Original Article

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Biochemical Correlation of FGF23 with other Biomarkers in Patients with End-stage Renal Disease on Haemodialysis: A Cross-sectional Study

Internal Medicine Section

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ABSTRACT

Introduction: In patients with End-Stage Renal Disease (ESRD) undergoing Haemodialysis (HD), Fibroblast Growth Factor 23 (FGF23), intact Parathyroid Hormone (iPTH), and homocysteine (Hcy) are frequently elevated and have each been associated with disordered mineral metabolism and increased cardiovascular risk. In addition to FGF23, both iPTH and Hcy play important roles in Chronic Kidney Disease (CKD)-related Mineral Bone Disorder (MBD) and Cardiovascular Disease (CVD) risk.

Aim: To evaluate the correlation of FGF23 with iPTH, Hcy, and routine biochemical parameters in patients with ESRD. Understanding these correlations may help identify new prognostic markers and inform treatment strategies in HD patients.

Materials and Methods: This cross-sectional study was conducted in the Department of Nephrology at Yeni Klinika Hospital, Baku, Azerbaijan between February 2024 and November 2024. ESRD patients who had been on dialysis for atleast three months were recruited. Data were collected from 103 patients who consented to participate. Patients were divided into two groups: the main group (n=75) with elevated FGF23 and Hcy levels, and the control group (n=28) with normal FGF23 and Hcy levels. Baseline laboratory parameters included Haemogram (Hg), C-reactive Protein (CRP), Glucose (Gluc), Creatinine (Crea), estimated Glomerular Filtration Rate (eGFR), Potassium (K), Sodium (Na), Calcium (Ca), Phosphorus (P), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), iPTH, Hcy, and FGF23. Descriptive statistics and frequency analysis were used to summarise demographic and clinical characteristics. The Chi-square (χ^2) test was used to compare categorical variables between groups, and the Mann-Whitney U test was applied to compare clinical parameters. Statistical significance was set at $p<0.05$. Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics version 25.0.

Results: The sample included 65 (63.1%) males and 38 (36.9%) females, with a mean age of 64±13.64 years, mean height of 170±6.9 cm, and mean weight of 79±13.04 kg. In the main group, FGF23 levels showed positive correlations with phosphorus (r=0.72, p=0.01), creatinine (r=0.78, p=0.01), iPTH (r=0.61, p=0.01), and Hcy (r=0.74, p=0.01). FGF23 was negatively correlated with eGFR (r=-0.64, p=0.01). No statistically significant correlation was observed with calcium levels (r=-0.12, p=0.29).

Conclusion: Changes in FGF23, iPTH, and Hcy levels, particularly when assessed alongside other biochemical parameters, may serve as early prognostic markers in HD patients. Monitoring these parameters could help guide prognosis and support timely treatment management in patients with ESRD.

Keywords: Chronic kidney disease, Fibroblast growth factor 23, Homocysteine, Intact parathyroid hormone, Mineral metabolism

INTRODUCTION

Patients with ESRD undergoing HD are at increased risk of mortality due to CKD-MBD and CVD complications, such as cardiorenal syndrome [1]. The elevated CVD risk in CKD patients is primarily attributed to pathologically altered phosphocalcic metabolism. CKD-MBD is characterised by disturbances in mineral balance and bone metabolism, including abnormal calcium (Ca) and phosphorus (P) levels, as well as elevated iPTH [2].

The FGF23, a key regulator of phosphate metabolism secreted by osteocytes, plays a central role in this process. Elevated FGF23 levels are associated with increased mortality in ESRD patients on HD [3]. Bouma-de Krijger A et al. reported no association between a single FGF23 measurement and all-cause mortality; however, rising FGF23 levels were linked to higher mortality risk [4]. FGF23 inhibits PTH secretion and active vitamin D3 synthesis, thereby reducing renal tubular phosphorus reabsorption and limiting intestinal phosphorus absorption [3,4].

In addition, FGF23 contributes to CVD pathophysiology, including left ventricular hypertrophy, myocardial injury, coronary atherosclerosis, and vascular calcification [5]. Vázquez-Sánchez S et al. reported direct effects of FGF23 on the cardiac myocardium, with elevated plasma levels associated with adverse cardiovascular outcomes such as arrhythmias and heart failure [6]. These effects are mediated by persistent hyperphosphatemia and deficiency of the cofactor Klotho. However, the relationship between FGF23 levels and CVD, including cardiorenal syndrome and MBD in HD patients, remains unclear [7].

Renal Hyperparathyroidism (rHPT) develops in the early stages of renal failure, increasing the risk of bone fractures, CVD, and mortality. Both PTH and FGF23 levels rise as kidney function declines, and in advanced kidney failure, their phosphaturic effects are impaired. This results in hyperphosphatemia and further elevations of both hormones. FGF23 levels should therefore be monitored in clinical practice, similar to iPTH levels. However, the optimal target range for iPTH remains debated, and further research is needed to establish evidence-based guidelines for ESRD patients on HD [8,9].

Chen W et al., reported elevated Hcy levels in CKD patients on HD [10]. Hyperhomocysteinemia (Hhcy) is an independent risk factor

for CVD, with an incidence of 85-90%, particularly when combined with biochemical abnormalities such as altered creatinine, albumin, calcium, and CRP levels. Hcy is therefore considered a prognostic biomarker in ESRD, and monitoring its levels is recommended in all CKD patients on HD.

At present, no single biomarker can reliably predict or track CKD progression. GFR and creatinine remain the standard markers for assessing kidney function and detecting early CKD [2,9]. However, limited research has investigated the simultaneous biochemical interrelationships among FGF23, iPTH, Hcy, CRP, lipids, and mineral metabolism markers in ESRD patients on chronic HD [10-12]. The present study aimed to address this gap by evaluating the cross-sectional correlation of FGF23 with iPTH, Hcy, and routine biochemical parameters in ESRD. Understanding these correlations may help identify new prognostic markers and guide treatment strategies for HD patients with ESRD.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Nephrology, Yeni Klinika Hospital, Baku, Azerbaijan between February 2024 and November 2024. The present study was conducted in accordance with the Declaration of Helsinki and approved by the Yeni Klinika Public Legal Entity Medical Research Ethics Commission (approval 012/24, protocol code 012) dated: 11/12/2024.

Sample size calculation: The sample size was determined using the G*Power 3.1 software. The ESRD patients who had undergone HD for atleast three months were approached, and data were collected from 103 patients who provided informed consent.

Patients were divided into two groups: the main group (with elevated FGF23 and Hcy levels) and the control group (with normal FGF23 and Hcy levels). Examinations were performed for both groups.

Inclusion criteria: Adult patients diagnosed with ESRD on maintenance HD and with absence of primary CVD were included in the study.

Exclusion criteria: Patients with presence of primary CVD or acute cardiovascular events, acute renal failure, recent surgery (within the past two months), HD due to non ESRD aetiologies (e.g., autoimmune or oncological diseases) were excluded from the study.

Study Procedure

Assessment parameters: Demographic information, including age, gender, primary disease, and co-morbidities, was collected. Standard biochemical parameters measured included creatinine, urea, sodium, potassium, calcium, phosphorus, AST, ALT and CRP. Target parameters included FGF23, iPTH, and Hcy levels. Cardiac evaluations of all HD patients were performed using color Doppler echocardiography and electrocardiography (ECG). Renal function was assessed using the CKD-EPI formula to calculate GFR (mL/min).

Biomarker measurement and reference values: Blood samples were collected prior to haemodialysis and centrifuged to obtain serum. Serum FGF23 levels were measured using an Enzyme-linked Immunosorbent Assay (ELISA). The human FGF23 ELISA kits used in this study were manufactured by Immutopics International (San Clemente, CA, USA; #60-6600). The normal reference range for FGF23 was 10.84-23.72 pg/mL, determined from the mean FGF23 value (17.28±6.44 pg/mL) in 28 healthy volunteers [2-4,13]. Intact PTH (iPTH) levels were measured using an Electrochemiluminescence Immunoassay (ECLIA, PTH Cobas®, Roche), with a normal reference range of 15-65 pg/mL [8,9,14]. Total Hcy concentrations were measured using the Fluorescence Polarisation Immunoassay (FPIA) method, with a reference range of 5-15 µmol/L [10,15,16]. Target reference ranges for phosphorus (1.13-1.78 mmol/L), calcium (2.1-2.4 mmol/L), and iPTH (150-300 pg/mL) in CKD patients were evaluated according to {Kidney Disease Outcomes Quality Initiative (K/DOQI)} [17-20].

STATISTICAL ANALYSIS

Descriptive statistics and frequency analysis were used to summarise demographic and clinical characteristics. The Chi-square (χ^2) test was applied to compare categorical variables between groups. The Shapiro-Wilk test indicated that the data were not normally distributed; therefore, non parametric methods were employed. The Mann-Whitney U test was used to compare clinical parameters between the main and control groups. Spearman's rank correlation was applied to assess relationships between FGF23 and other biochemical markers. Statistical significance was set at $p<0.05$. All analyses were performed using IBM SPSS Statistics version 25.0. Descriptive data are presented as mean±Standard Deviation (SD), while frequency and percentage values are reported for categorical variables. Chi-square analysis was used for proportional comparisons. Non parametric tests were selected based on the non normal data distribution revealed by the Shapiro-Wilk test. The Mann-Whitney U test evaluated differences between the main and control groups, while the Friedman test assessed differences between repeated measurements within groups. Spearman's correlation and regression analyses were conducted to examine multilevel relationships between FGF23 and other parameters.

RESULTS

The study included 103 patients receiving maintenance haemodialysis due to ESRD. Baseline clinical and laboratory characteristics are presented in [Table/Fig-1]. Among the 103 HD patients, there were 65 (63.1%) males and 38 (36.9%) females, with a mean age of 64±13.64 years. Baseline biochemical parameters, including Haemoglobin (Hg), CRP, glucose, creatinine, GFR, Potassium (K), Sodium (Na), Calcium (Ca), phosphorus (P), ALT, AST, iPTH, Hcy, and FGF23, were evaluated and are presented in [Table/Fig-1].

Parameters		n (%)	Control	Main	p**
Gender	Male	65 (63.1)	15 (54%)	50 (67%)	0.16
	Female	38 (36.9)	13 (46%)	25 (33%)	
Parameters		**Mean±SD**	**Mean±SD**	**Mean±SD**	**p*** **
Age (years)		64±13.64	67.2±13.9	61.23±12.9	0.09
Height (cm)		170±6.9	169.2±7.4	170.9±6.7	0.74
Weight (kg)		79 ±13.04	77.9±13.1	79.9±13.1	0.81
Vital parameters			**Mean±SD**	**Mean±SD**	**p*** **
Systolic blood pressure (mm/Hg)		140±17.83	140.5±19.7	140.1±17.1	0.91
Diastolic blood pressure (mm/Hg)		80±6.13	80.3±10.5	80.2±11.6	0.94
Pulse (per minute)		83±11.3	83.3±10.5	83.2±11.6	0.96
Laboratory parameters			**Mean±SD**	**Mean±SD**	**p**
HGB (g/dL)		9.3±11.9	9.7±1.7	11.2±13.8	0.26
HT (%)		30.4±6.36	30.7±7	30.3±6.2	0.95
CRP (mg/L)		12.31±18.67	10.2±9.45	14.6±12.6	0.11
eGFR (mL/min/ 1.73 m^2)		11±5.78	11.4±5.6	11.1±5.4	0.94
Creatinine (umol/L)		599±242.2	389.7±113.4	748.9±201.5	0.01*
Glucose (mmol/L)		6.2±3.2	6.4±4	6±2.9	0.61
Urine protein (mg/dL)		150±85.8	152.2±62.2	148.5±56.7	0.71
Potassium (mmol/L)		4.1±0.57	4.1±0.4	4.1±0.7	0.68
Sodium (mEq/L)		142±3.32	139.9±3.6	145.7±3.2	0.02*
Calcium (mmol/L)		2.34±3.17	2.2±1.8	2.7±2.0	0.11
Phosphorus (mmol/L)		1.7±1.94	1.1±1.4	1.7±2.0	0.02*

ALT (U/L)	22.1±13.06	22.6±15	22.7±12.3	0.74
AST (U/L)	22.4±12.56	22.4±14	22.6±11.9	0.78
FGF23 (pg/mL)	860.0±252.2	18.4±3.4	1703.6±1022.9	0.01*
İPTH (pg/mL)	153±93.7	121.5±27.1	235.2±91	0.03*
Homocysteine (umol/L)	19.1±6.8	8.2±3.3	30.0±5.2	0.01*

[Table/Fig-1]: Baseline clinical and laboratory characteristics (N=103).
HGB: Haemoglobin; HT: Haematocrit; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; ALT: Alanine transaminase; AST: Aspartate aminotransferase; FGF23: Fibroblast growth factor 23; iPTH: intact parathyroid hormone. Descriptive statistics: Quantitative data presented as mean±SD, categorical data presented as number (percentage) ***Mann-Whitney U test, **Chi-square test was performed. *p-value<0.05 considered significant

Age, height, and weight did not differ significantly between the study groups (p>0.05). Systolic and diastolic blood pressures, as well as pulse rates, were also similar between groups (p>0.05). Haemoglobin (g/dL), haematocrit (%), CRP (mg/L), eGFR (mL/min/1.73 m²), glucose (mmol/L), urine protein (mg/dL), potassium (mmol/L), calcium (mmol/L), ALT (U/L), and AST (U/L) showed no significant differences between groups (p>0.05).

Creatinine (µmol/L), sodium (mEq/L), phosphorus (mmol/L), FGF23 (pg/mL), iPTH (pg/mL), and Hcy (µmol/L) were significantly higher in the main group compared to the control group (p<0.05). Phosphorus levels were significantly higher in the main group (p=0.01), whereas calcium levels did not differ between groups (p=0.29). iPTH levels were also elevated in the main group (p=0.01). GFR levels were significantly lower in the main group compared to controls (p=0.01) [Table/Fig-2].

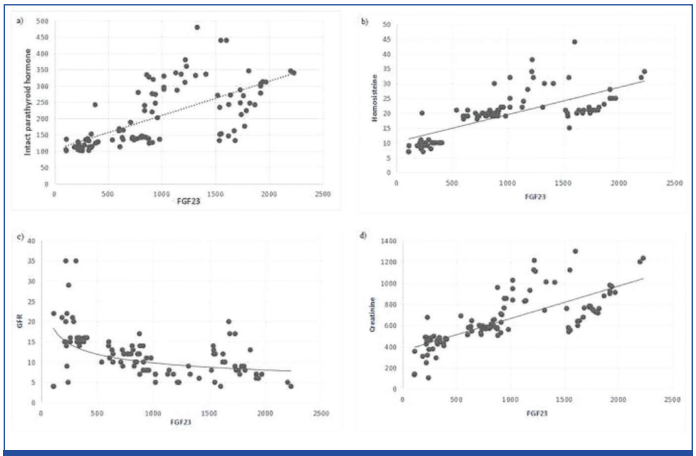
Patient characteristics (N=103)	Control (n=28) n (%)	Main (n=75) n (%)	p**
Phosphorus < t.r.r.	23 (82%)	20 (26.7%)	0.01*
Phosphorus > t.r.r.	5 (18%)	55 (73.3%)	
Calcium < t.r.r.	19 (67.9%)	59 (78.7%)	0.29
Calcium > t.r.r.	9 (32.1%)	16 (21.3%)	
iPTH < t.r.r.	22 (78.5%)	4 (5.3%)	0.01*
iPTH > t.r.r.	6 (21.5%)	71 (94.7%)	
GFR >15 mL/min/1.73 m²	23 (82%)	4 (5.3%)	0.01*
GFR <15 mL/min/1.73 m²	5 (18%)	71 (94.7%)	

[Table/Fig-2]: Analysis of laboratory characteristics according to study groups (N=103).
Categorical data presented as number (percentage). *p-value <0.05 considered significant **Chi-square test was performed

In the main group, FGF23 showed strong positive correlations with creatinine, phosphorus, iPTH, and Hcy levels, and a strong negative correlation with GFR (p<0.05). No significant correlation was observed between FGF23 and calcium (p>0.05). Similar correlation patterns were observed in the control group. In the main group, FGF23 and Hcy exhibited a strong positive linear correlation (r=0.74, p=0.01) [Table/Fig-3,4a-d].

Main group (n=75)		FGF23	p-value
Crea	r	0.78*	0.01
Ca	r	-0.12	0.29
P	r	0.72*	0.01
iPTH	r	0.61*	0.01
GFR	r	-0.64*	0.01
Hcy	r	0.74*	0.01
Control group (n=28)		**FGF23**	**p-value**
Crea	r	0.70*	0.01
Ca	r	-0.09	0.66
P	r	0.71*	0.01
iPTH	r	0.55*	0.01
GFR	r	-0.54*	0.01
Hcy	r	0.62*	0.01

[Table/Fig-3]: Analysis of the relationships between the changes in FGF23 and other biochemistry laboratory parameters in the main group (n=75) and control group (n=28).
**Correlation analysis was performed. *Significant relationship at 0.05 level



[Table/Fig-4]: Correlation of serum levels of fibroblast growth factor 23 with intact parathyroid hormone (a), serum homocysteine rate (b), glomerular filtration (c), and (d) creatinine (Main group).

Regression analyses were performed with Hcy (Model 1), iPTH (Model 2), and FGF23 (Model 3) as dependent variables. All models were statistically significant, with Analysis of Variance (ANOVA) p-values<0.001, indicating good model fit. Model 1 demonstrated the highest explanatory power (R^2=0.846), followed by Model 2 (R^2=0.814) and Model 3 (R^2=0.806) [Table/Fig-5].

Model	R	R^2	Adjusted R^2	Std. error of the estimate	ANOVA[a]
1	0.920[a]	0.846	0.809	2.92328	0.000[b]
2	0.902[a]	0.814	0.768	49.13951	0.000[b]
3	0.898[a]	0.806	0.758	607.83522	0.000[b]

[Table/Fig-5]: Model summaries.

DISCUSSION

This single-centre cross-sectional study demonstrated the following results. The mean FGF23 level in the main group was significantly higher than in the control group (p=0.01). In the main group, FGF23 levels were positively correlated with serum phosphorus, iPTH, and Hcy levels. This increase may represent an important factor contributing to CKD-MBD in HD patients.

Electrolyte imbalances such as hyperkalemia, hyperphosphatemia, and hypercalcemia are common consequences of CKD-MBD and have been associated with elevated FGF23 and PTH levels [21]. Nakagawa Y and Komaba H reported that elevated PTH and FGF23 levels can cause multi-organ damage in advanced CKD [9]. Our results support this observation, as patients in the main group demonstrated more pronounced disruptions in mineral metabolism (phosphate and calcium), altered PTH regulation, and impaired renal function, alongside elevated FGF23 levels. The positive relationship observed between FGF23 and iPTH in this study is consistent with findings from other reports suggesting an influence of FGF23 on parathyroid gland function [11].

Because FGF23 is strongly associated with phosphate levels, it plays a key role in phosphate regulation. Almquist M et al., also reported that elevated FGF23 levels reflect the body's adaptive response to phosphate accumulation [8]. In the present study, FGF23 and GFR exhibited an inverse correlation, suggesting that rising FGF23 levels as kidney function declines may contribute to kidney and cardiac complications. Zeng D et al., investigated FGF23 concentrations in 107 CKD patients and found an association with serum PTH and calcium levels, but not phosphate [2]. In contrast, the present study showed that patients with higher FGF23 and Hcy levels had

markedly increased creatinine, phosphate, and iPTH levels, along with reduced GFR. These findings reinforce the pathophysiological relevance of FGF23 and Hcy as markers of disease severity and potential contributors to CKD-related complications.

The present study highlights the significant correlation between elevated FGF23 and Hcy levels with impaired renal function and disrupted mineral metabolism in patients with advanced CKD. Monitoring these parameters may provide valuable insights into disease progression and help guide individualised treatment strategies. Similarly, Kruglova MP et al., demonstrated that Hcy is both a predictive and prognostic marker in CKD HD patients, with elevated levels observed in chronic renal failure [22].

Elevated PTH stimulates FGF23 synthesis in bone, while decreased renal Klotho expression increases serum phosphate load, further inducing FGF23 production. Elevated plasma FGF23 levels are strongly associated with impaired renal function, as reflected by higher creatinine levels and eGFR <60 mL/min/1.73 m^2 [23]. Consistently, this study also identified a negative correlation between FGF23 and eGFR.

These findings emphasise the need to monitor FGF23, iPTH, and Hcy levels alongside routine testing in CKD patients on HD. FGF23 and Hcy serve not only as markers of disease progression but also as potential therapeutic targets. Reducing FGF23 concentrations can be an important treatment goal in clinical practice, achievable through dietary phosphate restriction and the use of phosphate binders. Non calcium-containing phosphate binders, calcimimetics, and Haemodiafiltration (HDF) are effective methods to lower FGF23 levels in HD patients [24]. A recent study by Yang Q et al., proposed the use of the KHA-200 haemoperfusion device in HD patients, demonstrating that targeting blood urea nitrogen, creatinine, uric acid, potassium, phosphate, PTH, and Hcy significantly improved patient outcomes [25]. Therefore, the parameters highlighted in this study, including FGF23, should be considered in future treatment strategies.

Limitation(s)

The present study did not assess outcomes such as cardiovascular events, bone fractures, or mortality, which are commonly associated with elevated FGF23 and Hcy. In addition, factors such as the use of phosphate binders, vitamin D analogues, and variations in nutritional status were not controlled and may have influenced the results. Further studies are needed to evaluate whether FGF23 and Hcy directly contribute to organ damage and to determine their predictive value for clinical outcomes. Clinical trials should focus on interventions aimed at lowering FGF23 and Hcy to assess their impact on kidney function and overall patient health. Based on these findings, the inclusion of FGF23 and Hcy in CKD management guidelines—with an emphasis on bone-mineral changes and cardiovascular risk—is recommended.

CONCLUSION(S)

High levels of FGF23 and Hcy are associated with abnormal renal function and mineral imbalance. FGF23 shows a strong correlation with increased creatinine, phosphate, and iPTH levels, alongside reduced GFR. These parameters can be used to monitor disease progression and may serve as markers of disease severity in CKD patients undergoing HD. While GFR and creatinine remain standard markers for renal failure, the combined assessment of FGF23, iPTH, and Hcy can support prognostic evaluations and guide early treatment strategies in CKD management.

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- iThenticate Software: Sep 20, 2025 (21%)

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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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