FGF-23 as early marker of Left Ventricular Hypertrophy in non dialysis Chronic Kidney Disease patients

Doaa Salah Eldeen[1], Fawkia Eissa[1], Mona Naiem[2], Nivin Ghoraba[3], Shereen Elshaer[4]

[1]Department of Internal Medicine, Al Azhar University, Cairo, Egypt
[2]Department of Cardiology, Al Azhar University, Cairo, Egypt.
[3]Department of Clinical Pathology, Al Azhar University, Cairo, Egypt.
[4]Department of Biochemistry, Faculty of Pharmacy, Al Azhar University, Cairo, Egypt.
dsalah241@gmail.com

Abstract: Background: The family of FGFs consists of 23 proteins that regulate cell proliferation, migration, differentiation, and survival. FGF-23 is the most recently discovered FGF and functions as an endocrine hormone that regulates phosphorus homeostasis. Increased FGF23 production in chronic kidney disease (CKD) enhances urinary phosphate excretion to prevent hyperphosphatemia. Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease in CKD patients. We design this study to examine the relationship between increased plasma FGF 23 and LVH in patients with pre-dialysis CKD in order to understand the early mechanisms of LVH in CKD patients. **Methods:** FGF-23 measurement using ELIZA immunoassay and Conventional echo-Doppler study for LVH were done in 27 patients with pre-dialysis CKD (estimated glomerular filteration rate (eGFR) ≤ 60 mL/min/1.73m²) as well as 13 patients with preserved kidney function (eGFR) □ 60 mL/min/1.73m²) to serve as control. **Results:** The mean FGF-23 plasma level in patients with CKD (3.8 ± 2.2 pg/ml) was significantly higher than FGF-23 in those with preserved kidney function (0.5 ± 0.1 pg/ml). Within CKD patients, the FGF -23 levels were also significantly increased in group 4 compared with group 3 CKD (5.5 ± 1.3 pg/ml vs. 1.9±0.8 pg/ml). The increased FGF23 levels in CKD patients were negatively correlated with GFR and positively correlated with LVM and LVMI. **Conclusion:** Increased synthesis of FGF-23 in the course of declined GFR positively correlated to LVM and LVMI in patients with CKD and this positive correlation was present before appearance of hyperphosphatemia. FGF-23 may serve as sensitive marker of early calcium-phosphate disturbances and can predict occurrence of LVH in patients with CKD.

[**Doaa Salah Eldeen**, **Fawkia Eissa**, **Mona Naiem**, **Nivin Ghoraba**, **Shereen Elshaer FGF-23 as early marker of Left Ventricular Hypertrophy in non dialysis Chronic Kidney Disease patients]** Journal of American Science 2012; 8(8): 251-257]. (ISSN: 1545-1003). http://www.americanscience.org.37

Key words: Fibroblast growth factor 23; left ventricular hypertrophy; chronic kidney disease.

1. Introduction

Fibroblast growth factor-23 (FGF-23) is a 251-amino acid protein that is involved in the control of phosphate (P) and calcium (Ca) metabolism through binding to both FGF receptor (FGFRs) and its co-receptor (klotho) in the kidney and parathyroid glands. The activation of FGF-Rs is Klotho dependent as a Klotho/FGF-R complex binds to FGF-23 with higher affinity than does FGF-R or Klotho alone. It is synthesized and secreted by bone cells, mainly osteocytes ***(Yamashita et al., 2000).*** FGF-23 is a phosphaturic hormone, inducing urinary phosphate excretion by suppressing the expression of type IIa and IIc sodium/phosphate cotransporters in the brush border of renal proximal tubules (***Shimada et al., 2004).*** In addition, it inhibit gastrointestinal phosphate absorption by reducing intestinal IIb sodium/phosphate cotransporters activity in a vitamin D-dependent manner (by inhibiting 1α-hydroxylase which reduce the circulating 1, 25-dihydroxyvitamin D levels) (***Miyamoto et al., 2005).*** The principal physiological stimuli for increased FGF-23 expression both *in vitro* and *in vivo* are 1,25 dihydroxyvitamin D level and high dietary phosphate intake ***(Kolek et al., 2005 and Antoniucci et al., 2006).***

Chronic kidney disease (CKD) is a global public health problem that is estimated to affect many individuals' worldwide. Patients with CKD tend to develop hyperphosphatemia as a consequence of impaired renal P excretion and decreased 1,25-dihydroxyvitamin D production and hypocalcemia**.** In early stages of CKD, compensatory changes in renal P handling are sufficient to maintain a normal serum P level, but in more advanced CKD, these processes become no longer sufficient and overt hyperphosphatemia develops. The resulting increased P burden contributes directly to development of secondary hyperparathyroidism. PTH leads to induction of bone turnover to maintain serum Ca normal as well as increase the FGF-23 production by osteocytes through activation pathway with negative feedback control ***(Saji et al., 2009)***. The FGF-23 increases early in CKD in response to abnormal P metabolism and mediates its effect by promoting urinary phosphate excretion in the face of reduced nephron mass helping to restore serum P levels to normal in CKD stage 3 and in early stage 4. The increased P burden and subsequent overt hyperphosphatemia are associated with increased mortality and morbidity ***(Isakova et al., 2011).*** Several

studies have measured circulating FGF23 levels in predialysis and dialysis patients and reported progressively elevated FGF23 levels as serum creatinine or phosphate levels increase ***(Larsson et al., 2003 and Imanishi et al., 2004).***

Patients with CKD are at increased risk for cardiovascular events. Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease in those patients and is associated with markedly increased risk of mortality. Approximately 40% of patients with pre-dialysis CKD and up to 80% of patients initiating hemodialysis manifest LVH ***(London et al., 2003).*** Elevated serum phosphate concentrations, even within the normal range, are associated with LVH and increased cardiovascular mortality in both CKD and non-CKD populations. These results suggest that disordered phosphorus metabolism is a risk factor for LVH and cardiovascular disease ***(Tonelli et al., 2005)***. The circulating concentrations of FGF-23 increase early in the course of kidney disease, long before the development of hyperphosphatemia, and thus a high FGF-23 concentration is among the earliest markers of disordered phosphorus metabolism in CKD. Furthermore, increased FGF-23 concentrations were much stronger predictors of mortality than elevated serum phosphate concentrations, and the strongest associations between FGF-23 and mortality were observed in the normal range of serum phosphate ***(Nakai et al., 2010).***

These results suggest that increased FGF-23 may represent an early, more sensitive biomarker of disordered phosphorus metabolism than concomitant serum phosphate measurements. Elevated concentrations of FGF-23 have been shown to activate fibroblast growth factor receptors implicated in the development of cardiac hypertrophy ***(Virag et al., 2007).*** So, the hypothesis that elevated FGF-23 concentrations can be used as early, sensitive biomarker of LVH in asymptomatic patients with CKD need to be tested. We design this study to examine the relationship between FGF-23 and LVH in patients with pre-dialysis CKD in order to understand the early mechanisms of LVH in CKD patients which is essential for designing novel therapeutic strategies to attenuate cardiovascular disease in those patients.

2. Patients and Methods: Study Population:

This study was conducted in AL-Zahraa hospital of Al-Azhar University, Cairo, Egypt. The study population consisted of 40 patients with various stages of CKD according to The Kidney Disease Outcomes Quality Initiative (K/DOQI) 2002 (Patel et al., 2002): stage 1 kidney damage with normal or increased GFR (>90 mL/min/1.73 m2), stage 2 with mild reduction in GFR (60-89 mL/min/1.73 m2) stage 3 with moderate reduction in GFR (30-59 mL/min/1.73 m2) and stage 4 with severe reduction in GFR (15-29 mL/min/1.73 m2). Stage 5 with end stage kidney failure (GFR < 15 mL/min/1.73 m2) or dialysis were excluded from the study. Those patients were recruited from Internal Medicine Department. Patients were classified to 2 groups, 27 patients with CKD defined as sustained reduction (≥ 3 months) in estimated glomerular filtration rate (eGFR) of ≤ 60 ml/min/1.73² based on the simplified Modification of Diet in Renal Disease formula (Levey et al., 1999) and 13 patients with preserved renal functions (eGFR of ≥ 60 ml/min/1.73²) to serve as control. The early renal impairment in control group was proved by microalbuminuria and/or grade I to II nephropathy by abdominal US. Patients were eligible for the study if they were 30 years of age or older. All patients included in the study underwent a standard procedure consisting of detailed history (with special concern to smoking and co-morbidity with renal impairment) and complete physical examination. Blood pressure (BP) measurements were taken by sphygmomanometer as a mean of three times at different occasions in sitting position. Body surface area (BSA) was calculated from the equation BSA (m²) = ([Height (cm) x Weight (kg)]/ 3600)½ ***(Mosteller, 1987)***. Body mass index (BMI) was calculated using the equation BMI = weight (in kilograms) divided by the square of the height (in meters). Exclusion criteria include: Stage 5 kidney disease (eGFR < 15 ml/min/1.732), renal replacement therapy (dialysis or kidney transplant), known ischemic heart diseases or heart failure.

Conventional echo-Doppler study: Echo-Doppler study was performed at rest with the patient at steady state in both supine and left lateral position, using Vivid- 7GE system with multi frequency (2.5 MHz) matrix probe M3S. Echo-Doppler study was performed using the standard views from all accessible windows (parasternal long axis view, short axis view at the level of great vessels, apical four chamber view, and apical two chamber view) with ECG physio-signal displayed. Two dimensional guided M- mode measurements of left ventricular end diastolic dimension (LVEDD), left ventricular systolic dimension (LVS), interventricular septal thickness (IVS) and posterior wall thickness (PWT), were measured at the left ventricular (LV) short axis view at the level of chordae tendinae just beyond the mitral leaflet tips as recommended by the American Society of Echocardiography (ASE) (Sahn et al., 1978). Patients with structural valvular disorders or ejection fraction < 40% were execluded. Echocardiographic measurements of LVM were calculated using the American society of echocardiography (ASE) formula described by (Devereux et al., 1986): LVM (gm) = 0.80 {1.04x (LVEDD+IVS+PWT) 3- (LVEDD) 3} + 0.6 g. and was corrected to body surface area. LV hypertrophy (LVH) was defined as LVM/BSA>95

gm/m2 for women and > 115 gm/m2 for men (Lang et al., 2005).

Laboratory investigations: Blood samples were obtained from all patients and immediately centrifuged, separated into aliquots to prepare for further assays. Serum urea and serum creatinine were done using Hitachi 912 Auto-analyzer (Roch-Germany). The Cockcroft-Gault formula for estimating CrCl was used as follows: CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72) and CrCl (female) = CrCl (male) × 0.85. Serum phosphate, calcium and albumin were measured using standard commercial assays. FGF-23 assays were measured using ELIZA Kit according to manufacturer's protocol (Catalogue No. CSB-E10113h/Cusabio biotech). The microtiter plate provided in this kit has been pre-coated with an goat-anti-rabbit antibody. Standards or samples are then added to the appropriate microtiter plate wells with a HRP-conjugated FGF23 and antibody preparation specific for FGF23 and incubated. Then substrate solutions are added to each well. The enzyme-substrate reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of FGF23 in the samples is then determined by comparing the O.D. of the samples to the standard. The sensitivity for minimum detectable dose of human FGF23 is typically less than 0.5pg/ml.

Statistical methods: IBM SPSS statistics (V. 20.0, IBM Corp., USA, 2011) was used for data analysis. Data were expressed as Mean ± SD for quantitative parametric measures in addition to percentage for categorized data. Routine statistics was done after adjustment for age and BMI using analysis of co-variance. The following tests were done: (1) Comparison between two independent mean groups for parametric data using Student t test. (2) Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test. (3) Ranked Sperman correlation test to study the possible association between each two variables among each group for non-parameteric data. (4) Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly sig.

3. Results:

The description of demographic, laboratory and echocardiogram data of all 40 patients involved in the study classified according to level of kidney functions are represented in table (1). Results are expressed as mean ± standard deviation or percent as appropriate. There was none significant difference in age (47 ± 15 years vs. 54 ± 13 years), sex (59.3% females vs. 61.5 % females) or BMI (29.7± 3.3 kg/m² vs. 29.2±5.6 kg/m²) between control and CKD patients. The CKD participants (grades 3 and 4) were 33.3 % smokers and had one or more co-morbidities with renal disease in the form of diabetes mellitus (59.2%), hypertension (59.3%), autoimmune disease (3.7), or liver disease (3.7%). The participants with preserved kidney function (grades 1 and 2 CKD) were 38.5% smokers and the co-morbidity with renal disease including DM (61.5%), hypertension (46.1%) and bronchial asthma (7.7). The mean systolic and diastolic BP was normal in both groups; however systolic blood pressure show significant increase across the spectrum of CKD patients. The laboratory data were demonstrated a highly significant increase in serum FGF-23 in patients with CKD compared with those with preserved kidney functions. There was also significant decrease in serum calcium (which considered a main stimulus for PTH secretion and subsequently FGF-23). Furthermore, the mean serum phosphate concentration was within the normal range in all patients, including the group with CKD (3.9±0.6) which favour the idea that the FGF-23 is increased long before the development of hyperphosphatemia. Echo data also represented highly significant increased LVM and LVMI in patients with CKD compared with those with preserved kidney functions (155 ± 26 vs 250±75 and 88 ± 14 vs 137±38 respectively).

In order to further characterize the relationship between increased FGF-23 and progression of kidney functions, we classify the patients with CKD according to GFR into: grade 3 CKD with eGFR→ 60-30 (n=13) and grade 4 CKD with eGFR → 30-15 (n=14).

All demographic data were equally distributed between grades 3 and 4 CKD except for systolic and diastolic BP that showed significant increase in grade 4 compared to grade 3 CKD. Laboratory data showed significant decrease in serum calcium as kidney function deteriorates however, serum phosphorus remained unchanged. FGF-23 plasma level was increased as renal functions deteriorate (Figure 1) evident by highly significant increase in FGF-23 in grade 4 CKD compared by grade 3. There was no significant difference in the indices of cardiac structure and function across the spectrum of CKD except for LVM and LVMI which showed significant increases in grade 4 compared to grade 3 CKD (Table 2).

Table 3 represents significant positive correlation between plasma FGF 23 and GFR as well as LVM and LVMI (Figure 2) in patients with CKD. However, no significant correlations were founded between FGF-23 and serum calcium and phosphorus.

Table (1): Demographic, laboratory, and echocardiograpgic data of all patients according to kidney function.

Variables	eGFR □ 60 ml/min/1.73² N=13	eGFR ≤ 60 ml/min/1.73² N=27	P value	Significance
Demographic data:				
Age/years	47 ± 15	54 ± 13	0.139	NS
Female gender (%)	61.5	59.3	0. 890	NS
Co-morbidity (%): Diabetes mellitus Hypertension Bronchial asthma SLE Liver disease	 61.5 46.1 7.7 0.0 0.0	 59.2 59.3 0.0 3.7 3.7		
Smoking (%)	38.5	33.3	0.750	NS
BSA (m²)	1.8 ± 0.2	1.8±0.2	0.787	NS
BMI (kg/m2)	29.7± 3.3	29.2±5.6	0.764	NS
Systolic BP/mmHg	126 ± 9.6	135.7±17.6	0.032	S
Diastolic BP/mmHg	79 ± 7.6	83.7±10	0.127	NS
Laboratory data:				
Serum Calcium/(mg/dl)	8 ± 0.8	7.9± 0.9	0.198	NS
Serum Phosphorus/(mg/dl)	3.8 ± 0.5	3.9±0.6	0.348	NS
Serum Albumin/(mg/dl)	3.9 ± 0.4	3.3±0.5	0.002	HS
Serum Urea/(mg/dl)	58 ± 26	99± 40	0.001	HS
Serum Creatinin /(mg/dl)	0.9 ± 0.2	2.2±1	0.000	HS
eGFR (ml/min/1.73 m²)	96 ± 18	43±19	0.000	HS
FGF (pg/ml)	0.5±0.1	3.8± 2.2	0.000	HS
Echocardiogram M-mode left ventricular measurements				
IVSd/cm	1.1± 0.2	1.2±0.1	0.078	NS
LVIDd/ cm	4.8±0.5	5.2±0.7	0.068	NS
LVPWd/cm	1.1±0.2	1.2± 0.1	0.032	S
IVSs/cm	1.5±0.3	1.7±0.3	0.151	NS
LVIDs/cm	2.9± 0.7	3.1±0.6	0.418	NS
LVPWs/cm	1.5± 0.2	1.6±0.2	0.02	S
EDV/ml	105.5± 18.9	131.3± 46.3	0.017	S
ESV/ml	37± 10	40± 17	0.478	NS
EF%	70 ± 8	68±8	0.371	NS
LVM/g	155 ± 26	250±75	0.00	HS
LVMI	88 ± 14	137±38	0.00	HS

eGFR, estimated glomerular filtration rate, BSA, body surface area, BMI, body mass index, BP, blood pressure, FGF, fibroblast growth factor, IVS, inter ventricular septum, LVID, left ventricular internal dimensions, LVPW, left ventricular pulmonary wedge pressure, EDV, end diastolic volume, ESV, end systolic volume, EF, ejection fraction, LVM left ventricular mass, LVMI, left ventricular mass index, NS, non significant, S, significant, HS, highly significant.

Table (2): Comparison between demographic, laboratory and echocardiographic data of grades 3 and 4 CKD.

Variables	Grade 3 CKD N=13	Grade 4 CKD N=14	P value	Significance
Demographic data:				
Age/years	54 ± 12	54 ± 13	0.962	NS
BSA (m²)	1.8.±0.2	1.8± 0.1	0.667	NS
BMI (kg/m2)	28.4±6	30 ± 5	0.46	NS
Systolic BP/mmHg	127± 18	144± 13	0.015	S
Diastolic BP/mmHg	78.85	88 ± 6.7	0.014	S
Laboratory data:				
Serum Calcium/(mg/dl)	8.4 ± 0.6	7.5 ± 1	0.008	HS
Serum Phosphorus/(mg/dl)	3.9 ± 0.6	4 ± 0.6	0.563	NS
Serum Albumin/(mg/dl)	3.3 ± 0.7	3.2 ± 0.4	0.72	NS
Serum Urea/(mg/dl)	65 ± 21	127 ± 27	0	HS
Serum Creatinin /(mg/dl)	1.4 ± 0.5	2.9 ±1	0	HS
eGFR (ml/min/1.73 m²)	47 ± 5	26 ± 3	0	HS
FGF (pg/ml)	1.9 ± 0.8	5.5± 1.3	0	HS
Echocardiogram M-mode left ventricular measurements:				
IVSd/cm	1.1± 0.1	1.2±0.1	0.065	NS
LVIDd/ cm	5.0±0.6	5.3±0.9	0.235	NS
LVPWd/cm	1.1±0.1	1.2±0.1	0.101	NS
IVSs/cm	1.6±0.3	1.7±0.3	0.305	NS
LVIDs/cm	3.0±0.6	3.3±0.6	0.231	NS
LVPWs/cm	1.6±0.2	1.7± 0.2	0.076	NS
EDV/ml	118.6±31.6	143±55.3	0.169	NS
ESV/ml	35.9±13	43.5±19.3	0.236	NS
EF%	67.0±7.8	68.4±7.9	0.643	NS
LVM/g	215.4±25.5	281.2± 91.6	0.021	S
LVMI	119.8±11.7	153.7±46	0.018	S

eGFR, estimated glomerular filtration rate, BSA, body surface area, BMI, body mass index, BP, blood pressure, FGF, fibroblast growth factor, IVS, inter ventricular septum, LVID, left ventricular internal dimensions, LVPW, left ventricular pulmonary wedge pressure, EDV, end diastolic volume, ESV, end systolic volume, EF, ejection fraction, LVM left ventricular mass, LVMI, left ventricular mass index, NS, non significant, S, significant, HS, highly significant.

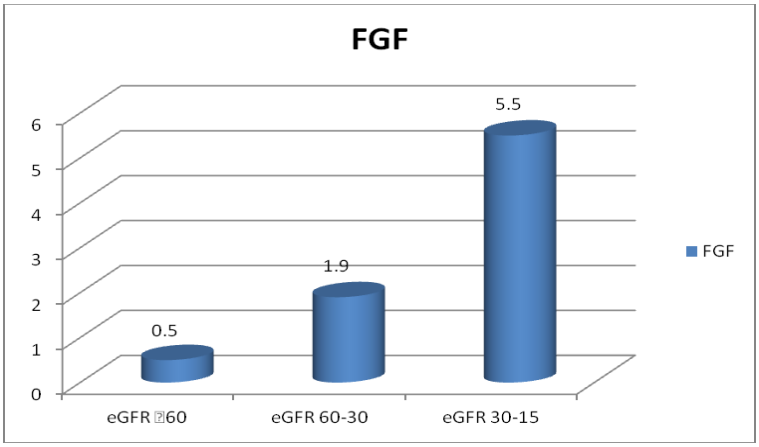

Figure (1): Elevated circulating FGF23 levels as renal functions deteriorate (as regards median values)

Table (3): Correlation between FGF-23 and serum calcium, phosphrous, creatinin, eGFR, LVM and LVMI in CKD patients

Variables	FGF-23		
	R	P	Sig.
Calcium (mg/dl)	-0.37	0.058	NS
Phosphorus (mg/dl)	0.175	0.384	NS
Creatinin (mg/dl)	0.526	0.005	HS
eGFR (ml/min/1.73 m²)	-0.631	0	HS
LVM/g	0.491	0.009	HS
LVMI	0.487	0.01	S

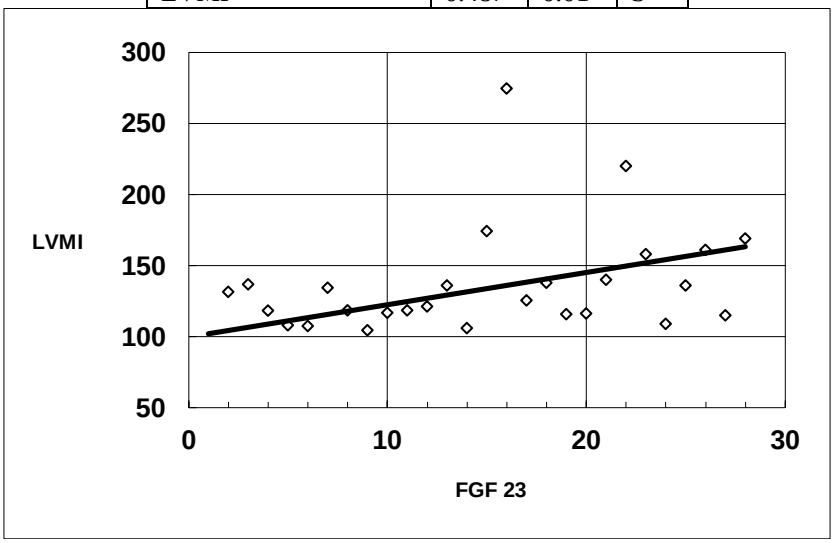

Figure (2): Linear regression analysis showing correlation between FGF-23 and LVMI among CKD patients

4. Discussion

Cardiovascular disease is the leading cause of death in all stages of CKD. One of the most important mechanisms of cardiovascular disorders is LVH that contributes to diastolic dysfunction, congestive heart failure, arrhythmia, and sudden death (***Go et al., 2004***). Our study was designed to characterize the FGF-23 role in the development of LVH in patients with CKD, aiming to elucidate additional mechanism of LVH helping to identify novel therapeutic targets for reducing the burden of cardiovascular disease in those patients.

Increased synthesis of FGF-23 in the course of declined glomerular filtration rate were characterized in our study by the increased plasma levels of FGF-23 in patients with CKD versus those with preserved kidney function as well as increased FGF-23 plasma levels in patients with grade 4 versus grade 3 CKD. The increased FGF 23 was negatively correlated to GFR in patients with CKD however; this increased FGF is independent of serum phosphate level which

remained normal in our study. Our results are in line with Stevens et al., 2011 from the Renal Unit at the Western Infirmary in Scotland who founded that FGF-23 concentration correlates negatively with eGFR in patients with diabetic nephropathy, biopsy-proven IgA nephropathy and CKD stages 3 and 4. Glomerular filtration rate may modulate FGF 23 levels independent of serum P as association of GFR with FGF 23 was also observed in subjects with normal or mildly impaired renal function (Marsell et al., 2008) and increased FGF 23 in patients with CKD develops earlier than increased phosphate or PTH (Isakova et al., 2011). Hence, FGF23 measurements may be a sensitive early biomarker of disordered phosphorus metabolism in patients with CKD and normal serum phosphate levels.

FGF-23 Levels are elevated, often more than 1000-fold, in patients with end-stage renal disease (ESRD) and hyperphosphataemia develops despite this marked elevation. Increased levels of FGF-23 may be due to reduced renal responsiveness which may reflect the reduction in the number of intact nephrons, and the resulting reduced expression of its co-receptor Klotho on distal convoluted cells (***Koh et al., 2001).*** De Borst et al., 2011 present another explanation that low levels of calcitriol (due to the loss of 1-alpha hydroxylase) increase renal renin production. Activation of the renin-angiotensin-aldosterone system (RAAS), in turn, reduces renal expression of klotho. The resulting high FGF-23 levels suppress 1-alpha hydroxylase, further lowering calcitriol. This feedback loop results in vitamin D deficiency, RAAS activation and high FGF-23 levels, and renal klotho deficiency, all of which associate with progression of renal damage.

The higher level of FGF-23 was significantly associated with higher risk of end stage renal disease (ESRD) and with an independently greater risk of death (Isakova et al., 2011). In advanced CKD, FGF-23 is strongly and independently associated with all-cause mortality (41%), cardiovascular events (56%), and initiation of chronic dialysis (20%) (Kendrick et al., 2011).

A valuable suggestion linking high FGF-23 to greater cardiovascular risk was offered by our study that revealed a significant correlation between elevated FGF-23 and LVMI in patients with CKD and this positive correlation was present before appearance of hyperphosphatemia as the mean phosphate level in our patients are within the normal range. So, FGF-23 may serve as sensitive marker of early calcium-phosphate disturbances and can predict occurrence of LVH in patients with CKD.

Our results augment Gutierrez and his colleagues, 2009 who presented a cross-sectional data from 162 subjects with pre-dialysis CKD and demonstrating that increased FGF-23 concentrations are associated with increased LVH independent of known risk factors in CKD.

In Stevens and his colleague's study, 2011, they assessed the relationship between FGF-23 and LVH in CKD using Cardiac magnetic resonance imaging. They concluded that FGF-23 concentrations correlate positively with LVMI and considered an independent predictor of LVH in CKD. The mechanism by which FGF-23 cause development of LVH in CKD patients may be a direct effects on the growth or matrix production of cardiac myocytes or that it has the potential to increase blood pressure.

Stevens et al., 2011 in vitro examined the effect of FGF-23 on endothelial cells and showed that FGF-23 stimulates the production of the cell adhesion molecules, E-selectin and VCAM. Higher levels of E-selectin and VCAM, indicate activation of the vascular endothelium and are present in patients with essential hypertension, who have endothelial dysfunction. However they did not prove direct causality with elevated FGF-23 and LVH.

Moreover, elevated concentrations of FGF-23 have been shown to non-selectively activate fibroblast growth factor receptors implicated in the development of cardiac hypertrophy (***Eswarakumar et al., 2005)***.

Further research needed to be continued in this area to ascertain the pathophysiological mechanism of FGF-23 on cardiac myocytes and development of LVH and also ascertain if lowering levels of FGF-23 translates to improved clinical outcomes in patients with CRF. FGF-23 can be lowered using routine clinical interventions that restrict dietary phosphorus absorption; these may suggest novel therapeutic strategies for ameliorating the development of LVH as well as improving the fatal prognosis of patients with CKD.

Summary and conclusion:

Increased FGF-23 in the course of decreased renal function may represent an early and sensitive biomarker of asymptomatic LVH in patients with CKD than concomitant serum phosphate measurements.
Recommendation: Further research needed to be continued in this area to ascertain the pathophysiological mechanism of FGF23 on cardiac myocytes and development of LVH and also to ascertain if lowering levels of FGF-23 translates to improved clinical outcomes in patients with CKD.

Corresponding author
Doaa Salah Eldeen
epartment of Internal Medicine, Al Azhar University, Cairo, Egypt.
dsalah241@gmail.com

References:

Antoniucci DM, Yamashita T, and Portale AA., 2006. "Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men". Journal of Clinical Endocrinology and Metabolism; 91 (8): 3144–3149.

Coresh J, Selvin E, Stevens LA, et al., 2007. Prevalence of chronic kidney disease in the United States. JAMA; 298(17): 2038–2047.

De Borst MH, Vervloet MG, ter Wee PM et al., 2011. Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF-23-klotho in chronic kidney disease. J Am Soc Nephrol. Sep;22 (9):1603-9.

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

Eswarakumar VP, Lax I and Schlessinger J., 2005. Cellular signalling by fibroblast growth factor receptors. Cytokine Growth Factor Rev.; 16(2):139–149.

Go AS, Chertow GM, Fan D et al., 2004. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med.; 351(13):1296–1305.

Gutiérrez OM, Januzzi JL, Isakova T et al., 2009. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. May 19;119(19):2545-52.

Imanishi Y, Inaba M, Nakatsuka K, et al., 2004. FGF-23 in patients with end-stage renal disease on hemodialysis. Kidney Int; 65:1943-1946.

Isakova T, Wahl P, Vargas GS, et al., 2011. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. Jun;79(12):1370-8.

Isakova T, Xie H, Yang W et al., 2011. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA;305(23):2432–2439.

Kendrick J, Cheung AK, Kaufman JS et al.,2011. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol. Oct;22(10):1913-22.

Koh N, Fujimori T, Nishiguchi S et al., 2001. Severely reduced production of klotho in human chronic renal failure kidney. Biochemical and Biophysical Research Communications; 280(4):1015–1020.

Kolek OI, Hines ER, Jones MD et al., 2005. "1α,25-dihydroxyvitamin D upregulates FGF23 gene expression in bone: the final link in a renal-gastrointestinal-skeletal axis that controls phosphate transport". American Journal of Physiology; 289 (6): 1036–1042.

Lang RM, Bierig M, Devereux RB, et al., 2005. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiography;18:1440-1463.

7/1/2012

Larsson T, Nisbeth U, Ljunggren O, et al., 2003. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney Int; 64: 2272-2279.

Levey AS, Bosch JP, Lewis JB et al., 1999. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med;130: 461–470.

London GM, Gu´erin AP, Marchais SJ et al., 2003. "Arterial media calcification in end stage renal disease: impact on all-cause and cardiovascular mortality". Nephrology Dialysis Transplantation; 18 (9): 1731–1740.

Marsell R, Grundberg E, Krajisnik T et al., 2008. Fibroblast growth factor-23 is associated with parathyroid hormone and renal function in a population-based cohort of elderly men. Eur J Endocrinol. Jan;158 (1):125-9.

Miyamoto K, Kuwahata M, Kato S et al., 2005. "Inhibition of intestinal sodium-dependent inorganic phosphate transport by fibroblast growth factor 23". Therapeutic Apheresis and Dialysis; 9(4): 331–335.

Mosteller RD., 1987. Simplified Calculation of Body Surface Area. N Engl J Med Oct 22;317(17):1098.

Nakai K, Komaba H and Fukagawa M., 2010. New insights into the role of fibroblast growth factor 23 in chronic kidney disease. J Nephrol. Nov-Dec; 23 (6):619-25.

Patel SS, Kimmel PL and Singh A., 2002. New clinical practice guidelines for chronic kidney disease: a framework for K/DOQI. Semin Nephrol. Nov; 22(6):449-58.

Sahn DJ, De Maria A, Kisslo J et al., 1978. The committee on M- mode standardization of mode echocardiography: results of a survey of echocardiographic measurements. Circulation; 58: 1072-1082.

Saji F, Shiizaki K, Shimada S et al., 2009. Regulation of fibroblast growth factor 23 production in bone in uremic rats. Nephron Physiol; 111:p59–p66.

Shimada T, Hasegawa H, Yamazaki Y, et al., 2004. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res.; 19:429-435.

Stevens KK, McQuarrie EP, Sands W et al., 2011. Fibroblast growth factor 23 predicts left ventricular mass and induces cell adhesion molecule formation. Int J Nephrol;2 (9): 7070.

Tonelli M, Sacks F, Pfeffer M et al., 2005. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation; 112: 2627–2633.

Virag JA, Rolle ML, Reece J et al., 2007. Fibroblast growth factor-2 regulates myocardial infarct repair: effects on cell proliferation, scar contraction, and ventricular function. Am J Pathol; 171: 1431–1440.

Yamashita T, Yoshioka M and Itoh N., 2000. "Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain". Biochemical and Biophysical Research Communications; 277(2): 494–498.