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## Impact of fibroblast growth factor-23 on blood pressure and pulse pressure in hemodialysis patients; a multicenter study

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### ABSTRACT

**Introduction:** Hypertension seems to be a major problem in dialysis patients. Fibroblast growth factor-23 (FGF-23) appears to be a risk factor for mortality in patients with end-stage renal disease (ESRD).

**Objectives:** This study aims to investigate FGF-23 and its association with blood pressure and pulse pressure among hemodialysis patients.

**Patients and Methods:** This cross-sectional multicenter study was performed on 135 patients aged 18 years and over with ESRD treated with hemodialysis. Systolic and diastolic blood pressure of all patients was measured. FGF-23, uric acid, Na and K were measured using blood test and fasting. We used univariate and multivariate linear and non-linear regression.

**Results:** The mean age of patients was 56.45±13.64 years. Around 60% of patients were male. The mean and median FGF-23 in patients was 855.07±43.33 pg/mL and 762.6 pg/mL (IQR=456.6-1430.3) respectively. After adjustment for age, gender, dialysis time, uric acid, Na, K and kt/V, FGF-23 had quadratic association with pulse pressure. We found, each 10-unit (pg/mL) increase in FGF-23 was significantly associated with 0.50 mm Hg decrease in minimum pulse pressure (P=0.002) and 0.42 mm Hg decrease in mean pulse pressure (P=0.009).

**Conclusions:** FGF23 had a significant association with dialysis vintage and a significant reverse association with minimum and mean pulse pressure.

### Implication for health policy/practice/research/medical education:

In this study we aimed to assess correlation between fibroblast growth factor-23 and pulse pressure and blood pressure in hemodialysis patients. FGF-23 had a significant reverse association with minimum pulse pressure and mean pulse pressure.

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### 1. Background

More than 1 million people in the world yearly die from end-stage renal disease (ESRD) (1). The number of patients also increases by 6% annually. Cardiovascular complications are the most common cause of mortality in dialysis patients, and hypertension is one of the most important risk factors of these complications (2,3). Hypertension is highly prevalent in patients with ESRD and it is found in 50%-90% of hemodialysis patients (4). Evidences suggest that hypertension is present in 69% of adults with incident myocardial infarction and 74% diagnosed with incident heart failure (5,6). According to a cohort study on

2535 hemodialysis patients in the United States, 86% of hemodialysis patients have had hypertension, which, despite the use of blood pressure medications in 76% of patients, only 30% had controlled blood pressure (7). Development of hypertension occurs in conjunction with the inability of the renal system to maintain mineral homeostasis (6). Therefore, hypertension seems to be a major problem in dialysis patients whose control is necessary to reduce the mortality of patients.

Based on the study by Fyfe-Johnson et al, high levels ( $\geq 60.6$  pg/mL) of fibroblast growth factor-23 (FGF-23) are associated with a little higher risk of hypertension in the

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normal people, independent of kidney function. Fibroblast growth factor-23 serum levels increase with chronic kidney disease (CKD) progression. Extremely high plasma levels of FGF-23 are often found in chronic dialysis patients (8). Studies show that elevated FGF-23 also is an independent risk factor for death in dialysis patients and CKD stages 2-4 (9,10).

Pulse pressure, as a reflection of arterial stiffness, may be an independent risk factor for progression of CKD and is the best predictor of cardiovascular disease and mortality from age 60 years and beyond (11).

## 2. Objectives

While FGF-23 appears to be a risk factor for mortality in patients with renal disease and CKD, it is important to investigate the mechanism of its action and its association with various variables. Therefore, this study aims to investigate FGF-23 and its association with blood pressure and pulse pressure among hemodialysis patients.

## 3. Patients and Methods

### 3.1. Data collection

This cross-sectional multicenter study was performed on 135 patients aged 18 years and over. Those were on maintenance hemodialysis from hemodialysis center of Imam Khomeini Hospital in Tehran province, and hemodialysis center of Razi hospital in Rasht. Some of the necessary data regarding the patient's age, gender and dialysis time were extracted from the records of patients using a data collection form.

### 3.2. Blood pressure and pulse pressure measurement in patients

Systolic and diastolic blood pressure of all patients was measured using Tiba medical Ambulo 2400 ambulatory blood pressure monitoring (ABPM) (made in the United States). The patient wore the device around his/her arm after the end of dialysis for a period of 24 hours. The minimum (min), mean and maximum (max) of diastolic and systolic blood pressure and also pulse pressure were measured. Pulse pressure was calculated by differencing diastolic from systolic blood pressure.

### 3.3. Biochemical markers measurement in patients

Uric acid, sodium (Na) and potassium (K) were measured using blood test and fasting. In addition,  $kt/V$  was calculated in all patients.

### 3.4. Measure of fibroblast growth factor 23

FGF-23 was measured by ELISA kit (pg/mL) from BIOTECH Company made in China before the beginning of dialysis session.

### 3.5. Ethical issues

Study related data was delivered to subjects and informed consent was provided before study. The research followed the tenets of the Declaration of Helsinki. This study was conducted as the nephrology fellowship thesis of Mahdih

Jamshidi (proposal code: 9311402003). The Ethics Committee of Tehran University Medical Science approved this study (ethical No. 29518).

### 3.6. Statistical analysis

For description of continuous data first of all normality assumption was assessed using the Kolmogorov-Smirnov test. If they had a normal distribution, mean and standard deviation were presented for them otherwise median and interquartile range were presented for them. For comparison of continuous variable among males and females, we used T-test for normal variables and Mann-Whitney U test for non-normal distributions.

We used univariate and multivariate linear and non-linear regression to investigate the association between FGF-23 and blood pressure. To better report and interpret the results, the FGF-23 was divided into 10. Hence each unit change in FGF-23 equals 10 pg/mL. Diastolic blood pressure (min, mean and max), systolic blood pressure (min, mean and max) and pulse pressure (minimum, mean and max) were modeled in separate models against FGF-23, dialysis time, age, gender, uric acid, Na, K and  $kt/V$ .

For systolic blood pressure (minimum, mean and max) because the residuals of the models were normal, we did not use any outcome transformation. For diastolic blood pressure (minimum, mean and max) and pulse pressure (minimum, mean and max) because residuals of the model did not show normal distribution after different transformations, to get the correct p-value and confident interval we used 300 bootstrap sampling. In addition, comparing the R-square indices of linear and non-linear models and also checking the scatter plots there was a quadratic relation between pulse pressure and FGF-23 (min, mean and max). We used `lincom` command in Stata software to evaluate the combined effect of linear and quadratic terms on the outcome in non-linear models. Data were analyzed by the Stata software (version 12). For all statistical tests,  $P < 0.05$  was considered statistically significant.

## 4. Results

Using the Kolmogorov-Smirnov test, maximum systolic blood pressure, maximum pulse pressure and also Na, K and uric acid had normal distribution hence mean and the standard deviation was presented for them. Other variables had non-normal distribution, thus median and interquartile range have been assessed for them.

Totally 135 dialysis patients were studied. The mean age of the patients was  $56.45 \pm 13.64$  years ( $54.28 \pm 14.24$  in male and  $59.72 \pm 12.11$  in female). Around 60% (81) of patients were male (sex ratio; 1.5 male/female). The median dialysis time in patients was 7 (IQR = 5-10) months. In addition, the mean and median FGF-23 in patients was  $855.07 \pm 43.33$  and 762.6 (IQR = 456.6-1430.3) pg/mL, respectively. The distribution of max systolic, max pulse pressure, Na, K and uric acid among males and females were calculated by *t* test. The distribution of dialysis time, FGF-23, min/mean

systolic blood pressure, min/mean/max diastolic blood pressure, min/mean pulse pressure and kt/V among males and females were calculated by Mann-Whitney U test.

The mean age, dialysis time, kt/V, FGF-23, systolic blood pressure, diastolic blood pressure, pulse pressure and biochemical markers did not show any significant difference between two sexes (*P*: NS). Description of study variables is presented in Table 1. There was a statistically significant association between FGF-23 and dialysis time adjusted for sex and age. For each month increase in duration of dialysis time, the concentration of FGF-23 increase to the amount of 58.66 pg/mL (*P*=0.001).

**4.1. Association of systolic blood pressure, diastolic blood pressure and pulse pressure with FGF-23**

As Table 2 shows, in univariate regression, no significant association between systolic (min, mean and max) and diastolic (min, mean and max) blood pressure with FGF-

23 was detected (*P*>0.05). Figures 1 to 3 shows scatter diagram, linear fit and also a lowess graph for locally weighted regression of pulse pressure (min, mean and max) versus FGF-23 respectively. As the graphs depict a nonlinear relation between FGF-23 and pulse pressure was seen.

After adjustment for age, gender, dialysis time, uric acid, Na, K and kt/V, FGF-23 had quadratic association with pulse pressure. We found, each 10-unit (pg/mL) elevation in FGF-23 was significantly related with 0.50 mm Hg decrease in min pulse pressure (*P*=0.002) and 0.42 mm Hg decrease in mean pulse pressure (*P*=0.009) and non-significantly associated with 0.29 mm Hg decrease in max pulse pressure (*P*=0.07), respectively (Table 2). The quadratic coefficients for the three models were 0.0024 (*P*=0.004), 0.0023 (*P*=0.01), 0.0016 (*P*=0.08) respectively.

**5. Discussion**

In this study, we aimed to investigate FGF-23 plasma

**Table 1.** Distribution of FGF-23, systolic, diastolic, pulse blood pressure and biochemical markers by sex among hemodialysis patients

Variables	Male (n=81)	Female (n=54)	Total (n=135)	P value*
	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	
Dialysis time (mon)	7 (5-10)	8 (4-11)	7 (5-10)	0.64
FGF-23 (pg/mL)	701.5 (423.3-1430.3)	822.5 (475-1424)	762.6 (456.6-1430.3)	0.45
Min systolic BP (mm Hg)	96 (88-116)	94.5 (81-117)	96 (84-117)	0.40
Mean systolic BP (mm Hg)	124.5 (116-142)	123.1 (110-144)	124.3 (112.3-144)	0.66
Min diastolic BP (mm Hg)	59 (50-65)	55 (48-66)	57 (49-65)	0.61
Mean diastolic BP (mm Hg)	74.7 (69.4-82.9)	74.5 (66-81.9)	74.7 (67.7-82.9)	0.43
Max diastolic BP (mm Hg)	94 (87-106)	92 (81-112)	94 (84-109)	0.72
Min pulse pressure (mm Hg)	34 (25-62)	40 (26-64)	34 (25-63)	0.94
Mean pulse pressure (mm Hg)	54.2 (43.2-76)	62.8 (43.4-78)	58.4 (43.2-77)	0.56
kt/V	1.2 (1.14-1.24)	1.19 (1.18-1.22)	1.2 (1.15-1.23)	0.65
	Mean (SD)	Mean (SD)	Mean (SD)	P value**
Max systolic BP (mm Hg)	157.01 (24.3)	158.7 (29.4)	157.7 (26.3)	0.71
Max pulse pressure (mm Hg)	82.5 (20.4)	85.5 (21.4)	83.7 (20.8)	0.41
Na (meq/L)	139.22 (3.91)	139.05 (4.63)	139.15 (4.2)	0.82
K (meq/L)	4.58 (0.63)	4.77 (0.84)	4.66 (0.72)	0.15
Uric acid (mg/dL)	6.5 (1.33)	6.49 (1.32)	6.50 (1.32)	0.94

BP=Blood Pressure, Q1-Q3=interquartile range.

\* Based on Mann-Whitney test; \*\* Based on *t* test.

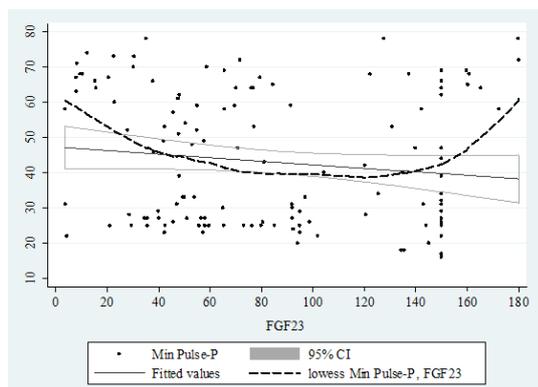
**Table 2.** The univariate and multivariate association of systolic, diastolic and pulse blood pressure with FGF-23 among hemodialysis patients

Dependent variables	Univariate			Multivariate				
	β	SE	P value	β	SE	95% CI	P value	R <sup>2</sup>
Min systolic BP (mm Hg)	-0.04	0.03	0.24	-0.06 <sup>a</sup>	0.04	-0.14, 0.01	0.11	0.09
Mean systolic BP (mm Hg)	-0.03	0.03	0.44	-0.03 <sup>a</sup>	0.04	-0.11, 0.05	0.46	0.08
Max systolic BP (mm Hg)	-0.06	0.04	0.16	-0.05 <sup>a</sup>	0.04	-0.15, 0.03	0.22	0.07
Min diastolic-BP (mm Hg)	-0.03	0.02	0.10	-0.03 <sup>a</sup>	0.02	-0.07, 0.01	0.20	0.11
Mean diastolic BP (mm Hg)	-0.02	0.02	0.24	-0.01 <sup>a</sup>	0.01	-0.05, 0.02	0.38	0.19
Max diastolic BP (mm Hg)	-0.01	0.03	0.60	-0.003 <sup>a</sup>	0.03	-0.05, 0.06	0.11	0.15
Min pulse pressure (mm Hg)	-0.05	0.03	0.11	-0.50 <sup>b</sup>	0.16	-0.81, -0.18	0.002	0.25
Mean pulse pressure (mm Hg)	0.009	0.03	0.77	-0.41 <sup>b</sup>	0.15	-0.73, -0.10	0.009	0.11
Max pulse pressure (mm Hg)	-0.003	0.03	0.91	-0.29 <sup>b</sup>	0.16	-0.62, 0.03	0.07	0.04

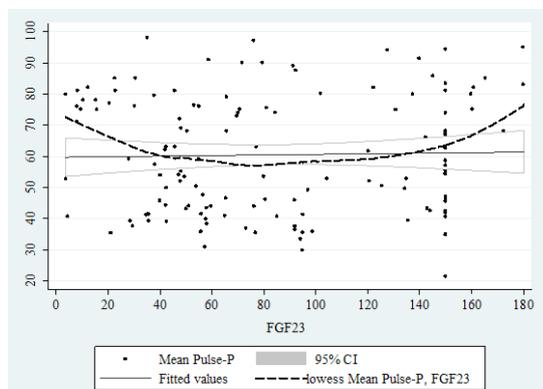
β, regression coefficient; SE=standard error; R2, coefficient of determination.

<sup>a</sup> Based on linear regression and adjusted for: age, sex, dialysis time, Uric Acid, Na, K and kt/V.

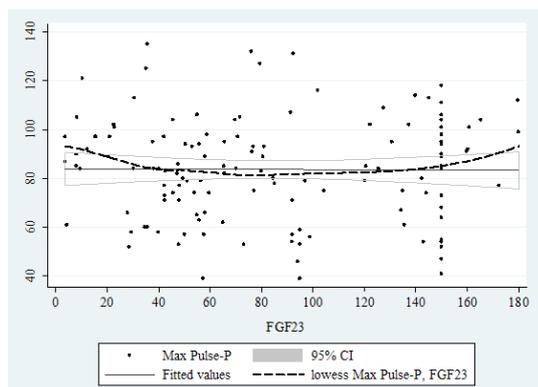
<sup>b</sup> Based on quadratic regression and adjusted for: age, sex, dialysis time, Uric Acid, Na, K and kt/V.



**Figure 1.** Lowess curve for linear and non-linear relationship between minimum pulse pressure and FGF-23.



**Figure 2.** Lowess curve for linear and non-linear relationship between mean pulse pressure and FGF-23.



**Figure 3.** Lowess curve for linear and non-linear relationship between maximum pulse pressure and FGF-23.

concentration and its association with blood pressure and pulse pressure among patients on maintenance hemodialysis. The mean age of our patients was  $56.45 \pm 13.64$  years and the median dialysis time in patients was 7 (IQR=5-10) months. In addition, the mean and median FGF-23 was  $855.07 \pm 43.33$  and  $762.6$  (IQR=456.6-1430.3) pg/mL, respectively.

In a study by Jean et al, the mean serum FGF-23

level was  $7060 \pm 1350$  RU/mL (median = 2740 RU/mL; IQR = 1192–8667 RU/mL) and linear regressions showed a significant correlation between log FGF-23 and age (mean age was  $66.6 \pm 14$  years and the duration of dialysis was  $68 \pm 75$  months) (12). In the study by Negishi et al, serum FGF-23 levels in dialysis patients were  $1171 \pm 553$  pg/mL. Mean dialysis duration was  $5.8 \pm 5.0$  years, confirming most of patients were on the long-term disease. They found the concentration of FGF-23 increases substantially with duration of disease. Recent results showed that the serum FGF-23 levels in dialysis patients were significantly higher than normal population ( $1171 \pm 553$  versus  $48 \pm 16$  pg/mL) (13). Nasrallah et al also reported that FGF-23 levels were more elevated in hemodialysis patients ( $4681.3 \pm 3906.1$  pg/mL) compared to controls ( $98.2 \pm 51.9$  pg/mL) (14). In the study of Kirkpantur et al, serum FGF-23 levels in hemodialysis patients were more than normal population (15). In addition, Hsu et al, in a population-based study in individuals who were referred for routine tests and no cardiovascular or renal disease (mean age of enrolled subjects was  $62 \pm 10$  years), detected the mean serum FGF-23 concentration was  $40 \pm 18$  pg/mL (median = 38 pg/mL; IQR = 30–46 pg/mL) (16). Therefore, all of the studies indicating a higher level of FGF-23 in renal disease and CKD patients.

In our study, no significant association between systolic and diastolic blood pressure with FGF-23 was seen. Contrary to our study results, Fragono et al examined the relationship of FGF-23 and cardiovascular disease in type 2 diabetes patients with diabetic nephropathy (stages 2–4) and with stable clinical status. Individuals with pulse pressure (PP)  $\geq 50$  mm Hg had higher levels of FGF-23. There was no difference between the two groups of patients regarding age of patients and duration of the disease (17). Besides, in the study of Hsu et al, patients with higher FGF-23 had higher systolic blood pressure, serum 25-OH vitamin D and phosphorus levels. They also found patients with higher FGF-23 had higher urine albumin to creatinine ratio (ACR) and age. Patients with more elevated FGF-23 also had more elevated pulse pressure, while this association remained significant after adjustment for demographic factors. Based on their study results, the relationship between FGF-23 and pulse pressure showed a positive correlation after age and sex adjustment (16). Our findings revealed that FGF-23 had a quadratic association with pulse pressure. The increase in FGF-23 was significantly associated with decrease in min and mean pulse pressure and non-significantly associated with decrease in max pulse pressure after adjustment for different variables. This also may be because of shorter duration of dialysis in our population and lower concentration of FGF-23 in our patients. We also found a quadratic (nonlinear) relationship between FGF-23 and minimum and mean pulse pressure (Figures 1 and 2).

Arulkumaran et al, in a study on 329 patients with CKD (mean estimated glomerular filtration rate of 39

mL/min/1.73 m<sup>2</sup>), showed a 10 mmHg higher pulse pressure was significantly related to a 10 percent greater relative risk of kidney function decline after approximately six months of follow-up (18). Effect of patient's drugs like antihypertensive, and also metabolic syndrome and diabetes, was not assessed in our study, however all of them can affect pulse pressure.

Limited data also suggest that antihypertensive agents differ in their effects on pulse pressure (19). Cushman et al, in a retrospective analysis including 1292 men with a diastolic blood pressure of 95 to 109 mm Hg (after one year of treatment), found that hydrochlorothiazide reduced pulse pressure by 8.6 mm Hg, clonidine by 6.3 mm Hg, diltiazem by 5.5 mm Hg, prazosin by 5 mm Hg, captopril by 4.1 mm Hg, and atenolol by 4.1 mm Hg (20). In a sub-study of the ASCOT trial, scientists calculate pulse pressure and central blood pressures of participants. The results suggested that atenolol had less improvement in pulse pressure, despite similar blood pressure reduction, than a calcium channel blocker regimen (21). Mulè et al showed increasing evidence suggests that patients with metabolic syndrome have an increased pulse pressure due to stiffer vessels (2).

Our study has some limitations. First, our study has a cross-sectional design and therefore any relationship cannot guarantee the causal association. Second, the sample size of the study was not very high, which may be a reason for not being significant in some of the results.

There are two assays for FGF-23 measuring. One assay detects only full-length/intact FGF-23. The second, the carboxy-terminal assay finds both intact and carboxy-terminal FGF-23. Carboxy-terminal FGF-23 has found excellent precision with coefficients of variation (CV) ranging from 4% to 10.5%, whereas the CVs for intact FGF-23 were not excellent (6%–37.5%). Moreover, the carboxy-terminal FGF-23 assay showed to associate better with progression of CKD based on plasma creatinine and estimated glomerular filtration rate (eGFR) (22). In our study, for measuring FGF-23, a kit based on detecting full-length/intact FGF-23 was used.

## 6. Conclusions

Fibroblast growth factor-23 had a significant association with dialysis vintage in hemodialysis patients. FGF-23 had a significant reverse association with minimum pulse pressure and mean pulse pressure.

## Limitations of study

This is a pilot study that requires more investigation by larger studies.

## Authors' contribution

FM and ER: Idea and writing the manuscript. MJ: Literature Review. MN: critique and thought. AA; statistical analysis. All authors read and approved the final manuscript.

## Conflicts of interest

All authors declare that they have no conflict of interest. Moreover, the funding agency did not play any role in the planning, conduct, and reporting or in the decision to submit the paper for publication.

## Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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