD

The study included 120 MHD patients as well as 20 controls. All MHD patients were treated in Shanghai's Ruijin Hospital in July 2011. All MHD patients met the following inclusion criteria: (1) age over 18 years old; (2) receiving hemodialysis three times a week, on a 4-hour schedule, using a dialysate calcium concentration of 1.5

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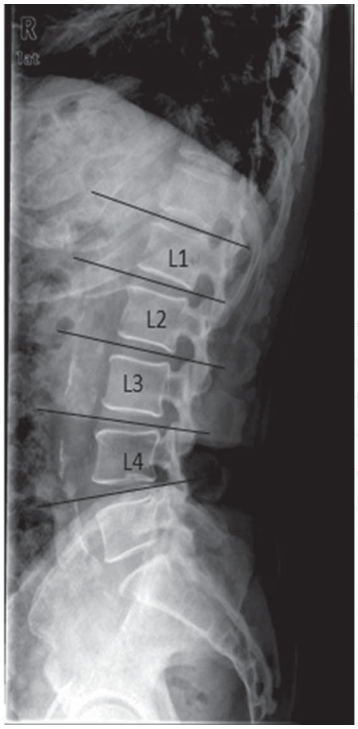

	Segment affected	Score		AAC score
		Anterior (0–3)	Posterior (0–3)	Total score (0–6)
L1	0	0	0	0
L2	1	2	0	2
L3	1	3	1	4
L4	1	3	1	4
Total	3	8	2	10

Figure 1. Aortic artery calcification score.

mmol/L; (3) no rapidly progressive kidney disease; and (4) no malignancy. The plasma samples of 20 controls were from the Medical Examination Center of Ruijin Hospital. This study was approved by the Institutional Review Board of the Ruijin Hospital, Shanghai Jiaotong University School of Medicine, and was in accordance with the principle of the Helsinki Declaration.

All clinic data of MHD patients were collected, including blood pressure, which were recorded using the mean of the precious 1 month, height and weight, medical history, and pre-dialysis blood tests, which included prealbumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein (TP), albumin, urea nitrogen (BUN), serum creatinine (SCR), uric acid (UA), parathyroid hormone (PTH), 25(OH)D, triglyceride, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum phosphate, and calcium. PTH was measured using an intact assay by a chemiluminescent method (Abbott i2000); serum 25(OH)D was measured by electrochemiluminescence immunoassay (Roche Cobas e601). The samples for measuring FGF23 were ethylene diamine tetraacetic acid (EDTA) plasma. We collected all the samples with other blood test samples on the same day in July 2011 before dialysis. After centrifugation for 10 min at 2000 rpm, all plasma was stored at –80° as soon as possible. The plasma FGF23 level was measured using a C-terminal assay [FGF23 (C-Term) enzyme-linked immunosorbent assay (ELISA), Immutopics Inc.]. Serum total calcium levels were corrected for serum albumin, calculated by measured Ca level in mg/mL + (4.0–albumin level in mg/mL). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Aortic artery calcification (AAC) was detected by a lateral lumbar X-ray plain at a voltage of 70 kV in 120 MHD patients and read by two radiologists using a semiquantitative score (Figure 1). This semiquantitative score was also used by others[2–5] and summarized as follows: calcified deposits along the anterior and posterior longitudinal walls of the abdominal aorta adjacent to each lumbar vertebra from L1 to L4 were assessed using the midpoint of the intervertebral space above and below the vertebrae as the boundaries. Calcifications were graded as follows: 0, no aortic calcific deposits; 1, less than one-third of the corresponding vertebral length; 2, one-third or more, but less than two-thirds of the corresponding length; 3, more than two-thirds of the corresponding length. Each patient's radiological semiquantitative score ranged from 0 to 4 for the segment affected, from 0 to 6 for each vertebral level, and from 0 to 24 for the total score. The blood tests and X-ray plain were be done within one month.

STATISTICAL ANALYSIS

Statistical Package for Social Analysis (SPSS) version 19.0 was used for data analysis. Results are expressed as mean ± SD, median (and range), or frequency (as percentage). Comparison between groups was performed by an unpaired t-test or the nonparametric Wilcoxon rank-sum test in case of non-normally distributed variables.

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Spearman's correlation was used for bivariate analysis. Stepwise multiple regression was done to demonstrate relationships between FGF23 and the other studied factors (criteria: enter $p \leq 0.05$, remove ≥ 0.10). One-way analysis of variance (ANOVA) and independent sample t-test were used to compare the variables according to quartiles of serum FGF23 level. Forward logistic regression was performed to determine significant associations between AAC and other variables, adjusted for potential confounders (criteria: enter $p \leq 0.05$, remove ≥ 0.10). Non-normally distributed variable FGF23, dialysis vintage, PTH, and triglyceride were Lg-transformed to achieve a normal distribution and used in statistical analysis. All statistical tests were performed at the two-sided 0.05 level of significance.

RESULTS

The demographic and clinical characteristics of MHD patients are presented in Table 1. Fifteen of 120 MHD patients (12.5%) with diabetes mellitus (DM).

Plasma FGF23 Levels

The plasma samples of 120 MHD patients and 20 health people were tested in our study. Plasma FGF23 levels were significantly higher among the dialysis patients compared to controls, with the FGF23 level of 27691.42 ± 55646.41 RU/mL in MHD patients versus 49.89 ± 23.94 RU/mL in healthy people ($p < 0.0001$). In MHD patients, the median plasma FGF23 level was 5601.27 RU/mL (interquartile range 1310.47–25783.44 RU/mL) and Lg FGF23 was 3.82 ± 0.79.

Significant correlations were observed between plasma FGF23 levels and Lg vintage ($r = 0.413$, $p < 0.001$; Figure 2A), Lg PTH ($r = 0.283$, $p = 0.002$; Figure 2B), serum phosphate ($r = 0.587$, $p < 0.001$; Figure 2C), total calcium ($r = 0.419$, $p < 0.001$; Figure 2D), 25 (OH)D ($r = 0.195$, $p = 0.033$; Figure 2E), BUN ($r = 0.263$, $p = 0.004$), and SCR ($r = 0.415$, $p < 0.001$; Figure 2F).

Because Lg FGF23 was normal distribution, stepwise multiple regression analyses showed that the independent parameters associated with FGF23 level were serum phosphate, total calcium, Lg PTH, SCR, and prealbumin ($R^2 = 0.638$, $p < 0.001$; Table 2).

Aortic Artery Calcification (AAC)

There were 73 patients (60.83%) with visible calcification in the abdominal aorta, whereas 56 patients (46.67%) with calcification in more than two segments, suggesting severe calcification. The median AAC score was 2.0 (0–21) and median AAC segments affected were 1.0 (0–4).

Table 1. Clinical characteristics of MHD patients.

Parameters	Results	Reference range
Number (n)	120	–
Sex male (%)	71 (59.2)	–
Age (years)	55.1 ± 14.9 (20–85)	–
BMI (kg/m^2)	21.71 ± 3.81	–
Vintage (month)	39.1 (1.0–225.5)	–
SBP (mmHg)	139.3 ± 13.3	–
DBP (mmHg)	81.6 ± 9.2	–
Pre-albumin (mg/L)	302.8 ± 73.9	180–380
ALT (IU/L)	14.3 ± 8.5	16–64
AST (IU/L)	14.6 ± 6.0	
ALP (IU/L)	90.9 (33.0–1001.0)	38.0–126.0
TP (g/L)	63.1 ± 6.0	
Albumin (g/L)	34.5 ± 4.1	35.0–55.0
BUN (mmol/L)	24.7 ± 6.3	2.5–7.1
SCR (umol/L)	1035.9 ± 264.1	Male: 62–115; Female: 53–97
UA (umol/L)	449.5 ± 77.0	160–430
iPTH (pg/ml)	1046.9 (8.5–86401.0)	130–600*
25 (OH) D (nmol/L)	50.9 ± 26.2	50.0–80.0
TG (mmol/L)	2.27 (0.41–14.58)	0.56–1.70
TC (mmol/L)	4.04 ± 1.08	2.33–5.7
HDL (mmol/L)	1.09 ± 0.34	
LDL (mmol/L)	2.22 ± 0.77	
cFGF23 (RU/ml)	27691.42 (69.94–351947.34)	–
LgFGF23	3.82 ± 0.79	–
P (mg/ml)	5.69 ± 1.86	2.5–4.5*
tCa (mg/ml)	9.43 ± 0.95	8.5–10.0*

Notes: *Reference range according to KDIGO CKD-MBD guideline. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TP, total protein; BUN, blood urea nitrogen; SCR, serum creatinine; UA, uric acid; iPTH, intact parathyroid hormone; TG, triglyceride; TC,cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; P, phosphate; tCa, total calcium.

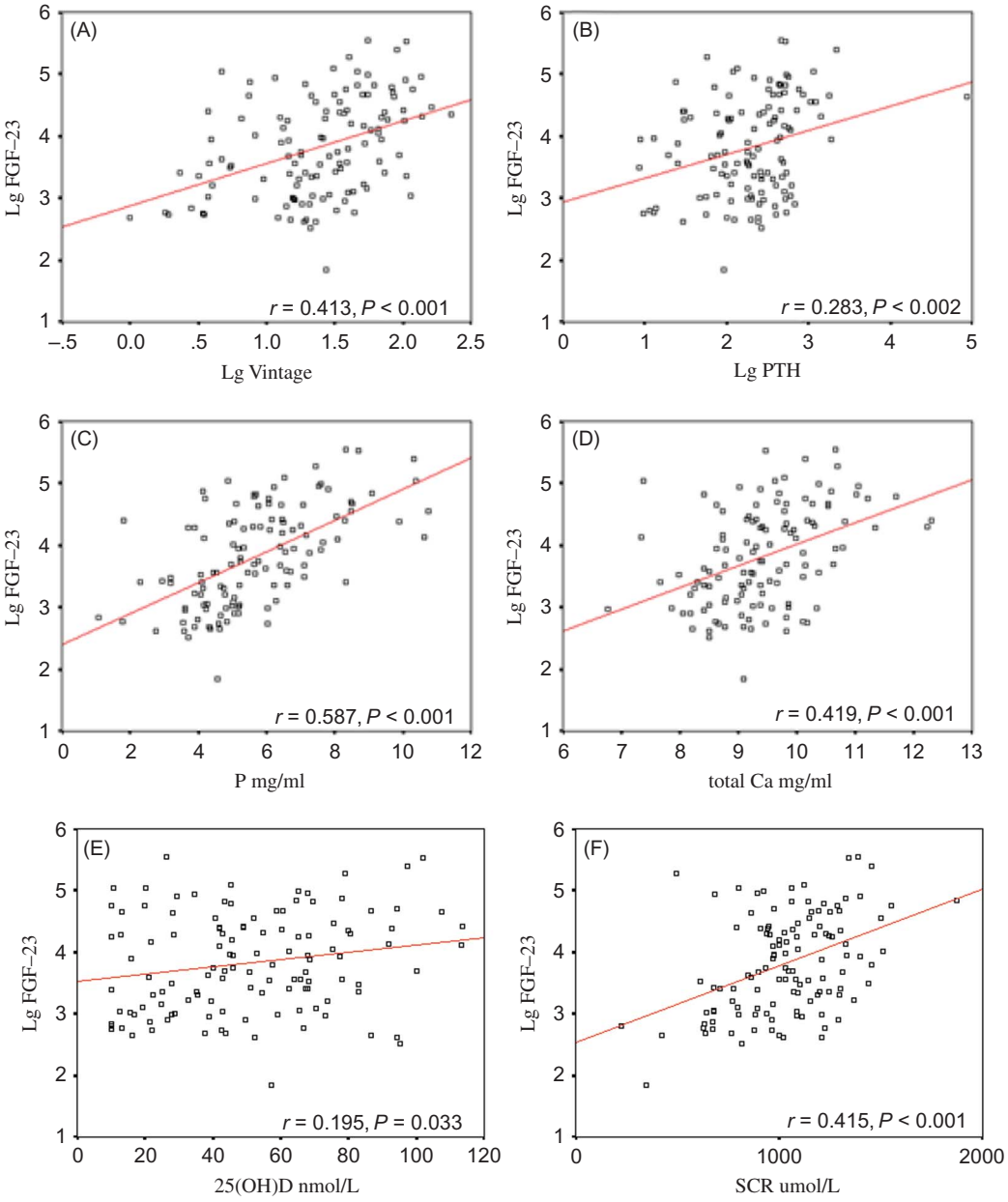

Figure 2. (A) Correlations between Lg FGF23 and Lg Vintage ($r = 0.413$, $p < 0.001$). (B) Lg PTH ($r = 0.283$, $p = 0.002$). (C) serum phosphate ($r = 0.587$, $p < 0.001$). (D) total calcium ($r = 0.419$, $p < 0.001$). (E) 25(OH)D ($r = 0.195$, $p = 0.033$). (F) SCR ($r = 0.415$, $p < 0.001$).

Aortic Artery Calcification (AAC) and FGF23

According to the FGF23 quartiles, the AAC score in the first quartile was 0.97 ± 1.59, which increased to 3.30 ± 4.81 in the second quartile, 4.93 ± 4.53 in the third quartile, and 6.50 ± 6.92 in the fourth quartile. The third and fourth FGF23 quartiles were associated with more severe AAC (Table 3).

Bivariate analysis showed that AAC score correlated in MHD patients with Lg FGF23 ($r = 0.371$, $p < 0.001$; Figure 3), phosphate ($r = 0.201$, $p = 0.028$), total calcium ($r = 0.216$, $p = 0.018$), Lg vintage ($r = 0.404$, $p < 0.001$), age ($r = 0.395$, $p < 0.001$), and diastolic blood pressure ($r = 0.395$, $p = 0.026$). Forward logistic analysis showed that the independent parameters associated with AAC were age, TP, and Lg FGF23 (Nagelkerke $R^2 = 0.395$, $p < 0.001$) (Table 4).

DISCUSSION

Vascular calcification is very common in CKD patients, especially in MHD patients. In 2004, Russo et al. reported that 40% of all CKD patients had vascular calcification as compared to 13% in a matched control

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Table 2. Stepwise multiple regression for factors associated with FGF23 P, Phosphate; Total Ca, total calcium; PTH, parathyroid hormone; SCR, serum creatinine.

		95% Condidence interval for β			
	β	Lower bound	Upper bound	R^2	P -Value
P	0.206	0.151	0.216	0.345	<0.001
Total Ca	0.392	0.290	0.494	0.209	<0.001
Lg PTH	0.318	0.143	0.494	0.043	<0.001
SCR	0.001	0.000	0.001	0.020	0.001
Pre-albumin	–0.002	–0.003	0.000	0.020	0.015

population.[6] Our study showed that 60.8% of MHD patients had visible calcification in the abdominal aorta. A lower prevalence of AAC (60.83%) detected by later lumbar X-rays that we found in MHD patients compared to other studies reporting a prevalence of 81–94% is probably attributable to a younger population (mean age 55.1 years in our study vs. 61.4 years in calcification outcome in renal disease (CORD) study vs. 66.9 years in Australia study)[3,4] or geographical location differences.[7]

Aortic artery calcification was shown to be associated with coronary artery calcification[5] and mortality.[2,8,9] Aortic artery calcification can be evaluated by different methods, mainly X-ray plain and computed tomography (CT). Non-contrast abdominal CT, considered as gold standard method, is highly reliable and sensitive for diagnosis of AAC, but it is expensive and delivers a substantial dose of radiation. Because of these limitations, it cannot be widely used in the clinic. Lateral lumbar X-ray is a simple method for detecting AAC with cheap price, available devices, and low radiation. Besides, we also used the AAC score to evaluate the severity of calcification. An AAC score has been reported to be highly correlated with coronary artery calcification.[5] In a previous study, FGF\23 has been reported to associate with peripheral calcification[10,11] in dialysis patients, but not with aortic calcification.[11] In our study, the main finding was that a single factor of FGF23 was independently correlated to aortic calcification on X-ray plain in MHD patients.

Why FGF23 relates to vascular calcification is still unknown. FGF23 is a novel bone-derived phosphaturic factor involved in mineral metabolism disorder. In our study, we also found that higher FGF23 levels were

Table 3. Baseline characteristics and AAC Score of MHD patients by quartiles of FGF23 level.

FGF-23 level	Q1 (<1311RU/mL)	Q2 (1311-5602RU/mL)	Q3 (5602-2578RU/mL)	Q4 (>25784RU/mL)	P Value
N	30	30	30	30	–
Age (year)	56.67 ± 15.9	55.4 ± 14.7	55.4 ± 14.0	53.1 ± 15.5	0.836
Sex male (%)	17 (56.7)	20 (66.7)	19 (63.3)	15 (50.0)	0.565
Vintage (month)	21.7 ± 21.4	28.6 ± 26.9	47.7 ± 46.1*	58.3 ± 40.4**	<0.001
Lg Vintage	1.13 ± 0.48	1.26 ± 0.45	1.49 ± 0.44*	1.63 ± 0.39**	<0.001
Pre-Alb (mg/L)	295.4 ± 63.7	305.0 ± 66.8	309.5 ± 86.3	301.5 ± 79.7	0.903
ALT (IU/L)	147 ± 8.5	17.1 ± 12.0	12.3 ± 5.0	12.9 ± 6.4	0.116
AST (IU/L)	16.4 ± 6.7	15.0 ± 6.2	13.4 ± 5.2	13.7 ± 5.7	0.209
ALP (IU/L)	83.5 ± 49.8	67.4 ± 18.7	112.6 ± 189.8	99.9 ± 80.3	0.386
TP (g/L)	63.6 ± 6.4	63.9 ± 5.6	62.2 ± 4.53	62.6 ± 7.2	0.655
ALB (g/L)	35.6 ± 3.6	34.4 ± 3.3	33.1 ± 3.3*	34.9 ± 5.4	0.108
BUN(mmol/L)	21.9 ± 5.5	24.3 ± 5.2	26.2 ± 6.5*	26.3 ± 7.2*	0.021
SCR (umol/L)	839.1 ± 262.7	1046.5 ± 212.2**	1097.0 ± 189.4**	1161.2 ± 275.6**	<0.0001
UA (umol/L)	449.5 ± 79.8	439.7 ± 70.5	450.1 ± 85.5	458.5 ± 74.3	0.831
iPTH (pg/mL)	222.9 ± 191.1	220.2 ± 166.9	306.1 ± 408.2	587.2 ± 500.0	0.298
Lg iPTH	2.12 ± 0.54	2.18 ± 0.44	2.17 ± 0.58	2.66 ± 0.62**	<0.001
25(OH)D(nmol/ml)	40.9 ± 26.2	51.1 ± 22.0	55.3 ± 24.4*	56.2 ± 30.0*	0.089
TG (mmol/L)	2.36 ± 2.57	2.52 ± 2.54	2.22 ± 1.81	1.99 ± 1.89	0.825
Lg TG	0.27 ± 0.27	0.28 ± 0.31	0.24 ± 0.30	0.19 ± 0.29	0.678
TC (mmol/L)	4.00 ± 1.25	3.78 ± 0.74	4.04 ± 1.16	4.33 ± 1.09	0.266
HDL (mmol/L)	1.05 ± 0.25	1.02 ± 0.35	1.06 ± 0.37	1.21 ± 0.38	0.158
LDL (mmol/L)	2.14 ± 0.95	2.04 ± 0.66	2.20 ± 0.68	2.47 ± 0.71	0.157
P (mg/mL)	4.33 ± 1.12	5.11 ± 1.40*	6.20 ± 1.79**	7.12 ± 1.76**	<0.001
tCa (mg/mL)	9.00 ± 0.79	9.08 ± 0.73	9.80 ± 1.04*	9.84 ± 0.93**	<0.001
SBP (mmHg)	138.6 ± 10.7	141.7 ± 13.1	139.0 ± 13.4	13708 ± 15.8	0.691
DBP (mmHg)	80.1 ± 8.9	83.8 ± 10.6	80.9 ± 7.1	81.5 ± 10.1	0.440
BMI (kg/m^2)	21.7 ± 3.5	22.5 ± 3.8	20.8 ± 3.8	21.9 ± 4.0	0.406
AAC seg.	0.84 ± 0.15	1.52 ± 0.28*	1.43 ± 0.26**	1.69 ± 0.31**	0.001
AAC Score	1.59 ± 0.29	4.82 ± 0.88*	4.53 ± 0.83**	6.92 ± 1.26**	<0.001

Notes: Results are expressed as mean ± SD or number of observations (precentage). ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TP, total protein; ALB, albumin; BUN, urea nitrogen; SCR, serum creatinine; UA, uric acid; iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; TG, triglyceride; TC, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; P, phosphate; tCa, total calcium; AAC seg., aortic artery calcification segments affected.
*$p < 0.05$, **$p < 0.001$, compared to the first quartile.

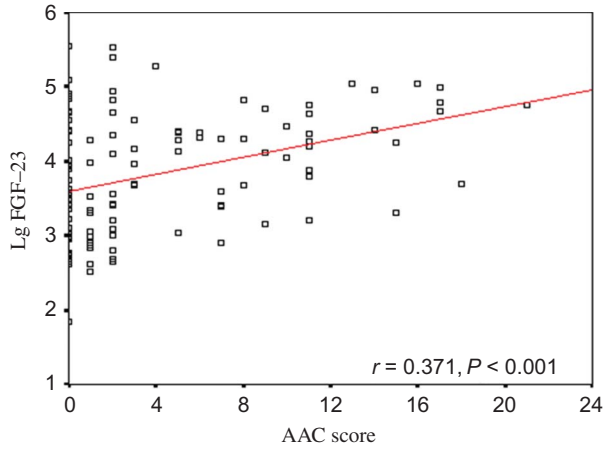

Figure 3. Bivariate correlation between Lg FGF23 level and AAC score ($r = 0.371$, $P < 0.001$).

Table 4. Forward logistic regression for factors associated AAC Score.

	Odds ratios	95% Confidence interval	*p*-value
Age (years)	1.088	1.050–1.128	<0.001
Lg FGF23	2.366	1.304–4.291	0.005
Total protein (g/L)	0.921	0.844–1.004	0.06

related to more severe secondary hyperparathyroidism, hypherphosphatemia, and hypercalcinemia. Increased FGF23 levels are observed in early CKD[12] and have been linked to increased mortality[13–16] and CVD, such as left ventricle hypertrophy[17–19] and vascular calcification[20] in CKD. Although the effects of FGF23 on cells of vascular wall have not been understood, it may play an important role in vascular calcification. FGF23 level increases with decreased kidney function and phosphate accumulates.[21] Recent studies have established a relationship between higher phosphate intake and FGF23 level[22] and have found that phosphate binder could reduce the FGF23 level.[23,24] FGF23 can promote renal phosphorus wasting and inhibit the conversion of 25(OH)D to the active 1,25-dihydroxyvitamin D form.[25–28] Because 25 (OH)D did not correlate with FGF23 or AAC score in multivariable models, AAC may not be the result of altered vitamin D levels. However, this point should be interpreted cautiously, because we did not measure the 1,25-dihydroxyvitamin D level in our study.

Another important protein for FGF23 effects is Klotho, a transmembrane protein expressed predominantly in the kidney. High levels of FGF23 as well as deficient renal Klotho expression are observed in CKD patients.[29] Some studies showed that, in the absence of Klotho, the increased FGF23 would bind to nonspecific low-affinity receptors[30] and may lead to a procalcification situation. However, serum Klotho levels were not tested in our study.

In multiple logistic regression analysis, the result also showed that TP is a protection factor of aortic calcification in MHD patients. Total protein is not only a nutrition factor, but also reflects the inflammation state of patients. The decreased TP level is associated with an inflammation situation in patients. So, in our study, patients with low TP may have a severe inflammation reaction and may have a link to aortic calcification.

There were a few limitations in our study. First, this study is cross-sectional and therefore does not show FGF23 level predicting the progression of vascular calcification or the detection of AAC by lateral lumbar radiographs predicting incident cardiovascular events and mortality in dialysis population. There is no longitudinal evaluation of the FGF23 level for cardiovascular events. Second, this is one single-center study and requires replication in other independent populations.

CONCLUSION

There is a high prevalence of AAC in Chinese hemodialysis patients. Lateral lumbar X-ray is a simple method for detecting AAC with cheap price, available devices, and low radiation. The plasma FGF23 level is significantly increased in hemodialysis patients, and our study is the first to find that FGF23 is independently associated with AAC detected by X-ray plain. Future studies might investigate the AAC and FGF23 level and mortality or cardiovascular events in Chinese hemodialysis patients, and whether FGF23 is a simple biomarker related to vascular calcification.

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