

Fibroblast Growth Factor-23: A Possible Cause of Pulmonary Hypertension and Left Ventricle Hypertrophy in Hemodialysis Patients

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Abstract

Assessment of blood level of fibroblast growth factor-23 (FGF-23) levels was done in forty patients with end-stage kidney disease (ESRD). We found that there were statistically significant positive correlations between FGF-23 and LVH, Phosphorus and Parathormone hormone. Statistically significant negative correlations were found between FGF-23 and corrected Calcium) and 25 (OH) vitamin D, but there was no significant correlation between FGF-23 and pulmonary artery systolic pressure. For prediction of FGF-23 Levels stepwise multiple linear regression analysis was done and revealed that the most 4 predictable values of FGF-23 are intact Parathormone hormone, corrected calcium, 25 (OH) vitamin D and SBP respectively. There were positive correlations between FGF-23 with LV mass and LV mass index. Statistically significant negative correlations were found between FGF-23 and LVIDs. A multiple discriminant functional analysis for prediction of LVH revealed that age, FGF-23, and Vitamin D are the most predictable variables. Hemodialysis patients with LVH had higher FGF-23 levels raising the possibility that FGF-23 may predict LVH.

Keywords: Parathormone; Hyperphosphatemia; Hypocalcemia; Hypercalcemia; Hyperparathyroidism

Introduction

It is estimated that there are more than 20 million in the United States have chronic kidney disease (CKD), which accounts for more than 10% of adults [1]. CKD patients have an increased risk of cardiovascular diseases (CVD), independent of hypertension, diabetes mellitus and albuminuria [2]. Endothelial dysfunction increased oxidative stress, inflammation, anemia, and CKD-mineral and bone disorders (MBD) increase as renal function deteriorates and these have been proposed to be responsible for the increased mortality seen in patients with CKD & ESRD [3].

CKD related mineral and bone disorders (CKD MBD) is a systemic disorder of mineral and bone metabolism and is associated with increased CVD & mortality. These disorders include hyperphosphatemia, hypocalcemia, hypercalcemia, hyperparathyroidism and vitamin D deficiency [4]. A recently described biochemical disorder that belongs to the CKD MBD is the elevated fibroblast growth factor-23 (FGF-23), which has been recently linked to worse outcomes of CKD patients, independent of other risk factors [5].

Fibroblast growth factor-23 (FGF-23) is a hormone that is mainly secreted by osteocytes. It is up-regulated by 1, 25 (OH) vitamin D and possibly by increased serum phosphate levels [6]. FGF-23 induces renal phosphate wasting by inhibiting the proximal tubular sodium phosphate co transporter type IIa (NPT2a) and suppressing the renal expression of CYP27B1, resulting in decrease of 1, 25 (OH) 2D3 synthesis [7].

FGF-23 concentrations start to increase with mild impairment of the glomerular filtration rate (GFR) in stage 2 or 3 of chronic kidney disease (CKD), before the increase of serum phosphate is detectable, but can reach levels 1,000-fold above normal in advanced renal failure [8].

Several studies suggested that serum levels of FGF-23 are increased in hemodialysis (HD) patients, and this increase is independently associated with increased mortality in patients who are beginning HD treatment [9]. Moreover, serum FGF-23 was shown to be independently associated with left ventricle hypertrophy (LVH) [10]. Pulmonary hypertension (PH) is another complication of several systemic disorders. The estimated prevalence of PH in hemodialysis patients ranges from 16 to 58% [11].

The pathogenesis of PH in patients with renal failure is complex. Possible causes include metabolic and hormonal derangements, high cardiac output due to arterio-venous fistulae (AVF), impaired endothelial function, fluid overload as well as other factors [12].

Aim of the Work

We aimed to study the relation between FGF-23 and left ventricle hypertrophy and pulmonary hypertension in hemodialysis patients, in the Dialysis Unit, Minia University Hospital.

Patients and Methods

This study is an observational cross-sectional study and it included 40 patients with end stage renal disease (ESRD); the participants were recruited from the Dialysis Unit, Minia University Hospital in the period from November 2013 to June 2014.

The study was explained to the patients and written informed consent was given by all patients.

Inclusion criteria included: all patients with end stage renal disease (ESRD) and are on hemodialysis, adult patients with age range 30-50 years of age and both males and females were included. Exclusion criteria included: patients with border line or normal renal function, patients with renal transplantation and patients younger or older than the previously mentioned age range.

All the patients were subject to the following:

- Complete clinical history taking.
- Thorough clinical examination.
- Laboratory investigations that included:

Serum creatinine

Blood urea

Complete blood count (CBC)

Serum phosphorus (Ph)

Serum calcium (Ca)

Serum intact parathormone hormone (iPTH)

Serum 25 hydroxyvitamin-D (25 (OH) vitamin D)

Serum fibroblast growth factor-23 (FGF-23)

Triglyceride (TG)

Total cholesterol (TC)

(Kt/v) calculated by Daugirdas second-generation formula.

- Echocardiography:

Echocardiography was performed by a single author (TTI) with 15 years' experience. Echocardiographic examination was performed using General Electric Vivid 3 ultrasound machine (GE Healthcare, Milwaukee, USA) with simultaneous ECG tracing. Echocardiography was performed with patients in semi-recumbent left lateral position with the probe located at the third or fourth intercostal space at the left sternal border. The measurements represent the mean of 3 consecutive cardiac cycles.

Measured parameters

- Internal dimension of the Left ventricle in end systole (LVIDs) and in end diastole (LVIDd) with estimation of the ejection fraction (EF) by M-mode in Parasternal long-axis (PSLAX) view [13].
- Left ventricle free wall thickness (LVPWT) and interventricular septum thickness (IVST) measured at the end of diastole by M-mode in PSLAX view [13].
- Left ventricular mass (LV Mass): LV Mass is calculated by Devereux's formula [14], as follows:

$$LV\ mass = 0.8 [1.04\{IVSd + LVIDd + PWTd\}^3 - LVIDd^3] \ 0.6g.$$

Normalization of left ventricular mass by body surface area (BSA):

LV mass / Body Surface Area (g/m^2), as BSA is calculated by Mosteller square root method [15].

$$BSA = \text{Height (m)} \times \text{Weight (Kg)} / 36$$

LV mass index was calculated as the ratio of LV mass to the BSA.

According to this formula, patients were considered to have LVH if the LV mass index was greater $>134\ g/m^2$ in men and $>110\ g/m^2$ in women [16].

Assessment of the pulmonary arterial systolic pressure (PASP) is done by measuring the maximal tricuspid regurgitation velocity (TR Vmax), then applying the modified Bernoulli equation to calculate the pressure values. Estimated right atrial pressure (RAP) must be included.

PASP measurement by Modified Bernoulli equation = tricuspid regurgitation gradient + (RAP).

$$PASP = (V_{max}^2 \times 4) + RAP.$$

- RAP presumed average 10 mmHg
- Normal value rest up to 35 mmHg

Statistical methods

The collected data were statistically analyzed using SPSS software version 20 (Statistical Package for Social Sciences). Descriptive statistics were done for numerical data by mean, standard deviation and minimum & maximum of the range, while they were done for categorical data by number and percentage.

Patients were classified into 2 groups according to the level of FGF23. Analysis of quantitative variables was done using independent sample t test between the 2 groups.

Not normally distributed data was tested after log transformation.

Chi square test was used for qualitative data between groups.

Correlation between two quantitative variables was done by using Pearson's correlation coefficient and for non-parametric variables Spearman's rho correlation test was used:

Correlation coefficient ranges from (0-1):- weak ($r=0-0.24$), fair ($r=0.25-0.49$), moderate ($r=0.5-0.74$), strong ($r=0.75-1$)

Stepwise multiple linear regression analysis was used for prediction of different variables. Stepwise multiple discriminant functional analysis was used for prediction of LVH. The level of significance was taken at ($p\ value \leq 0.05$). A post-hoc sample size calculation provided 100% power for the study.

Results

Mean age of patients was 41.5 ± 14.82 years. There were 23 (57.5%) men and 17 (42.5%) women. The body mass index (BMI) was $23.88 \pm 3.91\ kg/m^2$ while the systolic blood pressure (SBP) was $136.5 \pm 16.57\ mmHg$.

Seven patients were diabetic (17.5%), 4 patients had history of cardiovascular disease (10%), 26 patients were hypertensive (65%) and 6 patients were smokers (15%). Thirty three patients (82.5%) had proximal arterio venous fistula (AVF) and 7 patients (17.5 %) had distal AVF. Four patients died during the study (Table 1).

Variables:	Descriptive statistics (n=40)
WBCs $\times 10^3$ (cells/mm ³)	6.92 \pm 6.41
Hg (gm/dl)	9.99 \pm 1.77
Platelets ($\times 10^3$) (cells/mm ³)	170.4 \pm 50.26

Albumin (gm/dl)	3.87 ± 0.49	IVSs: (cm) ¹	1.63 ± 0.27
Urea (mg/dl)	137.07 ± 7.32	LVIDs: (cm) ¹	3.07 ± 0.93
Creatinine (mg/dl)	5.96 ± 0.57	LVPWs: (cm) ¹	1.44 ± 1.05
e GFR (ml/min 1.73 m ²)	10.12 ± 2.02	EF: (%) ¹	61.65 ± 8.99
Corrected Ca (mg/dl)	8.14 ± 0.23	LV mass: (gm) ¹	254.52 ± 60.25
Phosphorous (mg/dl)	6.34 ± 1.08	LV mass index: (gm/m ²) ¹	154.51 ± 36.23
iPTH (pg/mL)	451.03 ± 497.7	L VH: Yes / No ²	31 (77.5%) / 9 (22.5%)
25 (OH) Vit D (ng/mL)	42.59 ± 33.71	PASP: Pulmonary Arterial Systolic Pressure; IVSd: Interventricular Septal Thickness at Diastole; LVIDd: Left Ventricular Internal Dimension-diastole; LVPWd: Left Ventricle Posterior Wall Dimension in diastole; IVSs: Interventricular Septal thickness in systole; LVIDs: Left Ventricle Internal Dimension in systole; LVPWs: Left Ventricle Posterior Wall thickness at end systole; EF: Ejection Fraction; LV mass: Left Ventricular mass; LVH: Left Ventricular Hypertrophy.	
FGF-23 (pg/mL)	54.86 ± 16.82		
TG (mg/dl)	138.82 ± 47.81		
TC (mg/dl)	116.47 ± 44.96		
PASP: (mmHg) ¹	43.05 ± 12.41		
IVSd: (cm) ¹	1.12 ± 0.17		
LVIDd: (cm) ¹	4.99 ± 0.64		
LVPWd: (cm) ¹	1.11 ± 0.16		

Table 1: Laboratory and Echocardiography data of the study patients.

We classified patients into 2 groups, according to the level of FGF-23. No significant difference was noted in PASP, pulmonary HTN, IVSd, LVIDd, LVPWd, IVSs, LVPWs or EF (Table 2).

Variables	Low FGF23 (<44.55) (n=19)	High FGF23 (≥ 44.55) (n=21)	P value
SBP (mmHg) ¹	122.6 ± 12.4	149.04 ± 7	<0.001*
DBP (mmHg) ¹	75.7 ± 6.9	90.9 ± 7	<0.001*
PASP (mmHg)	41.4 ± 12.3	44.5 ± 12.6	0.437
Pulmonary HTN²			
Yes.	10 (52.6%)	15 (71.4%)	0.22
No.	9 (47.4%)	6 (28.6%)	
IVSd (cm) ¹	1.09 ± 0.15	1.15 ± 0.19	0.204
LVIDd (cm) ¹	5 ± 0.69	4.99 ± 0.6	1
LVPWd (cm) ¹	1.09 ± 0.15	1.12 ± 0.16	0.528
IVSs (cm) ¹	1.62 ± 0.29	1.64 ± 0.25	0.827
LVIDs (cm) ¹	3.38 ± 0.68	2.79 ± 1.04	0.045*
LVPWs (cm) ¹	1.61 ± 1.1	1.28 ± 0.96	0.333
EF (%) ¹	59.8 ± 11.01	63.2 ± 6.5	0.231
LV mass (gm) ¹	213.9 ± 57.3	291.2 ± 33.7	<0.001*
LV Mass index (gm/m ²) ¹	124.4 ± 26.7	181.7 ± 16.7	<0.001*
LVH ²	10 (52.6%)	21 (100%)	<0.001*

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WBCs: White Blood Cells; Hg: Hemoglobin; Ca: Calcium; iPTH: Intact Parathormone Hormone; 25 (OH) vit. D: 25-Hydroxyvitamin D; Kt/v: Integrated Fractional Clearance Expressed Per Dialysis; LVH: Left Ventricular Hypertrophy.

Table 2: Blood pressure and echocardiography data between patients with low and high fibroblast growth factor-23 (FGF-23).

In hemodialysis patients, FGF-23 significantly and positively correlated with SBP, DBP, phosphorous, intact parathormone hormone and LVH.

FGF-23 correlated significantly and negatively with corrected calcium and 25 (OH) vitamin D. FGF-23 didn't correlate with age, sex,

BMI, WBCs, Hg, platelets, albumin, urea, creatinine and kt/v (integrated fractional clearance expressed per dialysis), as shown in Table 3.

Variables	R	P value
Age (years)	0.226	0.161
Sex: male	0.134	0.41
BMI (gm/m ²)	-0.058	0.724
SBP (mmHg)	0.725	<0.001*
DBP (mmHg)	0.634	<0.001*
WBCs (cells/mm ³)	-0.147	0.367
Hg (gm/dl)	-0.101	0.534
Platelets (x10 ³) (cells/mm ³)	-0.051	0.756
Albumin (gm/dl)	-0.037	0.82
Urea (mg/dl)	-0.181	0.263
Creatinine (mg/dl)	-0.166	0.307
Corrected Ca (mg/dl)	-0.342	0.031*
Phosphorous (mg/dl)	0.702	<0.001*
iPTH (pg/mL)	0.962	<0.001*
25 (OH) Vit D (ng/mL)	-0.609	<0.001*
Kt/V	-0.09	0.581
LVH (cm)	0.717	<0.001*

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WBCs: White Blood Cells; Hg: Hemoglobin; Ca: Calcium; iPTH: Intact Parathormone Hormone; 25 (OH) vit. D: 25-Hydroxyvitamin D; Kt/v: Integrated Fractional Clearance Expressed Per Dialysis; LVH: Left Ventricular Hypertrophy.

Table 3: Correlation coefficient between plasma fibroblast growth factor (FGF-23) and other variables.

Multiple linear regression analysis for prediction of FGF-23 levels revealed that the most 4 predictable values of FGF-23 are iPTH, corrected Ca, 25 (OH) vitamin D and SBP respectively (Table 4).

Models	–	β	R	Adjusted R square	P value
1	Constant.	40.2	0.962	0.923	<0.001*
	iPTH	0.033			
2	Constant	113.97	0.969	0.936	<0.001*
	iPTH	0.032			
	Corrected Ca	-9.01			
3	Constant	142.44	0.975	0.947	<0.001*
	iPTH	0.035			
	Corrected Ca	-13.12			

	Vit D	0.082			
4	Constant	135.39	0.979	0.954	<0.001*
	iPTH	0.033			
	Corrected Ca	-14.96			
	Vit D	0.124			
	SBP	0.155			

Table 4: Multiple linear regression analysis for prediction of fibroblast growth factor (FGF-23) levels revealed 4 models.

FGF-23 revealed significant positive correlation with LV mass. FGF-23 also revealed significant negative correlation with LVIDs and FGF-23 didn't correlate with PASP, IVSd, LVIDd, LVPWd, IVSs, LVPWs and EF (Table 5).

Variables	r	P value
PASP (mmHg)	-0.024	0.881
IVSd (cm)	0.01	0.951
LVIDd (cm)	-0.124	0.445
LVPWd (cm)	0.028	0.865
IVSs (cm)	-0.114	0.482
LVIDs (cm)	-0.336	0.034*
LVPWs (cm)	-0.155	0.34
EF (%)	0.18	0.266
LV mass (gm)	0.554	<0.001*
LV Mass index (gm/m ²)	0.765	<0.001*

PASP: Pulmonary Arterial Systolic Pressure; IVSd: Interventricular Septal Thickness At Diastole; LVIDd: Left Ventricular Internal Dimension-Diastole; LVPWd: Left Ventricular Posterior Wall Dimensions In Diastole; IVSs: Interventricular Septal Thickness In Systole; LVIDs: Left Ventricular Internal Dimension In Systole; LVPWs Left Ventricular Posterior Wall Thickness At End Systole; EF: Ejection Fraction; LV mass: Left

Table 5: Correlation coefficient between fibroblast growth factor (FGF-23) and echocardiographic variables.

Increased PASP ≥ 35 mmHg was observed in 25 patients (62.5%) on hemodialysis. Patients with increased PASP have higher levels of Ph, iPTH and higher incidence of LVH and lower levels of 25 (OH) vitamin D. No significant difference in age, sex, BMI, duration of dialysis, Hg, corrected Ca, albumin, urea, creatinine, eGFR and FGF-23 level (Table 6).

	Increased PASP (n=25)	Normal PASP (n=15)	P value
–			
Age	43.6 \pm 13.8	37.8 \pm 16.2	0.235
Sex:			
Males.	12 (48%)	11(73.3%)	0.117
Females.	13 (52%)	4 (26.7%)	–
BMI	23.7 \pm 4.1	24.1 \pm 3.6	0.821
Cause of RF.			
HTN.	5 (20%)	4 (26.7%)	
DM.	4 (16%)	1 (6.7%)	0.773
GN.	2 (8%)	2 (13.3%)	–
Others.	14 (56%)	8 (53.3%)	–
Duration of dialysis.	4.4 \pm 2.3	5.3 \pm 3.8	0.365
Medications:			
B blockers.	8 (32%)	1 (6.7%)	0.063
CCB.	8 (32%)	5 (33.3%)	0.931
ACE inhibitors.	6 (24%)	7 (46.7%)	0.138
Hb	9.7 \pm 1.6	10.3 \pm 1.9	0.308
Corrected Ca ²⁺	8.19 \pm 0.28	8.1 \pm 0.18	0.243
Phosphorous	6.6 \pm 0.5	5.8 \pm 1.5	0.031*
iPTH	499.6 \pm 499.5	370.1 \pm 576.4	0.022*
Albumin	3.8 \pm 0.5	3.9 \pm 0.2	0.722
Urea	136.2 \pm 6.1	138.4 \pm 9.1	0.359
Creatinine	5.8 \pm 0.5	6.1 \pm 0.5	0.242
e GFR	9.8 \pm 2.04	10.5 \pm 1.9	0.338

FGF23	56.7 ± 17.7	51.6 ± 15.2	0.361
1,25 (OH) Vit D	31.6 ± 19.4	60.8 ± 44.1	0.006*
LVH	23 (92%)	8 (53.3%)	0.005*
AVF:-			
Proximal	23 (92%)	10(66.7%)	0.041*
Distal	2 (8%)	5 (33.3%)	–

Table 6: Data between patients with high and normal pulmonary arterial systolic pressure (PASP).

Discussion

Cardiovascular disease is a common complication in end-stage renal disease (ESRD) patients. The majority of deaths in hemodialysis (HD) patients are caused by cardiovascular events, followed by infection and stroke [17].

Left ventricle hypertrophy (LVH) is one of the most important cardiovascular complications in HD patient. Moreover, it is an independent risk factor for cardiovascular death in patients who are on maintenance HD therapy [18].

Pathogenesis of LVH in those patients can be divided into 3 categories [19]: 1) Afterload related, e.g. hypertension and arterial calcification; 2) Preload related, due to expansion of intravascular volume and large flow arteriovenous fistulae; and 3) Neither after load nor preload related. The aggressive control of blood pressure (BP) and anemia, in HD patients does not prevent LVH. Thus, it is possible that other factors play a role in the initiation and progression of LVH. Hyperphosphatemia is common in HD patients [20] and it was found that the control of serum phosphate level correlated well with the reduction in left ventricle mass index (LVMI). Thus, it was suggested that a novel mechanism may be responsible for the association of elevated serum phosphate and LVH and the consequent poor cardiovascular outcome in HD patients [21].

In our study, hemodialysis patients with LVH had higher FGF-23, raising the possibility that FGF-23 may predict LVH. We also found a significant positive correlation between FGF-23 and LVM index. This comes in agreement with the study by Hsu and Wu, 2009, who studied the association of FGF-23 and LVH in HD patients and revealed that LVH was significantly correlated with higher levels of FGF-23 [22].

Our result is also consistent with another study by Kirkpantur et al. 2011 who tested whether elevated FGF-23 levels are associated with left ventricular function as indicated by LV mass index (LVMI) and LV index of myocardial performance (MPI) in maintenance hemodialysis patients. Their study found that plasma FGF-23 level was associated with increased LVMI and MPI, independent of other known risk factors [23].

The renin-angiotensin system (RAS) is a key factor in increased cardiovascular morbidity and mortality. This is due to several effects, e.g. hypertension, baroreceptor dysfunction, endothelial dysfunction and LVH. Activation of the RAS by FGF-23 could be the explanation of the association of FGF-23 with LVH [24].

Another possible mechanism for the association of FGF-23 with adverse cardiovascular events is its effect on inflammation. Inflammation is common in ESRD patients and is associated with

significantly worse outcomes. Experiments suggest that FGF-23 increases the production of inflammatory markers such as lipocalin-2, tumor necrosis factor- α and the transforming growth factor- β [25]. Elevated serum FGF-23 levels have been found to be significantly correlated with these inflammatory markers in an observational study [26].

LVH is an adaptive response to increased cardiac workload; it has short-term beneficial effects on cardiac function, but detrimental effects on the long term [27].

A recently described gene, ST2, has been suggested by many authors to be implicated in cardiac muscle dysfunction. It is suggested that it plays a role in reducing the cardio-protective effects of IL-33. ST2 predicted mortality, according to recent studies. It was also correlated to systolic blood pressure, antihypertensive treatment and pulmonary & renal dysfunction [28]. This was not evaluated in our study.

Phosphatonins, such as fibroblast growth factor 23 (FGF-23), may act on multiple organs to regulate phosphate metabolism. FGF-23 decreases blood phosphate by reducing renal phosphate reabsorption and suppressing 1α -25 (OH) $_2$ D [29].

In the present study, FGF-23 positively correlated with PH level in hemodialysis patients. One possible explanation could be that the kidney, a principal target of FGF-23, was no longer responsive to FGF-23 in CKD. Renal klothoproduction is reduced in end-stage renal disease. This is an essential co-factor for FGF-23 activation. A second explanation could be that, in early stage CKD, serum FGF-23 is elevated to promote urinary excretion of phosphate and maintain serum phosphate levels. But in patients with advanced disease, overt phosphate loading may overcome this phosphate excretion despite markedly elevated FGF-23 levels [30].

In the present study, stepwise multiple linear regression analysis for prediction of FGF-23 levels revealed that the most 4 predictable values of FGF-23 are iPTH, corrected Ca, 25 (OH) vitamin D and SBP respectively. So, serum Ca, i-PTH and vit. D could be regulators of FGF-23 levels in patients on maintenance hemodialysis.

In our study, serum FGF-23 also correlated positively with i-PTH levels in hemodialysis patients. This result comes in agreement with a study by Urakawa et al. who found that excess FGF-23 stimulates PTH secretion as evidenced by the strong association between elevated FGF-23 levels and severity of hyperparathyroidism in CKD patients [31].

We also found that serum levels of FGF-23 and 25 (OH) vitamin D showed a trend towards negative correlation in patients on dialysis. This relation may be explained by the fact that 1, 25 (OH) $_2$ D directly

stimulates FGF-23 expression in osteocytes via a vitamin D response element (VDRE) in the FGF-23 promoter. Since FGF-23 targets the kidney to suppress 1, 25 (OH) 2D productions, the 1, 25 (OH) vitamin D stimulation of FGF-23 closes a feedback loop [32].

In our study, we also found that FGF-23 is negatively correlated with corrected calcium. This could be explained by the fact that FGF-23 suppresses **1- α -hydroxylase**, reducing its ability to activate **vitamin D**, impairing calcium absorption [33].

The present study demonstrates that PH was relatively common in the patients receiving HD. The prevalence of PH among hemodialysis patients ranges from 16 to 58%. This wide range is mainly due to the difference in the definition of PH, methodology and ethnicity of patients [34].

Many factors were suggested to contribute to the development of PH in patients with end-stage renal disease. For example, the increase in cardiac output in response to AVF in patients receiving HD, was suggested to be implicated in the pathogenesis of PH [35]. However, there is lack of any significant difference in cardiac output between the patients with and without PH [36]. Similarly, there is reduction in the cardiac output and PAP among HD patients who underwent renal transplantation regardless of the status of the AVF (whether it remains open or closed). This information suggests that there are other possible mechanisms for the development of PH [37].

Ramasubbu et al. reported that 63% of HD patients showed elevated pulmonary capillary wedge pressure (PCWP) [34]. They also noted a significant correlation between PAP and PCWP. In another study, significant increase in cardiac index, inferior vena cava (IVC) diameter and left atrial diameter were noted in PH patients receiving long-term HD [38]. These studies confirm that chronic volume overload may be responsible for the pathogenesis of PH. Other risk factors for PH include age, duration of chronic renal failure, hyperparathyroidism and increased pulmonary vascular stiffness [39].

In our study, increased PASP \geq 35 mmHg was observed in 25 (62.5%) patients receiving hemodialysis. Patients with pulmonary hypertension had significantly higher levels of PH, i-PTH and higher incidence of LVH and lower levels of 25 (OH) vitamin D.

This result comes in agreement with a study by Havlucu who revealed that patients with pulmonary hypertension had significantly longer duration of dialysis, higher serum levels of parathyroid hormone, calcium-phosphate product and higher probability of having an AVF [40].

Extraosseous pulmonary calcifications are found most commonly in patients with ESRD receiving hemodialysis [41]. Calcifications can occur in any tissue, but is found most commonly in the heart, lungs, kidney and stomach. In the lungs, calcium deposits have been found in the interstitium of the alveolar septum, bronchial walls and even in the walls of pulmonary vessels. Autopsy studies of hemodialysis patients have shown that pulmonary vascular calcifications occur frequently [42]. In its mild form, fine linear and granular deposits along the alveolar capillary wall were noted, while in severe forms, there were linear calcifications in the elastic laminae and muscle fibers and in some cases, these were accompanied by loose intimal fibrosis and narrowing of the vessel lumens [43]. Affected vessels become stiffer independent of age or hypertension. Studies have shown that elevated calcium phosphate product is associated with increase morbidity and mortality as well as the development of coronary, valvular and vascular

calcification [44]. In contrast to these findings, the relation between pulmonary artery calcification and PH was not demonstrated [45].

In summary, the results of the present study showed a high prevalence of LVH in ESRD patients and serum FGF-23 level was associated with LVH.

Our study had some limitations. The small sample size in our study was a drawback which may have affected some of the statistical results. Our study included only adult patients with ESRD; pediatric patients were not included. Accordingly, our results do not apply to pediatric patients. Finally, ST2-IL33 pathway was not evaluated in our study.

Ethical Statement

The study was approved by the institutional research ethics committee that conforms to the declaration of Helsinki. All patients provided a written informed consent prior to enrollment in the study.

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