Fibroblast Growth Factor-23 importance as a prognostic factor in hemodialysis patients

PCR como me Importancia del factor de crecimiento de fibroblastos-23 como factor pronóstico en pacientes en hemodiálisis diador del sistema de inmunidad innata y de los niveles de glucosa en sangre en adolescentes entrenados en fútbol

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Abstract

Background:
Initial complications evident in chronic kidney disease (CKD) are enhanced levels of Fibroblast growth factor 23 (FGF23) and phosphate homeostasis disorders. An increase in FGF23 is a highly sensitive indicator of phosphate toxicity and end-organ toxicity in the heart.

Objective:
The objective of the current research was to explore the correlation between the quantity of FGF23 and bone-mineral metabolism, anemia left ventricular hypertrophy (LVH), and dysfunction (LVEF).

Methods:
This research was executed at the nephrology units, dialysis department / Baghdad Teaching Hospital, and Basrah Teaching Hospital from 1st of January 2021 to 1 of March 2022. 60 patients undergoing hemodialysis for a minimum of six months were recruited for the research. Parameters assessed included hematocrit (Htc), hemoglobin (Hb), phosphorus (P), calcium (Ca), corrected albumin, and whole parathyroid hormone (iPTH). We further calculated if any correlation existed between these parameters and FGF23 levels. We also conducted left ventricular echocardiography of the recruited patients to evaluate the relation between FGF23, LVH, and LVEF.

Results:
We found a statistically significant positive correlation between serum FGF23 levels and iPTH ($P < 0.001$), and Ca values ($P < 0.001$). However, we were unable to find a substantial correlation between the levels of FGF23 and Hb ($P = 0.518$) and Htc ($P = 0.377$). FGF23 and LVH were also statistically correlated ($P<0.001$). A significant negative correlation of FGF23 was found with LVEF showing a decrease in LVEF with increasing levels of FGF23 ($P<0.001$).

Conclusion:
Elevated serum FGF-23 levels in hemodialysis patients showed a significant correlation with various studied parameters indicating its role in the development of hyperparathyroidism. Noticeably, our data showed a positive correlation between FGF23 and LVH and a negative correlation between FGF23 and LVEF suggesting that FGF23 is sufficient to forecast of overall death rate in patients suffering from CKD.

Keywords: chronic kidney disease, fibroblast growth factor 23, hemodialysis

Resumen

Fondo:
Las complicaciones iniciales evidentes en la enfermedad renal crónica (ERC) son niveles elevados del factor de crecimiento de fibroblastos 23 (FGF23) y trastornos de la homeostasis del fosfato. Un aumento de FGF23 es un indicador muy sensible de la toxicidad del fosfato y de la toxicidad de los órganos terminales en el corazón.

Objetivo:
El objetivo de la presente investigación fue explorar la correlación entre la cantidad de FGF23 y el metabolismo mineral óseo, la anemia, la hipertrofia ventricular izquierda (HVI) y la disfunción (FEVI).

Métodos:
Esta investigación se llevó a cabo en las unidades de nefrología, el departamento de diálisis/Hospital Universitario de Bagdad y el Hospital Universitario de Basora del 1 de enero de 2021 al 1 de marzo de 2022. Para la investigación se reclutaron 60 pacientes sometidos a hemodiálisis durante un mínimo de seis meses. Los parámetros evaluados incluyeron hematocrito (Htc), hemoglobina (Hb), fósforo (P), calcio (Ca), albúmina corregida y hormona paratiroidea total (PTHi). Además, calculamos si existía alguna correlación entre estos parámetros y los niveles de FGF23. También realizamos una ecocardiografía del ventrículo izquierdo de los pacientes reclutados para evaluar la relación entre FGF23, HVI y FEVI.

Resultados:
Encontramos una correlación positiva estadísticamente significativa entre los niveles séricos de FGF23 y la PTHi (P <0,001) y los valores de Ca (P <0,001). Sin embargo, no pudimos encontrar una correlación sustancial entre los niveles de FGF23 y Hb (P = 0,518) y Htc (P = 0,377). FGF23 y LVH también se correlacionaron estadísticamente (P <0,001). Se encontró una correlación negativa significativa de FGF23 con la FEVI que muestra una disminución de la FEVI con niveles crecientes de FGF23 (P <0,001).

Conclusión:
Los niveles séricos elevados de FGF-23 en pacientes en hemodiálisis mostraron una correlación significativa con varios parámetros estudiados que indican su papel en el desarrollo del hiperparatiroidismo. Notablemente, nuestros datos mostraron una correlación positiva entre FGF23 y HVI y una correlación negativa entre FGF23 y FEVI, lo que sugiere que FGF23 es suficiente para pronosticar la tasa de mortalidad general en pacientes que padecen ERC.

Palabras clave: enfermedad renal crónica, factor de crecimiento de fibroblastos 23, hemodiálisis.

Introduction

Chronic kidney disease
The health condition, chronic kidney disease (CKD), affects nearly 8-16% of the population worldwide[1]. It is defined by the occurrence of structural and functional abnormality of the kidney that is evident for more than 3 months of time duration. These abnormalities include glomerular filtration rate below 60 mL/min/1.73 m2, albuminuria, abnormalities in histology, urine sediment, or kidney damage evident by imaging, disorders in renal tubules, or history of kidney transplantation[2]. Prevalence of CKD has been found to be more in lower and middle countries as compared to high income countries[3]. Major contributing factors for CKD include diabetes and/or hypertension, however other causes like infection, environmental exposure and glomerulonephritis are also attribute to the development of CKD in Asian, African[4]. Various genetic factors have also been found to have a role in the development of CKD[5,6].

Fibroblast Growth Factor-23
Progression of CKD is multifactorial and associated effects. One such factor is FGF23, a phosphaturic hormone, also a circulating bone-derived factor that regulates the metabolism of bones and minerals[7]. FGF23, is a 251–amino acid hormone regulating the excretion of phosphate and was discovered during the studies conducted to explore autosomal dominant hypophosphatemic rickets and oncogenic osteomalacia[8]. This hormone is produced predominantly by the osteocytes and osteobalsts during the process of bone remodeling, but mRNA of FGF23 have also been found in heart, liver, thyroid/parathyroid, intestine and skeletal muscles. Increase in levels of FGF23 have been observed during mild renal injury which increases progressively during CKD due to increased secretion by osteocytes as well as their decreased catabolic metabolism by kidneys. Kidney is one of the major target organs for FGF23 and aberrant expression of FGF23 has been observed in CKD stage 4-5, where the level of FGF23 in serum could increase more than 1000 folds of the normal range[9]. Rise in levels of FGF23 is observed prior to the increased levels of calcium, phosphorus, or PTH levels and it has now been considered as the earliest detectable marker for chronic kidney disease (CKD) mineral bone disorder.

In this study, we aimed to ascertain this prognostic role of FGF23 in a cohort of CKD patients undergoing dialysis. The objective was to explore the association of FGF23 and other factors which effect the morbidity and mortality in dialysis patients. The prevalence of CVD in CKD patients, paralleled by increased levels of FGF23 as supported by many studies; strongly suggest the association of CVD with FGF23 levels. The 2D-Echocardiography for the recruited CKD patients undergoing dialysis could provide evidence for the association between FGF23 and functioning of heart. Herein, this study, based on echocardiography data, we also tried to establish a correlation between FGF23, LVH, and reduced left ventricular ejection fraction (LVEF).

Study setting and design

This cross-sectional observational study was conducted at the nephrology units, dialysis department of Baghdad teaching hospital and basrah teaching hospital during 1st of January 2021 to 1 of march 2022. This study recruited 60 patients: 34 males and 26 females. The included patient's age ranged between 25-70 years. All the recruited patients for this study were receiving hemodialysis replacement therapy minimum for last six months. Patients having chronic and active inflammatory disease (e.g., collagen tissue disease, malignancy, and diabetic foot) and incompliant patients were excluded from our study. Based on the serum level of PTH level less or more than 300 pg/mL, recruited patients were divided into two groups. Group A and Group B respectively(104).

Blood samples were collected from all the patients' post overnight fasting. Parameters studied included serum albumin, hematocrit (Htc), hemoglobin (Hb), calcium (Ca), phosphorus (P), intact PTH (iPTH), and FGF-23 levels. Calculation of Ca×P ratio was also done for each patient.

To evaluate the hemodialysis adequacy, Kt/V values were calculated for each patient using hemodialysis machine.

Biochemical Study

For all the biochemical studies, serum from the blood samples collected from the patients before dialysis was separated by centrifuging the collection tubes at 2000 g (10 min) to remove the serum and stored at -20^{0}c till the assays were conducted for measurement of FGF-23, phosphorus, calcium, albumin and PTH.

(I) Serum parathyroid hormone test

We used DEMEDITEC Intact-PTH ELISA kit (Demeditec Diagnostics GmbH, Germany) for the quantitative determination of Intact-PTH (Parathyroid Hormone) in the serum samples of the recruited patients. The protocol followed was as per the manufacturer's instructions. The normal range of serum PTH as per the kit was 10.4 to 66.5 pg/mL.

(II) Determination of serum fibroblast growth factor-23

Serum level of FGF-23 was determined using Human fibroblast growth factor-23(FGF-23) ELISA Kit supplied by Shanghai Yehua Biological Technology, China using the protocol provided by the manufacturer. The protocol in this kit consists of enzyme-linked immune sorbent assay (ELISA) based on biotin double antibody sandwich technology for the determination of FGF-23. The values in the assay range between 5pg/ml→1500pg/ml

(III) Determination of 1,25-dihydroxyvitamin D3

Determination of serum 1,25-dihydroxyvitamin D3 was done using CUSABIO (USA) kit as per the manufacturer's protocol. This kit is also based on the biotin double antibody sandwitch ELISA technology for calculating the serum level of human 1,25-dihydroxyvitamin D3(DVD, DHVD3). The normal values of the assay range between 2pmol/L→600pmol/L.

(IV) Determination of Serum Albumin

Serum albumin level was determined using Spinreact, (Spain) Albumin kit. The kit is based on the principal that albumin at a slightly acidic pH in the presence of bromocresol green changes the indicator's color from yellow-green to green-blue. The formed color intensity is proportional to the concentration of albumin in the sample. The reference values are in between 3.5 – 5 g/dl.

(V) Determination of Serum Calcium

Colorimetric determination of total calcium in the serum, without deproteinization, was determined using Biomérieux, (France) Ca-Kit. Ca+ forms a complex with methylthymol blue indicator (MTB) provided along with the kit in an alkaline medium to produce colored complex. Intensity of this Ca-MTB complex is measured at 612 nm and is proportional to the calcium quantity present in the sample presented as mg/dl. The reference range of this kit is 8.5- 10.5 mg /dl in serum.

Correction of the serum albumin concentration was done for the concentration of serum albumin. It was calculated as:

Serum albumin>4.0 g/dl, Corrected Calcium=Serum Calcium

Serum albumin<4.0 g/dl, Albumin-corrected calcium =Measured Ca [mg/dl] + 0.8 × (4 g/dl – measured albumin [g/dl])

(VI) Determination of Serum Phosphate

Linear chemical (Spain) kit was used to measure the serum phosphate levels as per the manufacturers' protocol. The kit is based on the principal that Inorganic phosphate and molybdic acid react to form a phosphomolybdic complex. It is further reduced in alkaline medium to produce blue molybdenum color. The blue color intensity is proportional to the amount of phosphorus in the sample.

Absorbance is measured at 740 nm and results are expressed as mg/dl. The reference range of kit is 2.5 – 5.0 mg/dl.

(VII) Determination of Blood Hemoglobin

Automated Beckman Coulter was used to measure the concentration of hemoglobin. The reference range for the hemoglobin results was 14.0 – 17.5 g/dl for male patients and 12.3 – 15.3 g/dl for female patients.

Echocardiography

For this study, we used 2D-Echocardiography Machine Vivid S5 which is provided with 3.5 MHz transducer probe for studying systolic and diastolic wall thickness and chamber dimensions. Left ventricular systolic dysfunction was measured by left ventricular ejection fraction (LVEF), and ejection fraction<55% was considered as systolic dysfunction. LVH was diagnose

when interventricular septum thickness or left ventricular posterior wall thickness ≥ 12 mm (105).

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) Statistical Software was used in this study for all the data analysis. We used one-way variance analysis for descriptive statistical methods viz. mean, standard deviation, median, and interquartile range. For conformity of variables to a normal distribution, logarithmic transformation was applied for FGF-23 and for PTH, square root transformation was applied. For comparison of two groups, independent t-test was used and for comparison of the variables with non-normal distribution, we used Mann-Whitney test. Qualitative data comparison was performed using Chi-square test. For defining the parameters which affect FGF 23, linear regression analysis was carried out. □< 0.05 was considered as statistically significant.

Results

We had recruited 60 patients who were followed up at nephrology unit, dialysis department of Baghdad teaching hospital and were undergoing dialysis replacement therapy for at least 6 months. These patients were divided into two study groups based on the serum PTH levels as mentioned above viz. Group A with PTH level below 300 pg/mL and Group B with serum PTH level above 300 pg/mL.

Demographic data

The mean age of all the recruited patients was 50.43 ± 12. Mean age individually of the patients recruited for the study in the Group A was 49.03 ± 11.52 and in the group B was 51.84 ± 12. Of all the patients recruited, 20 were male (57.1%) and 15 females (42.9%) in Group A and 14 males (56%) and 11 females (44%) in Group B. There was no significant difference between the mean age and gender distribution of the patients between both the groups (Table 1).

Table 1. Demographic data of patients

	iPTH <300	iPTH ≥ 300	All	P value
Number of Patients (%)	35(58.3)	25(42.7)	60	-
Age years (Mean±SD)	49.03 ± 11.52	51.84 ± 12.7	50.43 ± 12	0.376
Gender: Male(%)	20 (57.1)	14 (56)	34 (56.7)	0.93
Female(%)	15 (42.9)	11 (44)	26 (43.3)	0.75
T test, chi square was used				

Biochemical parameters

Serum Biochemistry

Serum biochemistries for the total cohort (*n* = 60) are presented in Table 2.

Table 2 biochemical profile of the study group.

Table 2. Disease characteristics of patients

	Mean	SD	Minimum	Maximum
Hemoglobin	8.21	1.5	4.90	12.90
Hct	26.05	4.71	14.90	41.90
Calcium	6.75	1.44	3.30	12.20
PO_4	5.95	1.7	3.00	13.40
Ca *x* PO_4 [a]	35.76	30.28 – 45.13		
iPTH[a]	232.9	133 – 903.8	40.25	1014
FGF-23[a]	334.5	260.8 - 1500	188	1500
Vitamin D_3 [a]	161.4	105.4 – 355.2	39.3	557
Albumin [a]	3.5	2.9 – 4.07	1.2	5.2
Kt/V [a]	0.95	0.7 – 1.3	0.95	1.96
[a] Data presented using median and interquartile range				

As mentioned above, depending on the parathyroid hormone level dialysis patients were divided into two groups viz. Group A(iPTH<300) and Group B (iPTH ≥300). Biochemical parameters viz. Hemoglobin, hematocrit, Vitamin D3, and Kt/V although had higher values in group B in comparison to group A but did not show any difference when compared between both the groups (P value > 0.05). Serum levels of calcium (p=0.007), phosphate (p<0.001), calcium phosphate product (p=0.043), FGF-23(p<0.001) and albumin (p=0.01) were found to be significantly higher in group A when compared with group B (Table 3).

Table 3. Biochemical data of patients divided by iPTH

	PTH <300		PTH ≥ 300		P value
Normal distribution	Mean	SD	Mean	SD	
Number	35		25		-
Hemoglobin	8.32	1.72	8.06	1.15	0.518
Hct	26.51	5.46	25.41	3.41	0.377
Calcium	6.38	1.05	7.34	1.6	0.007
PO_4	5.1	0.78	7.22	1.79	<0.001
Non normal distribution	Median	IQR	Median	IQR	
Ca *x* PO_4 product [a]	35.19	29.58 – 39.33	42	30.55 – 54.03	0.043
FGF-23[a]	271.57	235.5 – 328.4	1500	1138.5 – 1500	<0.001
Vitamin D_3 [a]	157.3	116.2 – 469.8	197.7	85.5 – 430.3	0.793
Albumin [a]	3.1	2.9 – 3.8	3.9	3.3 – 4.25	0.01
Kt/V [a]	0.93	0.7 – 1.24	0.99	0.79 – 1.34	0.525

[a]: median and IQR (interquartile range) used
t test for normally distributed variables, and Mann Whitney U test for non-normal distribution variables

Results of univariate analysis showed a statistically significant positive correlation between FGF23 values and iPTH values at a level of 78.2% (r^2: 0.612, p<.001). FGF23 and Ca also showed positive statistically significant correlation (r^2: 0.222, p<.001). We found a positive and statistically significant correlation between FGF23 and between FGF-23 values and PO_4 at a level of 28.1% (r^2: 0.366, p<.001) (table 4 and figure 3 ,4 and 5).

Table 4. Univariate Pearson correlation of Log_{10} FGF-23 and various variable

Variables	Standardized beta	R^2	P value
iPTH	0.782	0.612	<0.001
Ca	0.471	0.222	<0.001
PO_4	0.605	0.366	<0.001
Ca *x* PO_4 product	0.247	0.061	0.058
Albumin	0.064	0.004	0.629
Vitamin D_3	0.037	0.001	0.781
Kt/V	-0.088	0.008	0.575

R^2: coefficient of determination, standardized beta: correlation coefficient

Figure 3. Scatter plot of iPTH and Log_{10} (FGF-23)

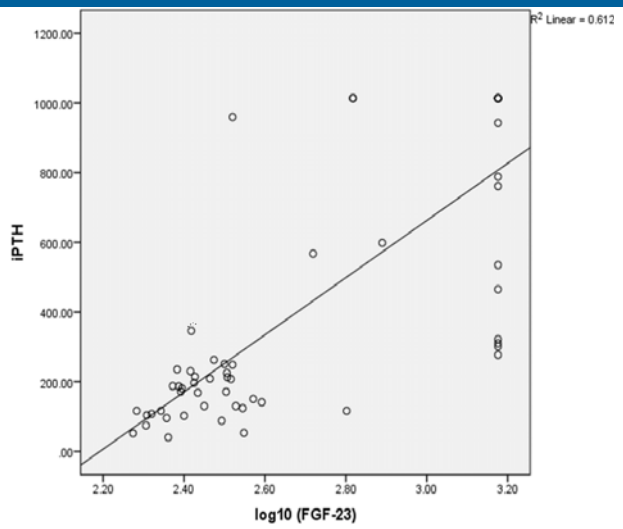


Figure 4. Scatter plot of Log_{10} FGF-23 and PO_4

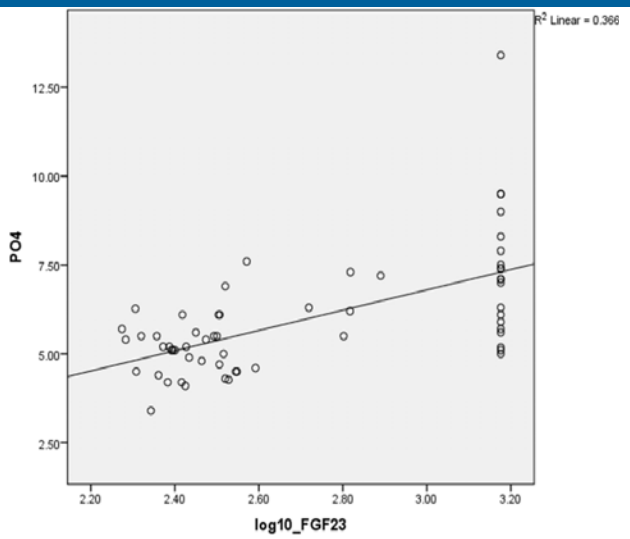
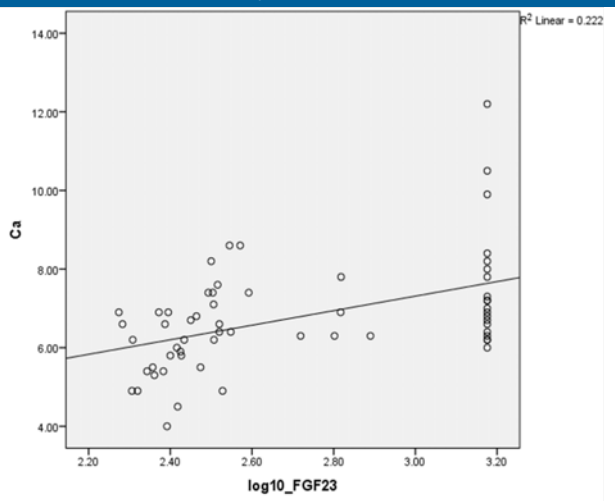


Figure 5. scatter plot of Log_{10} FGF-23 and Ca



No significant correlation was found between FGF-23 and Hb and Hct as illustrated in table 5.

Table 5. Univariate Pearson correlation of Log_{10} FGF-23 and various variable

Variables	Standardized beta	R^2	P value
Hb	-0.154	0.024	0.239
Hct	-0.111	0.012	0.399

R^2: coefficient of determination, standardized beta: correlation coefficient

In multivariate analysis, it was observed that iPTH and Log_{10} FGF-23 and PO_4 were positively correlated. This correlation remained significant after the adjustment to the effect of other variables in module (iPTH, Ca, calcium phosphate product, age, albumin, vitamin D_3 and Kt/V) meaning iPTH and PO_4 are independently correlated with Log_{10} FGF-23 (Table 6). It was calculated that the effect of iPTH was significant at the level of p=0.000. The effect of PO_4 was also found to be significant at the level of p=0.018 (Table 6). However, the correlation between Ca and FGF23 became insignificant with the effect of other variables (Table 6).

Table 6. Multivariable correlation of Log_{10} FGF-23 and various variable

Variables	Standardized beta	P value
Constant	-	0.000
iPTH	0.591	0.000
Ca	0.195	0.157
PO_4	0.338	0.018
Ca *x* PO_4 product	-0.222	0.134
Albumin	-0.029	0.776
Vitamin D_3	0.080	0.436
Kt/V	0.086	0.426

FGF23, LVH and Ejection function

FGF23 was found to have a statistically significant positive correlation with interventricular sep-tum end diastolic diameter (IVSd)/left ventricular posterior wall end diastolic diameter (LVPWd) (r: 0.428, p=.001). We found a statistically significant negative correlation between FGF23 levels and ejection fraction (r:-0.458, p<0.001) (Table 7, figure 6 and 7).

Correlation between FGF and EF and LVH			
	r	R^2	P value
EF	-0.458	0.210	<0.001
IVsd/PWd	0.428	0.184	0.001

Figure 6. Scatter plot of FGF23 level and Ejection fraction

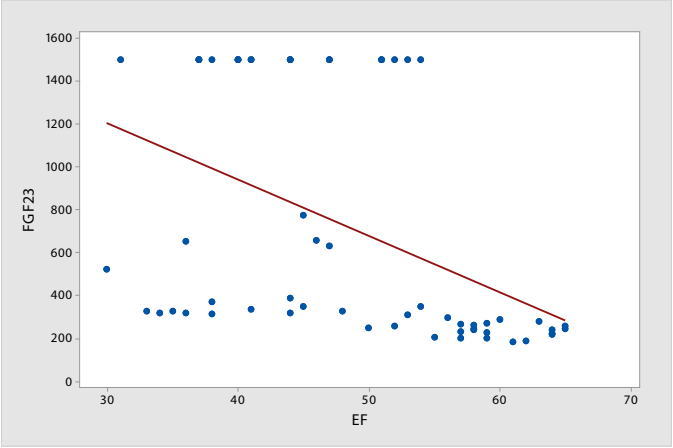
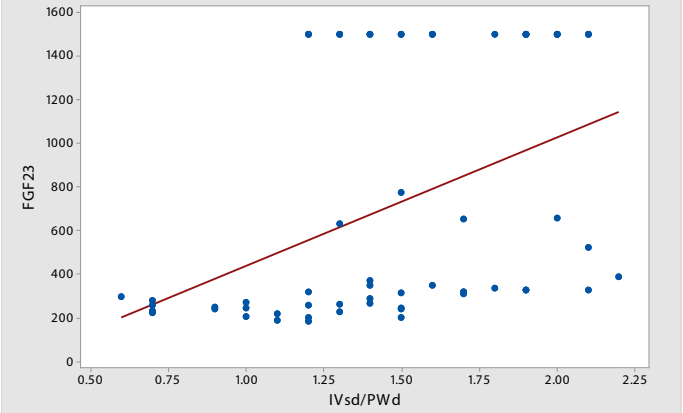


Figure 7. Scatter plot of FGF23 level and left ventricular hypertrophy



Discussion

Fibroblast growth factor-23 has an important role in mineral metabolism, metabolism of vitamin D, functions of parathyroid glands and excretion of phosphate from the kidney. It has been found that serum levels of FGF23 start increasing as soon as glomerular filtration rate falls below 90 mL/min/ per 1,73 square meters. Considering this, it has been thought that FGF23 could act as a prognostic marker which increases parallel with PO_4 levels from the early stages of CKD and contributes to the development of secondary hyperparathyroidism by suppressing levels of 1,25(OH)2D and increasing the excretion of PO_4[10]. Keeping this in view, in the present study In this study, we aimed to establish a correlation between FGF23 and parameters such as serum PO_4, iPTH, Ca which affect the rate of mortality and morbidity in the CKD patients undergoing dialysis.

60 patients were recruited for this study and these patients were divided in two groups based on the serum concentration of iPTH (Group A and Group B). Demographic data showed no significant difference between the recruited patients based on the age and gender in both the groups. The comparison was done between both the groups for various biochemical parameters. We did not find any significant difference between the values of hemoglobin, hematocrit, Vitamin D3, and albumin. Noticeably, the levels of Ca, PO_4 and FGF23 were found to be significantly high in group with high level of iPTH. Studies have shown that levels of FGF23 in serum increase prior to the increase in PTH in CKD[11]. As abovesaid, FGF23 contribute to the development of secondary hyperparathyroidism by suppressing levels of vitamin D, excretion of phosphorus[11]. Moreover, inhibition of enzyme 1-alpha-hydroxylase with increased production of FGF23 also leads to decreased calcium absorption in intestine leading to increase in PTH level. Our study data was in line with these findings as we observed high levels of FGF23 in group A with high level of PTH[12]. We also observed the increased levels of PO_4 in patients with high levels of PTH. Various studies have shown that increased level of PO_4 is related to increased PTH levels in CKD. It has been shown that in CKD patients, increase in serum phosphate is due to reduction in secretion of phosphate by the renal tubules and this promotes secondary hyperparathyroidism with increased concentration of PTH[13].It has also been explored that a progressive decline in GFR in CKD causes reduced levels of $1,25(OH)_2D$. This prolonged CKD-associated hypocalcemia and hyperphosphatemia also drives the parathyroid gland for the secretion of more PTH to normalize the levels of PO_4 and Ca. This further explains the remarkably increased levels of PO_4 in the high PTH group[14].

Studies have shown that secondary hyperparathyroidism could lead to anemia by inhibiting the production of red blood cells, increasing the fragility and thereby causing fibrosis of bone marrow. Since, their exists positive correlation between FGF23 and PTH, it is believed that FGF23 could contribute towards the development of anemia in the dialysis patients. Therefore, we tried to establish correlation between various blood parameters and FGF23 but we did not find any correlation between any parameter associated with blood such as hemoglobin and FGF23[15]. Similar results were obtained in the study conducted by Mirza et al[16]. In our study, we did not found significant difference in serum albumin levels of low and/ or normal or high serum FGF-23 patients.

A strong positive correlation was found between the levels of FGF23 and PTH levels. Various previous studies have shown similar to our study a strong correlation between serum FGF23 levels and iPTH levels. FGF23 and PTH regulate each other mutually in a negative feedback loop. In this loop, PTH stimulates the production of FGF23 and FGF23 in turn lead to suppression of PTH synthesis[17]. Study by Meir et al showed the activation of the nuclear receptor-associated protein-1 (Nurr1) is induced by PTH via the PTH receptor which further induces transcription of FGF23 in bone cells[18]. A recent study aimed at demonstrating the correlation of FGF23 with various factors recruited 89 patients of CKD undergoing dialysis. The data obtained was in coherence to our study showing significant positive correlation between serum levels of FGF23 and PTH values[19]. However, various studies have shown contradictory findings to our study. It has been well established that FGF23 requires αKlotho as a co-receptor for binding to its FGFR receptor. Expression of αKlotho has been found on kidney, parathyroid glands and epithelium of the choroid plexus which limits the organs which can be targeted by FGF23. Parathyroid glands express both FGFR and αKlotho indicating correlation between FGF23 and PTH. Contrary to our finding, some in vitro studies have shown that PTH mRNA expression and secretion of hormone is suppressed by FGF23[20]. An in vivo study data concluded negative regulation of PTH secretion by FGF23[20]. Study by DeLuca et al[21] supported our finding. It showed that FGF23 null mice that were overexpressing FGF23 showed increased serum levels of PTH inspite of normal calcium, $1,25(OH)_2D$, and hypophosphataemia supporting the fact that FGF23 induces production of PTH hormone[21]. A strong positive correlation was found between FGF23 and PTH in patient suffering from X-linked hypophosphataemia who are normocalcaemic and have low to normal $1,25(OH)_2D$[22]. Along with this, few studies wherein mice were overexpressing transgenic FGF23 caused secondary hyperparathyroidism[22]. Kawakami et al in their study also showed in concordance to our finding that FGF23 is a long-term inducer of proliferation of parathyroid cell and secretion of PTH, thereby one of the cause for secondary hyperparathyroidism in CKD[23].

Levels of circulating FGF23 increase exponentially during early CKD and are enhanced upto 1000 folds in the case of kidney failure[19]. These elevated levels of FGF23 are associated with all cause and cardiovascular mortality in the CKD patients[24], dysfunction of LV, atrial fibrillation and cardiac hypertrophy development[19,24].

These studies showing higher incidences of CVD in CKD patients along with the increase of FGF23 strongly recommend a strong correlation between CVD and levels of FGF23. This correlation could be established by conducting 2D- Echocardiography of the recruited CKD patients who were undergoing dialysis. Therefore, as another major objective of this study, we aimed at establishing a correlation between FGF23, LVH and LVEF. Our data suggested strong positive correlation of FGF23 with LVH. On the contrary, we found statistically significant negative correlation between FGF23 and LVEF. A study conducted by Mirza et al., evaluated the relation between FGF23 and LVH in a cohort of elderly people consisting of 795 swedish men and women. Similar to our findings, it was found that their exists strong association between elevated levels of serum FGF23 and increased risk of LVH [25]. Nielsen et al. conducted a cross-sectional study including 239 hemodialysis patients to establish the association between FGF23, LVH and LVEF. In concert to our findings, it was found that FGF23 was positively associated with LVH and negatively associated with LVE[F25]. Faul et al. also showed that elevated levels of FGF23 were associated with LVH in a large, racially diverse cohort of people suffering from CKD. They further showed in mice model that FGF23 led to the pathological hypertrophy of the cardiomyocytes isolated from the rats. This was mediated through FGF receptor–dependent activation of the calcineurin-NFAT signaling pathway, independent of Klotho as injecting FGF23 in wild type mice resulted in LVH as well as klotho deficient mice resulted in increased FGF23 levels and LVH[26]. In order to understand the mechanism by which FGF23 directly regulates LVH, it was found that FGF23 directly induced the hypertrophic growth of cardiomyocytes and led to cardiac hypertrophy in in vivo mice model which was further abolished by the inhibition of calcineurin but not by the use of inhibitors against MAP kinase, PI3 Kinase or inhibitors of Akt[27]. Later on FGFR4 was found to be the main molecule for efefctor function of FGF23 signalling in the heart which summarized that FGF23 induced cardiac hypertrophy is mediated by the FGFR4/PLCg/calcineurin pathway which activates NFAT and later on pro-hypertrophic NFAT target genes[28]. Another mechanism behind FGF23 induced LVH was that pro-hypertrophic properties of FGF23 might be the direct regulator of Na-Cl channel NCC in the distal renal tubules by FGF23, thereby making it a sodium-conserving hormone[28].

Conclusions

This study conducted to evaluate the prognostic value of FGF23 indicated that along with determining the levels of iPTH in the patients undergoing hemodialysis, measurement of FGF23 could serve as strong prognostic marker. Higher levels of FGF23 in the patients of secondary hyperparathyroidism emphasize the need to decipher the FGF23-klotho axis in detail. This would provide more evidence and elucidation of novel therapeutic measures for treatment of secondary hyperparathyroidism. Moreover, linear correlation of FGF23 with LVH and left ventricular dysfunction strongly recommend to keep an check on cardiac parameters in dialysis patients with high FGF23 levels to avoid any mortality with CVD associated with CKD to the best possible level.

Recommendation

1. Regular monitoring of FGF23 in follow up hemodialysis patients or in those at increased risk of CKD-BMD.

2. Administration of drugs that lower FGF23 in hemodialysis patients (phosphate binders and cinacalcet), in addition to dietary control (decrease phosphate intake)

3. Further studies are needed to clarify the effects of FGF23 on hemodialysis patients in detail.

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