Relation Between Fibroblast Growth Factor-23 and Red Cell Distribution Width in Patients with End-Stage Renal Disease Undergoing Hemodialysis

Elham Ramezanzade,[1] Masoud Khosravi,[2] Ali Monfared,[1]
Seyed Hossein Mirpour Hassankiadeh,[1] Masoomeh Namdar[1]

Original Paper

[1]Razi Clinical Research Development Unit, Razi hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[2]Urology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

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Introduction. Fibroblast growth factor-23 (FGF23) is responsible for regulating the metabolism of phosphorus and vitamin D by affecting the kidneys and parathyroid gland. Phosphate is present in the 2, 3-diphosphoglycerate (2,3DPG) ester composition, which can shift the O2-Hb dissociation curve to the right. Therefore, we hypothesized that maybe there is an association between red cell distribution width (RDW) and FGF23 level. The aim of this study was to investigate the relationship between iFGF23 and RDW in patients with end-stage renal disease undergoing hemodialysis.
Methods. This cross-sectional study was performed on 254 end-stage renal diseases (ESRD) patients undergoing hemodialysis who were admitted to Rasht Razi Hospital Hemodialysis Center, in 2017. We used Shapiro-Wilk, Spearman correlation coefficient, Mann– Whitney U-test, and Multiple Linear Regression Analysis. All statistical analyses were performed by SPSS software.
Results. The median age of patients was 60 years (IQR: 49 to 69). The mean and median iFGF23 concentration in patients were 59.5 ± 14.6 and 62 (IQR: 49 to 69) pg/mL, respectively. According to spearman test, iFGF23 had a statistically significant association with age (r = 0.856, $P < 0.001$), MCV (r = 0.202, $P < .001$), phosphorus (r = -0.176, $P < .05$), weight difference before and after dialysis (r = -0.264, $P < .05$), and Vitamin D (r = -0.201, $P < .05$). Also in multiple linear regression analysis, the variables of RDW, IDWG, iPTH, MCH, DM, HTN, Age, and CRP were considered as predictors of iFGF23 .
Conclusion. RDW was identified as one of the predictors of iFGF23 changes. Perhaps in the future, more value will be given to the role of RDW in dialysis patients.

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INTRODUCTION

End-stage Renal Disease (ESRD) is a destructive problem that lies in the medical, social, and economic areas requiring health care and careful follow-up. Also, because of high morbidity and mortality as well as economic and social side effects, it is a fundamental health problem in the community.[1] People with kidney disease, which are undergoing hemodialysis treatment, suffer from numerous pathological processes along with kidney disease, many of which are related to each other considering their mechanism.[2]

There are two groups of risk factors in ESRD including traditional and nontraditional. Some of the nontraditional significant risk factors are anemia, red cell distribution width (RDW),[3] as well as mineral metabolism markers, particularly fibroblast growth factor-23(FGF23).[4]

FGF23 is a phosphaturic hormone produced by osteocytes and remarkably contributes to systemic phosphate hemostasis and vitamin D metabolism.[5] In chronic kidney patients, it is a sensitive biomarker for impaired renal phosphate regulation. Its levels are increased in the early stages of renal dysfunction to increase renal phosphorus excretion.[6] Increased FGF23 levels in ESRD patients due to Klotho deficiency and other disorders such as elevated PTH, and decreased vitamin D levels are associated with increased mortality and are inversely related to glomerular filtration rate.[7] FGF23 itself is also directly associated with cardiovascular complications such as LVH. In the study, Gutierrez *et al.* confirmed that with reduction of glomerular filtration rate under 60 mm/min, FGF23 levels increase; this increase happens before other symptoms related to the non - natural state of minerals are caused and is independent of the amount of serum phosphate changes. The results indicate the relationship between higher level of FGF23 and cardiovascular calcification and mortality in dialysis patients.[8]

RDW is a strong indicator of adverse clinical outcomes in patients with acute and chronic heart failure,[9-12] coronary artery disease,[13] and acute kidney injury.[14] It is usually used to diagnose anemia, especially iron deficiency anemia. In addition, RDW is a prognostic marker for cardiovascular disease (CV) as well as the rate of death in different diseases such as diabetes, heart failure, stroke, and coronary artery disease, and in groups based on the general population.[15] To obtain RDW, as a quantitative marker of variability of erythrocyte size, the standard deviation of the erythrocyte size is divided by Mean Corpuscular Volume (MCV). Recently, it has been shown that RDW indicates well-documented malnutrition and inflammation, which raises the risk of cardiovascular complications and mortality in dialysis patients.[16]

Phosphate is present in ester compound of 2, 3-diphosphoglycerate (2,3DPG), which can shift the O2-Hb dissociation curve to the right, so oxygen is more easily separated from hemoglobin and delivered to the hypoxic tissues. Therefore chronic anemia becomes somewhat tolerable in ESRD patients. On the other hand, FGF23 regulates phosphate level which is an important component of 2,3 DPG structure.[17] So we hypothesized that maybe there is an association between Red cell Distribution Width and FGF23 level. Therefore we decided to evaluate is there any relationship between RDW as a convenient, available and inexpensive factor with this biomarker. Perhaps in the future, more value will be given to the role of RDW in dialysis patients.

MATERIALS AND METHODS

Data Collection

This cross-sectional study was conducted on 254 ESRD patients under hemodialysis treatment. The sampling method was a census so that all ESRD patients undergoing hemodialysis in Razi hospital in Rasht city, Iran, in the year 2017 were studied. The study design was approved by the ethics committee of the Guilan University of Medical Sciences, Iran (No. IR.GUMS.REC.1396.123). The study was conducted according to the criteria set by the declaration of Helsinki and each subject signed informed consent before participating in the study.

The exclusion criteria: 1) Patients with Decompensated Heart Failure, 2) Active enteric bleeding, 3) Acute liver failure, 4) Myocardial Infarction, 5) Stroke, 6) Patients with malignant hematological diseases, and 7) Patients undergoing dialysis for less than three months.

Demographic information about the patient's age, sex, BMI, history of smoking, history of hypertension, diabetes, and duration of dialysis were extracted from patients' records using the relevant form.

Measurement of Parathyroid Hormone (PTH), Mineral Factors (P, Ca), and 25-Hydroxyvitamin D in Patients

Ca and phosphorus (P) were measured in each patient's blood sample before dialysis using auditing kits; PTH with Siemens kits, China; and 25-hydroxyvitamin D was determined using the ELFA method (enzyme-linked fluorescent assay).

Measurement Biochemical Markers in Patients

RDW, C-reactive protein, Hemoglobin,

Hematocrit, Platelet, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin Concentration, Transferring Saturation, and Ferritin were measured in routine tests of patients.

Measurement of Fibroblast Growth Factor 23

iFGF23 was measured by ELISA kits before the beginning of dialysis sessions.

Statistical Analysis

First, the normality assumption of the continuous variable was evaluated using the Shapiro-Wilk test. If the data had a normal distribution, the mean ± standard deviation (SD) was reported; otherwise medians and interquartile ranges were reported. In order to determine the correlation between iFGF23 and demographic, clinical, and laboratory variables, the Spearman non-parametric correlation coefficient was used due to the non-normality of distribution of variables. Mann-Whitney U-test was applied to compare iFGF23 based on individual variables and underlying diseases. Multiple linear regression model was also utilized to determine the relationship of RDW predictor with iFGF23 by adjusting the effect of confounding variables.

Missing variables were deleted pairwise method. To analyze the data, SPSS (version 26) was used. $P < .05$ was considered statistically significant in all statistical tests.

RESULTS

Demographic, clinical, and laboratory data of 254 patients are summarized in Table 1.

The median age was 60 years (IQR: 49 to 69), and 57.9 % were male. Only 10.6 % of the study patients were smokers, and the dialysis time was 47.2 ± 51 months. 40.9% of the people in the study had diabetes, and 73.8% had hypertension. The mean of the Kt/V index was 1.3 ± 0.36, the minimum amount was 0.18, while the maximum amount was 2.46. The mean difference in weight between the two sessions of dialysis was 2.22 ± 1 kg. In the body mass index (BMI) analysis, most samples (50.84 %) were in the normal range, 27.31 % were overweight, 15.13 % were in class 1 obesity, and 4.2% in the range of class 2 obesity. The mean RDW value was 15.6 ± 2.3%. Furthermore, the mean and median of iFGF23 in patients were 59.5 ± 14.6 and 62 (IQR: 49 to 69) pg/mL; respectively (Table 1).

Table 1. Demographic, Clinical, and Biochemical Characteristics of Patients

Characteristics	All patients (n = 254)	Reference Values
Age, y	60 (49 to 69)	
Male Sex, n (%)	147 (57.9)	
Smoking (%)	10.6	
Dialysis time, mo	47.2 ± 51	
IDWG	2 (1.5 to 2)	
Kt/V	1.3 ± 0.36	
Hypertension (%)	73.8	
Diabetes Mellitus (%)	40.9	
Hemoglobin, g/dL	10.9 ± 1.8	12.5 to 16.1 (f)
		13.7 to 17.0 (m)
Hematocrit, L/L	0.35 ± 0.05	0.36 to 0.48 (f)
		0.40 to 0.52 (m)
MCV, /μm^3	90 (85 to 95)	80 to 102
MCH	28.7 (26.5 to 30.4)	27 to 33
MCHC	31 (30 to 32)	33 to 35
PLT, × 1000/mL	195 (154 to 254)	(150 to 450)
Ferritin, ng/mL	242 (42 to 506)	30 to 300
TSAT (%)	24.8 ± 7.3	< 45
CRP, mg/L	4 (1 to 11)	0 to 10
RDW (%)	15.6 ± 2.2	10.4 to 13.0
iFGF23 , pg/ml	62 (50 to 70)	20 to 50
iPTH, pg/mL	319 (217 to 417)	10 to 65
Ca, mg/dL	8.8 (8.3 to 9.5)	8.6 to 10.2
Phosphorus, mg/dL	5.7 ± 1.7	2.8 to 4.5 (Adults)
Phosphorus, mg/dL		4.0 to 7.0 (Children)
Vit. D, ng/mL	14 (10 to 19)	20 to 40

The Mann - Whitney U test showed that the amount of iFGF23 in the subgroup of sex ($P < .05$), diabetes ($P = .05$), and hypertension ($P < .05$) variables was statically significant, as the mean and median of iFGF23 in women undergoing dialysis were more significant than men. Also, the mean and median of iFGF23 in diabetic patients and patients with hypertension were more significant than those without diabetes and hypertension (Table 2).

According to the Spearman test, iFGF23 had a statically significant relation with age ($P < .001$, r = 0.856), MCV ($P < .05$, r = 0.202), phosphorus level ($P < .05$, r = -0.176), the weight difference before and after dialysis ($P < .05$, r = -0.265), and Vit. D ($P < .05$, r = -0.201), as it had a reverse relation with the weight difference before and after dialysis and phosphorus level but had a direct relation with

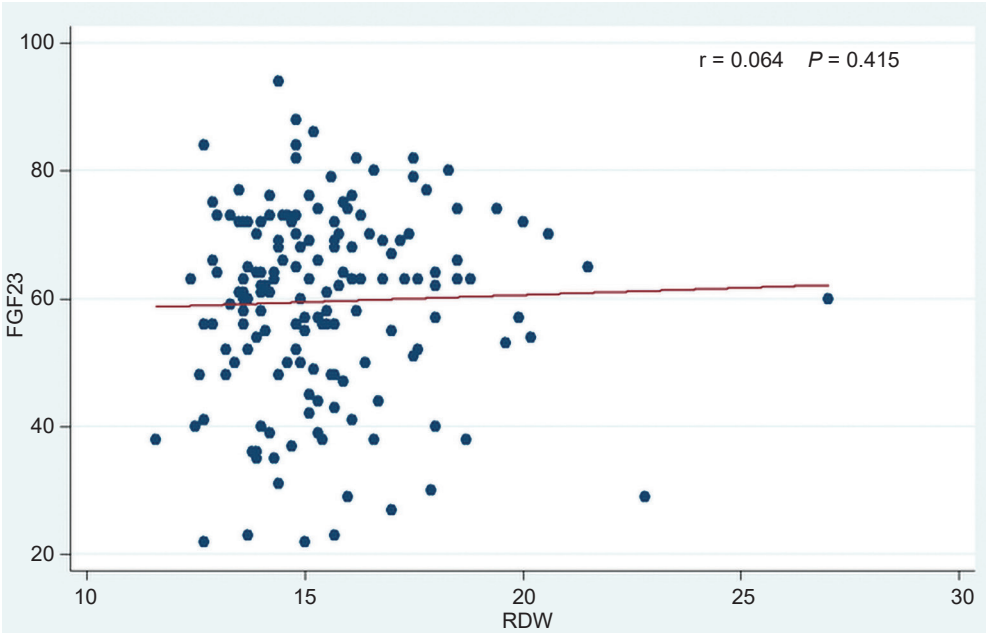
Table 2. Comparison of iFGF23 in Terms of Individual Variables and Underlying Diseases

Variables	iFGF23				*P*
	n	Mean	SD	Median	
Sex					
Female	107	61.91	14.21	65.00	< .05
Male	147	57.87	14.74	60.00	
Smoking					
Yes	27	55.42	11.63	56.00	> .05
No	227	59.93	14.90	63.00	
Diabetes Mellitus					
Yes	105	62.26	11.28	63.00	0.05
No	149	56.57	16.34	60.00	
Hypertension					
Yes	187	60.74	13.98	63.00	< .05
No	67	54.51	15.47	59.00	
BMI					
Underweight	6	73.20	12.52	66.00	> .05
Normal	121	58.01	14.21	60.00	
Overweight	65	60.33	13.96	63.00	
First-degree Obesity	36	63.48	13.58	63.00	
Second-degree Obesity	10	51.00	19.25	48.00	

age and MCV.

Figure shows the relation between iFGF23 and RDW based on the Spearman correlation coefficient. According to this coefficient (r = 0.064, $P > .05$), this correlation is not statically significant.

Multiple linear regression by backward LR method was used to investigate the relationship between iFGF23 and RDW with demographic variables, underlying diseases and blood parameters. Based on the results of Table 3, the variables RDW, IDWG (Interdialytic weight gain), iPTH, MCH, DM, HTN, and CRP were identified as predictors correlated with iFGF23 . As a result, after adjusting the effect of confounding variables (individual variables, blood parameters, and underlying diseases), there was a direct and meaningful relation between iFGF23 and RDW.



Relationship Between iFGF23 and RDW Based on Spearman Coefficient

Table 3. Multiple Linear Regression Model of the Association Between iFGF23 and RDW Adjusted for Demographic Variables, Underlying Diseases, and Blood Parameters[a,b]

Predictors	Unstandardized β	Standard Error	95% CI	*P*
RDW	0.711	0.283	0.151 to 1.271	< .05
IDWG	-2.147	0.580	-3.296 to -0.998	< .001
Hypertension	-3.428	1.365	-6.134 to -0.722	< .05
Diabetes Mellitus	-4.117	1.237	-6.569 to -1.665	< .01
MCH	0.542	0.187	0.171 to 0.913	< .05
CRP	0.129	0.048	0.034 to 0.225	< .05
iPTH	0.009	0.003	0.003 to 0.014	< .05
Age	0.767	0.042	0.684 to 0.850	< .001

[a]β, regression coefficient; CI, confidence interval.
[b]Dependent Variable: IFGF23

DISCUSSION

In this study, 254 ESRD patients were studied in the year 2017 at the center of dialysis in Guilan province, and their iFGF23 and serum RDW levels, demographic information, and laboratory markers were measured.

The current study, as its main finding, showed that iFGF23 and RDW were related in patients with ESRD after controlling potential confounding factors. In this research, the number of men present in the study (147 patient) was higher than women (107 patient), as presented by the gender distribution, which is compatible with other studies;[15, 18] on the other hand, iFGF23 in women undergoing dialysis showed higher values than men undergoing the same procedure which is similar to a study conducted by Joachim *et al.* (2011) to investigate the relationship between FGF23, sex and estrogen therapy.[19] The minimum and maximum dialysis time were three and 276 months, respectively. A significant correlation between the dialysis time and IFGF23 was not observed.[5, 15] The duration of dialysis in our patients was longer on a global scale, which could be due to the long waiting time for kidney transplantation or comorbidities that make them not suitable for transplantation, late referral for kidney transplantation well as economic issues. Considering underlying diseases, 41.6% of the studied samples had DM and 73.8% had HTN. People with DM or HTN had a higher mean and median iFGF23 than people without either of them. In the study of Van Breda *et al.*, 36.5 % of the study population was affected with DM and 78.8 % with HTN.[19] In the study of Sugimoto *et al.*, 33.7 % of people had DM, and there was not a significant relation between DM and FGF23.[5] Fayed *et al.* (2017), having reviewed the link between FGF23 and insulin resistance, referred to FGF23 as one of the most critical factors related to insulin resistance in patients with CKD. Researchers found that uremia, a disruption in phosphate metabolism, and FGF23 could be factors in insulin resistance in CKD patients.[20] In the study of Akabue *et al.*, the results showed that increased FGF23 was independently linked with higher risk of HTN. To justify its causes, it also stated that in CKD, the FGF23 could increase the production of renin through affecting the RAAS system (Renin - Angiotensin - Aldosterone System). Also, the FGF23 can regulate the RAAS system by inhibiting the angiotensin-converting enzyme 2.[21]

In our study, the median of the CRP factor is equal to 4 mg/L (IQR: 1 to 11), and it was determined as one of the predictive factors of iFGF23 changes on multiple regression analysis. In the study of Van Breda *et al.*, the mean of CRP was five mg/L (IQR: 2 to 11.3), and CRP was only slightly increased, suggesting that the samples were in a relatively low inflammatory state.[18] In the study by Sugimoto *et al.*, the mean ± SD to study the CRP factor was 0.8 ± 0.4 mg/dL, and there was no significant relation between CRP and FGF23.[5] In a study on 332 hemodialysis patients, age, serum Ca, P, PTH levels, the GNRI and the active vitamin D dose were the determinants of the serum FGF23 level in patients.[22] In the study by Weber *et al.*, serum phosphorus levels were positively associated with serum FGF23 levels in patients with ESRD.[23] However, in our study, patients with higher iFGF23 were older, but had lower serum phosphorus and vitamin D levels and no significant relationship was observed between iFGF23 and Ca. A positive relation was observed in the present study according to multiple regression

analysis after controlling the confounding variables between iFGF23 and iPTH. Also, in Marsell *et al.* study, multiple regression analysis showed a positive and significant relation between the FGF23 serum levels and PTH.[24] Furthermore, Serum FGF23 levels increase with the injection of PTH in mice.[25] So, the small and immediate changes in the FGF23 level can change the PTH secretion.

According to our study, the mean and median of iFGF23 in patients were 59.5 ± 14.6 and 62 (IQR: 49 to 69) pg/mL; respectively. The mean age of patients was 58.7 ± 14.9 years and was recognized as one of the predictors of iFGF23 changes. In the study by Sugimoto *et al.*, there was no relationship between age and FGF23.[5] In the study of Minoo *et al.*, serum FGF23 levels in patients undergoing dialysis were 855.07 ± 43.33 pg/mL, and the mean age of patients was 56.45 ± 13.64 years. [26]

In this study, according to multiple regression analysis after controlling the confounding variables, a significant relationship was observed between iFGF23 and RDW as the serum FGF23 levels positively correlated with the RDW level. In the study of Van Breda *et al.*, medians of iFGF23 and cFGF23 were equal to 107.3 (IQR: 65.1 to 162.2) pg/mL and 197.5 (IQR: 110 to 408.5) pg/mL; respectively. The result was that both the iFGF23 and the cFGF23 were increasing. A significant relationship between cFGF23 and RDW was observed in CKD and CHF patients, but there was not a significant relationship between iFGF23 and RDW in this study. In this study, different causes can explain this relationship. Among these factors: 1) Iron deficiency causes an increase in the breakdown of iFGF23 to cFGF23 by increasing FGF23 and thus affecting phosphate metabolism. 2) Inflammation, as a potential mechanism, explains the relationship between RDW and FGF23. High values of FGF23 are independently related to inflammation in patients with CKD. 3) The endothelial response to high amounts of FGF23 can cause the programmed cell death (eryptosis) of erythrocytes with compensatory increase in RDW; according to researchers, size of the study samples was small, and the results of this study were obtained on the elderly patients whom had both CKD and CHF. Results may not be generalizable to all CKD patients.[18] In our study, with a larger sample size that included ESRD patients rather than patients with the cardiorenal syndrome, a significant relationship was observed between RDW and iFGF23 with the control of confounding factors, which can complement the results of the above study.

There are some limitations to in the present study. RDW was not checked frequently and we failed to check FGF23 serially during hemodialysis. Moreover, it was necessary to check the cFGF23 factor to achieve more accurate and complete results, which was not possible due to the high cost of kits and international sanctions.

CONCLUSION

In this study, RDW was identified as one of the predictors of iFGF23 . RDW is therefore associated with this biomarker as a convenient, available and inexpensive agent. Perhaps more value will be given to the role of RDW in dialysis patients in the future.

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CONFLICTS OF INTEREST

The authors have declared that no conflicts of interest exist.

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Correspondence to:
Masoud Khosravi, MD
Associate Professor of Nephrology, Urology Research Center, Nephrology Department, Razi hospital, Sardar Jangal Street, Postal Code: 4144895655, Rasht, Iran
Tel: 0098 131 553 7500
E-mail: drmasoudkhosravi@gmail.com and masoud@gums.ac.ir

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