Circulating fibroblast growth factor 23 in children on peritoneal dialysis is associated with effective dialysis

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Received: 13 February 2015, Revised: 9 April 2015, Accepted: 22 April 2015

SUMMARY: Hacıhamdioğlu DÖ, Düzova A, Alehan D, Oğuz B, Beşbaş N. Circulating fibroblast growth factor 23 in children on peritoneal dialysis is associated with effective dialysis. Turk J Pediatr 2015; 57: 9-16.

Our purpose was to assess the relationship between serum fibroblast growth factor 23 (FGF23) and left ventricular function, carotid intima-media thickness (CIMT) and laboratory features in children on peritoneal dialysis (PD).

The study population consisted of 17 patients (11 female; median age 7.83 years, range 0.66-17.75) undergoing PD for 22 months (range 2-98). Serum FGF23, serum phosphorus, calcium, intact parathyroid hormone (iPTH), 25(OH) vitamin D, $1,25(OH)_2$ vitamin D and Kt/V urea, left ventricular mass (LVM) and LVM index (LVMI) were assessed.

Median FGF23 level was 29.92 pg/ml (22.7-74.76), phosphorus was 5.2 mg/dl (3.1-9.9), iPTH was 438 pg/ml (16-1446), 25(OH) vitamin D was 11 ng/ml (5-35), $1,25(OH)_2$ vitamin D was 11 pg/ml (2-106), Kt/V urea was 2.33 (1.01-3.84). FGF23 level was independently associated with Kt/V urea ($p<0.001$).

We found that effective dialysis may be the leading determinant of FGF level, independent from the calcium-phosphorus-PTH axis, in pediatric PD patients.

Key words: FGF23, Kt/V urea, left ventricular hypertrophy, CIMT.

Patients with chronic kidney disease (CKD) are considerably more likely to suffer from cardiovascular disease (CVD). CVD is a risk factor for progression of CKD and a significant cause of morbidity and mortality in these patients[1-3]. The connection between CVD and CKD appears to be mediated by several factors, and to date the underlying pathological mechanism is largely unknown. Abnormalities in bone and mineral metabolism are universal findings in patients with CKD and have emerged as a novel target for intervention.

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates serum phosphate levels[4, 5]. FGF23 has a phosphaturic effect that also reduces the formation of the biologically active 1,25-dihydroxyvitamin D [$1,25(OH)_2$ vitamin D][6]. Among adult patients with CKD, elevated FGF23 levels have been shown to be associated with left ventricular hypertrophy (LVH)[7], endothelial dysfunction[8] and increased carotid intima-media thickness (CIMT)[9], which are known to be risk factors for cardiovascular events and death[10,11]. Studies on pediatric hemodialysis patients have indicated that the highest FGF23 levels were associated with increased left ventricular mass index (LVMI)[12] and occurrence of coronary calcification[13].

FGF23 levels in dialysis patients are apparently associated with various factors, including phosphorous, LVH and CIMT. Despite all these data, the clinical parameters that affect serum FGF23 levels in children on peritoneal dialysis (PD) remain unclear. In this cross-sectional study, we aimed to evaluate the association between FGF23 and left ventricular hypertrophy, CIMT and clinical and laboratory features in children on peritoneal PD.

Material and Methods

Study population

The study population consisted of 17 pediatric patients undergoing continuous ambulatory

PD for more than 2 months. The exclusion criteria were (i) presence of congenital cardiac abnormality, (ii) presence of "uncontrolled" hypertension, defined as casual blood pressure (BP) measurements >95th percentile for age, gender, and height on three consecutive visits during the preceding 6 months, and (iii) evidence of active infection within two weeks prior to the study. Informed consent was obtained from both parents and children for patients aged 11–18 years and from parents only for those 10 years of age and under. The study was approved by the local Ethics Committee (HEK 12/116).

Clinical features and laboratory measurements

The following clinical information relevant to the analysis was collected: medical history and physical examination, including gender, age, weight, height, body mass index (BMI), BMI standard deviation score (SDS)[14] and body surface area (BSA); time on peritoneal dialysis; dwell volume, urine volume and ultrafiltration volume; and medications used. Blood chemistry parameters (creatinine, phosphorus, calcium, intact parathyroid hormone-İPHT, total cholesterol, low density lipoprotein-LDL, high density lipoprotein-HDL, triglycerides, 25(OH) vitamin D and complete blood count) were measured at our institution using standard automated techniques. 1,25$(OH)_2$ vitamin D levels were measured by radio immunoassay using a kit from Diasource (Belgium). The samples for FGF23 were centrifuged, and the serum decanted and aliquoted to separate tubes for storage at -80^{o}C within 4 hours following collection; samples were brought to room temperature, and the serum intact FGF23 concentrations were measured by a sandwich enzyme-linked immunosorbent assay system using a kit from Uscnlife (Wuhan, China).

We measured parameters of dialysis adequacy, including renal and peritoneal Kt/V urea, using standard methods[15, 16].

Echocardiography

Images were obtained on an echocardiographer (GE Medical System Vivid Five

Table I. Characteristics and Laboratory Values of the Study Population

Characteristics	Median	Range
Age (years)	7.83	(0.66-17.75)
Body mass index (kg/m^2)	14.42	(11.72-17.57)
BMI SDS (n:15)	-1.65	[(-4.56)-(-0.5)]
Body surface area (m^2)	0.77	(0.3-1.3)
Total time on PD (months)	22	(2-98)
Dwell volume (ml/m^2)	930	(500-1250)
Urine volume (ml/m^2) (11 pts. had anuria)	0	(0-2250)
RRF (ml/dk/1.73m^2) for 6 pts. with urine	11.2	(2.4-23.5)
Ultrafiltration (ml/m^2)	375	(0-1000)
Kt/V urea	2.33	(1.01-3.84)
Hemoglobin (g/dl)	10.1	(9.2-13.4)
Hematocrit (%)	30.4	(28-39.9)
Creatinine (mg/dl)	6	(2.02-11.91)
Triglycerides (mg/dl)	125	(47-364)
LDL cholesterol (mg/dl)	139	(69-197)
HDL cholesterol (mg/dl)	53	(32-97)
Calcium (mg/dl)	9.1	(8.2-11.8)
Phosphorus (mg/dl)	5.2	(3.1-9.9)
Calcium x phosphorus	49.5	(25.4-94)
iPTH (pg/ml)	438	(16-1446)
1,25$(OH)_2$ vitaminD3 (pg/ml)	11	(2-106)
25(OH) vitaminD (ng/ml)	11	(5-35)
FGF23 (pg/ml)	29.92	(22.7-74.76)

Echocardiographer). Measurements of left ventricular end-systolic dimension (LVESD) and left ventricular end-diastolic dimension (LVEDD) were taken according to the recommendations of the American Society of Echocardiography[17]. Measurements were performed by a single, well-trained individual (D.A.). Left ventricular ejection fraction (EF) and fractional shortening (FS) were measured[17,18]. Left ventricular mass (LVM) was calculated using the following equation—0.8 x {1.04 x [(LVEDD + left ventricular posterior wall thickness + interventricular septal thickness)^3 - LVEDD^3] + 0.6} g—and the LVMI was calculated for all patients[17]. The LVMI was obtained by dividing the LVM by height to the power of 2.7[18, 19]. The LVM and LVMI values were converted to z-scores according to the height age[19, 20].

In the literature, LVH in children has been defined as an LVMI that is greater than the 95th percentile for the age[21]. The age-independency of the LVMI has recently been questioned for infants and young children, and use of height-specific percentile charts or standard deviation scores (SDS) for LVMI to establish the diagnosis of LVH in children has been advocated[19, 20]. Assuming that growth retardation is common in children with CKD, and that the body composition, cardiac mass and cardiac output of a growth-retarded child could match that of a child of the same height who is at the 50th percentile for his/her age, we used values according to the height age[20].

CIMT measurements

A single, well-trained individual (B.O.) performed ultrasound (US) scanning using a B-mode ultrasound system with a 9.4-13.5 MHz linear probe (Sonoline Antares, Siemens Medical Systems, Erlangen, Germany). After at least 10 minutes of rest, with the patients in a supine position with slightly extended neck, CIMT was measured 1-2 cm below the bifurcation on the right and left common carotid arteries. CIMT was defined as the distance between the lumen–intima interface (upper border) and the media–adventitia interface (lower border) of the far wall and was measured manually using the caliper method. Five measurements were obtained on each side and averaged for each patient. The CIMT values were converted to z-scores according to age and height for those patients aged 6 years and above[22].

Statistical analysis

All statistical calculations were made using SPSS for Windows 15.0. Simple between-group comparisons were made using the Mann-Whitney U test. The results were expressed as medians (minimum-maximum). Statistical significance was defined as $p<0.05$. Nonparametric correlation analysis (Spearman rank correlation) was also used.

Results

Seventeen patients (6 male, 11 female) on continuous ambulatory PD were enrolled. The demographic and laboratory characteristics of the patients are presented in Table I. The patients' etiologies were renal agenesis (n: 1), congenital nephrotic syndrome (n: 1), cystic renal disease (n: 2), nephronophytisis (n: 2), cystinosis (n: 2), oxalosis (n: 2), vesicoureteral reflux (n: 2) and focal segmental glomerulosclerosis (n: 5). Phosphate binders, active vitamin D analogs and antihypertensives (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) were used by

Table II. Echocardiography and CIMT Characteristics

Features	Median	Range
EF (%)	66	(30-78)
FS (%)	34	(13-46)
LVM (g)	53.91	(15.22-119.07)
LVMI (g/m$^{2.7}$)	39.4	(21.9-137.8)
LVMI SDS for height age	-0.33	[(-1.65)-2.33]
CIMT (mm)	0.44	(0.30-0.70)
CIMT SDS (n=11)*	0.84	[(-0.67)-1.65]

CIMT: carotid artery intima-media thickness, EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, LVMI: left ventricular mass index, SDS: standard deviation score
*CIMT SDS was available for those patients aged 6 years and above

14 (82%), 12 (70.6%) and 7 (41%) patients, respectively.

Fifteen patients (88%) had low 25(OH) vitamin D levels (<30 ng/ml). Ten (83%) of 12 patients treated with active vitamin D analogs and 4 (80%) of 5 patients without treatment had low 25(OH) vitamin D levels.

Twelve (70%) patients had low $1,25(OH)_2$ vitamin D levels (<30 pg/ml). Seven (58%) of 12 patients treated with active vitamin D analogs and 5 (100%) of 5 patients without treatment had low $1,25(OH)_2$ vitamin D levels.

Six (35%) patients had high serum phosphorus levels according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative Guidelines[23]. Nine (52%) patients had high PTH levels (>300 pg/ml).

The prevalence of LVH (LVMI >95th percentile for height age) was 35% (6 patients). The baseline echocardiography and CIMT characteristics of the patients are presented in Table II.

Factors associated with FGF23

There were no statistically significant correlations between BMI SDS; time on PD; serum creatinine, phosphorus, calcium, calcium x phosphorus, LDL, iPTH, 25(OH) vitamin D and $1,25(OH)_2$ vitamin D levels; CIMT, CIMT SDS, LVM, LVMI and LVMI SDS for height; and FGF23. There were statistically significant negative correlations between age, body surface area, dwell volume, Kt/V urea and FGF23 levels (Table III). Differences in FGF23 levels between patients with LVMI>95th percentile (43.14 pg/ml, range: 22.70-74.76) and patients with LVMI≤95th (28.91 pg/ml, range: 22.98-64.11) did not reach statistical significance (p: 0.09). The strongest (-0.729; p: 0.001) correlation was between FGF23 and Kt/V urea (Table III, Fig.1).

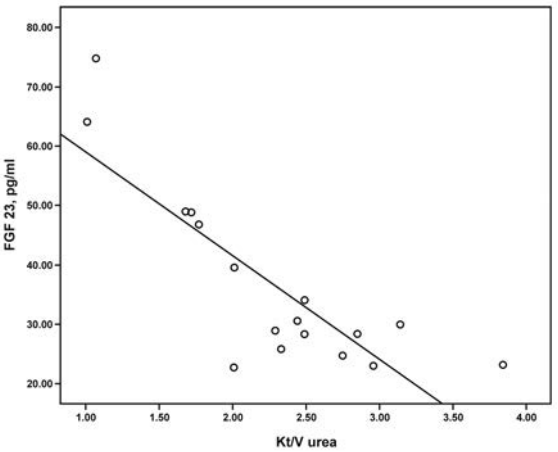

Fig. 1. Negative correlation of serum FGF 23 (pg/ml) with Kt/V urea, r=-0.729, p=0.001

Since the number of patients was limited, we performed multivariate regression analysis between the two covariants with the highest correlation coefficients in the linear regression analysis, i.e., Kt/V urea and dwell volume (ml/m^2). Kt/V urea was independently associated with FGF23 level (p<0.001); however, it was not independently correlated with dwell volume (p: 0.53)

The FGF23 level in patients with residual renal function (n: 6) (median: 29.92 pg/ml, range: 23.16-74.76) was comparable to that of those without residual renal function (median: 31.48 pg/ml, range: 22.7-64.11), (p: 0.964).

We also evaluated patients for residual renal function (RRF). Patients with RRF had higher Kt/V urea [respectively 2.7 (±0.74) and 2 (±0.64), p=0.04] and lower LVMI SDS [respectively -0.14 (±0.77) and 0.96 (±1.2),

Table III. Significant Correlation Analysis Results for FGF23 and Multivariable Regression Analysis of FGF23 and Kt/V urea and Dwell Volume

Features	Correlation coefficient	p* value	Multivariable regression analysis	
			Standard β	p value
Age	-0.515	0.035		
BSA	-0.589	0.013		
Dwell volume (ml/m^2)	-0.675	0.033	-0.34	0.53
Kt/V urea	-0.729	0.001	-0.65	< 0.001

BSA: Body surface area, *p<0.05

Table IV. Clinical Characteristics and Laboratory Values According to Age

Features	Age 0-4 years (n=5) Median (Range)	Age 5-10 years (n=5) Median (Range)	Age ≥11 years (n=7) Median (Range)
Gender (M/F)	1/4	3/2	4/3
Calcium (mg/dl)	9.4 (8.2-11.8)	9.2 (8.89-9.8)	8.62 (8.41-10)
Phosphorus (mg/dl)	7.04 (4.4-9.94)	4.52 (3.05-6.72)	5.46 (3.74-7.45)
25 (OH) vitamin D	25 (11-34.8)	15 (5.6-34)	8.8 (5-24)
1,25 $(OH)_2$ vitamin D	17 (8-106)	13 (<1.6-51)	7 (<1.6-32)
PTH (pg/ml)	508 (16-571)	203 (68.6-850)	433 (133-1446)
FGF23 (pg/ml)	47.78 (30.55-74.76)	28.35 (22.98-48.87)	28.31 (23.7-43.99)
LDL cholesterol (mg/dl)	121 (69-197)	152 (92-160)	153 (100-180)
Kt/V urea	1.77 (1.01-2.44)	2.85 (1.72-3.14)	2.33 (2.01-3.84)
LVMI ($g/m^{2.7}$)	58.53 (35-137.77)	29.81 (21.89-42.71)	36.39 (26.95-60.13)
LVMI SDS for height	1.28 [(-0.08)-1.65]	-0.13 [(-1.65)-1.28]	0.68 [(-1.28)-2.33]

F: female, FGF23: fibroblast growth factor 23, LDL: low density lipoprotein, LVMI: left ventricular mass index, M: male, PTH: parathyroid hormone, SDS: standard deviation score

p=0.03] than those without RRF. The difference in FGF23 levels did not reach statistical significance.

When we compared patients with and without angiotensin-converting enzyme inhibitor (ACE-i), we did not find a difference for Kt/V urea, FGF 23, LVMI SDS and CIMT SDS.

We stratified the subjects according to age (0-4, 5-10 and ≥11 years). In the youngest ages group (0-4 years), Kt/V urea was lower than that of other groups, while phosphorus, 25(OH) vitamin D, 1,25 $(OH)_2$ vitamin D, FGF23, LVMI and LVMI SDS were higher (Table IV).

Factors associated with CIMT SDS

Carotid intima-media thickness SDS was available in 11 patients. CIMT was ≥95th percentile in 3 patients and <95th in 8 patients. There were no significant correlations between serum FGF23, phosphorus, calcium, LDL, iPTH, 25 (OH) vitamin D and 1,25 $(OH)_2$ vitamin D levels and CIMT SDS .

Discussion

Data on FGF23 levels in pediatric patients undergoing PD are limited[24-26]. Van Husen et al.[24] reported that FGF23 levels in CKD stage 5 did not differ significantly between hemodialysis and PD; they also showed that residual renal function had no effect. In contrast, Wesseling-Perry et al.[25] showed that the absence of residual renal function was associated with higher FGF23 levels in children on PD. In adult patients undergoing PD, increased serum phosphate, loss of residual renal function, longer dialysis vintage, Kt/V urea, renal creatinine clearance and lower renal phosphate clearance were associated with elevated FGF23 levels[27, 28].

Herein, we have demonstrated that lower Kt/V urea was independently correlated with FGF23 level in children on PD. Nevertheless, this study did not confirm a correlation between FGF23 and phosphorous, calcium, PTH, 25(OH) vitamin D, 1,25$(OH)_2$ vitamin D, residual renal function and dialysis vintage. Recently, it was shown that FGF23 levels correlated significantly with calcium and inversely with Kt/V urea, indicating no relationship with phosphatemia in children on PD[26]. In that study, patients aged between 1.2 and 13.4 years; mean phosphate (5.4±1.0 mg/dl) and mean PTH (333±287 pg/ml) were lower and mean time on PD (13.5±14.5 months) was less than in our group. Despite these differences, both studies confirmed that FGF23 levels correlate significantly and inversely with Kt/V urea. These results suggest that effective dialysis might be the more important determinant for FGF23 levels in children undergoing PD. A prospective study is needed to examine the clearance of FGF23 in peritoneal dialysis or the deteriorated catabolism of FGF23 in renal failure.

A strong association of phosphatemia with

FGF23 has been reported [24]. However, we could not find such an association. Moreover, the subjects in the present study were distributed over a large age range, from 0.66 through 17.75, which may have contributed to the wide range of phosphorus values observed; this may mask the contribution of FGF23 to serum phosphorus metabolism. For this reason, we stratified the patients by age. We saw higher FGF23, serum phosphorus and LVMI SDS and lower Kt /V urea in younger patients. The cause of higher FGF and phosphorus in this age group may be related to inadequate dialysis.

Several recent studies indicate a relationship between FGF and LVH. The largest investigation was the CRIC study, in which 3,070 adult stage 2-4 CKD patients had baseline FGF23 measurements and underwent echocardiograms one year later. The investigators showed that ascending quartiles of FGF23 were significantly associated with increased LVMI and greater prevalence of concentric and eccentric LVH, independent of demographic, clinical and laboratory covariates[29]. There are several possible explanations regarding the underlying mechanisms. In an experimental study of mice, it was demonstrated that FGF23 directly induces pathological hypertrophy of isolated cardiomyocytes; this effect was independent of klotho, the co-receptor for FGF23 in the kidney and parathyroid glands[29]. In our study, we found no association between FGF23 and LVH or LVMI. The studies indicating a relationship between FGF23 and LVH were conducted in adult patients[25,29]. This suggests that long-term, high-level exposure to FGF23 may be required to induce LVH.

On the other hand, in a recently published study, adult patients treated with long nocturnal hemodialysis showed a lower LVMI and lower phosphate values; however, FGF23 was not associated with LVMI[30]. This result indicates that the pathogenesis of LVH in dialysis patients is likely multifactorial and needs further evaluation. In accordance with the aforementioned study, our study showed no correlation between FGF23 and LVMI SDS. However, these results may be related to the small size of the study populations.

Vitamin D deficiency is very prevalent in children with CKD[31]. In our study, fifteen patients (88%) had low 25(OH) vitamin D levels (<30 ng/ml). Risk factors for vitamin D deficiency include older age, female sex, geographic location and winter season. CKD may impose additional risk factors for vitamin D deficiency, including impaired cutaneous photosynthesis of calciferol due to uraemia[32], urinary losses of vitamin D-binding protein (DBP) and albumin, and decreased dairy intake due to phosphate restrictions. For the patients with vitamin D deficiency (6 male, 9 female), the median age was 9.25 years, and the median albumin was 3.9 g/dl. In our study, 7 (58%) of 12 patients treated with active vitamin D analogs had low $1,25(OH)_2$ vitamin D levels. $1,25(OH)_2$ Vitamin D deficiency has usually been attributed to reduced renal production of circulating $1,25(OH)_2$ vitamin D, and deficiency of its substrate 25(OH) vitamin D. However, advanced CKD has been shown to be strongly associated with lower 24,25-dihydroxyvitamin D [$24,25(OH)_2$ vitamin D] concentrations[33,34]. Significantly, this finding persisted after adjustment for both the concentration of available substrate 25(OH) vitamin D and the principal hormonal influences on vitamin D catabolism, PTH and FGF23. Thus, children with CKD not only have nutritional deficiency and decreased 1-α hydroxylation of 25(OH) vitamin D; they also exhibit altered catabolism and concentrations of free and bioavailable 25(OH) vitamin D.

Results regarding the effect of FGF23 on vascular calcification are conflicting. While some investigators were not able to find a significant relationship between FGF23 and vascular calcification in dialysis patients[35], others did report an association with coronary calcification scores in the hemodialysis setting[13]. Recently, it was shown that FGF23 levels were not associated with CIMT in 46 adult renal transplant recipients[36]. Although FGF23 is considered a marker for the prediction of vascular calcification, its exact role is undefined. The negative impact of FGF23 on the cardiovascular system may not directly involve an increase in atherosclerosis, at least in the earlier stages. In our study, we could not find an association between calcium, phosphate, vitamin D, PTH, FGF23 and CIMT.

The limited number of patients and absence of a control group are limitations of our study. Despite these limitations, we have shown

effective dialysis to be the leading determinant of FGF level, independent from the calcium-phosphorous-PTH axis, in pediatric PD patients with regulated blood pressure. Longitudinal studies in larger pediatric PD cohorts are necessary to investigate further this association.

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