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RESEARCH ARTICLE

The Relation between Fibroblast Growth Factor-23 and Left Ventricular Mass and Geometry in Hemodialysis Patients

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Abstract

INTRODUCTION :

Chronic kidney disease (CKD) is a major health problem that is associated with an increased risk of cardiovascular mortality and morbidity. Left ventricular hypertrophy (LVH) was found to be commonly met in patients with CKD. Hemodialysis patients with LVH mass was found to have poorer prognosis.Fibroblast growth factor-23 (FGF-23) is a circulating hormone, secreted by osteocytes and osteoblasts, and plays a critical role in regulation of bone and mineral metabolism. FGF-23 was found to be markedly elevated in CKD patients on regular dialysis and was found to be associated with LVH in these patients. However, little data are available about the relation between FGF-23 and different types of LVH and different LV geometries.

AIM OF THE WORK :

It was to study the relation between FGF-23 levels and LV mass and geometry in CKD patients under regular hemodialysis.

PATIENTS AND METHODS :

One hundred patients with CKD under regular hemodialysis were included in our study. Patients were excluded from the study if they had one or more of the following: known coronary artery disease, previous myocardial infarction or revascularization, significant valvular or congenital heart disease, or congestive heart failure. After giving an informed written consent, all subjects were subjected to full history taking; thorough clinical examination; complete 12-leads electrocardiography; echocardiography with measuring of of left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), fraction of shortening (FS), ejection fraction (EF), interventricular septal thickness (IVST), posterior wall thickness (PWT), left ventricular mass and mass index (LVMI), left ventricular end-diastolic volume and volume index (LVEDVI); laboratory tests measuring of blood urea and serum creatinine, serum electrolytes, complete blood count, lipid profile, and FGF-23 level. According to FGF-23 level were divided into two groups: **Group I**; patients with FGF-23 level < 123.5 RU/mL, **Group II**; patients with FGF-23 level ≥ 123.5 RU/ml.

RESULTS:

Regarding clinical and laboratory data there was no significant difference between the study groups except for a significantly higher phosphorus level in patients with FGF-23 level ≥ 123.5 RU/ml.The echocardiographic data, LVEDD, LVESD, IVST, PWT, LVMI, and LVEDVI, were significantly higher in patients with FGF-23 level ≥ 123.5 RU/ml. Also, there were significantly more patients with LVH and with thick and dilated LVH among patients with FGF-23 level ≥ 123.5 RU/ml.There was a significant positive correlation between FGF-23 level and LVMI (r = 0.446,

p <0.00001). Also, there was a significant positive correlation between FGF-23 level and LVEDVI (r = 0.454, p <0.00001).

CONCLUSION:

Among ESRD patients on regular hemodialysis, those with higher FGF-23 levels seem to have significantly higher LV mass, LV end diastolic volume, more incidence of LVH, and more incidence of thick and dilated LVH.

INTRODUCTION

Chronic kidney disease (CKD) is a major health problem that is associated with an increased risk of cardiovascular mortality and morbidity (1).Although CKD patients usually have many traditional risk factors for cardiovascular events such as hypertension (HTN), diabetes mellitus (DM), however these risk factors don't fully account for the burden of CVS disease (2).Left ventricular hypertrophy (LVH) was found to be commonly met in patients with CKD either in pre-dialysis patients or in regular dialysis patients (3). Hemodialysis patients with increased and/or increasing LV mass was found to have poorer prognosis (4).Fibroblast growth factor-23 (FGF-23) is a circulating hormone, secreted by osteocytes and osteoblasts, and plays a critical role in regulation of bone and mineral metabolism as it helps to maintain normal serum phosphate level (5).Fibroblast growth factor-23 was found to be markedly elevated in CKD patients on regular dialysis and was found to be associated with an adverse prognosis (6).Serum FGF-23 was found to be independently associated with increased left mass and LVH in patients with CKD (7). However, little data are available about the relation between FGF-23 and different types of LVH and different LV geometries.

AIM OF THE WORK:

It was to study the relation between FGF-23 levels and LV mass and geometry in CKD patients under regular hemodialysis.

PATIENTS AND METHODS:

This study had been carried out in the Dialysis Unit of Internal Medicine Department and in the Cardiology Department, Zagazig University Hospitals, during the period between January 2014 and March 2015.One hundred patients with CKD under regular hemodialysis (thrice weekly, 4 hours each session, for at least 6 months) were included in our study. Among them there were 59 males and 41 females, their mean age was 47.3±15.6 years.Patients were excluded from the study if they had one or more of the following:

- Known coronary artery disease.
- Previous myocardial infarction or revascularization.
- Significant valvular or congenital heart disease.
- Congestive heart failure (CHF) with NYHA class > I.

After giving an informed written consent, all subjects were subjected to the following:

1) Full history taking.
2) Thorough clinical examination, with measuring of weight and height.
3) Complete 12-leads electrocardiography:
4) Echocardiography: Echocardiographic and Doppler studies were performed for all patients using GE VIVID E9 machine with 2.5 MHz transducers. The following measures were taken:
   - M-mode measurements of left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), fraction of shortening (FS) and ejection fraction (EF), interventricular septal thickness (IVST), and posterior wall thickness (PWT).
   - Left ventricular mass (LVM) and mass index (LVMI): LV mass was calculated using the Cube's formula as following (8):

$$0.8 * 1.04 [(IVST+LVEDD+PWT)^3 - LVEDD^3] + 0.6 \text{ gm.}$$

Where IVST is the interventricular septal thickness, LVEDD is the left ventricular end-diastolic dimension, and PWT is the thickness of the posterior LV wall. All measures were taken at the end of diastole (8).Left ventricular mass index was obtained by dividing LVM by the body surface area (BSA) in square meters.

- Left ventricular hypertrophy was defined as left ventricular mass index $\geq$ 95 g/m^2 in women and 115 g/m^2 in men (8).
- Left ventricular end-diastolic volume (LVEDV): was calculated by lining the endocardial border of the left ventricle during the end of the diastole in the apical 4-chamber and apical 2-chamber views (9).
- Left ventricular volume index (LVEDVI): was calculated by dividing LVEDV by BSA (9).
- Left ventricular LV concentricity$^{0.67}$ was defined as LV mass/LV end-diastolic volume (LVEDV). LV concentricity$^{0.67}$ was considered increased if it was $\geq$ 9.1 $g/ml^{0.67}$ for men and $\geq$ 8.9 $g/ml^{0.67}$ for women) (9).

According to the 4-Tiered classification, LVH was divided into four types (9):

i. Indeterminate hypertrophy: neither increased concentricity$^{0.67}$ nor increased LVEDV/BSA.
ii. Dilated hypertrophy: increased LVEDV/BSA without increased concentricity$^{0.67}$.
iii. Thick hypertrophy: neither concentricity$^{0.67}$ without increased LVEDV/BSA.
iv. Both thick and dilated hypertrophy: increased both concentricity$^{0.67}$ and LVEDV/BSA.

5) Laboratory tests: Blood samples were taken from all patients after overnight fast in the non-dialysis day. The following laboratory test were done to all patients:

- Blood urea and serum creatinine.
- Serum electrolytes: Sodium, Potassium, Calcium, and Phosphorus.
- Complete blood count.
- Lipid profile.
- Fibroblast growth factor-23 level was measured using a second-generation, two-site, monoclonal antibody ELISA. Measurements were done according to the manufacturer's protocol (Kainos Laboratories International, Tokyo, Japan) (10). Measurements were made in duplicate and averaged.

We have used FGF-23 level of 123.5 relative unit/milliliter (RU/mL) as a cutoff point (11). Accordingly patients were divided into two groups:

Group I: patients with FGF-23 level < 123.5 RU/mL. This group included 55 patients, 33 males and 22 females; their mean age was 46.1±14.8 years.

Group II: patients with FGF-23 level $\geq$ 123.5 RU/mL. This group included 45 patients, 26 males and 19 females; their mean age was 48.4±16.1 years.

Statistical analysis: All data were analyzed using the SPSS 19 program. The Student's t-test, χ^2 test, and Pearson correlation analysis were used as appropriate. A p value < 0.05 was regarded statistically significant.

RESULTS:

We enrolled 100 CKD patients on regular hemodialysis in our study, 55 patients with FGF-23 level < 123.5 RU/mL, and 45 patients with FGF-23 level $\geq$ 123.5 RU/mL. Regarding clinical and laboratory data (table 1), there was no significant difference between the study groups concerning age, sex, or smoking, diabetes, hypertension, systolic and diastolic blood pressure, body mass index, duration of hemodialysis, blood hemoglobin, serum Sodium, Potassium, Calcium, blood urea nitrogen, serum cholesterol, or serum triglycerides.Mean serum Phosphorus was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (5.32±0.86 mg/dL versus 4.83±0.67 mg/dL, p = 0.0023).Regarding clinical and echocardiographic data (table 2), there was no significant difference between the study groups concerning FS or EF. Mean LVEDD was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (54.5±4.88 mm versus 57.4±5.11 mm, p = 0.0049). Mean LVESD was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (36.3±5.32 mm versus 39.1±5.83 mm, p = 0.015). Mean PWT was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (13.1±1.72 mm versus 11.6±1.42 mm, p < 0.00001). Mean IVST was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (12.9±1.87 mm versus 11.7±1.53 mm, p = 0.0008). Mean LV concentricity was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (9.72±1.87 $gm/mL^{0.67}$ versus 8.53±1.69 $gm/mL^{0.67}$, p = 0.0013).Mean LEVDVI was significantly higher in patients with FGF-23 $\geq$ 123.5 RU/mL than in patients with FGF-23 < 123.5 RU/mL (65.4±7.53 mL/m^2 versus 56±8.31 mL/m^2, p < 0.00001). There were significantly more patients with LVH among patients with FGF-23 $\geq$ 123.5 RU/mL (35, 77.8 %) than among patients with FGF-23 < 123.5 RU/mL (25, 45.5 %, p = 0.00014).There were significantly more patients with thick and dilated LVH among patients with FGF-23 $\geq$ 123.5 RU/mL (14, 31.1 %) than among patients with FGF-23 < 123.5 RU/mL (4, 7.3 %, p = 0.002).As shown in figure 1, there was a

significant positive correlation between FGF-23 level and LVMI (r = 0.446, p <0.00001) (figure 1A). Also there was a significant positive correlation between FGF-23 level and LVEDVI (r = 0.454, p <0.0001, (figure 1B).

Table 1: Clinical and laboratory data.

	FGF-23 < 123.5 RU/mL (n = 55)	FGF-23 ≥ 123.5 RU/mL (n = 45)	P
Age (Years)	46.1±14.8	48.4±16.1	> 0.05
Sex: Male Female	33 (60 %) 22 (40 %)	26 (57.8%) 19 (42.2%)	> 0.05
Smoking	13 (23.6%)	12 (26.7%)	> 0.05
Diabetes	16 (29.1%)	14 (31.1%)	> 0.05
Hypertension	34 (61.8%)	30 (66.7%)	> 0.05
SBP (mmHg)	139.1±26.5	144.5±24.7	> 0.05
DBP (mmHg)	78.3±18.2	81.2±16.5	> 0.05
BMI (kg/m^2)	25.6±4.9	27.1±5.3	> 0.05
Dialysis Duration (months)	38.3±15.2	41.2±18.6	> 0.05
Hemoglobin (gm/dL)	9.2±1.2	9.3±1.1	> 0.05
Na (mEq/L)	139.8±5.3	140.5±3.5	> 0.05
K (mEq/L)	5.1±1.1	5.4±0.92	> 0.05
Ca (mg/dL)	8.02±0.41	8.1±0.54	> 0.05
P (mg/dL)	4.83±0.67	5.32±0.86	0.002
Creatinine (mg/dL)	11.9 ±1.8	12.4 ± 1.7	> 0.05
BUN (mg/dL)	144.5±30.1	143.5±33.2	> 0.05
Albumin (g/dL)	3.75±0.361	3.86±0.432	> 0.05
Cholesterol (mg/dL)	165.2±41.5	155.3±47.5	> 0.05
Triglycerides (mg/dL)	134.5±51.6	143.2±50.3	> 0.05

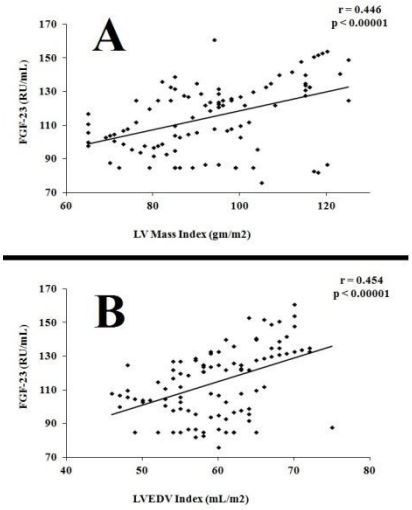
SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, BMI = Body Mass Index, BUN = Blood Urea Nitrogen.

Table 2: Echocardiographic data.

	FGF-23 < 123.5 RU/mL (n = 55)	FGF-23 ≥ 123.5 RU/mL (n = 45)	P
LVEDD (mm)	54.5±4.88	57.4±5.11	0.0049
LVESD (mm)	36.3±5.32	39.1±5.83	0.015
FS (%)	33.4±5.63	31.9±6.18	> 0.05
EF (%)	61.3±6.35	59.5±7.23	> 0.05
PWT (mm)	11.6±1.42	13.1±1.72	< 0.00001
IVST (mm)	11.7±1.53	12.9±1.87	0.0008
LVMI (gm/m^2)	84.2±19.6	106.4±17.4	< 0.00001
Concentricity ($gm/mL^{0.67}$)	8.53±1.69	9.72±1.87	0.0013
LVEDVI (mL/m^2)	56±8.31	65.4±7.53	< 0.00001
Total LVH	25 (45.5%)	35 (77.8%)	0.00014
Intermediate	9 (16.3%)	5 (11.1%)	> 0.05
Dilated	6 (10.9%)	9 (20%)	> 0.05
Thick	6 (10.9%)	7 (5.6%)	> 0.05
Thick and dilated	4 (7.3%)	14 (31.1%)	0.002

LVEDD = Left Ventricular End Diastolic Dimension, LVESD = Left Ventricular End Systolic Dimension, FS = Fraction of Shortening, EF = Ejection Fraction, PWT = Posterior Wall Thickness, IVST = Interventricular Septal Thickness, LVMI = Left Ventricular Mass Index, LVEDVI = Left Ventricular End Diastolic Volume Index, LVH = Left Ventricular Hypertrophy.

Figure 1: Correlation between FGF-23 level and LVMI (A), and LVEDVI (B).



DISCUSSION :

The mortality from cardiovascular complications in patients with end-stage renal disease (ESRD) is obviously higher than in the general population (12). Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in patient with ESRD. More than 50% of all deaths among ESRD patients are due to CVD (13).Classical coronary risk factors, like hypertension and diabetes mellitus, are much more prevalent among patients with ESRD and are associated with poor cardiovascular outcome. However, the increased burden of CVD in ESRD patients cannot be simply explained just by the increased incidence of traditional CVD risk factors (14).Fibroblast growth factor-23 is a phosphate-regulating hormone that is mostly produced by bone to reduce the serum phosphate concentration whenever needed (15).The serum levels of FGF-23 increase in patients with ESRD, and its levels are extremely high in hemodialysis patients (16). The high levels of FGF-23 in hemodialysis patients are due to the increased level of serum phosphorus in these patients in an attempt to reduce the abnormally high phosphorus level (17). In these patients, FGF-23 levels may reach up to 100-1000 times higher than the normal range (18). Elevated FGF-23 levels in patients with ESRD might be appropriate to compensate hyperphosphataemia. However, chronic elevation of FGF-23 might have adverse effects on organs other than the kidney and the parathyroid gland (6).Increased levels of FGF-23 in ESRD patients on regular hemodialysis were found to be associated with increased LV mass and LVH (19) and with an adverse outcome (20).Although increased LV mass was found to be associated with increased risk of cardiovascular events, patients with both thick and dilated hypertrophy were found to have more adverse outcome than patients with normal LVEDVI (21).Our study was carried out to investigate the relation between FGF-23 levels and LV mass and geometry in CKD patients under regular hemodialysis. We have found that LVEDD, LVESD, PWT, IVST, LVMI, concentricity index, and LVEDVI were significantly higher in patients with FGF-23 level ≥ 123.5 RU/mL.There were significantly more patients with LVH among patients with FGF-23 level ≥ 123.5 RU/mL. Also, there were significantly more patients with thick and dilated LVH among patients with FGF-23 level ≥ 123.5 RU/mL. We have also found significant positive correlation between FGF-23 level and LVMI and between FGF-23 level and LVEDVI .The increased risk of cardiovascular events with LVH, increased LV mass, and LV cavity dilatation, had been demonstrated by multiple population-based studies. The Framingham Heart Study established the relationship between LV mass and incident CVD in adults free of CVD aged ≥ 40 years and even beyond the traditional risk factors (22). The relation between FGF-23 level and LV mass and LVH was found to be direct, and even independent of renal function as well as variations mineral metabolism, which are related to FGF-23 secretion (15).It is not that clear whether increased FGF-23 level is a cause or a result of LVH. The volume overload, that is almost always present in patients with ESRD, is responsible, at least in part, for the development of LVH and LV dilatation (23). It was found that FGF-23 is produced at low levels in the heart (24, 25). So, one might predict that increased the workload and the size of the heart may in turn stimulate the local production of FGF23.On the other hand, FGF23 may have a direct endocrine effect on the heart, since the FGF-23 receptor co-factor alpha-Klotho was found to be expressed in heart (26). In addition, other members of the FGF family, such as FGF-1 and FGF-2, have been found have direct effects on growth and repair of the cardiovascular system (27, 28).However, the evidences that support the causal effect of FGF-23 on LV mass are much stronger that FGF-23 may be repositioned from being just a biomarker of CVD risk to a mechanism of the disease (17)

In addition to its association with LV mass, increased FGF-23 level was found to be associated with endothelium dysfunction and arterial stiffness (29), as well as with the severity of atherosclerosis (30). These effects may be partially responsible for the increased incidence of myocardial ischemia among ESRD patients under regular hemodialysis in addition to the increased incidence of CAD risk factors among these patients (14).

So, the association of vascular effect of FGF-23, its possible direct endocrine effect, as well as the volume overload in hemodialysis patients may explain the increased LVMI, LVEDVI, and increased number of patients with thick and dilated hypertrophy we have found among patients with FGF-23 level ≥ 123.5 RU/mL.We cannot exclude the possible effects of associated conditions commonly found in hemodialysis patients. For example, altered mineral metabolism was found to play an important role in the pathogenesis of LVH (31-33).

STUDY LIMITATIONS:

- Relatively small number of patients.
- Possibility for unmeasured confounding conditions.

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