Investigating the Relationship Between Blood Pressure and Serum FGF23 Level in Patients Undergoing Hemodialysis in Guilan Province, A Cross Sectional Study

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Introduction. The aim of current study is investigation of the impact of serum FGF23 levels on blood pressure of patients with end-stage renal disease (ESRD) undergoing hemodialysis.
Methods. Based on registry, 68 patients who underwent hemodialysis (HD) in the dialysis center of Shahid Beheshti hospital, Anzali, north of Iran, from April 2016 to May 2017 were enrolled. Enzyme-Linked ImmunoSorbent Assay (ELISA) was used to determine serum FGF23 levels. 24 hours blood pressure monitoring method, AMBB, was used to monitor the mean arterial pressure of patients. Spearman related analysis method was used to statistically analyze the correlation of serum FGF23 level with mean arterial pressure, age, HD duration, kt/v, URR weight gaining, cause of ESRD, and the mentioned laboratory parameters.
Results. Serum FGF23 levels of ESRD patients were not significantly related to age, time of HD and gaining weight. Furthermore, these parameters were not related to blood pressure. However, FGF23 expression levels in serum were positively correlated with phosphorous and calcium- phosphorous. The mentioned laboratory parameters had no significant correlation with 24 hours blood pressure changes. Meanwhile, the minimum diastolic pressure and intact parathyroid hormone (iPTH) level showed a significant direct linear correlation.
Conclusion. We suggest that understanding relationship between phosphate, FGF23 and cardiovascular disease can be applied in targeted phosphate-based treatment. Kidney failure and the non-dipper condition may be highly related to one another and lead to ESRD. Therefore, a special investment in controlling blood pressure and examining it with a tool such as ABPM can greatly help patients to progress effectively.

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INTRODUCTION

End-stage renal disease (ESRD) has been considered as one of the global public health concerns, with a dramatic growing rate according to the recent reports.[1-3] Aging of the population and global epidemic of diabetes are two main factors of the rising prevalence.[2] Although the favorable treatment in patients with ESRD is kidney transplantation, due to the high costs and failure of this method, long-term hemodialysis (HD) has

become the most common therapy used in these patients.[4] While HD is performed to remove accumulated toxins from the body,[5] it should be noted that the HD patients are 10 to 20 times more likely to be at risk for cardiovascular disease than normal population.[6] The inflamed kidneys and the process of HD also affect endothelial function, aggravating the risk of hypertension and cardiac problems.[7] Therefore, both physicians and patients should be aware of the consequences of HD.[8] To manage this condition in order to have a normal life, patients with chronic renal failure (CRF) need to be seriously trained on the facts of the disease, medications, dietary habits, and various measures.[9] Among other risk factors, phosphate metabolic disorder is considered as the most important factor to the mortality of patients with chronic kidney disease (CKD).[10,11] The regulatory impact of parathyroid hormone (PTH) and 25-hydroxyvitamin D3 (25-OH D3) in serum phosphate is known.[12,13] Recent studies have proven the effects of fibroblast growth factor 23 (FGF23) and Klotho gene as phosphorylation regulatory genes for cardiac remodeling in CKD patients.[14,15] In this study, the primary aim was to evaluate the correlation between expression levels of FGF23 with alterations of 24 hours blood pressure in HD patients. We also evaluated the separate correlations between 24 hours blood pressure and FGF23 levels with demographic and clinical characteristics of these patients.

MATERIALS AND METHODS

Inclusion Criteria

- All patients with ESRD undergoing HD in Shahid Beheshti Hospital, Bandare Anzali, northern Iran, during April 2016 to May 2017 were included in the study after signing written informed consent to participate in the study in accordance with the recommendations of the declaration of Helsinki.
- The age of enrolled patients ranged between 18-85 years old

Exclusion Criteria

Patient dissatisfaction to participate in the study as well as incomplete recorded data files

Clinical Data

Participants and sample collection. The clinical data of 68 ESRD patients including 39 males and 29 females were collected. The age of patients ranged from 20 to 84 years old with an average age of 58.44 ± 14.35 years. The HD duration was from 4 to 156 months with a median disease course of 42.33 ± 29.64 months. ESRD was confirmed by histopathology, laboratory detection and imaging. Ethics Committee of Guilan university of medical sciences approved this study with ID number # 78.2010. Also, methods were carried out in accordance with the approved guidelines with the declaration of Helsinki. A written consent form was completed for all the patients.

Sample Size

In order to estimate the correlation between alterations of 24 hours blood pressure with serum level of FGF23 in medium and higher levels ($r > 35$) with confidence interval (CI) 95% and power test 80%, 68 subjects were enrolled. Although this small sample size was one of our study limitations.

Blood Sample Collection

Blood samples from subjects were collected between 8:00 to11:30, in fasting condition and let them to be clotted for 1 hour at room temperature, followed by 1 hour at 4°C. Serum was then separated by centrifugation at 2000 g for 10 min at 4°C, aliquoted and stored at −80°C until use in 0.2 mL tubes strips (Sorfa Life Science).

Serum Measurement

Serum levels of calcium (mg/dL), phosphorus (mg/dL), PTH (pg/mL), uric acid (mg/dL), blood urea nitrogen, creatinine, 25-OH D3 (ng/mL) were measured by using the same laboratory kits (Pars Azmoon, Iran). FGF23 was detected using ELISA kit (Ab-cam, Cambridge, MA, USA) according to the manufacturer's instruction. Relevant software was utilized to draw a standard curve, and serum FGF23 level was calculated. The levels of serum FGF23 before and after HD were recorded, respectively.

Data Collection From Patients' Records

- Age, gender
- HD duration
- Antihypertensive drugs such as CCB, BB, AlphaB, ACEi, ARB, vasodilators, central acting drugs
- Causes for ESRD: diabetes, hypertension (HTN), glomerulonephritis (GN), obstruction, other

- HD adequacy: the adequacy of HD was evaluated using urea reduction ratio (URR) and kt/v (cc/min)

24 Hours Ambulatory Blood Pressure (ABPM)

Monitoring Method. The non-invasive method was used to indirectly monitor 24 hours ambulatory blood pressure and recorded the mean arterial pressure, systolic blood pressure, diastolic blood pressure, pulse pressure, dipper-non dipper, and severe HTN.

Statistical Analysis

SPSS 21 software was used for statistical analysis. $P < .05$ was considered to be statistically significant.

RESULTS

Table 1 depicts the demographic and clinical characteristics of the subjects and Table 2 shows the full interpretation of the clinical demographic profile and the implications of 24 hours blood pressure and FGF23. In this study the most antihypertensive drugs used by patients were beta blockers, calcium channel blockers, alpha blockers and ARB respectively. There was no significant relation between the demographic and clinical data with FGF23 levels. Instead of residual renal function, interdialytic weight gain and its correlation with FGF23 have been studied and no significant correlation was reported. However, the status of dipper and nondipper, as well as severe HTN, had a significant correlation with 24hours blood pressure alterations in patients. Non dipper group had significantly higher mean systolic, minimum and maximum systolic, and pulse pressure which were in accordance of previous studies.[16] While 24 hours diastolic blood pressure did not differ significantly between dipper and non-dipper subjects (Table 3). The higher age was significantly associated with a lower average 24 hours diastolic blood pressure and similarly minimum diastolic pressure (Table 4). From the measured laboratory parameters only phosphorous and "calcium x phosphorous" had a direct significant correlation with FGF23. Inspite of no correlation found between FGF23 and iPTH in this study, the minimum diastolic pressure with intact parathyroid hormone (iPTH) showed a significant direct linear correlation with moderate severity. There was no significant correlation between the measured laboratory tests and 24 hours blood pressure (Table 5). FGF23 level had no linear correlation with 24 hours blood pressure (Table 6).

Table 1. Description of the Demographic and Clinical Characteristics of the Subjects

	N (%)
Gender	
Female	27 (42.9)
Male	36 (57.1)
Dialysis Time	
Morning	29 (46)
Afternoon	34 (54)
Severe HTN	
No	48 (76.2)
Yes	15 (23.8)
Non-dipper	
No	34 (54)
Yes	29 (46)
Systolic Pressure (mean)	
< 140 mmHg	41 (65.1)
≥ 140 mmHg	22 (34.9)
Diastolic Pressure (mean)	
< 90 mmHg	54 (85.7)
≥ 90mmHg	09 (14.3)
Causes of ESRD	
DM	19 (30.2)
GN	03 (4.8)
HTN	26 (41.3)
PCKD	04 (6.4)
Obstructive Uropathy	04 (6.3)
Unknown	07 (11.11)
Antihypertensive Drugs	
Alpha Blocker	20 (31.7)
Beta Blocker	31 (49.2)
Diuretic	16 (25.4)
ACEi	08 (12.7)
Vasodilator	05 (7.9)
Calcium Channel Blocker	25 (39.7)
ARB	19 (30.2)
No Consumption	11 (17.5)

DISCUSSION

FGF23 is a protein with a main role of phosphate regulation.[17] It also inhibits the activation of vitamin D which leads to increased urinary phosphorus excretion.[18] The lack of vitamin D would consequently causes secondary hyperparathyroidism.[19] Therefore, normal levels of FGF23 have an important task in maintaining the normal function of endocritic axis in human body,[20] which will improve the diagnosis and treatment. Previous studies discussed the effect of FGF23 on high blood pressure, heart failure and arrhythmia by

Table 2. Description of the Demographic, Clinical Characteristics, and Outcomes of 24-h Blood Pressures and FGF23

	N	Mean	Median	SD	Minimum	Maximum
Age	63	58.44	59	14.35	20	84
Dialysis Duration	63	42.33	39	29.64	04	156
Phosphorous, mg/dL	63	05.06	05	0.93	03	7.6
Uric Acid, mg/dL	61	06.7	06.7	1.46	3.1	9.7
D3 25 OH, ng/mL	59	33.31	28	20.21	08	75
iPTH, pg/mL	59	365.32	301	270.07	25	1536
MAP, mmHg	63	92.43	93	17.90	58	142
Mean Systolic, mmHg	63	130.02	131	26.27	75	182
Mean Diastolic, mmHg	63	73.95	73	14.74	49	124
Pulse Pressure, mmHg	63	58.63	58	18.06	24	102
Kt/v, cc/min	63	01.31	01.26	0.26	0.66	1.9
MinSys, mmHg	63	101.68	96	25.23	54	161
MaxSys, mmHg	63	160.46	159	28.81	97	228
MinDia, mmHg	63	57.83	54	16.89	32	102
MaxDia, mmHg	63	93.05	87	23.52	56	200
URR	63	64.94	65	8.88	34	80
Ca x P	63	44.79	45	9.03	27	67
Ca, mg/dL	63	08.86	09	0.75	6.10	11
FGF23, pg/mL	61	1475.62	475	2382.26	80	9831
Inter dialytic Weight gain, kg	63	02.26	02	0.84	01	06

Table 3. Correlation Between FGF23 and 24-h Blood Pressure with Demographic and Clinical Characteristics of Subjects

	FGF23	*P*	MAP	*P*	MEAN SYSTOLIC	*P*	MEAN DIASTOLIC	*P*	PULSE PRESSURE	*P*
	Median (min - max)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Gender										
Female	548 (95 - 8259)	> .05	89.67 (16.94)	> .05	127.96 (28.35)	> .05	70.70 (13.02)	> .05	61 (21.35)	> .05
Male	423.5 (80 - 9831)		94.5 (18.55)		131.56 (24.90)		76.39 (15.64)		56.86 (15.23)	
Dialysis Time										
Morning	475 (95 - 9831)	> .05	90.17 (19.20)	> .05	128.66 (30.36)	> .05	71.17 (14.90)	> .05	60 (20.31)	> .05
Afternoon	452.5 (80 - 8259)		94.35 (16.76)		131.18 (22.62)		76.32 (14.39)		57.47 (16.12)	
Severe HTN										
No	514.5 (95 - 9831)	> .05	85.81 (13.25)	< .001	119.33 (18.42)	< .001	69.69 (11.53)	< .001	53.85 (15.67)	< .001
Yes	366 (95 - 4247)		113.60 (14.09)		164.20 (16.55)		87.60 (15.92)		73.93 (17.06)	
Non dipper										
No	681.5 (80 - 9831)	> .05	89.59 (20.95)	> .05	122.88 (26.73)	< .05	73.71 (18.06)	> .05	54.03 (16.72)	> .05
Yes	410 (82 - 8214)		95.76 (13.07)		138.38 (23.50)		74.24 (9.80)		64.03 (18.36)	

Table 4. The Relation of Measured Parameters in 24-h Blood Pressure Monitoring with the Studied Variables

	Min Sys Mean (SD)	*P*	Max Sys Mean (SD)	*P*	Min Dia Mean (SD)	*P*	Max Dia Mean (SD)	*P*
Gender								
Female	98.70 (25.41)	> .05	160.48 (33.24)	> .05	56.37 (15.91)	> .05	93.22 (29)	> .05
Male	103.92 (25.22)		160.44 (25.48)		58.92 (17.74)		92.92 (18.85)	
Dialysis Time								
Morning	98.24 (27.61)	> .05	158.21 (30.39)	> .05	55.55 (16.29)	> .05	90.07 (21.12)	> .05
Afternoon	104.62 (23.02)		162.38 (27.69)		59.76 (17.39)		95.59 (25.42)	
Severe HTN								
No	93.17 (19.17)	< .001	148.17 (20.04)	< .001	52.85 (13.18)	< .001	87.79 (17.55)	< .05
Yes	128.93 (23.26)		199.80 (12.23)		73.73 (18)		109.87 (31.91)	
Non-dipper								
No	96.09 (26.65)	< .05	152.29 (30.63)	< .05	55.68 (18.20)	> .05	92.12 (25.63)	> .05
Yes	108.24 (22.13)		170.03 (23.57)		60.34 (15.14)		94.14 (21.19)	

Table 5. Correlation Coefficient of FGF23 and 24-h Blood Pressure with Age, Dialysis Duration and Inter-dialytic Weight Gain

	FGF23	MAP	MEAN SYSTOLIC	MEAN DIASTOLIC	PULSE PRESSURE	Min sys	Max sys	Min Dia	Max Dia
Age									
Correlation Coefficient	0.078	-0.235	-0.128	-0.353**	0.101	-0.095	-0.229	-0.357**	-0.217
P	> .05	> .05	> .05	< .05	> .05	> .05	> .05	< .05	> .05
Dialysis Time									
Correlation Coefficient	0.197	-0.033	0.028	-0.148	0.224	-0.131	0.023	-0.173	-0.105
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
Inter-dialytic Weight Gain									
Correlation Coefficient	0.134	0.057	0.156	0.004	0.224	0.145	0.245	0.039	0.062
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
Phosporous									
Correlation Coefficient	0.343**	0.102	0.034	0.124	0.046	0.014	0.111	-0.016	0.160
P	< .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
Uric Acid									
Correlation Coefficient	-0.090	0.106	0.044	0.153	-0.130	0.132	0.099	0.146	0.084
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
iPTH									
Correlation Coefficient	0.197	0.143	0.123	0.118	0.109	0.088	0.175	0.258*	0.073
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	< .05	> .05
Kt/v									
Correlation Coefficient	0.203	-0.163	-0.169	-0.140	-0.059	-0.138	-0.085	-0.063	0.030
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
URR									
Correlation Coefficient	0.099	-0.156	-0.148	-0.146	-0.021	-0.078	-0.174	-0.055	-0.147
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
Calcium									
Correlation Coefficient	0.208	0.006	0.022	-0.048	0.033	-0.038	0.039	-0.154	-0.137
P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
Calcium x Phosporous									
Correlation Coefficient	0.413**	0.018	-0.030	0.030	0.012	-0.092	0.059	-0.136	0.091
P	< .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05

Table 6. Linear Correlation Coefficient of FGF23 with 24-h Blood Pressure with the Studied Patients

		MAP	MEAN SYSTOLIC	MEAN DIASTOLIC	PULSE PRESSURE	Min Sys	Max Sys	Min Dia	Max Dia
FGF23	Correlation Coefficient	-0.152	-0.204	-0.110	-0.084	-0.197	-0.148	-0.127	0.012
	P	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05

		Mean FGF23	*P*
Mean Systolic_cat	< 14 mmHg	475.00	> .05
	≥ 14 mmHg	452.50	
Mean Diastolic_cat	< 9 mmHg	440.00	> .05
	≥ 9 mmHg	716.00	

animal experiments.[21,22] Moreover, it is also helpful in maintaining mineralization of healthy bones and calcium-phosphorus metabolism.[23] In our study the vitamin D levels of 59 patients was 33.31 ± 20.21 and the median FGF23 level was 475. It is declared that the balance is disturbed in CKD patients. As kidney filtration function is significantly decreased in CKD patients, the serum FGF23 level can rise, leading to an increased secretion of phosphate, which in turn causes electrolyte disturbance in CKD patients. The disturbed electrolyte balance can lead to high blood pressure.[24] We found 23.8% of the ESRD patients had severe HTN. There was no correlation between FGF23 and 24 hours blood pressure. Previous studies also showed that high serum FGF23 levels had a certain correlation with the occurrence of angiocardiopathy, including ischemic heart disease, stroke, heart failure and atrial

fibrillation.[25,26] Unlike our study Li and colleagues reported that mean arterial pressure of long-stage CKD patients was significantly increased, and the increased level of blood pressure was positively correlated with the level of FGF23. It has been found that the role of FGF23 in promoting cardiovascular disease is essentially through the activation of renin-angiotensin-aldosterone system, which promotes the reabsorption of sodium in distal renal tubules, leading to high blood pressure, further causing cardiac hypertrophy and arrhythmia.[26] We observed that P and "calcium x phosphorous" had significant direct correlations with FGF23. Also, we noticed that increased level of iPTH was positively correlated with an increase in minimum diastolic pressure. It is stated that PTH has three mechanisms for controlling systolic and diastolic blood pressure, including cardiomyocyte effects and left ventricular hypertrophy on pacemaker cells and continuously increasing heart rate and effect on intracellular calcium which plays its role with the affection of the vascular endothelium and their smooth muscle wall.[27,28] PTH is related to inflammatory response and production of leptin, fibrinogen, CRP and IL-6 that would change the blood pressure.[29] Overall we conclude that FGF23 had no significant correlation with the underlying and clinical characteristics but phosphorous and "calcium x phosphorous" levels, which still manifests the important role of FGF23 in hemostatis of phosphorous. This factor will be increased progressively in CKD patients, as it is obvious that the GFR would be significantly decreased in the ESRD patients. This marker raises the notice to the risk of cardiovascular disorders too. Therefore, in effective therapeutic design, we need to know the relationship between phosphate, FGF23 and cardiovascular disease. The precise planning of healthcare sector executives on targeted phosphate-based therapy can be applied. Furthermore, serum levels of phosphate and FGF23 can target general health education policies for patients and pharmaceutical agents. Finally the positive relation between PTH levels and the minimum diastolic blood pressure as well as higher systolic blood pressure in nondipper patients with HTN attracts our notice to the non-dipper status, which is mostly considered as a risk factor for the development of nephropathy. Taking into account that high blood pressure in the population is the second most common cause of ESRD disease, and as the relationship between kidney and hypertension is obvious, it seems that poor kidney function and non dipper status may strongly interact with each other meanwhile may lead to kidney failure, thus we suggest that controlling blood pressure and examining it with ABPM can greatly help patients to progress and has health benefits. It would be better to evaluate the 24 hours blood pressure and FGF23 after HD for each patient. Also, we did not access to the clinical records of all patients. It seems that the high incidence of chronic renal failure is due to blood pressure and diabetes which has dormant nature. Therefore, through enhancing the health level and awareness of people in the community and changing the lifestyle of patients with diabetes and blood pressure, the complications of these disorders as well as renal insufficiency would be controlled. Screening of high-risk groups for the diagnosis of hypertension and diabetes is important for early diagnosis of patients and provide first round care programs to prevent from irreversible renal damages. It is also recommended that similar studies be conducted at a wider and preferably provincial level in order to access the maximum information. Besides, it is noteworthy that the ability of this study to eliminate the effects of all the distorters was weak and the results can be used as a hypothesis and preliminary study for the future studies.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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