Fibroblast growth factor-23 is independently associated with the left ventricular mass index in hemodialysis patients

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Context
Left ventricle (LV) hypertrophy is an important cardiovascular complication in chronic kidney disease that leads to LV dysfunction and increased mortality. Studies that tested the association between fibroblast growth factor (FGF)-23 and LV structural and functional changes in hemodialysis (HD) patients have shown conflicting results.
Aims
The aim of this work was to study whether FGF-23 has a direct association with LV structural and functional changes in HD patients.
Settings and design
This is a cross-sectional study.
Materials and methods
Demographic data of 95 HD patients were recorded in a predefined data sheets. The blood samples for FGF-23 and other laboratory variables were collected and measured by the standard methods. Echocardiography area length method was used to calculate left ventricular mass index (LVMI), and modified Simpson's rule was used to measure ejection fraction. Transmitral Doppler and tissue Doppler of septal e′ were used to measure LV diastolic function.
Statistical analysis
Multivariate analysis was carried out.
Results
There were significant positive correlations between FGF-23 and LVMI (r=0.285, P=0.005) and LV E/e′ ratio (r=0.391, P=0.001), while there were insignificant correlations with other echocardiographic parameters including chamber dimensions, chamber volumes and PASP. Multivariate analysis showed a significant association between LVMI and FGF-23 level after adjustment for age and systolic BP (P=0.0001).
Conclusion
FGF-23 is independently associated with LVMI in HD patients. This result suggests a direct role of elevated FGF-23 in the pathogenesis of LV hypertrophy in patients with HD.

Keywords:
fibroblast growth factor-23, hemodialysis, left ventricular mass index

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Introduction

Fibroblast growth factor (FGF)-23 is a hormone secreted by osteocytes to regulate phosphate and vitamin D metabolism. While its primary role is the regulation of bone-mineral metabolism, FGF-23 has a strong association with adverse cardiovascular (CV) outcomes and mortality in chronic kidney disease (CKD) patients independent of abnormalities of bone-mineral metabolism. High levels of FGF-23 are independently associated with increased CV events [1], vascular calcification [2], left ventricular hypertrophy (LVH) [3], arterial stiffness, endothelial dysfunction [4], and levels of inflammatory markers [5], suggesting that FGF-23 may serve as a CV biomarker in CKD. We aimed to study the association between FGF-23 and echocardiography-driven LV structural and functional changes in hemodialysis (HD) patients, which can explain the association of FGF-23 with adverse CV outcomes in HD patients, and deepen our knowledge about the potential mechanisms of this association.

Materials and methods

We conducted a cross-sectional study, carried out on 95 patients who underwent regular HD in the Nephrology Unit of Assiut University Hospital from January 2017 to December 2017.

All patients gave informed consents before their inclusion in the study; illiterate participants gave their consent by fingerprints. The study was approved by the Ethical Committee of Faculty of Medicine at Assiut University.

Demographic, clinical, and laboratory data

Patients' demographic data and medical history including age, sex, history of hypertension, diabetes, smoking index (number of cigarette/number of years), duration of dialysis and drug history were recorded. BMI was calculated as the weight (kg) divided by the square of the height (m^2). Body surface area (BSA) was calculated using the following equation: BSA (m^2)= 0.007184×(height) 0.725×(weight) 0.425. Blood pressure of the patients was recorded. Venous blood samples were collected from our patients after dialysis sessions and analyzed in the Nephrology Unit Laboratory. Laboratory measurements including serum levels of creatinine, blood urea nitrogen, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose, serum levels of calcium, phosphorous, alkaline phosphatase, intact parathyroid hormone, 25-hydroxyvitamin D level, uric acid and albumin were measured using standard kits. The blood samples for intact FGF-23 (iFGF-23) were centrifuged, separated and frozen immediately after collection and were assessed by the ELISA method.

Echocardiographic data

All echocardiograms were performed with an HDI 5000 instrument (Philips Medical Systems, Bothell, Washington, USA) equipped with a broad band harmonic transducer. A standard echocardiography was used on the basis of apical four and two-chamber views; 2D echocardiograms of the LV short axis were recorded at three levels: mitral valve, midpapillary muscle level, and apex. All echocardiograms were analyzed at Assiut University Internal Medicine Echocardiography Laboratory. LA and LV dimensions were calculated using 2D-guided M-mode calculations. The mean value of three measurements of the technically best cardiac cycles was taken from each examination. LV diastolic function was calculated using transmitral E wave velocity using pulsed Doppler with a sample size of 0.7 mm just above MV leaflet tips; septal e' wave was measured by tissue Doppler with a sample size of 4.0 mm at the level of the MV septal annulus, and E/e′ velocity ratio. Modified Simpson's rule was used to calculate LV volumes and ejection fraction. Pulmonary artery systolic pressure was estimated using TVR pressure gradient plus estimated right atrial pressure, which was estimated form inferior vena cava diameter and percentage of inspiratory collapse.

LV mass was assessed by area length method wherein a standard parasternal short view at papillary muscles' level was used for measuring both the epicardial and endocardial LV dimensions, and standard apical four view was used to measure the LV length.

Statistical analysis

The statistical analysis was performed using SPSS (version 19.0; SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to test normality. The continuous variables were presented as the means±SD, and categorical variables were reported as percentages. Spearman's correlation was used to measure correlation among variables. Multivariate analysis was used to test the association between left ventricular mass index (LVMI) and FGF-23, systolic blood pressure (BP) and age. A *P* value less than 0.05 was considered statistically significant.

Table 1 Clinical data characteristics and laboratory

Variables	
Age (year)	44.00±15.33
BMI (kg/m^2)	25.41±4.43
BSA (m^2)	1.71±0.43
DM	45 (51.2)
HTN	57 (65.1)
Smoking index	635±132.1
Duration of dialysis (years)	6.54±4.37
HB level (g/dl)	10.54±1.56
SBP (mmHg)	154.34±15.33
DBP (mmHg)	85.32±11.67
BUN (mg/dl)	50.42±19.70
Serum creatinine (mg/dl)	7.82±1.16
FBG (mg/dl)	222±23.31
Na (mEq/l)	133.43±4.56
K (mEq/l)	5.02±0.55
Albumin (g/dl)	3.32±0.42
Calcium (mg/dl)	8.83±0.42
Phosphorus (mg/dl)	5.45±1.62
Calcium phosphate product	54.61±17.13
iPTH (pg/ml)	282.31±328.45
ALP (U/l)	162.43±129.59
LDL-C (mg/dl)	155.35±65
HDL-C (mg/dl)	23±27.21
Triglyceride (mg/dl)	225±44.77
Serum uric acid (mg/dl)	8.8±4.31
FGF-23 (pg/ml)	42.88±35.67
Serum iron(mg/dl)	143.98±37.97
Ferritin (ng/ml)	4049.22±1887.82
TIBC (mg/dl)	215.15±39.24

Values are expressed as the means±SD, number (percentage). ALP, alkaline phosphatase; BUN, blood urea nitrogen; DM, diabetes mellitus; FBG, fasting blood glucose; FGF-23, fibroblast growth factor-23; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; iPTH, intact parathormone; K, potassium; LDL-C, low-density lipoprotein cholesterol; Na, sodium; TIBC, total iron binding capacity.

Results

Demographic and clinical characteristics

The study was carried out on 95 regular HD patients. Demographic and clinical characteristics are shown in Table 1.

Laboratory data

The mean FGF-23 in our sample was 42.78 pg/ml (with a range between 2.6 and 220 pg/ml). Other laboratory data are shown in Table 1.

Echocardiographic data

LA dimensions, LV dimensions, LV volumes, LV systolic and diastolic functions, and PASP are shown in Table 2.

Table 2 Echocardiographic parameters

	Mean±SD	Range
LA (cm)	4.41±0.70	2.7–6.2
LVEF (%)	56.85±11.06	27.1–79
LVESD (cm)	3.57±0.76	2–5.7
LVEDD (cm)	5.14±0.74	3.1–7.1
LV mass (g)	235.97±82.09	62.5–462
LV mass index (g/m^2)	149±44	31–332
LVEDV (ml)	133±35	24–244
LVESV (ml)	49±33	17–134
E velocity (m/s)	0.96±0.25	0.4–1.6
e′ (m/s)	0.10±0.04	0.04–0.21
E/e′	11.27±4.97	2.95–30
PASP (mmHg)	39.48±15.23	17–95

LA, left atrium; LV, left ventricle; LVEDD, left ventricle end-diastolic dimensions; LVESD, left ventricle end-systolic dimensions; PASP, pulmonary artery systolic pressure.

Correlations data

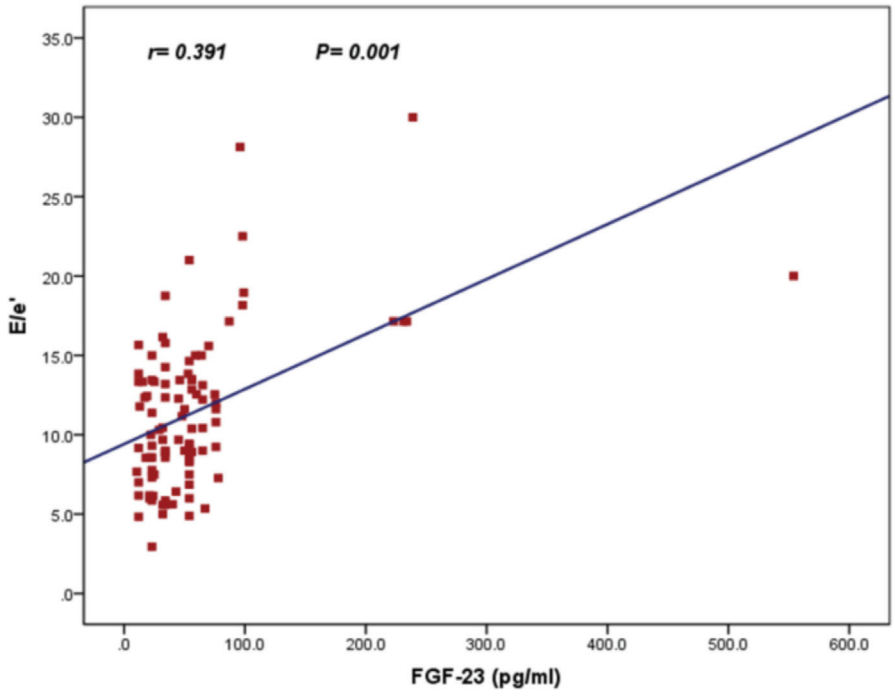
Table 3 shows the association between FGF-23 and various echocardiographic indices. Briefly, there was significant positive correlation between FGF-23 and both indexed LV mass (r=0.285, P=0.005) (Fig. 1) and E/e′ ratio (r=0.391, P=0.001) (Fig. 2), While there were insignificant correlations between FGF-23 and LA dimension nor LVEF, LV systolic dimensions, LV diastolic dimensions, LV systolic volume, LV diastolic volumes, E velocity, e', velocity, and PASP.

Table 3 Correlations between fibroblast growth factor-23 and echocardiographic parameters

	FGF-23 (pg/ml)	
	r-value	*P* value
LA (cm)	−0.129	0.237
LVEF (%)	0.183	0.092
LVESD (cm)	−0.077	0.480
LVEDD (cm)	0.006	0.954
LVEDV (ml)	0.677	0.870
LVESV (ml)	0.675	0.654
LV mass (g)	0. 741	0.342
LV mass index (g/m^2)	0.285	0.005
E velocity (m/s)	−0.145	0.182
e′ (m/s)	0.144	0.186
E/e′	0.391	0.001
PASP (mmHg)	−0.169	0.120

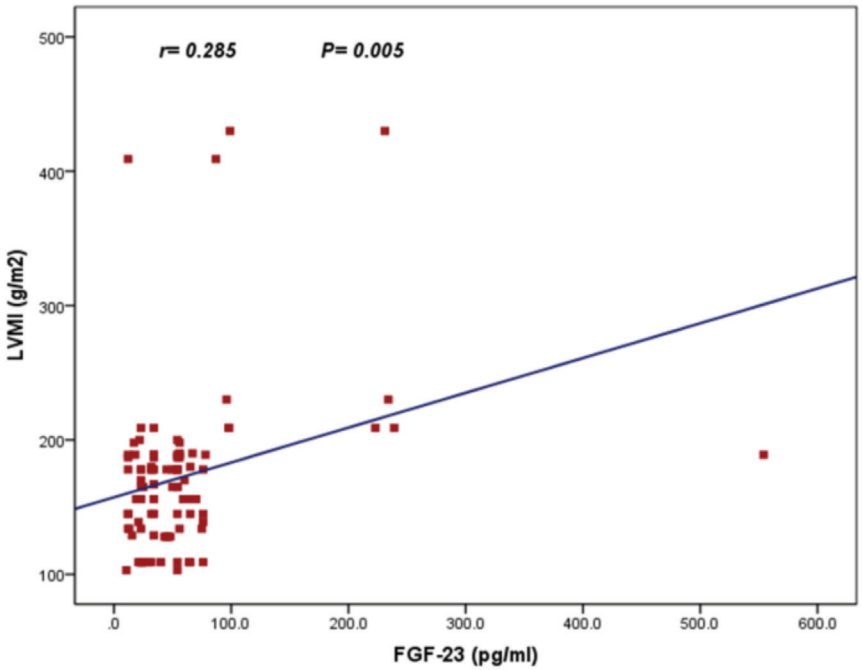
FGF-23, fibroblast growth factor-23; LA, left atrium; LV, left ventricle; LVEDD, left ventricle end-diastolic dimensions; LVESD, left ventricle end-systolic dimensions; PASP, pulmonary artery systolic pressure.

Figure 1



Correlation between fibroblast growth factor-23 and E/e′ ratio.

Figure 2



Correlation between fibroblast growth factor-23 and left ventricular mass index.

Table 4 Multivariate analysis (coefficients and modal summary)

Model	Standard coefficients	*t* value	*P* value	VIF
FGF-23	0.696	16.341	*0.0001*	*1.01*
SBP	0.335	7.105	*0.0001*	*1.01*
Age	0.130	4.136	*0.0035*	*1.01*
S: 0.359883	R^2: 86.61%	R^2 (adjusted): 82.68%	R^2 (predictive): 80.11%	

FGF-23, fibroblast growth factor-23; SBP, systolic blood pressure; VIF, variance inflation factor.

Multivariate analysis data

Our regression model R^2 was 82.68%, which explains most of the LVMI changes. Inflation value was 1.01, which excluded significant co-linearity. LVMI changes were significantly associated with FGF-23 changes after adjusting for age and systolic BP (Table 4).

Discussion

The current study showed a significant positive correlation between FGF-23 and indexed LV mass and a significant positive correlation between FGF-23 and E/e′ ratio as a diastolic function parameter. LVH is an important CV complication in CKD that leads to left ventricular (LV) dysfunction, heart failure and arrhythmic sudden cardiac death [6]. The prevalence of LVH in the general population is 15–21% [7], while in intermediate stages of CKD it is 50–70%, and up to 90% in HD patients [8]. One mechanism that could explain the association between FGF-23 and increased LV mass is by increasing blood pressure. FGF-23 can increase BP by several mechanisms: (a) suppression of angiotensin-converting enzyme-2 (ACE2) expression [9], (b) increasing RAAS activity through vitamin D activation suppression [10], and (c) increasing renal Na^+ reabsorption and plasma volume [11]. However, regression of LVH after kidney transplantation suggests that factors other than chronic hypertension explain the high prevalence of LVH in CKD [12]. In the current study, the multivariate analysis showed that indexed LVM was significantly associated with FGF-23 level after adjustment for systolic blood pressure and age. This stimulates searching for other mechanisms that could explain the association between FGF-23 and LVMI.

Cross-sectional clinical studies demonstrated an association between FGF-23 and LVM that was independent of renal function and other calcium phosphate metabolism-related parameters [13] and urine ACR, and that association was much stronger in older persons with CKD [14]. Follow up clinical studies showed that stage 3 CKD patients exhibited increasing LVM despite stable GFR, BP, and ejection fraction [15].

However, some clinical studies did not show a significant relation between FGF-23 and adults [16] or children with CKD [17]. These negative results can be explained by the heterogeneity of participants, small sample size, methods of FGF-23 measurement (iFGF-

23 vs. cFGF-23), and the time interval between samples and echocardiographic examination.

An animal study has demonstrated that FGF-23 both directly induces hypertrophy of isolated mice cardiomyocytes and after intraventricular or intravenous injection of FGF-23. Moreover, administration of an FGF receptor blocker to the 5/6 nephrectomy rat model of CKD attenuates the severity of LVH, without reducing the animals' markedly elevated blood pressure [3]. These results establish a direct causal role for elevated FGF-23 in the pathogenesis of LVH and suggest that the association of FGF-23 with adverse outcomes can be attributed to the development of LVH in patients with HD.

Conclusion

In the current study, there were significant positive correlations between FGF-23 and both LV mass and E/e′ ratio, while there were insignificant correlations between FGF-23 and other echocardiographic indices. The association between the LVMI and the FGF-23 level was significant even after adjustment for age and systolic BP.

Study limitations and recommendations

Financial factors interfered with recruiting more patients in our study due to lower type II error in testing the association between FGF-23 with other echocardiographic parameters such as PASP. Further research for modulation of FGF-23 activity could improve the LVM and the CV outcomes in HD patients.

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Conflicts of interest

There are no conflicts of interest.

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