

Research Article**Clinical significance of FGF-23 in Chronic Kidney Disease Patients****Manar Raafat¹, Mona Madkour², Amna Metwaly³, Fatma Mohammad Nasr^{3*}, Osama Mosbah¹, Noha El-Sheikh¹**¹Department of Nephrology, Theodor Bilharz Research Institute, Cairo, Egypt²Department of Hematology, Theodor Bilharz Research Institute, Cairo, Egypt³Department of Intensive Care, Theodor Bilharz Research Institute, Cairo, Egypt***Corresponding author**

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Abstract: Fibroblast growth factor 23 (FGF-23) is a potent regulator of serum phosphate level. In CKD, circulating FGF-23 levels gradually increase with declining renal function. Higher FGF-23 level was associated with higher atherosclerosis score. We aimed to study the correlation between FGF-23 and the parameters that have effects on morbidity and mortality in CKD patients and to establish its role as biomarker of cardiovascular disease risk in these patients. This study comprises 80 subjects divided into three groups: group I (40 patients with CKD on regular HD), group II (20 patients with CKD on conservative treatment) group 3 (20 healthy subjects as a control). All patients and controls were subjected to the following: echocardiography, carotid duplex and laboratory investigations including serum calcium, phosphate, parathyroid hormone, alkaline phosphatase, creatinine, blood urea, Iron profile (serum iron, serum ferritin, T_{sat}, TIBC, FGF23). The laboratory data showed significant increase in creatinine, urea, phosphorus, CaPh product, PTH and FGF-23 with significant decrease in serum calcium and ferritin in group 1 & 2 compared to the controls. There were a statistically significant increase in IVST, PWT, LVM, LVMI and CIMT in group 1 & 2 compared to the controls. FGF-23 showed a positive correlation with creatinine, urea, PTH, CaPh, LVMI & CIMT and negative correlation with ferritin, Hb & HCT. We concluded that elevated FGF-23 level was independently associated with faster progression of CKD, therapy-resistant secondary hyperparathyroidism and increased cardiovascular risk in CKD patients and so, could represent a promising therapeutic target that might improve the fatal prognosis of patients with CKD.**Keywords:** CKD, Hemodialysis, FGF-23, PTH, LVM, CIMT.

INTRODUCTION

Patients with chronic kidney disease (CKD), particularly end-stage renal disease (ESRD), face an increased risk of mortality, mainly due to cardiovascular disease (CVD) [1, 2]. Clinical studies have reported CKD as an independent risk factor for CVD from its early stages [2]. Among ESRD patients, the risk of cardiovascular mortality has been found to be 10–100 times greater than in healthy individuals [3]. Structural and functional alterations of the cardiovascular system, such as endothelial dysfunction, arterial stiffening, left ventricular hypertrophy (LVH), and vascular calcification, contribute to the risk of CVD [4].

This increased cardiovascular mortality occurs due to the interplay of traditional (e.g. hypertension, dyslipidaemia, diabetes) and non-traditional cardiovascular risk factors that comprises primarily microinflammation, oxidative stress and particularly deranged calcium phosphate metabolism [5].

Studies have revealed that hyperphosphataemia, hyperparathyroidism [6-8] and

hypovitaminosis D [9] to be independently associated with cardiovascular morbidity and mortality in CKD. Additionally, studies have indicated that substitution of vitamin D [10], pharmacological lowering of parathyroid hormone [11] and intake of phosphate binders [12] might improve cardiovascular outcome [5].

Fibroblast growth factor 23 (FGF-23), a 251-amino-acid protein is synthesized and secreted by osteoblasts and osteocytes. It is a potent regulator of serum phosphate levels. Along with its co-receptor Klotho, FGF-23 induces renal phosphate excretion by suppressing renal Na/Pi co-transporter activity in proximal tubule. Moreover, it reduces intestinal phosphate absorption by the inhibition of the 25-hydroxyvitamin D3 1- α -hydroxylase, that catalyzes the rate-determining step of synthesis of calcitriol [13].

In CKD, levels of circulating FGF-23 gradually increase with declining renal function. FGF23 levels can be up to 1000-fold above the normal by the time patients reach end-stage renal disease [14].

In healthy individuals and wild-type mice, lower serum iron concentrations has been found to be correlated with elevated FGF23 levels measured with a C-terminal (cFGF23) but not an intact (iFGF23) assay [15, 16]. It suggests that iron deficiency stimulates FGF23 synthesis but may not lead to increased circulating levels of biologically active hormone, perhaps because it is cleaved by furin within osteocytes into fragments [17], that are released and can be detected with the C-terminal assay. FGF23 levels has also been found to increase in response to intravenous iron in patients with end-stage renal disease (ESRD) undergoing hemodialysis, but with small change [18].

Higher FGF-23 level was reported to be associated with higher atherosclerosis score [19]. Some studies have linked FGF-23 to peripheral vascular calcification and/or coronary artery calcification score, whereas other studies have failed to show such an association [20, 21]. Currently it is thought that, at least in early CKD, FGF-23 indirectly contributes to decreased vascular calcification through maintaining a normal serum phosphate level. Finally, the relation between FGF-23 and left ventricular hypertrophy has been evaluated, which is another strong cardiovascular risk factor in CKD. Serum FGF- 23 has been reported to be positively associated with left ventricular mass index (LVMI) and increased risk of having left ventricular hypertrophy. Particularly, such associations were found in the highest FGF-23 tertile (>48 pg/mL) and were strengthened when restricted to subjects with eGFR <60mL/min/1.73m² [22].

Aim

In this study, we aimed to demonstrate the correlation between FGF-23 and the parameters that have effects on morbidity and mortality in CKD patients and to establish its role as biomarker of cardiovascular disease in these patients.

MATERIALS AND METHODS

This study was carried out in nephrology department of Theodor Bilharz Research Institute; it comprises 80 subjects divided into three groups:

Group 1: Including 40 patients with CKD on regular hemodialysis (HD), 3 times per week in 4 hours sessions. They were 25 males and 15 females.

Group 2: Including 20 patients with CKD on conservative treatment. They were 15 males and 5 females.

The etiology of renal failure was variable among the two studied patient groups.

Group 3: Including 20 age and sex matched healthy subjects as a control group. They were 13 males and 7 females.

Informed written consents were obtained from all patients according to the Declaration of Helsinki and the ethical committee of hospital approved this study.

All patients and controls in this study were subjected to the following:

A-History taking: laying stress on symptoms of cardiac complications e.g. previous anginal episodes, thrombotic events, etc.

B-Clinical examination: to confirm the diagnosis and to detect signs of CV complications with measurement of arterial blood pressure and pulse.

C-Echocardiography

Standard transthoracic M-mode, two dimensional, continuous and pulsed wave Doppler echocardiograms were obtained soon after a session of routine HD using a high resolution (ALT 5000 HDI) Toshiba Memo 30 scanner equipped with a 2.5 MHz transducer. M mode measurements were used to evaluate interventricular septum thickness and left ventricular posterior wall thickness at end diastole and left ventricular internal dimensions both in systole and diastole aiming to calculate left ventricular mass, fractional shortening (FS) and ejection fraction (EF).

D-Carotid Duplex

Ultrasonographic studies on common carotid arteries were performed using an ultrasound machine (Toshiba Memo 30 scanner) equipped with a 7.5 MHz high resolution transducer. The carotid intima-media thickness (CIMT) was defined as a low-level echo gray band that does not project into the arterial lumen and was measured during end-diastole as the distance from the leading edge of the second echogenic line of the far walls of the distal segment of the common carotid artery, the carotid bifurcation and the initial tract of internal carotid artery on both sides.

E- Laboratory Investigations

Blood sampling was performed after a 12-hrs fast. In HD group blood samples were obtained before the first session of the week. Ten ml venous blood was obtained by clean venipuncture from the antecubital vein and divided as follows: 2 ml into EDTA anticoagulated vacuum tube for complete blood picture and 8 ml into a plain vacuum tube, serum was separated after blood clotting by centrifugation and was stored at -20°C for further determination of Serum calcium, serum phosphate, serum parathyroid hormone, serum alkaline phosphatase, serum creatinine, blood urea, Iron profile [serum iron, serum ferritin, Transferrin Saturation (TSAT)], Total Iron Binding Capacity (TIBC), and serum Fibroblast Growth Factor (FGF23).

Complete blood picture and routine renal function tests were assessed using automated analyzer.

Serum Calcium: "Quantichrom TM Calcium Assay Kit" quantitative determination of calcium ion Ca⁺⁺ by calorimetric method (612 nm), Bio Assay Systems .

Serum Phosphorus: "Quantichrom TM Phosphate Assay Kit" quantitative determination of phosphate by colorimetric method (620 nm), Bio Assay systems (2007)

Alkaline Phosphatase (ALP): "Alkaline Phosphatase Kit" (Biomed diagnostics, Germany), Normal level ranges between 39 to 117 U/L.

Parathormone level : Parathormone level was measured by enzyme linked immunosorbent assay (ELISA) using kit manufactured by BioSource, Neville, Belgium with minimal detectable concentration of 2 pg/ml (Intra-assay coefficient of variations (CVs) 1.1-2 % and Inter-assay CVs 2.9-7.1%).

Serum Iron: Quantitative colorimetric determination of iron (STAMBIO laboratory, Normal Iron level is 50 - 150 ug /dl).

Serum Ferritin: Immuno-enzymometric Sequential Assay type 4 (Ferritin Test System, Normal ferritin level is 15 - 200 ug/l for males and 30-300 ug/l for females).

Transferrin Saturation Ratio (TSAT): Calculated from total iron level and Iron Binding Capacity. $TSAT = (S. IRON / TIBC) \times 100$, Johnson and Catherine). Normal T_{sat} is 20 - 50%

Total Iron Binding Capacity (TIBC): Quantitative colorimetric determination of unsaturated Iron Binding Capacity in serum (STAMBIO Laboratory, Normal level is 250 - 410 ug /dl).

Fibroblast Growth Factor (FGF23): Serum FGF-23 levels were determined using Human FGF-23 ELISA Kit (cat. number EZHFGF-23-32K) purchased from Millipore (USA) following the manufacturer's instructions.

Millipore Human FGF-23 ELISA Kit employs the quantitative sandwich enzyme immunoassay technique. FGF-23 levels were expressed as pg/mL.

This assay recognizes recombinant and natural human FGF23.

All assays were carried out according to manufacturer's instructions.

Statistical Analysis

Data were expressed as the mean \pm standard deviation (SD) for numerical variables. Association between variables was assessed by Pearson correlation coefficient. The threshold for significance was a p-value ≤ 0.05 . Statistical analysis was performed with the aid of the SPSS computer program, version 17.

RESULTS

The demographic data of the patients group and the control group revealed mean ages 48.89 ± 14.52 , 47.08 ± 17.04 and 43.17 ± 10.24 years respectively. In group 1 (HD group) 25 were males (62.5%) and 15 were females (37.5%), in group 2 (renal impairment group) ,15 were males (75%) and 5 were females (25%) and in group 3(control group), 13 were males (65%) and 7 were females (35%) (Table1).

The laboratory data showed significant increase in creatinine, urea, phosphorus, calcium x phosphorus product, PTH and FGF-23 with significant decrease in serum calcium and ferritin in group 1 & 2 compared to the controls and significant increase in creatinine , PTH & FGF-23 in group 1 compared to group 2. There was significant decrease in serum iron and TIBC in group 1 compared to group 3 and significant decrease in transferrin saturation in Group 2 compared to Group 3 (Table 2).

The echocardiographic data and the carotid duplex data showed a statistically significant increase in interventricular septum thickness (IVST), posterior wall thickness (PWT) , left ventricular mass (LVM), left ventricular mass index (LVMI) and carotid intima media thickness (CIMT) with significant decrease in FS and EF in group 1 and 2 compared to the controls (Table 3).

There was negative correlation between both Creatinine & urea and Calcium & Ferritin and Positive correlation between both creatinine & urea and phosphorus & PTH (Table 4).

There was positive correlation between creatinine & urea and IVST, PWT and LVM with a negative correlation between urea and both FS & EF (Table 5).

FGF-23 showed a positive correlation with Creatinine, urea, PTH, calcium x phosphorus product, LVMI and CIMT and it showed negative correlation with ferritin, Hb & HCT (Table 6).

LV mass showed a positive correlation with PTH and a negative correlation with serum Ca (Table7).

There was negative correlation between Hb and both urea and LV mass index (Table 8).

Table 1: Demographic data of the studied groups

	Group 1	Group 2	Group 3
Age (years)	48.89 ±14.52	47.08 ±17.04	43.17±10.24
Sex			
Male	25(62.5%)	15(75%)	13(65%)
Female	15(37.5%)	5(15%)	7(35%)
Duration of disease (years)	10.61 ±6.50	10.58 ±7.66	.
Duration of dialysis (years)	2.56 ±1.92	.	.

Table 2: Laboratory data of the studied groups

	Group 1	Group 2	Group 3	p value 1&3	p value 2&3	p value 1&2
Cr.(mg/dl)	7.02 ±2.27	3.00±1.7	.61±.18	<.01	<.01	<.01
Ur. (mg/dl)	114.3 ±37.76	100.86±32.86	27.76±6.95	<.01	<.01	
Ca.(mg/dl)	8.44±1.12	8.39±1.09	9.44±.64	<.01	< 0.05	
Ph. (mg/dl)	5.52±1.60	5.14±1.39	3.64±.75	<.01	<.01	
CaPh(mg ² /dl ²)	46.62±15.86	42.49±10.49	34.53±7.95	<.01	<.01	
ALP(U/L)	119.19±87.05	125.67±156.89	138.42±86.75			
PTH(pg/dl)	437.58±416.71	200.58±152.39	52.42±10.13	<.01	<.01	<.01
HB(gm/dl)	10.21±1.43	9.90±2.37	11.59±1.79			
HCT%	32.37±4.75	29.66±7.76	34.28±4.54			
Iron (ug/dl)	44.40± 25.09	50.67± 22.66	68.17± 24.79	<.01		
TIBC(ug/dl)	172.73± 98.44	226.42± 42.87	222.83±43.41	< 0.05		<.01
Tsat%	28.13± 13.36	22.26± 8.00	31.12±11.18		< 0.05	
Ferritin(ug/dl)	60.00±20.55	71.83±20.88	110.00±30.67	<.01	<.01	
FGF23(pg/ml)	122.4± 36.7	97.4±27.2	63.3±17.4	<.01	<.01	< 0.05

Cr.: serum creatinine, ur.: blood urea, Ca.: serum calcium, Ph.: serum phosphorus, CaPh: calcium x phosphorus product, ALP: serum alkaline phosphatase, PTH: parathormone, HB: hemoglobin, HCT: hematocrit, iron: serum iron, TIBC: total iron binding capacity, Tsat: transferrin saturation, FGF-23: fibroblast growth factor-23.

p< 0.05=Significant, p<0.01= highly significant

Table 3: Echocardiographic and CIMT data of the studied groups

	Group 1	Group 2	Group 3	p value 2&3	p value 2&3	p value 1&2
LVD(cm)	5.01±.65	5.01±.48	4.99±.71			
LVS(cm)	3.26 ±.58	3.38±.65	2.97±.46			
FS%	35.80± 6.0	31.67±7.92	40.50±3.48	<.01	<.01	
EF%	64.85± 8.01	52.67±8.11	70.67±5.42	<.01	<.01	<.01
IVST(cm)	1.16± .22	1.11±.20	.94±.10	<.01	< 0.05	
PWT(cm)	1.15± .19	1.12±.19	.94±.10	<.01	< 0.05	
LV mass(gm)	224.244± 58.30	214.04±59.14	168.27±34.66	<.01	< 0.05	
LVMI	129.60± 35.4	116.04±30.34	88.65±17.66	<.01	<.01	<.01
CIMT(cm)	1.11±.18	.98±.13	.42±.12	< 0.05	<.01	< 0.05

LVD: left ventricular diastolic diameter, LVS: left ventricular systolic diameter, FS: fraction shortening, EF: Ejection fraction, IVST: Interventricular septum thickness, PWT: Posterior wall thickness, LV mass: left ventricular mass, CIMT: carotid intima media thickness

p< 0.05=Significant, p<0.01= highly significant

Table 4: Correlation between Creatinine & Urea and other Laboratory parameters

	Creatinine		Urea	
	R	p	R	p
Ca	-.275*	.020	-.258*	.030
Ph	.553**	.000	.555**	.000
PTH	.371**	.001	.304**	.01
Ferritin	-.428**	.000	-.384**	.001

*p< 0.05=Significant, **p<0.01= highly significant

Table 5: Correlation between Creatinine & Urea and Echocardiographic parameters

	Creatinine		Urea	
	R	p	R	p
LV mass	.435**	.000	.278*	.026
FS			-.340**	.006
EF			-.289*	.020
IVST	.409**	.001	.379**	.002
PWT	.421**	.001	.296*	.018

*p< 0.05=Significant, **p<0.01= highly significant

Table 6: Correlation between FGF-23 and other parameters

	FGF	
	R	p
Creatinine	.430**	.000
Urea	.389**	.001
Ferritin	-.387**	.001
Hb	-.368**	.002
HCT	-.301*	.011
PTH	.385**	.001
CaPh	.362**	.002
CIMT	.375**	.002
LVMi	.276*	.047

*p< 0.05=Significant, **p<0.01= highly significant

Table 7: Correlation between LV mass and other Parameters

	LV mass	
	R	p
Creatinine	.435**	.000
Urea	.278*	.026
Ca	-.279*	.026
PTH	.255*	.042

*p< 0.05=Significant, **p<0.01= highly significant

Table 8: Correlation between Hb and other parameters

	HB	
	R	p
Urea	-.242*	.042
LV mass index	-.310*	.025

*p< 0.05=Significant

DISCUSSION

Fibroblast growth factor 23 (FGF-23) is an endocrinal hormone. It is secreted by osteocytes and osteoblasts concerning phosphate homeostasis [23]. It has been shown to have a key role in the “bone-parathyroid-kidney” axis and the regulation of the metabolism of Po4/Ca/vitamin D [24].

FGF-23 elevation has been associated with mortality for early stage chronic kidney disease (CKD) and hemodialysis (HD) patients [25].

In the current study there is significant increase in FGF-23 in HD patients (group 1) and CKD patients (group 2) compared to control group (group 3) and in group 1 compared to group 2 (p<0.05). Also there is a positive correlation between FGF-23 and serum creatinine and blood urea (p<0.01).

In agreement of our results Gutierrez *et al.*, in 2005 stated that in CKD, circulating FGF-23 levels gradually increase with declining renal function such that by the time patients reach end-stage renal disease, FGF23 levels can be up to 1000-fold above the normal range [14].

The increase in FGF-23 level starts at a very early stage of CKD as a physiological compensation in order to stabilize serum phosphate levels as the number of intact nephrons declines [26]. In contrast, it had been hypothesized that increased FGF-23 levels in CKD result primarily due to decreased renal clearance [27]. FGF-23 levels depend on an increased secretion due to an end-organ resistance to the phosphaturic stimulus of FGF-23 due to the deficiency of necessary Klotho cofactor [28, 29]. Other explanations for the early rise in the level of FGF-23 could be the release of unidentified FGF-23 stimulatory factors or loss of a

negative feedback factor(s) which normally suppress FGF-23, by the failing kidney [30].

Mizuiru *et al.*, in 2014 reported that high FGF-23 levels are associated with increased mortality in HD patients and can be caused by hyperphosphatemia and loss of residual renal function [31].

In our study we found significant increase in serum phosphorus, CaPh product and PTH with significant decrease in serum calcium in both group 1&2 compared to control group ($p<0.01$). Also FGF-23 showed a positive correlation with PTH and CaPh product ($p<0.01$).

In early stages of CKD, the phosphate levels are initially maintained in normal range due to increase per nephron phosphate excretion. But in the later stages of CKD, hyperphosphataemia occurs, as phosphate load overwhelms FGF-23-induced phosphaturia in remaining functional nephrons [14, 27].

In the presence of progressive CKD, serum FGF-23 levels increase along with the declination of renal function and increased serum phosphate and PTH concentration [27, 29, 14]. In the pre dialysis patients and patients who were on maintenance hemodialysis, high FGF-23 levels had been correlated with those of phosphate, pointing to a disrupted feedback loop that result in very high levels of serum FGF-23 [32].

Several studies have reported that FGF-23 levels are increased in patients with CKD and also have been reported that this hormone is related to the development of secondary hyperparathyroidism [24, 33]. It has been suggested that serum FGF23 levels are early contributors to the development of secondary HPT by suppressing of serum vitamin D and calcium levels [14, 34, 35].

In our research we demonstrated significant negative correlation between FGF-23 and serum Hb & HCT. Braithwaite *et al.* had confirmed this relationship [36]. This could be attributed to the fact that systemic effects of prolonged phosphate deficiency as a result of high FGF-23 level including abnormal erythrocyte, leukocyte and platelet function resulted from reduced AMP and 2,3, diphosphoglycerate levels [37].

Iron deficiency is an environmental trigger stimulating the FGF23 expression and hypophosphatemia in autosomal dominant hypophosphatemic rickets (ADHR). Unlike osteocytes in ADHR, normal osteocytes couple increased FGF23 production with commensurately increased FGF23 cleavage ensuring that normal phosphate homeostasis is maintained in iron deficiency. Simultaneous measurement of FGF23 by intact and C-terminal assays has supported it by providing minimally invasive insight into FGF23 production and cleavage in bone.

These findings also suggest a novel mechanism of FGF23 elevation in patients with CKD, those are often iron deficient demonstrating increased FGF23 production and decreased FGF23 cleavage, consistent with an acquired state mimicking the ADHR molecular pathophysiology [38].

In the current study there was a significant decrease in serum iron and total iron binding capacity (TIBC) in group 1 compared to group 3 ($p<0.01$ and $p<0.05$ respectively), with significant decrease in transferrin saturation in group 2 compared to group 3 ($p<0.05$) but there was no correlation between serum iron and FGF23 level.

In a study done by Akalin and his colleagues in 2014 they found no significant difference between the patients with severe secondary hyperparathyroidism and high serum FGF-23 levels and the patients with controlled secondary hyperparathyroidism and low and/or normal serum FGF-23 levels in terms of serum iron and ferritin levels and iron binding capacity [39].

As regard serum ferritin we demonstrated a negative significant correlation with FGF-23 in both group 1&2 ($p<0.01$) although it is a well-known acute phase reactant. Durham *et al.*, in 2007 [40]; Imel *et al.*, in 2007 [41] and Schouten *et al.*, in 2009 [42] reported elevated C-terminal FGF-23 in patients with low serum ferritin. Also this was in agreement with Braithwaite *et al.*, 2012 [36] and Prats *et al.*, 2013 [43] who stated that ferritin could be taken as a strongest inverse predictor of FGF-23 in subjects with and without elevated CRP.

The echocardiographic and CIMT data showed a statistically significant increase in interventricular septum thickness (IVST), posterior wall thickness (PWT), LV mass, LVMI and CIMT and significant decrease in FS and EF in group 1 and 2 compared to the control group. Also FGF-23 showed a positive correlation with LVMI and CIMT ($P<0.05$, $P<0.01$ respectively).

Higher FGF23 is associated with left ventricular hypertrophy (LVH), which is an important mechanism of congestive heart failure, and arrhythmia, and a potent risk factor for mortality in CKD [44, 45]. Thus, LVH explains the link between higher FGF23 and greater risk of mortality. Studies carried out in CKD, ESRD, and non-CKD populations have reported that the elevated FGF23 levels are independently associated with greater left ventricular mass index and greater prevalence of LVH [46-49].

Also, Dzgoeva *et al.*, in 2014 proved that FGF-23 is strongly associated with LV lesion to the point that some consider FGF-23 as a biomarker for cardiovascular disease and structure [50, 51].

The endothelium and vessel wall are targets of injury in CKD. Higher FGF23 levels were found to be independently associated with endothelial dysfunction that is marked by lower flow-mediated vasodilatation of the brachial artery, in patients with CKD stages 3–4 [52] and in an older, predominantly non-CKD population [53]. The data on FGF23 and vascular calcification are murky. Some studies have reported an independent association [54, 55] and others reporting none [56, 57].

The associations between FGF- 23, vascular dysfunction, atherosclerosis, and left ventricular hypertrophy are all progressively strengthened in patients with a lower eGFR despite normal phosphate levels. This finding supports the hypothesis that FGF-23 may reveal information about phosphate-related toxicity which cannot be obtained by measurements of serum phosphate [30].

However Sany *et al.*, in 2014 had another opinion and found that in dialysis patients LVMI were correlated weakly with the FGF-23 levels [58]. Thus, FGF-23 alone may not be a parameter that can be used for evaluation of the cardiac status in HD patients. Wald *et al.*, 2014 [59] and Scialla *et al.*, 2014 [60] agreed to that opinion and demonstrated that FGF-23 was not associated with either LVMI or LVEDV and proved that aggressive blood pressure reduction and avoidance of volume overload may confer LVM regression and improve clinical outcomes.

Existing therapeutic approaches for CKD-MBD might affect the serum concentration of FGF23. Because FGF23 is a phosphaturic hormone, its level might be modifiable by dietary phosphate restriction or using phosphate binder [4]. Vitamin D receptor activators are used commonly for the treatment of secondary hyperparathyroidism. Studies have reported that active vitamin D therapy is associated with improved survival in dialysis patient [61, 62]. Vitamin D increases the FGF23 level but improves outcomes in CKD patients. Conflicting data exist in relation to their effects on CVD. Active vitamin D promotes vascular calcification by upregulating osteoblastic markers and also by increasing calcium transport into the VSMCs [63]. In contrast, inhibitory effects of vascular calcification by vitamin D are reported in other studies [64].

In addition to these therapies, novel treatments are under investigation. For example, Shalhoub and his colleagues demonstrated that FGF23 antibodies ameliorated the development and progression of most features of secondary hyperparathyroidism in a rat model of CKD. However, perhaps because of the hyperphosphatemia, vascular calcification and death were increased after the treatment [35]. Results of this study imply that targeting FGF23 in CKD must be fine-tuned. They show that tissue-specific/selective blockade

of FGF23 receptor inhibitors demands further investigation [4].

CONCLUSION

FGF-23 is a regulator of calcium-phosphate metabolism. Elevated FGF-23 levels were independently associated with faster progression of CKD, therapy-resistant secondary hyperparathyroidism, and increased cardiovascular risk in CKD patients. Thus, FGF-23 could represent a promising therapeutic target that might improve the fatal prognosis of patients with CKD.

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