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Original Article

The association of fibroblast growth factor 23 with atherosclerosis and arterial stiffness in peritoneal dialysis patients

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Abstract

Aim: Increased serum fibroblast growth factor-23 (FGF-23) levels are associated with adverse cardiovascular events in chronic kidney disease patients. The aim of our study was to investigate the association of FGF-23 with atherosclerosis and arterial stiffness in patients with peritoneal dialysis (PD).

Material and Methods: This cross-sectional study was performed in 55 (34 (61.8%) male/21 (38.2%) female) PD patients with a mean age of 53.1±11.4 years. The presence of atherosclerosis was determined by carotid artery-intima media thickness (CA-IMT) and the presence of arterial stiffness was determined by brachial-ankle pulse wave velocity (baPWV). Residual renal function was determined by residual glomerular filtration rate (rGFR), renal creatinine clearance (CCr), and residual urine output. FGF-23 and soluble klotho (s-KL) levels were determined by enzyme-linked immunosorbent assay.

Results: CA-IMT ($p < 0.001$), baPWV ($p = 0.003$), log10 FGF-23 ($p < 0.001$) were higher and s-KL ($p < 0.001$) was lower compared with the healthy controls. rGFR ($p= 0.007$), residual diuresis ($p = 0.004$) and renal CCr ($p = 0.001$) were higher in patients with $\log_{10}$ FGF-23 ≤ 2.16 than $\log_{10}$ FGF-23 > 2.16. In multiple regression analysis there was an inverse relationship between $\log_{10}$ FGF-23 and rGFR ($p = 0.032$), residual diuresis ($p = 0.048$), renal CCr ($p = 0.045$). There was no relationship with $\log_{10}$ FGF-23 and CA-IMT, baPWV ($p > 0.05$).

Conclusion: Increased atherosclerosis and arterial stiffness were detected in PD patients compared to healthy subjects. There was no relationship between FGF-23 and atherosclerosis and arterial stiffness in PD patients.

Keywords: Peritoneal dialysis; Fibroblast growth factor-23; Atherosclerosis; Arterial stiffness.

INTRODUCTION

Cardiovascular (CV) diseases are the most common causes of increased mortality and morbidity in peritoneal dialysis (PD) patients. Risk factors such as diabetes, hypertension, hyperlipidemia, as well as uremia and dialysis treatment are thought to be effective in the development of atherosclerosis in PD patients (1). Direct absorption of glucose in dialysis fluid and increased serum lipid levels due to loss of substances regulating lipoprotein synthesis secondary to peritoneal protein clearance in PD patients are thought to cause atherogenic effect (2).

The development of arterial stiffness in PD patients is an independent predictor of CV diseases (3). Covic et al. reported that increased arterial stiffness development in PD patients was associated with uremia-related malnutrition-inflammation (4). Szeto et al. reported that the development of arterial stiffness in PD patients was associated with systolic blood pressure and serum Ca levels (5). Jung et al. reported that the development of arterial stiffness in PD patients was associated with mean blood pressure and serum triglyceride (Tg) levels (6).

Fibroblast growth factor-23 (FGF-23) is a phosphatonin synthesized from osteocytes and osteoblasts and

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plays a role in the maintenance of serum phosphate (P) balance. Soluble klotho (s-KL) gene is found in the kidney, parathyroid gland, and other endocrine organs, besides bone tissue. In the presence of its coreceptor s-KL, FGF-23 acts by binding to renal FGF receptors. Parallel to the progression of renal failure, serum FGF-23 levels are elevated in order to maintain normal serum P balance (7). It causes renal P excretion by inhibiting sodium (Na)-dependent P carriers NaP-IIa and NaP-IIc in the proximal tubule. It also inhibits conversion of 25-hydroxy(OH) vitamin(Vit)D_3 to its active form 1.25$(OH)_2$VitD_3.

Studies investigating the relationship between FGF-23 and atherosclerosis in patients with end-stage renal disease have conflicting results. Balci et al. reported a correlation between the development of atherosclerosis and FGF-23 and carotid plaques determined by carotid artery-intima media thickness (CA-IMT) in hemodialysis (HD) patients (9). In studies with FGF-23 deficient mice, Shimada reported that FGF-23 had a protective effect on atherosclerosis and arterial stiffness (10). Inaba et al. reported that there wasn't an association between FGF-23 and vascular calcification that cause atherosclerosis and arterial stiffness in patients with HD (11).

The relationship between FGF-23 and increased mortality in chronic kidney disease (CKD) patients is known, but the underlying cause is still being investigated. In addition, although there are studies in normal populations, pre-dialysis CKD and HD patients in the literature, the number of studies examining the association and affecting factors between FGF-23 and atherosclerosis and arterial stiffness in PD patients is low and the results are contradictory. For that reason, the aim of our study was to investigate the association of serum FGF-23 levels with atherosclerosis determined by CA-IMT and with arterial stiffness determined by brachial-ankle pulse wave velocity (baPWV).

MATERIAL AND METHODS

Patient selection

This cross sectional study was performed with 55 peritoneal dialysis (PD) patients (34 (61.8%) male/21 (38.2%) female) whose mean age was 53.1 ± 11.4 and who were being followed at Antalya Research and Education Hospital Nephrology Clinic between September 2018 and January 2019. Forty-three (78.2%) patients were treated with continuous ambulatory peritoneal dialysis (CAPD) at three or four 2 L exchanges per day and 12 (21.8%) patients were treated with automated peritoneal dialysis (APD) at three or four 5 L exchanges per night, using standard dialysates containing glucose. The patients were compared with 45 healthy subjects with no known comorbid disease or drug use history. Patients who declined to participate in the study, has a history of known cardiac intervention (stent, bypass, coronary angiography, valve replacement...), heart disease (left ventricular ejection fraction <45%, myocardial infarction, arrhythmia...), peripheral vascular disease, stroke, transient ischemic attack, previous renal replacement, peritonitis during last 3 months, malignancy or parathyroidectomy were excluded. Patients over 18 years of age, who were getting treatment for PD for more than 6 months and accepted to involve in the study were included. The aim of the study was explained to all participants, and written informed consents were obtained. The study was approved by Antalya Training and Research Hospital Ethics Committee.

Collection of data and laboratory measurements

Venous blood samples taken from the entire study group after 10-12 hours of nightly fasting were centrifuged and stored at -80°C. 24-hour urine samples of PD patients were collected. Levels of serum calcium (Ca), phosphate (P), total cholesterol (T-C), triglyceride (Tg) and high density lipoprotein cholesterol (HDL-C) were calculated using Beckman coulter commercial kits in a Beckman coulter AU5800 (Beckman coulter Instrumentation, San Diego, CA, USA) autoanalyser. Low density lipoprotein cholesterol (LDL-C) levels were measured by (T-C)-(HDL-C)- (Tg/5) formula determined by Friedewald et al. (12). Fibroblast growth factor-23 (FGF-23) level was determined by enzyme-linked immunoadsorbent assay (ELISA). 1.25 hydroxy$(OH)_2$Vitamin(Vit)D_3 level was determined by (ELISA) (Bioassay Technology Laboratory, Shanghai, China). 25(OH)VitD_3 level was measured with chemiluminescence method using Liason (DiaSorin, MN, USA) device. For all parameters, the inter- and intra-assay coefficients of variation were < 10%; 1.25 $(OH)_2$VitD_3 measurement range was determined to be 0.2-60 ng/mL; measurement sensitivity was determined to be 0.07 ng/mL; FGF-23 measurement range was determined to be 15.6-1000 pg/mL, and measurement sensitivity to be 9.38 pg/mL.

Demographic characteristics (gender, age, body mass index), etiology of end-stage renal disease (ESRD), comorbid diseases and antihypertensive medications and phosphate lowering drugs used were recorded. Blood pressure values were determined by taking the average of measurements from both arms with a sphygmomanometer after a resting period of at least 15 minutes by the same nurse while there was no dialysate in the abdomen of the patients. Patients with previous history of hypertension (HT), history of antihypertensive drug use, or systolic blood pressure/diastolic blood pressure ≥ 140/90 mmHg were considered hypertensive. Body mass index (BMI) was calculated using the formula of weight divided by height squared.

Determination of dialysis adequacy

The weekly total Kt/Vurea (K = dialyzer clearance of urea), (t = treatment time), (V = patient's volume of urea distribution) and the weekly total creatinine clearance values of patients were determined according to standard methods (13). Residual renal function (RRF) was determined by the presence of residual glomerular filtration rate (rGFR), renal creatinine clearance (CCr), and residual urine output. The value of rGFR was determined

as the sum of 24-h urine urea and creatinine clearances (14). Peritoneal equilibrium test (PET) was performed to determine peritoneal transport rates (PTR) (15). After the dialysate was left in the abdominal cavity for 8 to 12 hours at night, 2 liters of 2.27% dialysis solution was placed in the abdominal cavity. Dialysate glucose concentrations, dialysate, and serum creatinine levels were determined at 0, 2, and 4th hours. Second and 4. hour dialysate glucose was divided to 0. hour dialysate glucose, and 2. and 4. hour dialysate creatinine was divided to 0. hour serum creatinine to classify patients into 4 PTR groups as high (H), high-average (HA), low (L), and low-average (LA) (H ≥ 0.81, HA=0.65–0.80; L < 0.50, LA=0.50–0.64). Those with low and low-medium permeability were considered to be L-PTR, those with high to medium permeability were considered to be H-PTR.

Determination of carotid artery intima-media thickness

All measurements were performed by the same radiologist using a B-Mode Ultrasonography (USG) device (Hitachi Hi-Vision avius, , 2-5 mHz linear probe, Tokyo, Japan) while the participants were in the supine position and their necks were extended. Measurements were made from the right and left common carotid artery, carotid artery bifurcation, and proximal 2 cm of the internal and external carotid arteries. The thickness of the carotid artery intima-media was determined by transversal examination ranging from vessel lumen echogenicity to media-adventitia echogenicity (16). Measurements were made on both sides, right and left, and average values were obtained from the measurements. CA-IMT > 0.9 mm was considered as development of atherosclerosis.

Determination of brachial-ankle artery pulse wave velocity

Arterial stiffness was measured with the brachial-ankle pulse wave velocity (baPWV) instrument (D-52222, 2007, Stolberg, Germany) by the same nurse while the abdomens of the PD patients were empty. The PWV value was determined by calculating the latency difference between the blood pressure curves at two different points of the arterial system. The interval between the start and end of the brachial and ankle waves obtained from brachial and tibial arteries were determined as transit time (TT). The distance between the suprasternal notch and brachium (B) was calculated by 0.2195 X length (cm) - 2.0734 formula and the distance between suprasternal notch and ankle (A) was calculated by 0.8129 X length (cm) + 12.328 formula. The baPWV value was determined by the formula (A-B)/TT (17). The augmentation index (AIx) value was determined by dividing theamount of elevation of arterial pressure wave due to reflected wave to pulse pressure.

STATISTICAL ANALYSIS

The statistical analysis was made using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). Descriptive statistics were expressed as mean ± standard deviation, and median (minimum-maximum) for continuous variables and n (%) for categorical variables. Mann-Whitney U test was used for quantitative variables with non-normal distribution and Student's t-test was used for quantitative variables with normal distribution for comparison of patient characteristics with healthy control group and for comparison according to mean $\log_{10}$ FGF-23 level. Age and gender adjusted multiple linear regression analysis was used to examine parameters independently associated with FGF-23. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 55 PD patients, 34(61.8%) male and 21(38.2%) female, with a mean age of 53.1±11.4 years were included in the study. The average PD duration was 44.1 ±31.2 months. Demographic and clinical characteristics of the patients are given in Table 1. Mean SBP was 129.3±25.1 mmHg and mean DBP was 80.5±16.9 mmHg. The etiology of ESRD was diabetes mellitus in 13(23.6%) patients, hypertension in 26(47.3%) patients, chronic glomerulonephritis in 8(14.5%) patients, polycystic kidney disease in 2(3.6%) patients, nephrolithiasis in 5(9.1%) patients, and other reason in 1(1.8%) patient. Four (7.3%) patients were using angiotensin converting enzyme inhibitor, 7(12.7%) were using angiotensin-II receptor blocker, 23(41.8%) were using calcium channel blocker, 24(43.6%) were using beta-receptor blocker, 11(20%) were using alfa-receptor blocker, and 22(40%) were using diuretics. 30(54.5%) of the patients were using Ca-acetate/Ca-phosphate, 11(20%) were using sevelamer, 3(5.5%) were using cinacalcet and 34(61.8%) were using calcitriol. 43(78.2%) patients were applying CAPD and 12(21.8%) patients were applying APD. rGFR was 5.9±5.7 mL/min/1.73 m^2 and residual diuresis was 942.9±1552.4 mL/day. 8(19%) patients had residual diuresis ≤ 100 mL/day. The mean renal Kt/Vurea was 0.84±0.82 and the mean CCr was 56.98±52.53 mL/min /1.73 m^2. The mean value of CA-IMT was 0.7±0.2 mm and CA-IMT was > 0.9 mm in 7(12.7%) patients. The mean baPWV and AIx values were determined as 7.8±1.7 m/sec and 20.9±10.9%, respectively. Patients were compared with 45 healthy control subjects with a mean age of 47.7±10.3 years (Table 1).

Laboratory values of patient's are summarized in table 2. The mean CaXP product was 43.2±12.5 mg / dL, 25(OH) $VitD_3$ level was 12.4±6 ng/mL and 1.25 $(OH)_2VitD_3$ level was 28.5±18.4 ng/mL. The mean T-C, tg, HDL-C, and LDL-C levels were 199.6±53.9 mg/dL, 251.9±262.9 mg/dL, 39.3±10.8 mg/dL, and 114.4±34.1 mg/dL, respectively. The mean $\log_{10}$ FGF-23 level was 2.16±0.39 pg/mL and s-KL level was 13.9±3.1 (Table 2).

The patients had significantly higher levels of CA-IMT, baPWV, CaXP product, $\log_{10}$ FGF-23 (all $p < 0.001$), T-C ($p=0.003$), and LDL-C ($p=0.006$), and significantly lower 1.25 $(OH)_2VitD_3$ ($p < 0.027$), 25(OH)$VitD_3$ and s-KL (all $p < 0.001$) levels than the healthy individuals (Table 3).

The mean $\log_{10}$ FGF-23 level was 2.16 pg/mL. Patients with $\log_{10}$ FGF-23 ≤ 2.16 had higher levels for rGFR ($p=0.007$), residual diuresis ($p=0.004$), renal Kt/Vurea ($p=0.004$), renal CCr ($p=0.001$), T-C ($p=0.018$), and LDL-C ($p=0.027$) compared with patients $\log_{10}$ FGF-23 > 2.16.

There was no significant difference between the two groups regarding CA-IMT and baPWV (all p > 0.05) (Table 4).

There was no relation between log_{10} FGF-23 and CA-IMT (r = -0.084, p = 0.542) and baPWV (r= 0.075, p = 0.586). There was inverse relation between log_{10} FGF-23 and rGFR (r = -0211, p = 0.005).

In age and gender adjusted multiple linear regression analysis; there were independent inverse relations between log_{10} FGF-23 and rGFR (p = 0.032), residual diuresis (p = 0.048), renal CCr (p = 0.045), T-C (p = 0.027), and LDL-C (p = 0.007). There was no relation between FGF-23 and CA-IMT and baPWV (Table 5).

Table 1. Demographic and clinical characteristics of patient and healthy control group

	PD patients (n = 55) Mean ± S.D./n (%)	Healthy control group (n = 45) Mean ± S.D./n (%)
Age (years)	53.1 ± 11.4	47.7 ± 10.3
Gender (Male/Female)	34 (61.8%) / 21 (38.2%)	21 (46.7%) / 24 (53.3%)
BMI (kg/m^2)	28.1 ± 4.9	26.7 ± 4.2
Time on dialysis (months)	44.1 ± 31.2	
SBP (mmHg)	129.3 ± 25.1	118.1 ± 11.6
DBP (mmHg)	80.5 ± 16.9	78.3 ± 9.9
Etiology of ESRD		
Diabetic nephropathy	13 (23.6%)	
Hypertensive nephrosclerosis	26 (47.3%)	
Chronic glomerulonephritis	8 (14.5%)	
Polycystic kidney disease	2 (3.6%)	
Nefrolitiasis	5 (9.1%)	
Unknown or missing data	1 (1.8%)	
Use of antihipertansive medications		
ACE inh/ARB	4 (7.3%) / 7 (12.7%)	
Ca-channel blocker	23 (41.8%)	
Beta-receptor blocker	24 (43.6%)	
Alfa-receptor blocker	11 (20%)	
Diuretic	22 (40%)	
Use of phosphate-binders		
Ca-acetate/Ca-phosphate	30 (54.5%)	
Sevelamer	11 (20%)	
Use of Vit D/Vit D analogs	3 (5.5%)	
Calcimimetics	34 (61.8%)	
Calcitriol		
CAPD	43 (78.2%)	
APD	12 (21.8%)	
rGFR (mL/min/1.73 m^2)	5.9 ± 5.7	
Residual diuresis (mL/day)	942.9 ±1552.4	
100 ≤	8 (19%)	
Renal Kt/Vurea	0.84 ± 0.82	
Renal CCr (mL/min/1.73 m^2)	56.98 ± 52.53	
CA-IMT (mm)	0.7 ± 0.2	0.66 ± 0.7
0.9 >	7 (12.7%)	
baPWV (m/sec)	7.8 ± 1.7	6.6 ± 0.9
AIx (%)	20.9 ± 10.9	23.8 ±13.8

Data are presented as mean ± S.D and n(%). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESRD, end-stage renal disease; ACE inh, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; Ca, calcium; Vit, vitamin; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; Kt/V=K,urea clearance; t, time, V, urea distribution volume; CCr, creatinine clearance; CA-IMT, carotid artery intima-media thickness; baPWV, brakial ankle pulse wave velocity; AIx, augmentation index; S.D., standard deviation

Table 2. Laboratory values of patient and healthy control group

	Patients (n= 55) Mean ± S.D.	Healthy control group (n = 45) Mean ± S.D.
CasXP product (mg/dL)	39.1 ± 14.1	31.6 ± 4.7
25(OH)VitD (ng/mL)	12.4 ± 6	21.1 ± 10.9
1.25(OH)2VitD3 (ng/mL)	28.5 ± 18.4	40.1 ± 17
T-C (mg/dL)	199.6 ± 53.9	195 ± 41.7
Triglyceride (mg/dL)	251.9 ± 262.9	147 ± 96.9
LDL-C (mg/dL)	114.4 ± 34.1	119.4 ± 33.5
HDL-C (mg/dL)	39.3 ± 10.8	48.8 ± 13.9
Log_{10} FGF-23 (pg/mL)	2.16 ± 0.39	2.08 ± 0.3
s-KL (ng/mL)	13.9 ± 3.1	18.2 ± 3.6

Data are presented as mean ± S.D. Abbreviations: Ca, calcium; P, phosphate; OH, hydroxy; T-C, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FGF-23, fibroblast growth factor-23; s-KL, soluble klotho

Table 3. Comparison of patient characteristics with healthy control group

	Patients (n = 55)	Healthy control group (n = 45)	p-value
CA-IMT (mm)	0.7 (0.5-1.2)	0.5 (0.5-5)	**<0.001**
baPWV (m/sec)	8 (4.7-10.8)	6.5 (4.8-9)	**<0.001**
CasXPs product (mg/dL)	43.2 ± 12.5	31.6 ± 4.7	**<0.001**
25(OH)VitD (ng/mL)	12.2 (4-26.7)	18.1 (6.9-58.9)	**<0.001**
1.25(OH)2VitD3 (ng/mL)	13.1 (2.1-56.5)	25.2 (4.2-66.2)	**<0.027**
T-C (mg/dL)	192 (115-476)	188 (117-285)	**<0.003**
Triglyceride (mg/dL)	191 (15-1848)	109 (38-453)	0.779
LDL-C (mg/dL)	114 (57-193)	90 (52-194)	**<0.006**
HDL-C (mg/dL)	39 (24-72)	46 (28-92)	0.460
Log_{10}FGF-23 (pg/mL)	2.16 ± 0.39	2.08 ± 0.29	**<0.001**
s-KL (ng/mL)	13.9 ± 3.1	18.2 ± 3.6	**<0.001**

Mann-Whitney U test, Student's t-test

Table 4. Comparison of patient characteristics according to mean log_{10} FGF-23 levels

	Log_{10} FGF-23 > 2.16 pg/mL (n = 28)	Log_{10} FGF-23 ≤ 2.16 pg/mL (n = 27)	p-value
rGFR (mL/min/1.73 m^2)	2.25 (0.2-18.2)	6.76 (0.6-20.4)	**0.007**
Residual diuresis (mL/day)	500 (50-10000)	1000 (20-2000)	**0.004**
Renal Kt/Vurea	0.32 (0.02-1.87)	1.11 (0.15-2.92)	**0.004**
Renal CCr (mL/min/1.73 m^2)	19.3 (0.04-139.7)	70.89 (6.4-173.93)	**0.001**
CA-IMT (mm)	0.7 (0.5-1.2)	0.7 (0.5-1)	0.298
baPWV (m/sec)	8.1 ± 1.7	7.6 ± 1.6	0.310
T-C (mg/dL)	180 (121-476)	204 (115-289)	**0.018**
Triglyceride (mg/dL)	185.5 (15-1848)	192 (79-796)	0.596
LDL-C (mg/dL)	40 (24-57)	124.7 ± 38.7	**0.027**
HDL-C (mg/dL)	104.4 ± 25.9	39 (28-72)	0.899

Mann-Whitney U test, Student's t-test

Table 5. Factors associated with log_{10} FGF-23 in multivariate analysis			
	βeta	Standard error	p-value
rGFR (mL/min/1.73 m^2)	-1.348	0.003	**0.032**
Residual diuresis (mL/day)	-0.645	0.012	**0.048**
Renal Kt/Vurea	0.551	0.199	0.199
Renal CCr (mL/min/1.73 m^2)	-1.032	0.004	**0.045**
CA-IMT (mm)	-0.078	0.429	0.663
baPWV (m/sec)	-0.098	0.080	0.776
T-C (mg/dL)	-1.667	0.005	**0.027**
Triglyceride (mg/dL)	0.869	0.001	0.086
LDL-C (mg/dL)	-1.260	0.005	**0.007**
HDL-C (mg/dL)	-0.621	0.011	0.086
Mann-Whitney U test, Student's t-test			
Multiple linear regression analysis (R = 0.634; R2 = 0.402; p = 0.183)			

DISCUSSION

In our study, the presence of atherosclerosis was investigated by measuring USG and CA-IMT values, since the determination of CA-IMT in CKD patients was considered to be an adequate index in the early diagnosis of atherosclerotic changes (18). In this study, PD patients had significantly higher T-C and LDL-C levels and significantly higher atherosclerosis than healthy subjects. Avram et al. reported increased atherosclerosis development in PD patients (19). Johansson et al. reported that elevated serum lipid levels due to direct absorption of glucose in peritoneal dialysate fluid in PD patients lead to the development of atherosclerosis (20). Kronenberg et al. reported that atherosclerosis in PD patients was associated with increased serum lipid levels secondary to loss of protein from the peritoneal membrane (21).

Development of arterial stiffness in PD patients causes increased CV mortality (22). Chung et al. reported increased arterial stiffness development in PD patients (23). Jung et al. reported development of arterial stiffness 1 year after (6) and Szeto et al reported approximately 2 years after initiation of treatment (5) in PD patients. Sipahioglu et al. reported that the presence of arterial stiffness detected by brachial-ankle pulse wave velocity (baPWV) in PD patients was an independent predictor of increased CV mortality (24). We used baPWV device to detect presence of arterial stiffness in our study because it is non-invasive, easy to use, and give similar results with aortic pulse wave velocity which is known to be the gold standard (25) and we found increased arterial stiffness development in PD patients compared with healthy individuals.

Results of the studies that show the association between FGF-23 and CV complications are controversial. Asicioglu et al. reported that there was a relationship between elevated serum FGF-23 levels and adverse CV events in PD patients (26). Zeng et al. suggested that increased serum FGF-23 levels play a role in the pathogenesis of initiation and progression of atherosclerosis in PD patients (27). In contrast Moldovan et al. reported that serum FGF-23 was not associated with atherosclerosis and arterial stiffness development in HD patients (28). Janda et al. reported no association between FGF-23 and atherosclerosis determined by CA-IMT in PD patients (29).

In our study, there was no relation between FGF-23 and atherosclerosis determined by CA-IMT and arterial stiffness development determined by baPWV in PD patients. The results may be due to two factors. First; Page et al. reported that serum P levels were maintained at normal intervals in PD patients with RRF due to elevated P-excretion (30). Kuhlman et al. reported normal serum P levels related with low serum FGF-23 levels secondary to increased total renal P clearance in PD patients with RRF (31). Jimbo et al. reported that in the presence of normal serum P levels, FGF-23 alone has no effect on the development of atherosclerosis and arterial stiffness in vessels (32). In our study, there was no relation between FGF-23 and atherosclerosis determined by CA-IMT and arterial stiffness development determined by baPWV in PD patients. In our study the patients were divided into two groups according to low and high FGF-23 levels, and in patients with low FGF-23 levels there were high rGFR, renal CCr, and residual urine output which were accepted to indicate presence of RRF. In addition, multivariate analysis showed an inverse relationship between FGF-23 and RRF markers. Yamada et al. reported that the presence of RRF in PD patients was associated with a reduction in FGF-23-mediated CV mortality (33). Second; Ozdemir et al. reported that the cause of atherosclerosis development in PD patients was associated with high serum total C and LDL-C levels (34). In our study, high total C and LDL-C levels were observed in patients with low FGF-23 levels. In addition, multivariate analysis showed an inverse

relationship between FGF-23 and total C and LDL-C. Ashikaga et al. reported an inverse relation between high FGF-23 and high total C and LDL-C which are risk factors for the development of atherosclerosis; therefore, they suggested that FGF-23 mediated mortality develops outside this pathway mediated by FGF-23, itself (35).

In our study there are some limitations that affect the results. First; our study was conducted in a single-center, with small number of patients. Second; our study had a cross-sectional design. Therefore long term effects of serum FGF-23 levels on atherosclerosis and arterial stiffness development and causality couldn't be observed. Third; relatively short duration of treatment period of PD patients (mean 44 months) may have affected the outcomes associated with RRF. Fourth; antihypertensive, antihyperlidemic and phosphate binding drugs which have effects on serum Ca, P, lipid levels and presence of RRF were not stopped due to ethical reasons. Fifth; patients' serum P levels were measured, but peritoneal and urinary P levels were not evaluated.

CONCLUSIONS

In conclusion, in our study we observed increased atherosclerosis and arterial stiffness in PD patients compared to healthy subjects. There was no relationship between FGF-23 and the development of atherosclerosis and arterial stiffness in PD patients. There was an inverse relationship between FGF-23 and the presence of RRF and T-C and LDL-C which are risk factors for atherosclerosis. The development of atherosclerosis and arterial stiffness in PD patients occurs due to risk factors independent from FGF-23. There is a need for multi-center, randomized, controlled follow-up studies with more PD patients to investigate the effect of FGF-23 on CV events and the mechanisms of its action.

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REFERENCES

1. Prichard S. Major and minor risk factors for cardiovascular disease in peritoneal dialysis. Perit Dial Int 2000;20 S154-9.
2. Attman PO, Samuelsson OG, Moberly J, et al. ApolipoproteinB-containing lipoproteins in renal failure: the relation to mode of dialysis. Kidney Int 1999;55:1536-42.
3. Gao N, Kwan BC, Chow KM, et al. Arterial pulse wave velocity and peritoneal transport characteristics independently predict hospitalization in Chinese peritoneal dialysis patients. Perit Dial Int 2010;30:80-5.
4. Covic A, Goldsmith DJ, Florea L, et al. The influence of dialytic modality on arterial stiffness, pulse wave reflections, and vasomotor function. Perit Dial Int 2004;24:365-72.
5. Szeto CC, Kwan BC, Chow KM, et al. Prognostic value of arterial pulse wave velocity in peritoneal dialysis patients. Am J Nephrol 2012;35:127-33.
6. Jung JY, Hwang YH, Lee SW, et al. Factors associated with aortic stiffness and its change over time in peritoneal dialysis patients. Nephrol Dial Transplant 2010;25:4041-8.
7. Fukagawa M, Kazama JJ. With or without the kidney: the role of FGF23 in CKD. Nephrology Dialysis Transplantation 2005;20:1295–1298.
8. Adragao T, Pires A, Lucas C, et al. A simple vascular calcification score predicts cardiovascular risk in hemodialysis patients. Nephrol Dial Transplant 2004;19:1480-8.
9. Balci M, Kirkpantur A, Gulbay M, et al. Plasma fibroblast growth factor-23 levels are independently associated with carotid arteryatherosclerosis in maintenance hemodialysis patients. Hemodial Int 2010;14:425-32.
10. Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of FGF23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest 2004;113:561-8.
11. Inaba M, Okuno S, Imanishi Y, et al. Role of fibroblast growth factor-23 in peripheral vascular calcification in non-diabetic and diabetic hemodialysis patients. Osteoporos Int 2006;17:1506-13.
12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
13. Canada-USA (CANUSA) peritoneal dialysis study group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol 1996;7:198-207.
14. Van-Olden RW, Krediet RT, Struijk DG, et al. Measurement of residual renal function in patients treated with continuous peritoneal dialysis. J Am Soc Nephrol 1996;7:745-50.
15. Twardowski ZJ, Nolph KO, Khanna R, et al. Peritoneal equilibration test. Perit Dial Bull 1987;7:138-47.
16. Szeto CC, Chow KM, Woo KS, et al. Carotid intima media thickness predicts cardiovascular diseases in Chinese pre-dialysis chronic kidney diseases patients. J Am Soc Nephrol 2007;18:1966-72.
17. Yokoyama H, Shoji T, Kimoto E, et al. Pulse wave velocity in lower-limb arteries among diabetic patients with peripheral arterial disease. J Atheroscler Thromb 2003;10:253-8.
18. Rossi A, Bonfante L, Giacomini A, et al. Carotid artery lesions in patients with nondiabetic chronic renal failure. Am J Kidney Dis 1996;27:58-66.
19. Avram MM, Fein PA, Antignani A, et al. Cholesterol and lipid disturbances in renal disease: the natural history of uremic dyslipidemia and the impact of hemodialysis and continuous ambulatory peritoneal dialysis. Am J Med 1989;87:55N-60N.
20. Johansson AC, Samuelsson O, Attman PO, et al. Dyslipidemia in peritoneal dialysis-relation to dialytic variables. Perit Dial Int 2000;20:306-14.
21. Kronenberg F, Konig P, Neyer U, et al. Multicenter study of lipoprotein (a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. J Am Soc Nephrol 1995;6:110-20.
22. Wang AY. Cardiovascular risk factors in peritoneal dialysis patients revisited. Perit Dial Int 2007;27:S223-7.

23. Chung AW, Yang HH, Kim JM, Sigrist MK, Brin G, Chum E, Gourlay WA, Levin A. Arterial stiffness and functional properties in chronic kidney disease patients on different dialysis modalities: an exploratory study. Nephrol Dial Transplant 2010;25:4031-41.
24. Sipahioglu MH, Kucuk H, Unal A, et al. Impact of arterial stiffness on adverse cardiovascular outcomes and mortality in peritoneal dialysis patients. Perit Dial Int 2012;32:73–80.
25. Yamashina A, Tomiyama H, Arai T, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. Hypertens Res 2003;26:615-22.
26. Asicioglu E, Kahveci A, Arikan H, et al. Fibroblast Growth Factor-23 Levels Are Associated with Vascular Calcifications in Peritoneal Dialysis Patients. Nephron Clin Pract 2013;124:89-93.
27. Zeng Y, Feng S, Han OY, et al. Role of fibroblast growth factor-23 in the pathogenesis of atherosclerosis in peritoneal dialysis patients. Genet Mol Res 2015;14:719-29.
28. Moldovan D, Moldovan I, Rusu C, et al. FGF-23, vascular calcification, and cardiovascular diseases in chronic hemodialysis patients. Int Urol Nephrol 2014;46:121-8.
29. Janda K, Krzanowski M, Chowaniec E, et al. Osteoprotegerin as a marker of cardiovascular risk in patients on peritoneal dialysis. Pol Arch Med Wewn 2013;123:149-55.
30. Page DE, Knoll GA, Cheung V. The relationship between residual renal function, protein catabolic rate, and phosphate and magnesium levels in peritoneal dialysis patients. Adv Perit Dial 2002;18:189-91.
31. Kuhlmann MK. Phosphate elimination in modalities of hemodialysis and peritoneal dialysis. Blood Purif 2010;29:137-44.
32. Jimbo R, Kawakami-Mori F, Mu S, et al. Fibroblast growth factor 23 accelerates phosphate-induced vascular calcification in the absence of Klotho deficiency. Kidney Int 2014;85:1103-11.
33. Yamada S, Tsuruya K, Taniguchi M, et al. Relationship Between Residual Renal Function and Serum Fibroblast Growth Factor 23 in Patients on Peritoneal Dialysis. Ther Apher Dial 2014;18:383-90.
34. Ozdemir FN, Güz G, Sezer S, et al. Atherosclerosis risk is higher in continuous ambulatory peritoneal dialysis patients than in hemodialysis patients. Artif Organs 2001;25:448-52.
35. Ashikaga E, Honda H, Suzuki H, et al. Impact of fibroblast growth factor 23 on lipids and atherosclerosis in hemodialysis patients. Ther Apher Dial 2010;14:315-22.