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Plasma fibroblast growth factor-23 levels are independently associated with carotid artery atherosclerosis in maintenance hemodialysis patients

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Abstract
Fibroblast growth factor-23 (FGF-23) has been suggested to play a role in vascular calcification in chronic kidney disease. Common carotid artery intima-media thickness (CIMT) assessment and common carotid artery (CCA) plaque identification using ultrasound are well-recognized tools for identification and monitoring of atherosclerosis. The aim of this study was to test that elevated FGF-23 levels might be associated with carotid artery atherosclerosis in maintenance hemodialysis (HD) patients. In this cross-sectional study, plasma FGF-23 concentrations were measured using a C-terminal human enzyme-linked immunosorbent assay kit. Carotid artery intima-media thickness was measured and CCA plaques were identified by B-Mode Doppler ultrasound. One hundred twenty-eight maintenance HD patients (65 women and 63 men, mean age: 55.5 $\pm$ 13 years, mean HD vintage: 52 $\pm$ 10 months, all patients are on HD thrice a week) were involved. The mean CIMT were higher with increasing tertiles of plasma FGF-23 levels (0.66 $\pm$ 0.14 vs. 0.75 $\pm$ 0.05 vs. 0.86 $\pm$ 0.20 mm, $P<0.0001$). Log plasma FGF-23 were higher in patients with plaques in CCA than patients free of plaques (3.0 $\pm$ 0.17 vs. 2.7 $\pm$ 0.23, $P<0.0001$). Significant correlation was recorded between log plasma FGF-23 and CIMT (r=0,497, P=0.0001). In multiple regression analysis, a high log FGF-23 concentration was a significant independent risk factor of an increased CIMT. Further studies are needed to clarify whether an increased plasma FGF-23 level is a marker or a potential mechanism for atherosclerosis in patients with end-stage renal disease.

Key words: FGF-23, hemodialysis, carotid artery, atherosclerosis

INTRODUCTION

Atherosclerotic cardiovascular disease is a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD).[1,2] Accumulating evidence revealed that there is an increased incidence and accelerated worsening of atherosclerosis in patients on maintenance hemodialysis (HD). Abnormalities of mineral metabolism are a prevalent condition in chronic kidney disease and are important determinants of bone and vascular system in this patient population. Several studies have shown that hyperphosphatemia, increased serum PTH, and low 1,25(OH)2 D3 levels are independently associated with an increased total and cardiovascular mortality in patients with ESRD.[3–5] These observations have raised interest in understanding mineral metabolism regulation and its consequences in patients with CKD.

Fibroblast growth factor 23 (FGF-23), a novel hormone secreted by osteoblasts, is an important negative regulator of phosphate and vitamin D metabolism. Initially, FGF-23

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was described as the cause of rare hypophosphatemic syndromes characterized by hypophosphatemia, renal phosphate wasting, low serum levels of 1,25(OH)2 D3, and osteomalacia or rickets.[6,7] Fibroblast growth factor 23 induces renal phosphate wasting by inhibiting the proximal tubular sodium phosphate cotransporter type IIa (NPT2a) and suppressing the renal expression of CYP27B1, resulting in the decrease of 1,25(OH)2 D3 synthesis.[8]

Several studies have indicated that serum levels of FGF-23 are elevated in HD patients,[9,10] and recently, elevated FGF-23 concentrations are independently associated with an increased risk of mortality in patients who are beginning HD treatment.[11] As data on the association between FGF-23 and atherosclerosis are limited in patients with chronic kidney disease, the aim of this study was to test if elevated FGF-23 levels might be associated with carotid artery atherosclerosis in maintenance HD patients.

SUBJECTS AND METHODS

Subjects

One hundred thirty-seven HD patients were screened based on the following inclusion/exclusion criteria: 18 years or older, stably treated with HD for at least 1 year, Kt/V >1.2 during the previous 6 months, and no signs of liver disease, clinically evident active infection, autoimmune disease, or known malignancy. Overall, participants were 128 maintenance HD patients (65 women and 63 men, mean age 55.5 ± 13 years, mean HD time: 52 ± 10 months, on HD thrice a week). The patients suffered from ESRD due to diabetic nephropathy (n=34), hypertensive nephrosclerosis (n=30), chronic glomerulonephritis (n=27), chronic pyelonephritis (n=15), and polycystic disease (n=10). The renal diagnosis was unknown in 12 patients.

Patients were prescribed treatments including $CaCO_3$ (27%), sevelamer (11%), Ca-acetate (41%), alfacalcidol (62%), warfarin (18%), and erythropoietin (70%). The mean erythropoietin dose was 145 U/(kg/wk) achieving a mean hemoglobin (Hb) level of 11.4 g/dL; $<10\%$ of patients had Hb <10 g/dL.

All patients were receiving conventional 4 hour-HD with polysulfone dialyzers F6HPS and F7HPS (Fresenius AG, Bad Homburg, Germany) thrice a week, with bicarbonate dialysate, and low-molecular-weight heparin for standard anticoagulation. Mean blood flow rate was 300 mL/min during an HD session (range: 250–340 mL/min). Dialysate fluid composition was sodium 140 mEq/L, potassium 1 to 3 mEq/L, calcium 3 mEq/L, and bicarbonate 33 mEq/L. Dry weight was considered optimal when the patients had no residual symptoms of orthopnea, dyspnea, and edema during the interdialytic period. Urea (Kt/V) values were calculated according to Daugirdas second-generation formula.[12]

Blood pressure (BP) of the patients were measured with a conventional mercury manometer before each HD session. Hypertension was defined as a systolic BP of 140 mmHg or above, diastolic BP of 90 mmHg or above, and patients on antihypertensive medication.[13] Average values of systolic and diastolic BP obtained in the first 3 weeks of the study were used in statistical analysis. Patients were on antihypertensives: angiotensin-converting enzyme inhibitors (n=22), angiotensin receptor blockers (n=14), beta blockers (n=30), and calcium channel blockers (n=28). No patient was on statin therapy.

The study was approved by the local Ethics Committee of Diskapi Training and Research Hospital and all the patients provided written informed consent before entering the study.

Biochemical assays

Venous blood samples were drawn after an overnight fasting from HD patients. Blood sample was obtained from a HD patient directly through an arteriovenous fistula or central catheter on a midweek nondialysis day. Serum total cholesterol and triglycerides were quantified by commercial colorimetrical assay methods (GPO-PAP and CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) was quantified by the phosphotungustic acid precipitation method. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula (LDL-C=CHO–TG/5–HDL-C) where CHO is serum total cholesterol and TG is triglycerides. C-reactive protein (CRP) was detected by rate nephelometry (IMAGE). Serum biochemical parameters (creatinine, blood urea nitrogen, glucose, electrolytes, albumin, and complete blood count) and intact parathormone levels were studied by means of a computerized autoanalyzer (Hitachi 717; Boehringer-Mannheim). We have measured serum CRP levels of all patients thrice a year in order to monitor a cardiovascular event. Serum albumin levels are routinely measured monthly with other biochemical parameters in the routine follow-up of the patients in our institution. Thus, mean values of serum chemistries (total of 12 values) and CRP levels (total of 3 values) over 12 months have been considered into account in statistical analysis.

Common carotid B-mode Doppler ultrasound

A high-resolution B-mode ultrasound of the common carotid arteries (CCA) with scanning on the longitudinal axis until the bifurcation and on the transversal axis was performed using an instrument generating a wide band ultrasonic pulse with a middle frequency of 7.5 MHz (Siemens Elegra Ultrasonography Systems, Tokyo, Japan). For each carotid artery, 2 longitudinal measurements were obtained by rotating (180° increments) the vessels along the axis. All patients were blindly examined by 1 experienced operator. Carotid intima-media thickness (CIMT) is measured at 1 cm proximal to the bifurcation on each side as described previously.[14]

Plasma FGF-23 levels

Plasma FGF-23 concentrations were measured using a C-terminal human ELISA (Immunotopics, San Clemente, CA, USA).[6] Measurements were made in duplicate and averaged. The sensitivity of the second generation Human FGF-23 C-terminal ELISA as determined by the 95% confidence limit on 20 duplicate determinations of the 0 RU/mL Standart is 1.5 RU/mL. The intra-assay and interassay variation of plasma FGF-23 measurements were 5% and 5% to 7.3%, respectively.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Whether the distributions of continuous variables were normally or not was determined by using Shapiro Wilk test. Data were shown as mean, standard deviation, median, and interquartile range. Degrees of associations between continuous variables were calculated by the Spearman's correlation coefficient.

The study population was divided in tertiles according to CIMT and FGF-23 levels and baseline characteristics of the study population in the 3 tertiles were compared by means of analysis of variance for continuous data and chi-square statistic for categorical data. Non-normally distributed variable FGF-23 was also log-transformed to achieve a normal distribution and used in subsequent statistical analysis. A P value <0.05 was considered statistically significant. Linear regression analyses were performed to examine relationships between CIMT and clinical variables. Multiple regression analysis was performed to assess the combined effects of clinical variables on CIMT.

RESULTS

The demographic and clinical characteristics of the HD patients according to the CIMT and FGF-23 tertiles are depicted in Tables 1 and 2, respectively. Age, prevalance of Type 2 diabetes mellitus, systolic BP, serum phosphate, calcium phosphate product, serum intact parathormone, CRP, and log FGF-23 levels were higher with increasing tertiles of CIMT (Table 1). Patients in the highest FGF-23 tertile had higher serum levels of intact PTH, phosphate, and calcium-phosphate product (Table 2).

Plasma FGF-23 levels

Median plasma FGF-23 level was 958 RU/mL (interquartile range 106–1894 RU/mL) and mean log FGF-23 was 2.9 ± 0.29. Log FGF-23 levels were not significantly different in patients with a history of Type 2 diabetes mellitus (2.9 ± 0.29 vs. 2.9 ± 0.26, P=0.96) and smoking (2.93 ± 0.25 vs. 2.89 ± 0.26, P=0.60) compared with those with out. However, patients with a history of coronary artery disease had higher levels of log FGF-23 than those with out (3.00 ± 0.22 vs. 2.82 ± 0.26, P=0.002). Significant correlations were observed between plasma FGF-23 levels and serum phosphate (r=0.469, P<0.0001; Figure 1a) and intact PTH levels (r=0.374, P=0.001; Figure 1b).

Risk factors for increased CIMT

Carotid IMT significantly correlated with age (r=0.24, P=0.04), smoking (r=0.06, P=0.047), diabetes (r=0.17, P=0.001), systolic BP (r=0.236, P=0.047), serum CRP (r=0.290, P=0.013), phosphate (r=0.413, P=0.0001), and intact parathormone levels (r=0.246, P=0.036).

Plasma FGF-23 levels and CIMT

The mean CIMT were higher with increasing tertiles of plasma FGF-23 levels (Table 2). Log plasma FGF-23 levels were higher in patients with plaques in CCA than patients free of plaques (3.0 ± 0.17 vs. 2.7 ± 0.23, P<0.0001). Significant correlations were recorded between log plasma FGF-23 levels and CIMT (r=0,497, P=0.0001; Figure 2).

Linear regression analysis

Independent variables included in the multivariable model were the variables found to correlate significantly with CIMT. Among these, age, systolic BP, presence of Type 2 diabetes mellitus, serum CRP, phosphate and intact parathormone levels, and increased log FGF-23 concentrations were the only parameters that remained

Table 1 Characteristics of the study population according to CIMT tertiles

Parameter	CIMT tertile 1 (<0.70 mm)	CIMT tertile 2 (0.70–1.00 mm)	CIMT tertile 3 (>1.00 mm)	P value
Number (n, %)	41 (32%)	43 (33.6%)	44 (34.4%)	
Male/female	20/22	22/23	21/20	
Age (y)	52 ± 13	55 ± 14	59 ± 11	0.045
Body mass index (kg/m^2)	23.8 ± 1.7	24 ± 1.8	24 ± 1.2	0.73
HD duration (mo)	50 ± 8	51 ± 11	52 ± 10	0.28
Diabetes (n, %)	5 (12%)	11 (26%)	18 (41%)	0.04
Smoking (n, %)	2 (5%)	9 (21%)	14 (32%)	0.15
Hypertension (n, %)	24 (59%)	23 (53%)	24 (55%)	0.34
Systolic blood pressure (mmHg)	134 ± 20	140 ± 18	148 ± 20	0.03
Diastolic blood pressure (mmHg)	75 ± 20	80 ± 18	79 ± 20	0.52
Medications				
ACEI/ARB	20 (49%)	23 (53%)	25 (57%)	0.42
Betablockers	13 (32%)	10 (23%)	13 (30%)	0.66
CCB	15 (37%)	17 (40%)	17 (39%)	0.86
$CaCO_3$	13 (32%)	11 (26%)	11 (25%)	0.74
Ca-acetate	20 (49%)	23 (53%)	20 (45%)	0.54
Sevelamer-HCl	4 (10%)	5 (12%)	5 (11%)	0.80
Alfacalcidiol	26 (64%)	27 (63%)	26 (59%)	0.88
Hemoglobin (g/dL)	10.7 ± 1.0	11.2 ± 1.0	11.0 ± 0.7	0.96
Calcium (mg/dL)	8.9 ± 0.8	9.1 ± 0.6	9.0 ± 0.4	0.64
Phosphorus (mg/dL)	4.3 ± 0.9	4.8 ± 1.1	5.5 ± 1.9	0.004
Ca-Phosphorus product (mg^2/dL^2)	38 ± 6	44 ± 5	49 ± 7	0.002
Intact parathormone level (pg/mL)	112 (68–136)	328 (200–426)	598 (356–992)	0.004
Serum creatinine (mg/dL)	10.6 ± 2.0	10.5 ± 2.8	10.4 ± 2.6	0.88
Serum albumin (g/dL)	4.1 ± 0.4	3.9 ± 0.3	3.7 ± 0.3	0.035
Total cholesterol (mg/dL)	151 ± 46	154 ± 44	148 ± 42	0.56
Triglycerides (mg/dL)	146 ± 50	150 ± 35	141 ± 48	0.40
LDL-C (mg/dL)	88 ± 28	90 ± 24	87 ± 21	0.36
HDL-C (mg/dL)	42 ± 14	42 ± 16	43 ± 18	0.76
C-reactive protein (mg/dL)x	1.4 ± 1.0	1.6 ± 1.2	2.0 ± 1.6	0.035
Kt/V	1.33 ± 0.28	1.32 ± 0.40	1.34 ± 0.26	0.84
Log FGF-23x	2.72 ± 0.23	2.87 ± 0.28	3.02 ± 0.21	0.0001

ACEI/ARB=angiotensin converting enzyme inhibitors, or receptor blockers; CCB=calcium channel blockers; CIMT=carotid artery intima-media thickness; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

significantly associated with CIMT (Table 3). The results did not differ significantly when further adjusted for vitamin D and phosphate binder use (data not shown).

DISCUSSION

In the present study, plasma FGF-23 level was shown to be associated with an increased CIMT, independent of established known risk factors. The significant and positive association of plasma level with CIMT, raises the possibility of a specific pathophysiologic effect of FGF-23 on atherosclerosis, distinct from its effects on serum phosphorus and intact parathormone.

Fibroblast growth factor 23 has emerged as a novel important negative regulator of circulating phosphate and 1,25(OH)2D3 levels.[15] Fibroblast growth factor 23 levels are progressively elevated in patients with chronic kidney disease and when the patients reach ESRD, FGF-23 levels are often 100- to 1000-times higher than the normal range.[11] Despite the fact that elevated FGF-23 levels in progressive chronic kidney disease seem to be appropriate to compensate hyperphosphatemia, chronically elevated FGF-23 might have actions on organs other than kidney and parathyroid gland.

Recently, increased FGF-23 concentrations have been reported to be independently associated with mortality

Table 2 Characteristics of the hemodialysis population according to FGF-23 tertiles (mean ± SD)

Parameter	FGF-23 tertile 1 (<454 RU/mL)	FGF-23 tertile 2 (454–1023 RU/mL)	FGF-23 tertile 3 (>1023 RU/mL)	P value
Number (n, %)	41 (32.1%)	44 (34.3%)	43 (33.6%)	
Male/Female	19/20	22/23	22/22	
Age (y)	54 ± 14	55 ± 14	56 ± 13	0.51
Body mass index (kg/m^2)	24.0 ± 3.2	23.9 ± 2.6	24.2 ± 3.1	0.76
HD duration (mo)	49 ± 7	52 ± 11	51 ± 10	0.35
Diabetes (n, %)	11 (27%)	13 (29.5%)	10 (23%)	0.77
Smoking (n, %)	7 (17%)	9 (20%)	9 (21%)	0.82
Hypertension (n, %)	24 (58.5%)	22 (50%)	25 (58%)	0.59
Systolic blood pressure (mmHg)	138 ± 27	140 ± 22	144 ± 19	0.30
Diastolic blood pressure (mmHg)	77 ± 19	80 ± 17	79 ± 19	0.40
Medications				
ACEI/ARB	22 (54%)	24 (55%)	22 (51%)	0.36
Betablockers	14 (24%)	11 (25%)	11 (26%)	0.84
CCB	16 (39%)	17 (39%)	16 (37%)	0.56
$CaCO_3$	11 (27%)	12 (27%)	12 (28%)	0.92
Ca-acetate	19 (46%)	23 (52%)	21 (49%)	0.68
Sevelamer-HCl	4 (10%)	6 (13%)	4 (10%)	0.82
Alfacalcidiol	24 (59%)	27 (61%)	28 (65%)	0.54
Hemoglobin (g/dL)	10.9 ± 1.1	11.2 ± 0.9	11.3 ± 0.8	0.77
Calcium (mg/dL)	9,1 ± 0.4	9,0 ± 0.6	9,1 ± 0.7	0.78
Phosphorus (mg/dL)	4.3 ± 1.0	4.9 ± 0.9	5.2 ± 1.6	0.002
Ca-phosphorus product (mg^2/dL^2)	39 ± 6	44 ± 6	48 ± 9	0.002
Intact parathormone level (pg/mL)	121 (76–144)	345 (230–412)	566 (458–992)	0.01
Serum creatinine (mg/dL)	10.5 ± 2.8	10.6 ± 2.4	10 ± 2.0	0.69
Serum albumin (g/dL)	4.0 ± 0.6	3.9 ± 0.4	3.8 ± 0.2	0.055
Total cholesterol (mg/dL)	148 ± 49	156 ± 41	149 ± 42	0.71
Triglycerides (mg/dL)	143 ± 55	151 ± 29	143 ± 40	0.46
LDL-C (mg/dL)	89 ± 24	87 ± 27	88 ± 20	0.62
HDL-C (mg/dL)	40 ± 15	42 ± 19	40 ± 13	0.87
C-reactive Protein (mg/dL)	1.8 ± 1.3	1.8 ± 1.6	1.6 ± 1.9	0.95
Kt/V	1.35 ± 0.33	1.32 ± 0.27	1.34 ± 0.30	0.69
CIMT (mm)	0.66 ± 0.14	0.75 ± 0.05	0.86 ± 0.20	<0.0001

ACEI/ARB = angiotensin converting enzyme inhibitors, or receptor blockers; CCB = calcium channel blockers; CIMT = carotid artery intima-media thickness; FGF-23 = fibroblast growth factor-23; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

among patients who are beginning HD treatment[11] and also among patients treated with long HD sessions.[16] Plasma FGF-23 levels emerged as an independent correlate of CIMT in maintenance HD patients in the present work. The results lend further support to our hypothesis that plasma FGF-23 level is involved in the high cardiovascular risk of maintenance HD patients and these findings may add evidence to explain the link between elevated FGF-23 levels and mortality in ESRD population.

The significant relation between altered mineral metabolism, increased cardiovascular risk, and morbidity-mortality in patients with chronic kidney disease[3] raised the possibility whether plasma FGF-23 is independently associated with cardiovascular risk factors. A cross-sectional study involving healthy individuals and early chronic kidney disease (PIVUS cohort) revealed that a higher FGF-23 was linked to several dynamic measurements of vascular function, impaired vasoreactivity measured by an invasive forearm technique, and an increased arterial stiffness measured by pulse-wave velocity.[17] Furthermore, the total body atherosclerosis score (AS) was determined by a magnetic resonance imaging-based angiography in a subsample of the community-based PIVUS cohort.[18] That study showed that the 1 SD increase of serum FGF23 level was associated with a 43% to 49% increased odds of having a high total

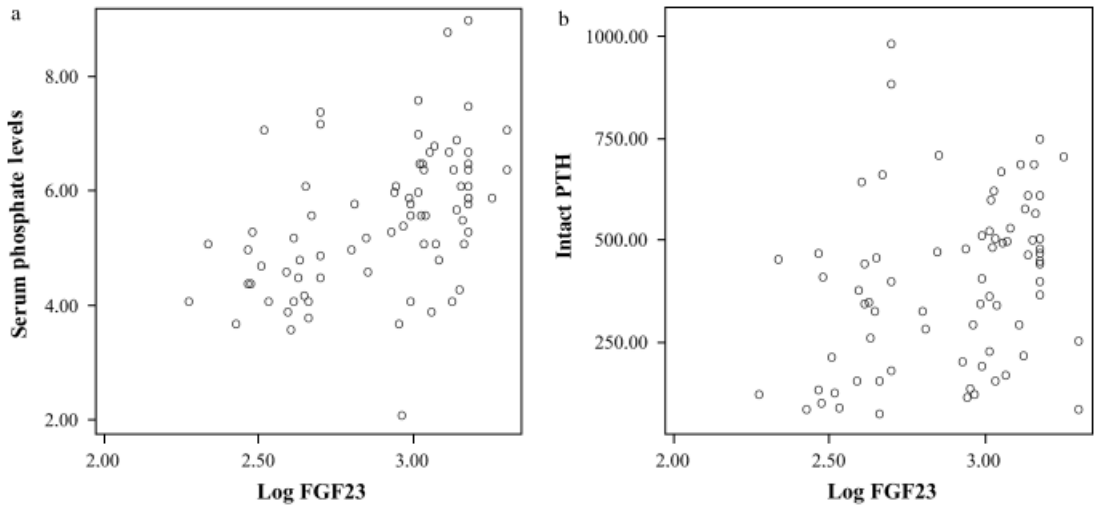

Figure 1 (a) Correlations between log FGF-23 and serum phosphate ($r=0.469$, $P<0.0001$) and (b) intact parathormone levels ($r=0.374$, $P=0.001$).

body AS vs. a low total body AS in both crude and adjusted models.[18] More recently, based on clinical studies, Larsson stated that the associations among FGF-23, vascular dysfunction, and atherosclerosis were all progressively strengthened in patients with a lower eGFR despite normal phosphate levels, supporting the hypothesis that FGF-23 may provide information about phosphate-related toxicity that cannot be obtained by measurements of serum phosphate levels.[15]

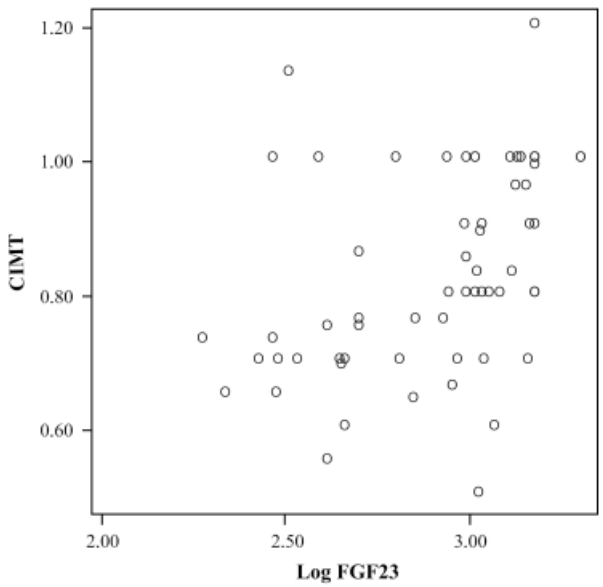

Figure 2 Correlation between log FGF-23 and carotid artery intima-media thickness (CIMT) ($r=0.497$, $P=0.0001$).

The relation between FGF-23 and cardiovascular calcification has also gained interest in dialysis patients. Recent studies have showed that FGF23 is linked to peripheral vascular, aortic, and coronary artery calcification in HD patients.[16,19–22] In agreement with these results, the present work showed positive correlation between log FGF-23 and CIMT, further suggesting that the plasma FGF-23 level might be a marker of vascular changes in maintenance HD patients.

The positive relation between atherosclerosis, vascular calcification, and plasma FGF-23 level is still largely obscure.[21,23–25] According to recent clinical evidence, firstly, it may be speculated that the plasma FGF-23 level may not only be a biomarker of early cardiovascular changes induced by altered mineral homeostasis, but that

Table 3 Multiple regression analysis of factors associated with CIMT (n = 128 patients)

Parameter	β	P
Age	0.220	0.040
Systolic blood pressure	0.237	0.048
Smoking	0.128	0.903
Diabetes	0.338	0.002
Serum CRP levels	0.135	0.018
Serum albumin levels	−0.190	0.280
Serum phosphate levels	0.159	0.026
Serum intact parathormone levels	0.272	0.025
Log FGF-23	0.328	0.001

CIMT = carotid artery intima-media thickness; FGF-23 = fibroblast growth factor-23.

FGF-23 itself directly influences the cardiovascular system as well.[15] However, as Klotho is not expressed in the vasculature, it appears unlikely that FGF-23 affects vascular tissues in an endocrine fashion.[15] Secondly, supraphysiological concentrations of FGF-23, observed in many dialysis patients, may induce unspecific, Klotho-independent, FGF receptor signaling.[15] FGF receptors, FGFR1 and FGFR4, are expressed in tunica media of several artery and veins.[26] Activation of these FGF receptors with FGFs may yield to neointimal hypertrophy and fibrosis. FGF-2 is an important mediator of vascular smooth muscle proliferation following arterial injury that results in neointimal growth.[27,28] Moreover, it has been shown that FGF-2 is responsible for a significant portion of smooth muscle cell proliferation in the tunica media stimulated by endothelial denuding injury to the rat carotid artery.[29] Finally, an increased expression of basic FGF and FGFR-1 in vascular smooth muscle cells of unstable plaques in carotid arteries have been reported more recently.[30]

Based on the above mentioned data, we might speculate that chronically and remarkably elevated FGF-23 levels in dialysis patients may induce hypertrophic and fibrotic response in the carotid arteries of uremic patients by binding to FGF receptors. However, this hypothesis remains to be proven, and unfortunately, does not work in the kidney, as Klotho-null mice were not able to correct elevated serum phosphate and 1,25(OH)2D3 levels despite markedly elevated levels of FGF-23.[31] Moreover, patients with X-linked hypophosphatemic rickets and tumor-induced osteomalacia who have high circulating FGF-23 but not chronic renal disease, do not experience an increased cardiovascular risk.[15]

There are several limitations of this cross-sectional study. Owing to the design of the study, we measured CIMT in which changes generally occur by time. Then, we tried to find out associations of these with single point in time measurements of plasma FGF-23 levels. Uncertain possible variations in plasma FGF-23 levels may occur. Moreover, the study was performed in 1 center in Turkey, revealing limitations in number and race of patients. Furthermore, no causal relationship could be observed; only association data were presented.

In conclusion, plasma FGF-23 concentration is independently associated with CIMT and the presence of CCA plaque(s) in maintenance HD patients. Further prospective studies are needed to clarify whether an increased plasma FGF-23 level is a marker or a potential mechanism for peripheral arterial atherosclerosis in patients with ESRD.

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