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Case Report

A Clinical Case Using FGF-23 Biomarker to Prognosticate LVH in Renal Disease

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Received: July 27, 2018; **Published:** August 30, 2018

Abstract

A 31-year-old man with a history of end-stage renal disease (ESRD) due to hypertension and biopsy proven focal sclerosis glomerulonephritis presented with several hours of shortness of breath due to hypertensive urgency. During his admission, he was found to have severe concentric left ventricular hypertrophy with markedly elevated fibroblast growth factor 23 (FGF-23) level at 24,100 RU/mL (normal < 180 RU/mL). Serum FGF-23 levels can be measured using an enzyme-linked immunosorbent assay to quantify the serum FGF-23 level. Elevation of FGF-23 in patients with chronic kidney disease (CKD) is correlated with increased risk for developing left ventricular hypertrophy, heart failure, coronary artery disease and cardiovascular death. Patients with CHF have a threefold higher risk of hospitalization than those in the lowest quartile and elevated FGF-23 levels are associated with a 4.4-fold increased risk of new-onset left ventricular hypertrophy (LVH). Additionally, patients with an FGF-23 level greater than 172 RU/mL have been observed to have a lower median survival compared to those with FGF-23 less than 172 RU/mL (2.3 years versus 6 years). FGF-23 appears to cause LVH is by binding to cardiac myocyte FGFR4 receptors. Investigation into pharmacologic treatment has been very limited to date and future investigation may consider targeting of FGF-23 substrates and receptors. In conclusion, in patients with renal failure and LVH, elevation of FGF-23 poses elevated risk for cardiovascular morbidity and mortality. Once the pathway of FGF-23 mediated LVH is better understood, potential pharmacologic treatment of elevated FGF-23 levels may be possible.

Keywords: *FGF-23; LVH; Renal Disease*

Abbreviations

ANP: Atrial Natriuretic Peptide; BNP: Brain Natriuretic Peptide; CHF: Congestive Heart Failure; CRIC: Chronic Renal Insufficiency Cohort study; ESRD: End-Stage Renal Disease; FGF-23: Fibroblast Growth Factor 23; FGFR: Fibroblast Growth Factor Receptor; FGFR4: Fibroblast Growth Factor Receptor 4; HCM: Hypertrophic cardiomyopathy; HD: Hemodialysis; LVH: Left Ventricular Hypertrophy; LVMI: Left Ventricular Mass indexed to Height; IV: Intravenous

Introduction

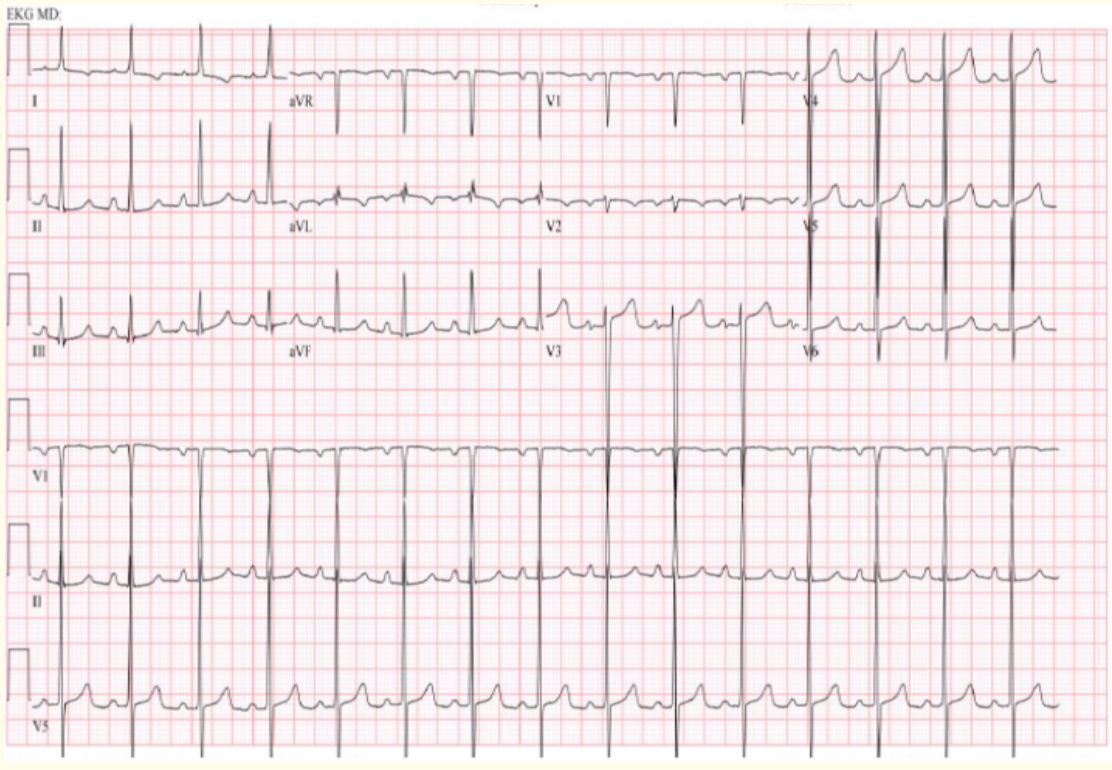
Cardiovascular disease remains a major cause of death for millions of patients with chronic kidney disease (CKD) [1]. Left ventricular hypertrophy (LVH) is a common mechanism of cardiovascular disease that occurs in 50 - 80% of patients with chronic kidney disease stages I-IV (CKD) [1]. Left ventricular hypertrophy has been recognized as a significant independent risk factor that portends an increased risk of mortality by 10 to 30 fold in patients with CKD and end-stage renal disease (ESRD) [2]. Despite treatment of known risk factors, cardiovascular mortality in CKD continues to cause significant disease and novel treatment of CKD induced cardiovascular dysregulation is needed to further reduce cardiac mortality.

Investigations into novel mechanisms of LVH in CKD lead to the recognition of fibroblast growth factor-23 (FGF-23) and its association with cardiovascular disease. FGF-23 is a hormone that regulates phosphate homeostasis via a novel bone and kidney axis [3]. Abnormal elevations of FGF-23 appear in the earliest stages of CKD and studies have observed a positive association between elevated levels and increased risk of cardiovascular events including myocardial infarction, congestive heart failure and death [3]. Furthermore, elevations of FGF-23 are independently associated with an increased risk for LVH and FGF-23 has shown promise as a marker for prognostication of LVH in CKD [3]. In our patient with ESRD and LVH we elected to obtain a serum FGF-23 level, which was markedly elevated and undertook a review of the recent literature to delineate his future risk of cardiovascular events.

Clinical Case

A 31-year-old man with a history significant for end-stage renal disease (ESRD) due to early onset hypertension and biopsy proven focal sclerosis glomerulonephritis presented to the hospital with several hours of unresolved shortness of breath. He had not missed any doses of medications. He denied associated dizziness, chest pain, abdominal pain, nausea or diaphoresis. He had not missed any dialysis sessions and his prior dialysis session was uneventful with a normal run time. In the emergency department his blood pressure was elevated to 220/120 and he was started on intravenous (IV) nicardipine with mild improvement of his blood pressure and shortness of breath. As an out-patient he was managed with carvedilol 25 mg twice daily, hydralazine 100 mg three times daily and clonidine 0.2 mg three times daily.

His physical exam was notable for a loud S4, a normal jugular venous pressure and no signs of systemic volume overload. A chest X-ray was without cardiomegaly or additional cardiopulmonary abnormalities (Figure 1a) and an ECG was notable for left ventricular hypertrophy with a strain pattern (Figure 1b). His admission labs were notable for sodium 139, potassium 5.9, calcium 10.0, phosphorus 4.9, BUN 49, creatinine 10.04 and troponin I < 0.10 (patient summary, table 1).



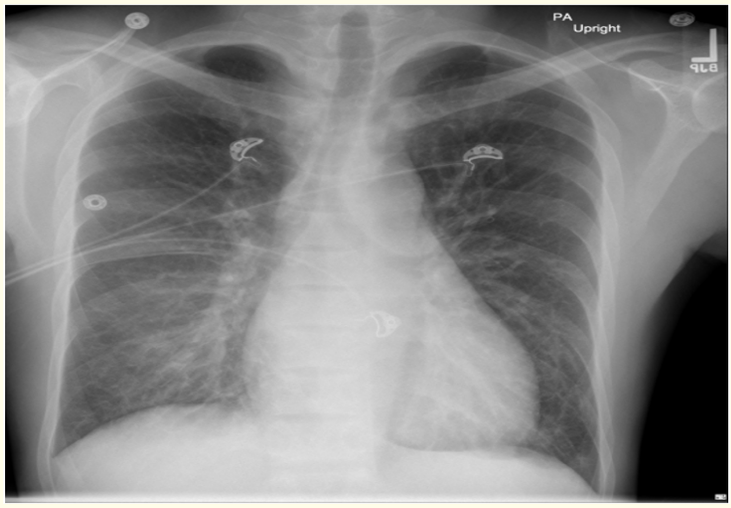


Figure 1: *A - Admission Chest X-ray revealed a normal cardiopulmonary silhouette without acute infiltrate. B - Admission ECG was notable for normal sinus heart rate with severe LVH criteria and possible left atrial enlargement.*

Patient Characteristics			
Presentation	31 year old male presenting with shortness of breath		
Past Medical History	End-stage renal disease on hemodialysis Hypertension Secondary Hyperparathyroidism		
Physical Exam	Vital Signs	RR 16, HR 85, BP 220/156	
	Skin	No rashes, bruises, excoriation or sores	
	Head and Neck	Normal thyroid gland, moist mucous membranes	
	Pulmonary.	Bilaterally clear to auscultation. No rhonchi, crackles or wheezing appreciated.	
	Cardiovascular	Regular rate and rhythm. Normal S1, with a loud S2 and S4 appreciated.	
	Abdomen	Abdomen was soft without pain to light or deep palpation in all four quadrants.	
	Vascular	Radial and dorsalis pedis pulses bilaterally equal. JVP 7 cm H_2O.	
	Extremities	No lower extremity edema.	
Laboratory Results		Patient Result	Normal
	Sodium	139	135 - 145 mmol/liter
	Potassium	5.9	3.6 - 5.0 mmol/liter
	Calcium	10.0	8.4 - 10.2 mg/dL
	Phosphate	4.9	2.44.1 mg/dL
	Blood Urea	49	6 - 23 mg/dL
	Creatinine	10.0	0.67 - 1.17 mg/dL
	Aspartate Transaminase	29	10 - 50 U/L
	Alkaline Phosphate	216	40 - 129 U/L
	Troponin I	< 0.10	< 0.10
	Hemoglobin	11.9	12.4 - 173 g/dL
	Platelets	262	150 - 450 K/uL

Table 1: *A summary of the patient's past medical history, physical exam and admission labs. Respiratory rate (RR), Heart rate (HR), Blood Pressure (BP)*

His blood pressure subsequently improved with medication adjustments and volume removal with hemodialysis; however, his dyspnea minimally improved. A transthoracic echocardiogram during admission was notable for septal and posterior lateral wall hypertrophy and increased left ventricular mass consistent with severe concentric left ventricular hypertrophy (LVH) and preserved systolic function (LVEF 50 - 55%) (Figure 2a, 2b). There was no significant left ventricular outflow obstruction at rest (Figure 2c, 2d) and diastolic parameters were consistent with pseudo normalization.

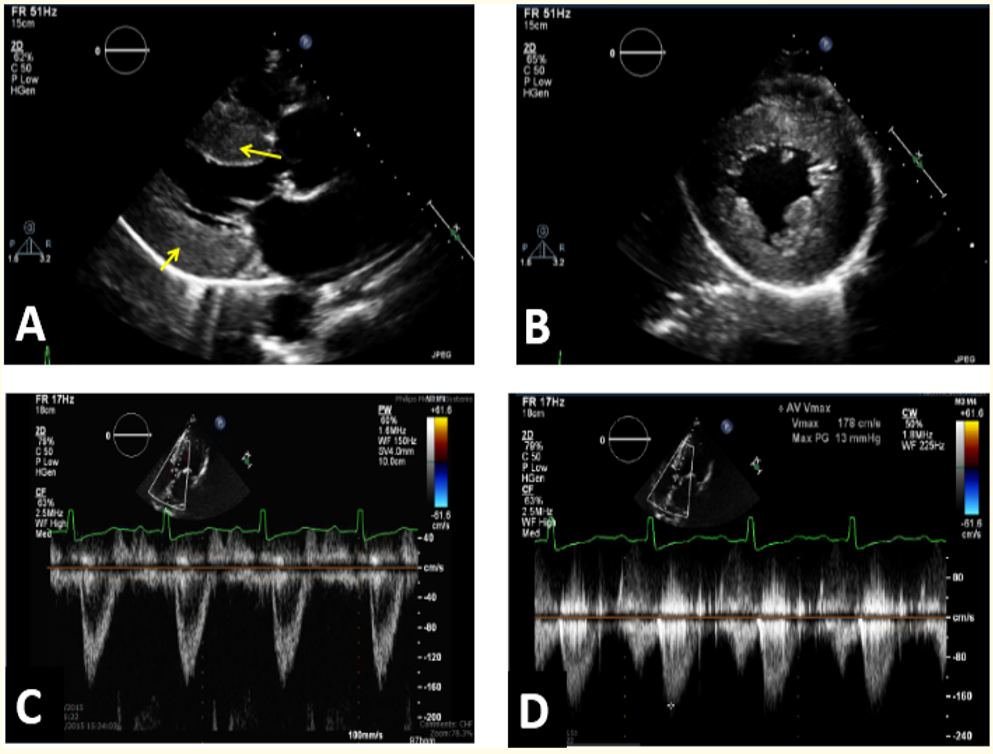


Figure 2: *A, B: Parasternal long and short axis during systole demonstrates septal and posterior-lateral wall hypertrophy (IVSd-1.7 cm, LVPWd-1.7 cm respectively), yellow arrows. Using the previous dimensions as well as LVEDD-4.9 cm The LV mass as indexed to basal surface area (BSA) was calculated to be (LV mass = 202.6 grams/m^2) consistent with severe concentric LVH. C, D. The presence of LVOT obstruction is assessed by using pulse wave and continuous wave Doppler. In our patient, the peak velocities across the LVOT were within normal range < 2.7 m/s and Doppler wave forms were early-peaking. These findings exclude hypertrophic obstructive cardiomyopathy (HOCM).*

These imaging finds were consistent with severe LVH versus possible familial hypertrophic cardiomyopathy (HCM). Clinically, the patient had no history of palpitations, pre-syncope or cardiac arrest. A detailed family history was unremarkable and there was no known family history of sudden cardiac death, hypertension, heart failure or myocardial infarction. As such, familial HCM was unlikely making additional genetic testing for HCM unwarranted. However, clinical prognostication of left ventricular hypertrophy in an ESRD population was possible at our center and an EDTA serum sample was sent to the Mayo medical lab (Rochester, MN) for FGF-23 level analysis by an immunometric enzyme assay [4]. The assay uses two purified goat antibodies that bind to the carboxyl terminal end of the FGF-23 molecule. One antibody coats the microtiter wells and a second is biotinylated. Next, horseradish peroxide is conjugated to avidin and 3.3', 5,5'-tetramethylbenzidine substrate provides a colored product, which is read in a microtiter plate spectrophotometer to determine the level [4].

Recent literature has suggested that patients with elevations in fibroblast growth factor 23 (FGF-23), a history of both chronic kidney disease and LVH carry a worse overall prognosis due to an increased risk for cardiovascular death [3,5]. In our patient the FGF-23 assay was significantly elevated at 24,100 RU/mL (normal < 180 RU/mL). As will be explained in our discussion, elevations to this magnitude are predictive of a worse survival due to increased risk of cardiovascular death. Our patient's blood pressure was stabilized to normal target range (less than 140/90 mmHg) and he was discharged with scheduled follow-up with his nephrologist and cardiologist.

Discussion

FGF-23 is a recently characterized biomarker that has gained attention for its use in prognostication of mortality in patients with ventricular hypertrophy and heart failure. Left ventricular hypertrophy is a prevalent condition in patients with hypertension and chronic kidney disease. Soon after the discovery of FGF-23 in patients with CKD, investigation into FGF-23 commenced. FGF-23 is a hormone secreted by osteocytes in response to elevated levels of serum phosphate, calcium and/or calcitriol acting primarily through a bone-kidney axis to maintain phosphate homeostasis [6,7]. Low level secretions of FGF-23 are considered physiologic; however, in patients with chronic renal disease the response to derangements in calcium and phosphate metabolism is exaggerated. Although FGF-23 works to maintain phosphate homeostasis, elevated FGF-23 levels are considered abnormal.

Similar to elevations of ANP and BNP in heart failure, elevated FGF-23 may be an independent risk factor for progressive heart failure, left ventricular hypertrophy, coronary artery disease and decreased survival [6-8]. A study involving 3,860 patients with CKD stages 2 - 4 over an average of 3.7 years observed 360 patients hospitalized for CHF. Hospitalized patients with FGF-23 levels in the highest quartile (> 239 RU/mL vs < 96 RU/mL) had a threefold higher risk of hospitalization than those in the lowest quartile (HR 8.18, 95% CI, 5.47 to 12.24) [3]. Higher baseline FGF-23 levels (> 239 RU/mL vs < 96 RU/mL) was associated with an increased rate of incident heart failure up to one year after initial levels were measured (43.5 vs. 6.8 per 1000 person years in 2487 patients without a history of heart failure) [3].

In a second prospective study, 149 patients not on dialysis with LVH were followed over 4.8 years and determined that elevated FGF-23 levels greater than 104 RU/mL predicted patients at an increased risk of cardiovascular events including incident myocardial infarction, coronary stenting, coronary bypass, coronary angioplasty, stroke and death (HR of 2.49, 95% CI 1.40 - 4.39) [5]. Individuals with FGF-23 greater than 172 RU/mL had a lower median survival compared to those with FGF-23 less than 172 RU/mL (2.3 years versus 6 years) (Figure 3) [9]. This association has been further characterized in a large national cohort of 3,070 patients with CKD. Patients with elevated FGF-23 levels in the highest quartile had a 4.4-fold increased risk of new-onset LVH (P = 0.001; 95% CI, 1.8 - 10.6). This risk appeared to increase logarithmically with those in the highest FGF-23 quartile having a 7.0 fold increased risk compared to the lowest quartile [10]. Overall, individuals with CKD and elevated FGF-23 had a 2.5-fold greater relative risk of eccentric hypertrophy and concentric hypertrophy versus normal ventricular geometry (P < 0.001; 95% CI, 2.1 - 3.0) [10]. Furthermore, elevated FGF-23 levels were positively associated with step-wise increase in left ventricular mass indexed to height (LVMI) as well as increased rates of developing eccentric and concentric LVH [10].

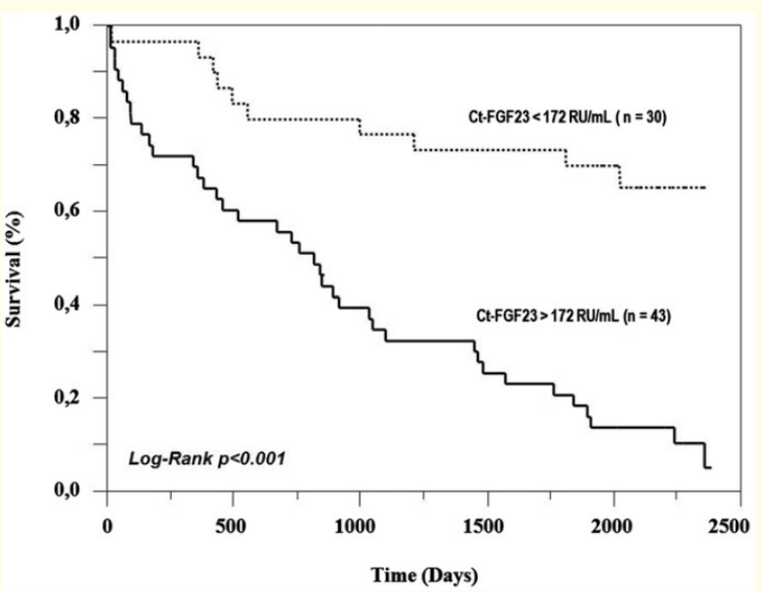


Figure 3: *A Kaplan-Meier curve for survival in 149 patients with heart failure with reduced ejection fraction in patients with an FGF-23 > 172 RU/mL versus patients with an FGF-23 < 172 RU/mL. Median survival for patients with an FGF-23 level > 172 rU/mL was 2.3 years versus more than six years for patients with an FGF-23 > 172 RU/mL [9]. Image credited to Dr. Gruson at the Université Catholique de Louvain (Brussels, Belgium), used with permission.*

FGF-23 appears to also model cardiovascular event risk for patients without known cardiac disease. In a prospective multiethnic cohort of 6,547 patients without known cardiovascular disease was followed over an average of 7.5 years to assess the relationship between FGF-23 and cardiovascular outcomes. A positive association between FGF-23 and left ventricular mass was observed with an estimated 1.2-g greater left ventricular mass for each 20-pg/mL higher serum FGF-23 concentration (95% confidence interval, 0.2 - 2.2 gram increase) [11]. The incidence of new heart failure was > 2-fold when comparing the highest to lowest quartiles of FGF-23 (< 30.5 RU/mL vs 46.4 - 223 RU/mL) [11]. In addition each 20-pg/mL greater FGF-23 concentration was associated with an estimated 19% greater risk of heart failure (HR 1.19; 95% CI, 1.03 - 1.37) and a 14% greater risk of incident coronary heart disease (HR 1.14; 95% CI, 1.01 - 1.28) [11].

The molecular basis of FGF-23

Under normal conditions, FGF-23 primarily acts through the bone-renal axis to exert its effects and maintain metabolic homeostasis. Renal specific responses are regulated by klotho, a transmembrane co-receptor protein, which forms a high affinity bond with FGF-23 and the fibroblast growth factor receptor (FGFR) to direct organ specific receptor stimulation in the kidney [7,12].

Although cardiac myocytes lack transmembrane klotho protein, FGF-23 appears to directly induce cardiac myocyte hypertrophy and activate the expression of various genes linked to cardiac hypertrophy [10]. These effects appear to suggest that cross activity exists through an alternative myocyte receptor. High affinity binding of FGF-23 to cardiac fibroblast growth factor receptor 4 (FGFR4) receptors in the setting of a systemic soluble and transmembrane klotho protein deficiency can cause receptor activation and LVH in the setting of prolonged FGF-23 elevation [10,13]. Binding of FGF-23 to FGFR4 receptors in cultured cardiac myocytes stimulated the PLCγ-calcineurin-NFAT pathway independent of klotho protein co-stimulation and appears to serve as the dominant signaling cascade pathway leading to LVH (Figure 4) [10,13]. Reactivation of fetal β-myosin heavy chain (β-MHC) expression while reducing expression of adult α-myosin heavy chains in myocytes occurs after exposure to FGF-23 treatment leading to cardiac myocyte hypertrophy (Figure 5) [10]. It has also been observed that, FGF-23 exposure increases levels of known markers of heart failure including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) [10].

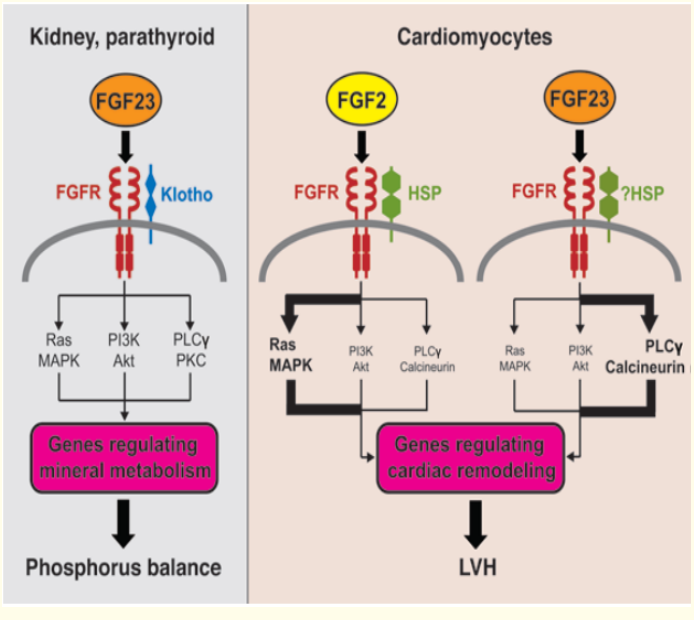


Figure 4: *In the kidney and parathyroid gland, FGF-23 binding to FGFR requires the co-receptor klotho protein to induce the signaling cascade leading to genetic activation. In cardiomyocytes, FGF-23 binds to FGFR receptors (specifically FGFR4 receptors) to active the PLCγ-calcineurin-NFAT independent of klotho protein, which results in LVH [10]. Image credited to Dr. Christian Faul, University of Miami Miller School of Medicine (Miami, FL), used with permission.*

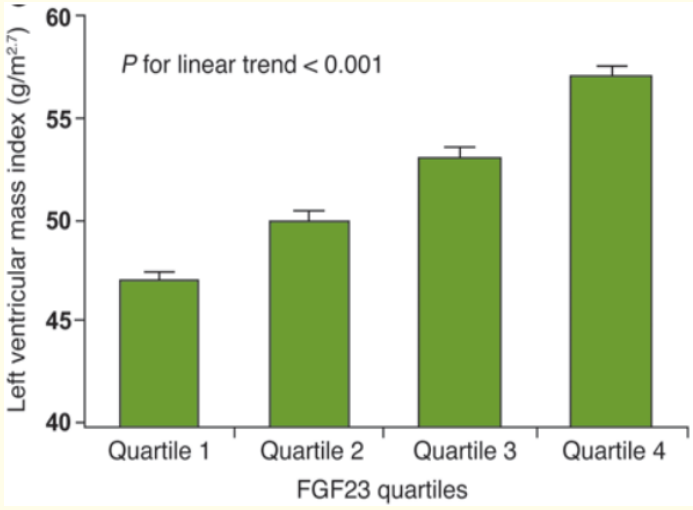


Figure 5: *Patients in the Chronic Renal Insufficiency Cohort study (CRIC) study with increasing quartiles of FGF23 were associated with increased left ventricular mass (P for linear trend < 0.001) [10]. Image credited to Dr. Christian Faul, University of Miami Miller School of Medicine (Miami, FL), used with permission.*

Therapeutic challenges

To date there have been few studies investigating the attenuation of the FGF-23 pathway in relation to the risk reduction of cardiac outcomes and LVH. Research into anti-FGF-23 compounds to reduce LVH has been very limited. Exploration of anti-FGF-23 compounds and antibodies remain largely pre-clinical. As with many endocrine pathways, isolated treatment of a metabolic problem often leads to cascade of events and unintended consequences. To date the primary strategy to reduce FGF-23 has been restriction of phosphate intake which has been shown to modestly reduce FGF-23 levels [7]. ACE inhibitors have also been investigated as a potential therapy. A small retrospective, non-randomized cohort of patients with type 2 diabetes and stage 1 CKD with proteinuria observed a mild reduction in FGF-23 levels (40.5 RU/mL vs 28.0 RU/mL, P < 0.001) for patients treated with ramipril (N = 64) over 12 weeks [14]. Although FGF-23 level decreased approximately 31% in patients receiving ramipril, it is unclear if the effect is clinically significant as both values were within normal limits and the follow-up was too short to observe cardiovascular outcomes [14]. Future studies are needed to clarify if ACE inhibitors may attenuate abnormal FGF-23 levels and improve clinical outcomes.

Additionally, cyclosporine (a calcineurin inhibitor) has previously been correlated with a reduction of left ventricular mass. Since the PLCγ-calcineurin-NFAT pathway appears to be one of the primary pathways for FGF-23 mediated LVH, future studies may be warranted to investigate the therapeutic implications of adding cyclosporine in patients with elevated FGF-23.

Conclusion

Our patient had significantly elevated levels of FGF-23 suggesting that he is at an increased risk for developing CHF, developing coronary artery disease and cardiovascular death. FGF-23 can be measured using an enzyme-linked immunosorbent assay to quantify the level of FGF-23 in serum samples. At this time FGF-23 appears to be helpful in cardiovascular prognostication of patients with chronic kidney disease and LVH. LVH in the context of severe FGF-23 may represent a severe pathological process for which no clearly beneficial pharmacologic treatment exists. Overall, the data supports the theory that elevated FGF-23 may be a marker for patients at an increased risk of developing CHF, increased risk for CHF hospitalizations and a marker for increased mortality in patients with LVH [6,7,9]. Once the pathway of FGF-23 mediated LVH is better understood, potential pharmacologic treatment of elevated FGF-23 levels may be possible.

Acknowledgements

We would like to thank our colleagues at the University of Texas Southwestern for their insight and expertise as well as the staff, staff support and of courses our patient for providing us with the support and permission to author this paper. We would also like to especially thank Dr. Christian Faul at the University of Miami Miller School of Medicine (Miami, FL) and Dr. Gruson at the Université Catholique de Louvain (Brussels, Belgium) for providing permission to use their images in our paper.

List of Support/Grant Information

None.

Disclosures

Speakership for Boehringer-Ingelheim, compensation is less than $10,000.

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Volume 5 Issue 9 September 2018