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FGF-23, Inflammation and Iron Metabolism in the Early Stages of Autosomal Dominant Polycystic Kidney Disease

Erken Evre Otozomal Dominant Polikistik Böbrek Hastalığında FGF-23, İnflamasyon ve Demir Metabolizması

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Abstract: To investigate the correlation of Fibroblast Growth Faktör-23 (sFGF-23) with iron status, inflammation and carotid intima-media thickness (CIMT) in the early stages of autosomal dominant polycystic kidney disease (ADPKD). Forty ADPKD patients (24 female) with normal creatinine levels and 40 healthy volunteers (21 female) were included in the study. Serum FGF-23 levels were measured using the ELISA technique. The associations between sFGF-23 with CIMT, hs-CRP, neutrophil lymphocyte ratio (NLR) and iron parameters were evaluated using correlation analysis. Patients' sFGF-23 levels were significantly higher [245 (182-963) pg/mL; vs. 219.6 (34-494) pg/mL], (P< 0.001). NLR and hs-CRP were also found to be statistically higher in patients than controls (P< 0.001 and P= 0.003, respectively). CIMT was significantly higher in the patient group (P= 0.037). There were statistically significant negative correlations between sFGF-23 and calcium, hemoglobin, hematocrit, serum iron, ferritin, and NLR (P= 0.009, P= 0.035, P= 0.002, P= 0.033, P= 0.017, P= 0.023, respectively), and positive correlations with phosporus, total iron binding capacity and sFGF-23 (P= 0.010, P= 0.049, respectively). There was no statistically significant correlation between sFGF-23 and PTH, hs-CRP and CIMT. In multivariate lineer regression analysis, serum phosphorus level was statistically significiant independent risk factor for the determinantion of sFGF-23 level [B: 0.318, OR:130,662(32,715-228,610), P=0.010]. Our study results support an inverse relationship between sFGF-23 and iron deficiency but no relationship between sFGF-23 and inflammation and atherosclerosis in the early stages of ADPKD.

Keywords: autosomal dominant polycystic kidney disease, Fibroblast growth factor-23, Inflammation, Iron metabolism

Özet: Bu çalışmanın amacı erken evre Otozomal Dominant Polikistik Böbrek Hastalığı'nda (ODPBH) serum Fibroblast Growth Faktör-23 (sFGF-23) düzeyleri ile demir metabolizması, inflamasyon ve karotis intima-media kalınlığı (KİMK) arasındaki ilişkiyi araştırmaktır. Çalışma Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesinde gerçekleştirildi. Çalışmaya 40 ODPBH hastası (24 kadın) ile 40 kişilik sağlıklı kontrol (21 kadın) grubu alındı. Serum FGF-23 düzeyleri ELİSA yöntemi ile çalışıldı. Tüm çalışma popülasyonundan KİMK ölçümü yapıldı. Serum FGF-23 düzeyleri ile KİMK, hs-CRP, nötrofil/lenfosit oranı (NLO) ve demir parametreleri arasındaki ilişki korelasyon analizi ile değerlendirildi. Hasta grubunun sFGF-23 düzeyi istatistiksel olarak anlamlı düzeyde daha yüksekti. Hasta grubunda 245(182-963) pg/mL, kontrol grubunda 220(34-494) pg/mL, (P< 0.001). NLO ve hs-CRP düzeyi hasta grubunda kontrol grubuna göre istatistiksel olarak daha yüksekti (sırasıyla, P< 0.001, P= 0.003). Ayrıca KİMK hasta grubunda, kontrol grubuna göre anlamlı düzeyde daha yüksek saptandı (P= 0.037). sFGF-23 düzeyleri ile kalsiyum, hemoglobin, hematokrit, serum demir, ferritin ve NLO arasında anlamlı negatif korelasyon (sırasıyla, P= 0.009, P= 0.035, P= 0.002, P= 0.033, P= 0.017, P= 0.023), sFGF-23 ile fosfor ve total demir bağlama kapasitesi arasında ise anlamlı pozitif korelasyon saptandı (P= 0.010, P= 0.049). sFGF-23 düzeyi ile PTH, hs-CRP ve KİMK arasında ise korelasyon saptanmadı. Multivariate lineer regresyon analizinde serum fosfor düzeyi sFGF-23 tahmininde bağımsız değişken olarak saptandı. Erken evre ODPBH'da sFGF-23 düzeyi demir eksikliği ile ilişkiliyken inflamasyon ve ateroskleozis arasında ilişki saptanmadı.

Anahtar Kelimeler: demir Metabolizması, FGF-23, İnflamasyon, Otozomal dominat polikistik böbrek hastalığı

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1. Introduction

Fibroblast growth factor-23 (FGF-23), secreted by osteocytes and osteoblasts, is involved in phosphorus and vitamin D metabolism.1 In chronic kidney disease (CKD), FGF-23 secretion is stimulated by a decrease in urinary phosphorus excretion.2 Although FGF-23 receptors are commonly present in all tissues, a transmembrane protein called klotho, synthesized in kidney is needed for effects on kidney, parathyroid and intestine.3

It was reported that FGF-23 is associated with progression of CKD, higher risk of cardiovascular complications and mortality.4 Serum FGF-23 (sFGF-23) is related to the endothelial dysfunction (ED), left ventricular hypertrophy (LVH) and arterial stiffness.5 In normotensive autosomal dominant polycystic kidney disease (ADPKD) patients with preserved renal function, cardiovascular abnormalities like ED and LVH were increased compared to the normal population.6 In addition, FGF-23 was found to be increased in patients with ADPKD compared to patients with the same stage CKD without polycystic disease.7

An independent association between severe inflammation and FGF-23 was demonstrated in patients with CKD.8 Increased inflammation was also identified in accordance with the stage of renal failure in ADPKD.9 A relationship between iron status and FGF-23 metabolism was mentioned in a few studies. In these studies, it was emphasized that iron deficiency is an important stimulator of FGF-23 gene transcription10, and FGF-23 production has been shown to increase in response to the iron deficiency.11 In patients with CKD proteolytic cleavage of FGF-23 is impaired, thus active intact FGF-23 (iFGF-23) and inactive C-terminal fragment (cFGF-23) forms of FGF-23 may be detected in CKD patients with iron deficiency.12 In a recent study, it has been argued that FGF-23 is associated with kidney function and fibrinogen, but not with iron status parameters in patients with the early stage of CKD.2

The aim of this study is to investigate the correlations between and FGF 23 with iron status, inflammation and carotid intima media thickness (CIMT) in patients with the early stage of ADPKD.

2. Material and Methods

The study was completed in Bursa Yuksek Ihtisas Training and Research Hospital after the local ethical committee approval (Date: 06.11.2013, No: 2). Written informed consent was obtained from each participant.

Fourty ADPKD patients (24 females, mean age of 44.6±9.7 years) with family history, imaging techniques and clinical findings with normal creatinine levels and glomerular filtration rate (GFR) of >60 mL/dk/1.73m², and 40 healthy volunteers (21 females, mean age of 43.9±8.6 years) were included in this study.

Patients with malignancy, acute coronary artery disease or acute cerebrovascular event within the last 6 weeks, decompensated liver disease, New York Heart Association class 3 or 4 heart failure, surgical procedures in the last month, severe burns and smokers were excluded.

Hypertension was defined as average systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg or usage of antihypertensive drugs. Body Mass Index (BMI) was calculated according to the formula of kilograms divided by height in meters squared (kg/m²).

Laboratory Analysis

Venous blood samples were taken in the morning after 12 hours of fasting. Complete blood count, sodium (Na), potassium (K), calcium (Ca), phosphorus (P), glucose, blood urea nitrogen (BUN), creatinine (Cr), uric acid, lipid profile (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides), albumin, total protein, parathyroid hormone (PTH), iron (Fe), total iron binding capacity (TIBC), ferritin, and

high-sensitivity C-reactive protein (hs-CRP) levels were studied with routine laboratory methods. The ratio of the absolute neutrophil count to absolute lymphocyte count (NLR) was calculated. Protein excretion was calculated in 24-hour urine collection. Glomerular filtration rate (GFR) was calculated according to the modified Modification of Diet in Renal Disease method. Blood samples were centrifuged at 3,000 rpm for five minutes to separate the serum for intact sFGF-23 measurements, and then stored at -80 °C until the assay.

The FGF-23 measurement was performed using Enzyme Linked Immuno Sorbent Assay (ELISA) kit (Catalog No. 201-12-0060, Sunred Biological Technology, Shanghai China). Test range was between 10 ng/L and 1,500 ng/L with a sensitivity of 5.147 ng/L. Intra-assay and inter-assay coefficient of variations (CV) were <10% and <12%, respectively.

The carotid artery intima media thickness (CIMT) was measured by the same device [Toshiba SSA - 240 Ultrasound (Toshiba, Tokyo, Japan)] in all participants using the 7.5 MHz linear array transducer. The measurement was performed bilaterally through the 1cm proximal of the bifurcation of the two main carotid arteries while the patient was in a supine position with the head in slight extension. Three measurements were obtained when the intima layer was seen in the anterior and posterior walls, and the arithmetical mean of these three random measurements was used.

Statistical Analysis

SPSS for Windows 15.0 package program (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Normality distribution of the variables was analyzed by the Shapiro Wilk test. The variables distributed normally were presented as mean±standard deviation, whereas the variables not distributed normally were presented as a median(25th-75th inter quartile range). For normally distributed variables, comparisons between the two independent groups were performed using the student's t-test. For the variables not distributed normally, comparison of the two groups was performed using the Mann Whitney U test. Categorical variables were compared using the Chi-square test. The relationship between the variables was evaluated with Spearman or Pearson correlation analysis as appropriate. All of the reported P values were two-tailed, and those less than 0.05 were considered to be statistically significant.

3. Results

The study included 24 female patients in a total of 40 patients (mean age of 44.6±9.7 years) and 21 female control subjects among 40 people (mean age of 43.9±8.6 years). There were no significant differences between the groups in terms of age, gender, BMI, systolic blood pressure and diastolic blood pressure. However, 24 patients (60%) in the study group had hypertension (P< 0.001). Demographic characteristics of the patient and control group, comorbid disease distribution and laboratory data are presented in Table 1.

White blood cell (Wbc) count, creatinine, K, blood urea nitrogen (BUN), albumin and proteinuria were significantly higher in the patient group compared to control group (P< 0.001, P< 0.001, P= 0.029, P< 0.009, P< 0.048, P<0.001, respectively). GFR was significantly lower in the patient group (patient group 83±15.5 mL/min/1.73m2, controls 99±18.7 mL/min/1.73m2) (P< 0.001) (Table 2). Patients' median sFGF-23 levels were significantly higher [245 (182-963) pg/ml vs. 220 (34-494) pg/ml, P< 0.001)]. Furthermore, NLR, hs-CRP and CIMT were also significantly higher in patients than controls (P< 0.001, P= 0.003 and P= 0.037, respectively) (Table 3).

Table 1. Demographic and Clinical Characteristics of Patients and Controls

	Patients (n=40)	Controls (n=40)	*P*
Gender (M/F)	16/24	19/21	0.652
Age (years)	44.6±9.7	43.9±8.6	0.752
BMI (kg/m²)	27.1±4.6	25.5±2.8	0.078
SBP (mmHg)	130(180-90)	130(140-90)	0.299
DBP (mmHg)	80(90-60)	80(90-60)	0.199
DM (n, %)	5 (12.5)	-	0.055
HT (n, %)	24 (60)	-	<0.001
COPD (n, %)	2 (5)	-	0.494
CAD (n, %)	4 (10)	-	0.116
CVD (n, %)	-	-	-
PAD (n, %)	1 (2.5)	-	1

Normally distributed parameters are given as mean±standart deviation, while non-normally distributed parameters are given as median(25th-75th Inter Quartile Range). BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, CVD: Cerebrovascular Disease, PAD: Peripheral Arterial Disease.

Table 2. Comparison of Laboratory Parameters Between Patients and Controls

	Patients (n=40)	Controls (n=40)	*P*
WBC (µL)	7.7 (5.5-13.9)	6.5 (4.2-9.9)	<0,001
Hb (g/dL)	13.4±1.6	13.4±1.8	0.865
Hct (%)	40.1±4.2	39.0±5.1	0.307
BUN (mg/dL)	13.3 (8.4-27.3)	11.9 (7.0-45.5)	0.009
Cr (mg/dL)	0.9±0.2	0.8±0.1	<0.001
GFR (mL/min/1.73m²)	83±15.5	99±18.7	<0.001
Glucose (mg/dl)	92 (71-182)	89 (72-117)	0.163
Na (mEq/L)	139±3	138±2	0.392
K (mEq/L)	4.2 (3.8-5.1)	4.1 (3.6-5.2)	0.029
Ca (mg/dL)	9.3±0.4	9.3±0.5	0.689
Phosphorus (mg/dl)	3.2±0.5	3.2±0.5	0.881
Ca x P (mg^2/dL^2)	29.7±4.3	30.0±4.9	0.751
Uric Acid (mg/dL)	5(2-9)	5(2-7)	0.990
Total protein (gr/dL)	7.6±0.3	7.4±0.6	0.092
Albumin (gr/dL)	4.4 (3.7-4.8)	4.2 (3.6-5.2)	0.048
Total Cholesterol (mg/dL)	182 (114-278)	198 (138-299)	0.290
LDL (mg/dL)	115±38	127±37	0.175
HDL (mg/dL)	45 (25-80)	44 (16-67)	0.272
TG (mg/dL)	111 (31-500)	98 (56-388)	0.725
PTH (pg/mL)	71±42	60±27	0.167
Proteinuria (g/24 hours)	0.2 (0.1-1.2)	0.1 (0.1-0.1)	<0.001
Iron (mg/dL)	69 (14-197)	78 (18-240)	0.379
Ferritine (ng/mL)	39 (3-366)	58 (2-281)	0.664
TIBC (pg/dL)	272±79	254±93	0.331

WBC:White Blood Cell Count, BUN: Blood Urea Nitrogen, GFR: Glomerular Filtration Rate, TIBC: Total Iron Binding Capacity

Table 3. Comparison of the FGF-23, NLR, hs-CRP and CIMT Between Patients and Controls

	Patients (n=40)	Controls (n=40)	*P*
FGF-23 (pg/mL)	245 (182-963)	220 (34-494)	<0.001
NLR	1.9 (1.0-5.6)	1.6 (0.9-5.7)	<0.001
hs-CRP (mg/dL)	6.2 (3.1-32.8)	4.0 (3.1-14.6)	0.003
CIMT (mm)	0.6 (0.4-0.9)	0.5 (0.4-0.8)	0.037

NLR: Ratio of the neutrophil count to lymphocyte count, CIMT: Carotid intimae media thickness

Correlation analysis between FGF-23 and laboratory parameters are shown in Table 4. sFGF-23 was negatively correlated with Ca (*P*= 0.009) and positively correlated with P levels (*P*= 0.010). In addition, there was a statistically significant negative correlation between FGF-23 and hemoglobin (Hb), Hct, serum iron (Fe) and ferritin (*P*= 0.035, *P*= 0.002, *P*= 0.033, *P*= 0.017, respectively). There was a statistically significant positive correlation between sFGF-23 and phosphorus and TIBC (*P*= 0.010, *P*= 0.049, respectively), and a statistically significant negative correlation between sFGF-23 and NLR (*P*= 0.023) There was no statistically significant correlation between FGF-23 and PTH, hsCRP and CIMT.

In multivariate lineer regression analysis, serum phosphorus level was statistically significiant independent risk factor for the determinantion of sFGF-23 level [B: 0.318, OR:130,662(32,715-228,610), *P*=0.010], (Table 5).

Table 4. Corelation Analyses of FGF-23 in Patients Group

	Patients (n:40)	
	r	*P*
Hb (g/dL)	-0.335	0.035
Hct (%)	-0.341	0.002
Fe (µg/dL)	-0.338	0.033
TIBC (µg/dL)	0.221	0.049
Ferritine (ng/mL)	-0.267	0.017
Ca (mg/dL)	-0.409	0.009
P (mg/dL)	0.404	0.010
Ca×P (mg^2/dL^2)	0.340	0.032
PTH (pg/mL)	0.092	0.574
hs-CRP (mg/dL)	0.273	0.089
NLR	-0.359	0.023
CIMT (mm)	0.018	0.911

TIBC: Total iron binding capacity, NLR: Ratio of the neutrophil count to lymphocyte count, CIMT: Carotid intimae media thickness.

Table 5. Multivariate Lineer Regression Analysis of Variables in Predicting FGF-23

Multivariate Lineer Regression Analysis			
	B	OR(95%Cl)	*P*
Hb	-0.105	-12,452(-47,801-22,897)	0.485
Iron	-0.073	-0,305(-1,527-0,918)	0.621
Ferritin	0.077	0,241(-0,545-1,026)	0.543
NLR	-0.166	-35,711(-84,900-13,479)	0.152
PTH	0.160	0,906(-0,421-2,232)	0.178
CRP	-0.099	-3,919(-12,660-4,822)	0.374
Proteinuria	0.144	173,551(-109,984-457,087)	0.226
CIMT	0.087	123,179(-192,340-483,697)	0.439
Phosphorus	0.318	130,662(32,715-228,610)	0.010
Calcium	-0.111	-50,804(-163,243-61,636)	0.371

4. Discussion

This study is the first study to investigate the relationship between FGF-23 and iron status and inflammation in ADPKD patients. In this study, sFGF-23, NLR, hs-CRP and CIMT were significantly higher in patients with early stage of ADPKD. A negative correlation, supporting a possible relationship between sFGF-23 and NLR and iron parameters, was detected. However, there was no correlation between FGF-23 and hs-CRP, PTH, and CIMT.

ADPKD patients with normal kidney function had significantly higher levels of FGF-23 than CKD patients and controls. This may be associated with the mutations in the PKD1 or PKD2 genes in bone skeletal cells.[7] In an experimental animal study using rodent models of polycystic kidney disease, sFGF-23 level increased up to 10 times due to the target organ resistance to sFGF-23. Increased FGF-23 levels are thought to be caused by renal cysts rather than bone cells.[13] In another study, increased sFGF-23 level and resistance to its effect, is thought to be caused by a reduction in co-factor klotho, and klotho reduction is correlated with the reduction of GFR.[14] According to our study, sFGF-23 levels were higher in patient group, similar to the literature. Significantly lower GFR in patients may contribute to the higher sFGF-23 levels. Although there is no statistical difference in terms of phosphorus level between groups, a positive correlation between phosphorus and sFGF23 levels in all cohorts indicates sFGF-23 may be important for phosphorus metabolism even in the early stages of the disease. The most important missing part in this hypothesis is the absence of the relationship between in vivo circulating levels of klotho and transmembrane klotho. Moreover, many studies show the effect of sFGF-23 on the vascular bed regardless of the presence of klotho.

In the early stage of ADPKD, sFGF-23 levels were significantly higher than healthy controls, and lower arterial compliance is determined independently of hypertension in these patients. However, no correlation was observed between sFGF-23 and arterial dysfunction.[15] In another study of early-stage ADPKD, patients had higher CIMT and left ventricular mass index (LVMI) than control group.[16] Moreover, several studies have found higher CIMT in the early stages of APKD independent of blood pressure.[6] In a study conducted in hemodialysis patients, FGF-23 and CIMT were found to be higher compared to the control group and there was a significant correlation between soluble Klotho levels and CIMT.[17] However, there is no study in the literature exploring the correlation of sFGF-23 with CIMT in stage 1-2 ADPKD. In our study, traditional CV risk factors such as age, BMI, blood pressure values, blood glucose and lipid levels were similar between the two groups, but CIMT was significantly higher in the patient group. This may be a sign of early onset endothelial dysfunction in the early stage of ADPKD, but the presence of significant hypertension in the patient group is confusing. In the patient group, sFGF-23 was significantly higher, but in correlation analysis sFGF-23 was not correlated with CIMT. We argue that it would be useful to evaluate the association between FGF-23 and subclinical atherosclerosis with larger studies in patients with early stage ADPKD.

Inflammation increases FGF-23 production and secretion by the HIF-1α pathway.[18] A recent study emphasized that acute inflammation led to increases in osseous FGF-23 mRNA expression with elevated inactive cFGF-23 but not active iFGF-23. Chronic inflammation produced similar results with an increase in iFGF-23 level.[18] In a study of 3115 elderly subjects, a significant correlation was found between hs-CRP and iFGF-23 and cFGF-23.[19] In a CRIC cohort, there was a significant positive correlation between FGF-23 and inflammatory markers, IL-6, CRP and TNF-α in patients with CKD.[20]

In a recent study of the early stage of ADPKD, NLR was higher in patient group.[16] Increased levels of hs-CRP and NLR support the presence of subclinical inflammation that may play a role in the progression of atherosclerosis. In our study, both hs-CRP and NLR were higher in the patient group. This is the first study in the literature evaluating the relationship between sFGF-23 and inflammation in the early stages of ADPKD in

which a negative correlation was observed between sFGF-23 and NLR, whereas no correlation was detected between sFGF-23 and hs-CRP.

Recently, studies about sFGF-23 and iron metabolism are increasing. In studies, an inverse relationship between iron status and sFGF-23 was mentioned and iron deficiency was emphasized as an important stimulus of sFGF-23 transcription. It was also found that serum FGF-23 levels were increased in hemodialysis patients after iron dextran therapy.[21] In another study oral ferric citrate treatment for 12 weeks significantly decreased iFGF-23 levels in predialysis CKD patients.[22] Restoring iron deficiency with ferric carboxy maltose treatment induced a decline in serum phosphate with parallel to the decline in FGF-23 in CKD patients.[23] In a recently published study it was reported that serum iron was inversely correlated with cFGF-23, but not with iFGF-23 in 2000 pre-menopausal women.[24] In another study conducted in peritoneal dialysis patients, patients with high sFGF-23 level had lower hemoglobin and transferrin saturation, and they used more recombinant erythropoietin.[25] Our study results support an inverse relation between iron deficiency and FGF-23 both in the normal population and the early stages of ADPKD.

This cross-sectional study has some limitations. Vitamin D was not measured and fractional excretion of phosphate in urine was not calculated. Only serum intact sFGF-23 was assessed. When CIMT measurement results are interpreted, the presence of hypertension and diabetes mellitus in patient group, and a significant decrease of GFR in control group should be taken into account although the serum creatinine level is in the normal range. Patients under hemodialysis treatment without polycystic kidney disease could be included in the study as an another control group. Measurement of erythropoietin levels could be useful, since erythropoietin production was preserved in patients with polycystic kidney disease.

5. Conclusion

In the early stage of ADPKD, sFGF-23, NLR, and hs-CRP levels were significantly higher than healthy controls. CIMT was also higher in patient group. However, no significant correlation was detected between FGF-23 and inflammatory and endothelial dysfunction markers but a statistically significant correlation supporting the possible role of sFGF-23 in iron metabolism was detected.

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