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; 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)
  - Serum phosphorus (Ph)
  - Serum creatinine
  - 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)

\( LV \text{ mass} = 0.8 \times [1.04( IVSd+LVIDd+PWTd) - LVIDd^3]^{0.6g} \)

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

\[ \text{LV mass} \times \text{Body Surface Area} \times (g/m^2) \times 36 \]

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.

\[ \text{PASp} = (V_{max}^2 \times 4) + \text{RAP} \]

- 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 \((p \text{ value} \leq 0.05)\). 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 ± 3.91 kg/m^2 while the systolic blood pressure (SBP) was 136.5 ± 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 arterial 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 \((\times 10^3)\) \(\times 10^3\) (cells/mm^3) | 6.92 ± 6.41 |
| Hg (gm/dl)                 | 9.99 ± 1.77                   |
| Platelets \((\times 10^3)\) (cells/mm^3) | 170.4 ± 50.26                |
### 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) | 122.6 ± 12.4 | 149.0 ± 7 | <0.001* |
| DBP (mmHg) | 75.7 ± 12.9 | 90.9 ± 7 | <0.001* |
| PASP (mmHg) | 41.4 ± 12.3 | 44.5 ± 12.6 | 0.437 |

#### Pulmonary HTN

- **Yes.** 10 (52.6%) 15 (71.4%) 0.22
- **No.** 9 (47.4%) 6 (28.6%) 0.204
- IVSd (cm) | 1.09 ± 0.15 | 1.15 ± 0.15 | 0.528
- LVIDd (cm) | 5 ± 0.69 | 4.99 ± 0.6 | 0.827
- LVPWd (cm) | 1.09 ± 0.15 | 1.12 ± 0.16 | 0.045*
- IVSs (cm) | 1.62 ± 0.29 | 1.64 ± 0.25 | 0.333
- LVIDs (cm) | 3.38 ± 0.68 | 2.79 ± 1.04 | 0.231
- LVPWs (cm) | 1.61 ± 1.1 | 1.28 ± 0.96 | <0.001*
- EF (%) | 59.8 ± 11.01 | 63.2 ± 6.5 | <0.001*
- LV mass (gm) | 213.9 ± 57.3 | 291.2 ± 33.7 | <0.001*
- LV Mass index (gm/m²) | 124.4 ± 26.7 | 181.7 ± 16.7 | <0.001*
- LVH² | 12 (63.2%) | 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).

- **Variables** | **Low FGF23 (<44.55)** (n=19) | **High FGF23 (≥ 44.55)** (n=21) | **P value** |
- Albumin (gm/dl) | 3.87 ± 0.49 | 1.63 ± 0.27 | 0.21 |
- Urea (mg/dl) | 137.0 ± 7.32 | 3.07 ± 0.93 | 0.21 |
- Creatinine (mg/dl) | 9.56 ± 0.57 | 1.44 ± 1.05 | 0.21 |
- eGFR (ml/min 1.73 m²) | 10.12 ± 2.02 | 61.6 ± 8.99 | 0.21 |
- Corrected Ca (mg/dl) | 8.14 ± 0.23 | 31.5 ± 36.23 | 0.21 |
- Phosphorous (mg/dl) | 6.34 ± 1.08 | 1.17 ± 1.65 | 0.21 |
- iPTH (pg/mL) | 451.03 ± 497.7 | 31 (77.5%) / 9 (22.5%) | 0.21 |
- 25 (OH) Vit D (ng/mL) | 42.59 ± 33.71 | 31 (77.5%) / 9 (22.5%) | 0.21 |
- FGF-23 (pg/mL) | 41.4 ± 12.3 | 31 (77.5%) / 9 (22.5%) | 0.21 |
- TG (mg/dl) | 138.82 ± 47.81 | 31 (77.5%) / 9 (22.5%) | 0.21 |
- TC (mg/dl) | 116.47 ± 44.96 | 31 (77.5%) / 9 (22.5%) | 0.21 |

**PASP:** Pulmonary Arterial Systolic Pressure; **IVSd:** Interventricular Septal Thickness at Diastole; **LVIDd:** Left Ventricular Internal Diameter-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 Ventricle mass; **LVH:** Left Ventricular Hypertrophy.

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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 \texttt{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/m²)             | -0.058| 0.724   |
| SBP (mmHg)              | 0.725 | <0.001* |
| DBP (mmHg)              | 0.634 | <0.001* |
| WBCs (cells/mm³)        | -0.147| 0.367   |
| Hg (gm/dl)              | -0.101| 0.534   |
| Platelets (x10⁶) (cells/mm³) | -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* |

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 R² | P value            | \texttt{P value} |
|--------|----|--------|-------|-------------|--------------------|-----------------|
| 1      | Constant | 40.2   | 0.962 | 0.923       | <0.001*            | 0.962           |
|        | iPTH | 0.033  |       |             |                    |                 |
| 2      | Constant | 113.97 | 0.969 | 0.936       | <0.001*            | 0.979           |
|        | iPTH | 0.032  |       |             |                    | 0.954           |
|        | Corrected Ca | -9.01 |       |             |                    | <0.001*         |
| 3      | Constant | 142.44 | 0.975 | 0.947       | <0.001*            | 0.975           |
|        | iPTH | 0.035  |       |             |                    | 0.954           |
|        | Corrected Ca | -13.12 |       |             |                    | <0.001*         |

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).
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).

| 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/m²) | 0.765 | <0.001* |

| –               | Increased PASP (n=25) | Normal PASP (n=15) | P value |
|-----------------|-----------------------|---------------------|---------|
| Age             | 43.6 ± 13.8           | 37.8 ± 16.2         | 0.235   |
| Sex:            |                       |                     |         |
| Males.          | 12 (48%)              | 11(73.3%)           | 0.117   |
| Females.        | 13 (52%)              | 4 (26.7%)           |         |
| BMI             | 23.7 ± 4.1            | 24.1 ± 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 ± 2.3          | 5.3 ± 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 ± 1.6             | 10.3 ± 1.9          | 0.308   |
| Corrected Ca2+  | 8.19 ± 0.28           | 8.1 ± 0.18          | 0.243   |
| Phosphorous     | 6.6 ± 0.5             | 5.8 ± 1.5           | 0.031*  |
| iPTH            | 499.6 ± 499.5         | 370.1 ± 576.4       | 0.022*  |
| Albumin         | 3.8 ± 0.5             | 3.9 ± 0.2           | 0.722   |
| Urea            | 136.2 ± 6.1           | 138.4 ± 9.1         | 0.359   |
| Creatinine      | 5.8 ± 0.5             | 6.1 ± 0.5           | 0.242   |
| e GFR           | 9.8 ± 2.04            | 10.5 ± 1.9          | 0.338   |
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Table 6: Data between patients with high and normal pulmonary arterial systolic pressure (PASP).

|        | High PASP (n=16) | Normal PASP (n=16) | p-value |
|--------|-----------------|--------------------|---------|
| 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%)          |         |

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 LVMI. 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 correlated with LVMI and 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-a 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.

Phosphatonin, 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 1a-25 (OH)2D [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 overwhelm 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) 2D 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-a-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 ≥ 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 difference in cardiac output between the open or closed AVF (whether it remains open or closed). This information suggests that there are other possible mechanisms for the development of PH [37].

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This result comes in agreement with a study by Havluco 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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References

1. (2011) Chronic Kidney Disease Surveillance System, Centers for Disease Control and Prevention Atlanta.
2. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, et al. (2011) Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 79: 1341-1352.
3. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM (2002) The elephant in the uraemia: oxidant stress as a unifying concept of cardiovascular disease in uraemia. Kidney Int 62: 1524-1538.
4. Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K (2010) Outcomes associated with serum calcium level in men with non-dialysis-dependent chronic kidney disease. Clin J Am Soc Nephrol 5: 468-476.
5. Ezumza I, Quares LD, Kovesdy CP (2014) [FGF23 and the heart]. G Ital Nefrol 31.
6. Bergwitz C, Jüppner H (2012) FGF23 and syndromes of abnormal renal phosphate co-transport activity and 1 alpha, 25-dihydroxyvitamin D3 production. J Biol Chem 278: 2206-2211.
7. Saito H, Kusano K, Kinosaki M, Ito H, Hirata M, et al. (2003) Human fibroblast growth factor-23 mutants suppress Na+-dependent phosphate transport in kidney cells. J Biol Chem 278: 2206-2211.
8. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, et al. (2011) Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 79: 1370-1378.
9. Gutiérrez OM, Mannstadt M, Isakova T, Rauch-Hain JA, Tamez H, et al. (2008) Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med 359: 584-592.
10. Hsu HJ, Wu MS (2009) Fibroblast growth factor 23: a possible cause of left ventricular hypertrophy in hemodialysis patients. Ann J Med Sci 337: 116-122.
11. Ramasubbu K, Deswal A, Herdejuren C, Aguilar D, Frost AE (2010) A prospective echocardiographic evaluation of pulmonary hypertension in chronic hemodialysis patients in the United States: prevalence and clinical significance. Int J Gen Med 3: 2279-286.
12. Fabbian F, Cantelli S, Molino C, Pala M, Longhini C, et al. (2010) Pulmonary hypertension in dialysis patients: a cross-sectional Italian study. Int J Nephrol 2011: 283475.
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography.

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Committee on Standards, Subcommittee on Quantification of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 2: 358-367.

Devereux RB, Alonso DR, Lutas EM, Gottdieb G, Campo E, et al. (1986) Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 57: 450-458.

Mosteller RD (1987) Simplified calculation of body-surface area. N Engl J Med 317: 1098.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, et al. (2006) Recommendations for chamber quantification. Eur J Echocardiogr 7: 79-108.

Nakai S, Watanabe Y, Masakane I, Wada A, Shoji T, et al. (2013) Overview of Regular Dialysis Treatment in Japan (as of 31 December 2011). Ther Apher Dial 17: 561-611.

London GM, Pannier B, Guerin AP, Blancher J, Marchais SJ, et al. (2001) Alterations of Left Ventricular Hypertrophy in and Survival of Patients receiving Hemodialysis: Follow-Up of an Interventional Study. J Am Soc Nephrol 12: 2759-2767.

Glassock RJ, Pecottis-Filho R, Barberato SH (2009) Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol 4 Suppl 1: S79-91.

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, et al. (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15: 2208-2218.

Ayus JC, Mizani MR, Achinger SG, Thadhani R, Go AS, et al. (2005) Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. J Am Soc Nephrol 16: 2778-2788.

Hsu HJ, Wu MS (2009) Fibroblast growth factor 23: a possible cause of left ventricular hypertrophy in hemodialysis patients. Am J Med Sci 337: 116-122.

Kirkpantur A, Balci M, Gurbuz OA, Afsar B, Canbakan B, et al. (2011) Mosteller RD (1987) Simplified calculation of body-surface area. N Engl J Med 317: 1098.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, et al. (2006) Recommendations for chamber quantification. Eur J Echocardiogr 7: 79-108.

Nakai S, Watanabe Y, Masakane I, Wada A, Shoji T, et al. (2013) Overview of Regular Dialysis Treatment in Japan (as of 31 December 2011). Ther Apher Dial 17: 561-611.

London GM, Pannier B, Guerin AP, Blancher J, Marchais SJ, et al. (2001) Alterations of Left Ventricular Hypertrophy in and Survival of Patients receiving Hemodialysis: Follow-Up of an Interventional Study. J Am Soc Nephrol 12: 2759-2767.

Glassock RJ, Pecottis-Filho R, Barberato SH (2009) Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol 4 Suppl 1: S79-91.

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, et al. (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15: 2208-2218.

Ayus JC, Mizani MR, Achinger SG, Thadhani R, Go AS, et al. (2005) Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. J Am Soc Nephrol 16: 2778-2788.

Hsu HJ, Wu MS (2009) Fibroblast growth factor 23: a possible cause of left ventricular hypertrophy in hemodialysis patients. Am J Med Sci 337: 116-122.

Kirkpantur A, Balci M, Gurbuz OA, Afsar B, Canbakan B, et al. (2011) Serum fibroblast growth factor 23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients. Nephrol Dial Transplant 26: 1346-1354.

Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, et al. (2011) FGF23 induces left ventricular hypertrophy. J Clin Invest 121: 4393-4408.

Dai B, David V, Martin A, Huang J, Li H, et al. (2012) A Comparative Transcriptome Analysis Identifying FGF23 Regulated Genes in the Kidney of a Mouse CKD Model. PLoS One 7: e44161.

Munoz Mendoza J, Isakova T, Ricardo AC, Xie H, Navaneethan SD, et al. (2012) Fibroblast growth factor 23 and Inflammation in CKD. Clin J Am Soc Nephrol 7: 1155-1162.

Glassock RJ, Pecottis-Filho R, Barberato SH (2009) Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol 4 Suppl 1: S79-91.

Ciccione MM, Cortese F, Gesualdo M, Riccardi R, Di Nunzio D, et al. (2013) A novel cardiac bio-marker: ST2: a review. Molecules 18: 15314-15328.

Berndt T, Kumar R (2007) Phosphatonin and the regulation of phosphate homeostasis. Annu Rev Physiol 69: 341-359.

Nabeshima Y (2008) Discovery of alpha-Klotho and FGF-23 unveiled new insight into calcium and phosphate homeostasis. Clin Calcium 18: 923-934.

Ura kawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, et al. (2006) Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 444: 770-774.

Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Sciall a J, et al. (2011) Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 79: 1370-1378.

Fukagawa M, Nishi-Kono T, Kazama JJ (2005) Role of fibroblast growth factor 23 in health and in chronic kidney disease. Curr Opin Nephrol Hypertens 14: 325-329.

Ramasubbu K, Deswal A, Herdejüren C, Aguilar D, Frost AE (2010) A prospective echocardiographic evaluation of pulmonary hypertension in chronic hemodialysis patients in the United States: prevalence and clinical significance. Int J Gen Med 3: 279-286.

Dagli CE, Sayarlıoğlu H, Dogan E, Acar G, Demirpolat G, et al. (2009) Prevalence of and factors affecting pulmonary hypertension in hemodialysis patients. Respiration 78: 411-415.

Tarras F, Benjelloun M, Medkouri G, Hachim K, Benghanem MG, et al. (2006) Doppler echocardiograph evaluation of pulmonary hypertension in patients undergoing hemodialysis. Hemodial Int 10: 356-359.

Nakhoul F, Yigla M, Gilman R, Reisner SA, Abassi Z (2005) The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. Nephrol Dial Transplant 20: 1668-1692.

Agarwal R (2012) Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. Nephrol Dial Transplant 27: 3908-3914.

Harp RJ, Stavropoulos SW, Wasserstein AG, Clark TW (2005) Pulmonary hypertension among-end stage renal failure patients following hemodialysis access thrombectomy. Cardiovasc Intervent Radiol 28: 17-22.

Havlucy V, Kursat S, Ekmecki C, Celik P, Serter S, et al. (2007) Pulmonary hypertension in patients with chronic renal failure. Respiration 74: 503-510.

Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI (2002) Calcium deposition with or without bone formation in the lung. Am J Respir Crit Care Med 165: 1654-1669.

Yigla M, Nakhoul F, Sabag A, Tov N, Gorevich B, et al. (2003) Pulmonary hypertension in patients with end-stage renal disease. Chest 123: 1577-1582.

Conger JD, Hammond WS, Alfrey AC, Contiguglia SR, Stanford RE, et al. (1975) Pulmonary calcification in chronic dialysis patients. Clinical and pathologic studies. Ann Intern Med 83: 330-336.

Block GA, Hulbert-Sharon TE, Levin NW, Port FK (1998) Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 31: 607-617.

Amin M, Fawzy A, Hamid MA, Elhendy A (2003) Pulmonary hypertension in patients with chronic renal failure: role of parathyroid hormone and pulmonary artery calcifications. Chest 124: 2093-2097.