https://doi.org/10.48047/AFJBS.6.2.2024.4346-4356

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Fibroblast Growth Factor 23 as a Risk Factor of Left Ventricular Hypertrophy in Children on Regular Hemodialysis

Amal Mohamed Abd El-Latef [1], Hany El-Sayed Ibrahim [1], Saad Sabry Osh [2], Mona Mohamed Morsy Mohamed [1]

[1] Pediatric Department, Faculty of Medicine, Zagazig University, [2] Clinical Pathology Department, Faculty of Medicine, Zagazig University.

Corresponding author: Mona Mohamed Morsy Mohamed

Email: m.mohamed23@medicine.zu.edu.eg

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

doi:10.48047/AFJBS.6.2.2024.4346-4356

Abstract: Background: Left ventricular hypertrophy (LVH) is the most common cardiovascular abnormality in children with CKD, with a reported prevalence of 17%–49%.
Aim: To evaluate the role of FGF23 as early predictor of LVH in children on regular hemodialysis, aiming at reducing morbidity, mortality of these children.
Methods: This was a prospective cross-sectional observational study that was conducted on 48 children on regular hemodialysis at Nephrology Unit, Pediatric Department in Zagazig University Hospitals.
Results: FGF23 levels were significantly higher in the group with LVH compared to the non-LVH group (mean ± SD: 752 ± 246 vs. 535 ± 208 Pg/mL, p=0.002). NT pro-BNP levels were also significantly higher in the LVH group. There was a statistically significant negative correlation between FGF23 levels and fractional shortening (r=-0.442, p=0.002), and a positive correlation between FGF23 and NT pro-BNP levels (r=0.391, p=0.006). However, no significant correlations were found between FGF23 and BMI, dialysis duration, CBC, urea, serum albumin tests or serum PTH. Positive correlation between FGF23 and patient age negative correlation between FGF23 and 25(OH)D levels. Positive correlation between FGF23 and serum creatinine.
Conclusion: FGF23 has a role for early prediction of LVF in children on regular hemodialysis which helps in reducing morbidity, mortality of these children.

Keywords: *Fibroblast Growth Factor 23, Left Ventricular Hypertrophy, Children, Regular Hemodialysis.*

Introduction

The mortality risk of patients with chronic kidney disease [CKD] receiving dialysis treatment is approximately 20-fold greater than that of the general population and is largely due to cardiovascular [CV] disease **[1].**

In children, LVH can be identified in the early stages of CKD and tends to progress with age. It constitutes a major cause of CV morbidity and mortality in young adults who have been on dialysis treatment since childhood **[2]**.

Traditional CV risk factors, such as elevated serum cholesterol, hypertension, or obesity, do not account for the increased mortality, but disturbances of mineral metabolism, including hyperphosphatemia, secondary

hyperparathyroidism and vitamin D deficiency have been identified as non-classical risk factors for CV mortality in these patients with CKD **[3]**.

Fibroblast growth factor 23 [FGF-23], a phosphaturic hormone that also reduces the activity of renal 1-alpha-hydroxylase and renal synthesis of 1,25-dihydroxy-vitamin D [1,25$[OH]_2$D], plays a central role in maintaining mineral homeostasis in early stage CKD **[4].**

FGF-23 is elevated in adults and young patients with advanced CKD. Elevated serum FGF-23 concentrations have been identified as strong predictor of future mortality in adults at the initiation of hemodialysis [HD] and are independently associated with LVH in adults on HD and those with predialysis CKD. However, these associations are recognized in older patients who have had longer exposure than children to the metabolic derangements and confounding comorbidities of CKD known to impact CV mortality. The life expectancy of pediatric patients with advanced CKD continues to improved thus, early identification of potential CV risk factors may further benefit their long-term outcome **[5]**.

The aim of the current study was to evaluate the role of FGF23 as early predictor of LVH in children on regular hemodialysis, aiming at reducing morbidity, mortality of these children.

Patients and Methods

This prospective cross-sectional observational study was conducted at Nephrology Unit, Pediatric Department in Zagazig University Hospitals. Inclusion Criteria included all children on regular hemodialysis and their age between 5 and 15 years.

Every patient was subjected to full history taking, general assessment. Children receiving routine hemodialysis had routine investigations that included parathyroid hormone (PTH), calcium, and phosphorus. Specific investigations (FGF-23 by ELISA, serum N-terminal prohormone B-type natriuretic peptide (NT Pro BNP), and 25-hydroxycholecalciferol) and echocardiography were measured.

Clinical information and lab techniques:

Data on all demographics, dialysis duration, weight during interdialysis, and types of hypertension were documented. The measurements of height, weight, and body mass index were given as an average and a range. Serum parathyroid hormone, 25OH vitamin D, calcium, phosphorus, magnesium, albumin, urea, creatinine, salt, postassium, ferritin, albumin, CBC, and serum ferritin were all determined. The sandwich enzyme linked immunosorbent assay (ELISA) assay, which recognizes intact molecules, was used to quantify the concentration of FGF23 in plasma. The assay was refrigerated until processing, with a 100 PG/mL upper limit of normal. The Elecsys 2010 system analyzer Roche diagnosed normal range for serum N-terminal prohormone B type natriuretic peptide (NT-ProBNP), a recognized indicator of cardiac stress and hypertrophy, is 0-125 PG/ml.

Echocardiography

Pediatric echocardiography staff conducted all doppler echocardiograms and M-mode tracings.

The following parameters were measured

A) Left ventricular dimensions (LVD): Measured from the derived M-mode echocardiography in the parasternal long ads, view. To assess the following parameters:

- Interventricular septum thickness at end-diastole (IVSd)(cm)
- Interventricular septum thickness at end-systole (IVSs)(cm)
- Left ventricular internal diameter at end-diastole (VIDd) (cm)
- Left ventricular internal diameter at end-systole (LVIDs) (cm)
- Left ventricular posterior wall at end-diastole (LVPWd) (cm)
- Left ventricular posterior wall at end-systole [LVPWs] (cm)

B) Left ventricular systolic functions were determined as well through estimation of:

- Ejection fraction (EF%). This method derived from a 2D image is recommended to assess the LV EF **(Feng et al., 2002)**

$$EF\ (\%)\ SV / EDV * 100$$

- Fractional shortening (FS%) **(Srinivasan et al., 2017)**

$$FS = [(LVEDD-LVESD)/ LVEDD] * 100\%$$

C) Left ventricular mass (LVM gm) **(Perdrix et al., 2011)**:

$$LVM = 0.8\ \{1.04[([LVDd + IVSd + PWD] - LVDd^3)]\} +0.6$$

D) Left ventricular mass index (LVMI gm/m2) was calculated by using LVMI calculator: LVMI calculated using the following equation **(Richey et al., 2010)**:

LVMI LVM/body surface area

Reference Range	Female	Male
Mildly abnormal	43-95	49-115
Moderately abnormal	96-108	116-131
Severity abnormal	>122	<149

Measurements were determined with standard techniques in accordance with the recommendations of the American Society Echocardiography (ASE).

Administrative design:

The study protocol was submitted for approval by Zagazig University Institutional Review Board.

STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates Non-significant difference. Independent T-test: was used in order to compare between two independent groups with parametric quantitative data. Mann-Whitney test: was used in order to compare between two independent groups with non-parametric quantitative data. Pearson correlation coefficient: used to measure the strength of a relationship between two variables.

Results:

Table (1) showed comparison of lab investigations between participants with and without left ventricular hypertrophy, FGF23 (Pg/mL) in LVH group ranged from 219 to 969 with mean ± SD = 752 ± 246 **,**while in No LVH group the FGF23 (Pg/mL) ranged from 248 to 922 with mean ± SD = 535 ± 208 with statistical significant difference (p= 0.002) between the two groups. The NT pro-BNP (pg/mL) in LVH group ranged from 2435 to 18000 with mean ± SD = 10212 ± 4325 while in No LVH group the BNP (pg/mL) ranged from 150 to 18107 with mean ± SD = 6991 ± 4813 with statistical significant difference (p= 0.03) between the two groups. Serum 25OHD (ng/mL) in LVH group ranged from 16 to 33 with mean ± SD = 26.1 ± 4.45 while in No LVH group the Serum 25OHD (ng/mL) ranged from 22 to 33 with mean ± SD = 28 ± 2.82 with no statistical significant difference (p= 0.148) between the two groups. Serum PTH (pg/mL) in LVH group ranged from 17 to 1076 with mean ± SD = 439 ± 353 while in No LVH group the Serum PTH (pg/mL) ranged from 3.35 to 2841 with mean ± SD = 580 ± 590 with no statistical significant difference (p= 0.622) between the two groups.

Table (2) showed a significant positive correlation between FGF23 and age of the studied population (r=0.321, P=0.026), while there was no significant correlation between FGF23 with BMI and dialysis duration. Table (2) also showed a significant positive correlation between FGF23 levels and serum creatinine levels among studied populations (r=0.304, P=0.036), while there was no significant correlation between FGF23 levels with CBC, urea or serum albumin tests (P >0.05).

Table (3) showed a statistically significant negative correlation between FGF23 levels with fractional shortening (r=-0.442, P=0.002). Also, there was significant positive correlation between FGF23 levels with NT pro-BNP levels (r=0.391, P=0.006).

Table 1: Comparison of laboratory investigations between participants with and without left ventricular hypertrophy

	LVH group (n = 18)	**No LVH group (n = 30)**	**Test of Sig.**	**p-value**
FGF23 (Pg/mL)				
Mean ± SD.	752 ± 246	535 ± 208		
Median (IQR)	887 (245)	498 (359)	124	**0.002**
Range (Min-Max)	(219 – 969)	(248 – 922)		
NT pro-BNP (pg/mL)				
Mean ± SD.	10212 ± 4325	6991 ± 4813		
Median (IQR)	11010 (4591)	6935 (7241)	168	**0.03**
Range (Min-Max)	(2435 – 18000)	(150 – 18107)		
Serum 25OHD (ng/mL)				
Mean ± SD.	26.1 ± 4.45	28 ± 2.82		
Median (IQR)	27(7.5)	28 (4)	202	0.148
Range (Min-Max)	(16 - 33)	(22 - 33)		
Serum PTH (pg/mL)				
Mean ± SD.	439 ± 353	580 ± 590		
Median (IQR)	379 (581)	451 (504)	238	0.622
Range (Min-Max)	(17 – 1076)	(3.35 – 2841)		

***MW:** Mann-Whitney test* ***SD:** standard deviation* ***IQR:** interquartile range*

***p**: p value for comparing between the studied groups*

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.001: Highly significant

Table 2: Pearson's correlation coefficients (r) between FGF23 (Pg/mL) with patients' characters and laboratory results among studied patients

	FGF23 (Pg/mL)	
	r	**p**
Age	0.321	**0.026**
Dialysis duration	0.228	0.119
BMI	0.192	0.190
Hypertension	0.048	0.747
Hemoglobin	-0.187	0.204
Serum ferritin	-0.145	0.325
Serum iron	0.137	0.353
WBCs	-0.182	0.216
Platelets	0.101	0.496
Urea	-0.013	0.930
Serum creatinine	0.304	**0.036**
Serum albumin	0.346	0.160
PT	0.002	0.990
PTT	0.125	0.396
INR	-0.132	0.389

Table 3: Pearson's correlation coefficients (r) between FGF23 (Pg/mL) and echocardiography findings, 25 (OH)D, PTH levels among studied patients

	FGF23 (Pg/mL)	
	r	**p**
Ejection fraction	-0.088	0.550
Fractional shortening	-0.442	**0.002**
NT pro-BNP (Pg/mL)	0.391	**0.006**
Serum 25 (OH)D	-0.156	0.289
Serum PTH	0.167	0.263

Discussion

In the current study there a significant positive correlation between FGF23 and age of the studied population [r=0.321, P=0.026], while there was no significant correlation between FGF23 with BMI and dialysis duration. There was a significant positive correlation between FGF23 levels and serum creatinine levels among studied populations [r=0.304, P=0.036], while there was no significant correlation between FGF23 levels with CBC, urea or serum albumin tests [P >0.05].

The results of **Seeherunvong et al. [6]** study demonstrate a strong relationship between elevated concentrations of FGF-23 according to the C-terminal FGF-23 assay and increased LVMI, and that higher FGF-23 levels aggregate with LVH in young children and adolescents receiving chronic HD. Compared to other CV risk factors, FGF-23 was among the strongest factors associated with elevated LVMI in this cohort of patients.

Similar outcome studies are not available in pediatric patients, but the extremely high rates of cardiac death in children on dialysis, which reach 1,000-fold higher than that of the general pediatric population, are due to similar causes **[7]**.

LVH is present in 75 % of adults starting dialysis and in 82–85 % of pediatric patients on chronic HD **[2].** The 55 % prevalence rate of LVH in **Seeherunvong et al. [6]** study is substantially lower than that reported in most previous studies. This difference probably reflects the stricter criteria used by us to define LVH by adjusting the LVMI to the height–age value **[8]** rather than to chronological age **[9].**

The observed LVH rate and the proportions of patients with concentric and eccentric LVH in **Seeherunvong et al. [6]** study are very similar to those reported by **Bakkaloglu et al. [10]** [48 % prevalence of LVH] in a large pediatric cohort receiving chronic peritoneal dialysis and employing similar height-adjusted criteria.

In **Mitsnefes et al. [11]** study of children with predialysis CKD to date, they find that among children and adolescents with eGFR≥45 ml/min per 1.73 m^2, higher plasma FGF23 concentrations were independently associated with a higher prevalence of LVH. This association was strongest in participants with FGF23 levels ≥170 RU/ml in whom the odds of LVH was three times higher than in those with FGF23 levels <100 RU/ml. Further, when analyzed as a continuous variable, each doubling of FGF23 was associated with a two-fold higher odds of LVH. The associations were significant before and after adjustment for confounders including hemoglobin level and SBP, the latter a strong independent predictor of LVH in children with CKD **[12].**

Mitsnefes et al. [11] by contrast, the association of FGF23 with LVH was attenuated at lower eGFR of 45 ml/min per 1.73 m^2], when high SBP and higher BMI were significant predictors. These findings suggest that in children with eGFR of 45 ml/min per 1.73 m^2 and above, in whom BP can often be normal, FGF23 is an important determinant of left ventricular structure, whereas with advanced CKD, factors including hypertension and high BMI are relatively stronger determinants of LVH than FGF23.

Mitsnefes et al. [11] data showing strong dose-dependent associations of higher FGF23 with greater risk of LVH are consistent with studies in adults with predialysis CKD **[13].**

Further, **Mitsnefes et al. [11]** finding that FGF23 is a novel CKD-related cardiovascular risk factor in children is potentially of even greater importance because unlike adults, most children with CKD do not have multiple comorbidities such as preexisting advanced cardiac disease, peripheral vascular disease, or diabetes. A potential mechanism of FGF23-induced cardiac hypertrophy has been recently revealed in a series of experimental studies.

Regarding comparison of lab investigations between participants with and without left ventricular hypertrophy, FGF23 [Pg/mL] in LVH group ranged from 219 to 969 with mean ± SD = 752 ± 246 **,**while in No LVH group the FGF23 [Pg/mL] ranged from 248 to 922 with mean ± SD = 535 ± 208 with statistical significant difference [p= 0.002] between the two groups. The NT pro-BNP [pg/mL] in LVH group ranged from 2435 to 18000 with mean ± SD = 10212 ± 4325 while in No LVH group the BNP [pg/mL] ranged from 150 to 18107 with mean ± SD = 6991 ± 4813 with statistical significant difference [p= 0.03] between the two groups. There was no statistical significant difference between the two groups as regard Serum 25OHD and Serum PTH.

Abdel-hady et al. [14] study showed a significant correlation between FGF23 and LVH measured by LVMI, whereas phosphorus did not show any significant correlation at this stage. This could indicate that FGF23 could be an early marker of LVH before serum phosphorus increases.

In agreement with our study, **Gutiérrez et al. [2]** reported that FGF23 is associated independently with LVMI and LVH in patients with CKD.

A study by **Stevens et al. [15]** examined the relationship between FGF23 and LVH measured using the gold standard technique, Cardiac MRI, and reported a direct relationship between LVH and FGF23, but they did not prove a causality with elevated FGF23 on LVH.

Our study showed that there was a statistically significant negative correlation between FGF23 levels with fractional shortening [r=-0.442, P=0.002]. Also, there was significant positive correlation between FGF23 levels with NT pro-BNP levels [r=0.391, P=0.006].

In **Abdel-hady et al. [14]** study, predialysis CKD patients showed a high prevalence of LVH measured by LVMI [73.3%], mainly a concentric pattern rather than an eccentric pattern.

Clinical and experimental data support an important association between vitamin D and adverse cardiac remodeling **[16, 17]. Ky et al. [17]** found that higher serum 25OHD and 1,25$[OH]_2$D concentrations associated with lower left ventricular mass in 1431 adult participants from the Chronic Renal Insufficiency Cohort Study. **Mitsnefes et al. [11]** also observed that higher serum 25OHD concentrations were associated with lower odds of LVH. Unlike the findings of **Ky et al. [17]**, **Mitsnefes et al. [11]** observed no effect modification by vitamin D of the association between FGF23 and LVH. The major strengths of the present study include a large representative cohort of children with predialysis CKD from multiple pediatric nephrology centers across North America and standardized collection of demographic, clinical, laboratory, and echocardiographic data **[18]**.

Elevated FGF-23 level, in addition to hypertension, was the only other variable significantly correlated to LVMI; FGF-23, and no other variable, correlated significantly to IVST, another marker of myocardial hypertrophy. Elevated FGF-23 levels were associated independently with increased mortality in patients starting HD and with LVH in adults with predialysis CKD and on maintenance HD **[19].** In **Seeherunvong et al. [6]** group of patients, the duration of dialysis did not correlate with FGF-23 levels, suggesting that the association of FGF-23 with LVMI may already be evident in young patients shortly after starting HD treatment, as has been reported in adults, and likely was present before dialysis **[20]**. The strong association of the results of the C-terminal FGF-23 assay with LVMI compared to the less robust association of the results of the intact assay is probably a result of the limited number of samples tested with the latter assay. Of note, FGF-23 concentrations measured by C-terminal or intact molecule assays are highly correlated and accurately reflect the biologically active hormone **[21].**

Shimada et al. [21] showed that whether the markedly elevated FGF-23 concentrations in the patients on dialysis could be cardiotoxic and eventually result in LVH independent of other factors remains debatable. The fibroblast growth factor receptor-1 [FGFR1] is expressed in cardiomyocytes, but under physiologic conditions FGF-23 has a low affinity for FGFR1 and requires activation by the obligatory coreceptor Klotho, which is conspicuously absent in normal cardiomyocytes. It is conceivable that the elevated FGF-23 concentrations seen in CKD and dialysis patients could bind non-selectively to these receptors in the absence of Klotho, subsequently inducing myocardial hypertrophy. **Faul et al. [22]** recently described FGF-23-mediated development of LVH in wild-type mice receiving intramyocardial or intravenous injections of FGF-23. Furthermore, **Faul et al. [22]** showed that Klothodeficient mice with elevated FGF-23 concentrations were observed to exhibit LVH. **Seeherunvong et al. [6]** preliminary observations demonstrated upregulation of the FGFR1 in myocardial tissue of uremic rats with cardiac hypertrophy.

Since BP also exerted significant associations with LVMI, **Seeherunvong et al. [6]** study cannot categorically support the notion that FGF-23 constitutes the sole and independent cause of the elevated LVMI and LVH in HD patients.

Bakkaloglu et al. [10] illustrated that Hypertension is a known predictor of LVH in patients on dialysis. While we observed an association of systolic and diastolic BP measurements with LVH in the correlation analysis, those associations were no longer present following multivariable regression analysis, and time-averaged BP measurements were below the 95th percentile in most patients. The attenuating effects of a pan-FGF receptor blocker on LVH without effects on the severity of hypertension in uremic animals with elevated FGF- 23 concentrations supports a prominent role of FGF-23 in the development of LVH **[23]**.

The patients with concentric LVH tended to have higher FGF-23 levels than those with eccentric LVH, remodeling, or normal LV geometry. This finding, in addition to the positive correlations of FGF-23 with LVMI and IVST, suggests a possible role of FGF-23 in the development of concentric LVH—but not eccentric LVH—as also noted in adults with CKD **[2]**.

In **Seeherunvong et al. [6]** study, patients with eccentric LVH had considerably increased LVEDD, but not IVST. Anemia could result in increased cardiac output and contribute to the increased LVEED and eccentric LVH **[23].**

Conclusion:

FGF23 has a role for early prediction of LVF in children on regular hemodialysis which helps in reducing morbidity, mortality of these children**.**

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med, 2004; 351(13), 1296-1305.
2. Mitsnefes MM, Barletta GM, Dresner IG, Chand DH, Geary D, Lin JJ, et al. Severe cardiac hypertrophy and long-term dialysis: the Midwest pediatric nephrology consortium study. Pediatr Nephrol. 2006; 21:1167–1170
3. Pilz S, Tomaschitz A, Drechsler C, de Boer RA. Vitamin D and heart disease. Kidney Int. 2011; 1[Suppl]:S111–115
4. Hasegawa H, Nagano N, Urakawa I, Yamazaki Y, Iijima K, Fujita T, et al. Direct evidence for a causative role of FGF23 in the abnormal renal phosphate handling and vitamin D metabolism in rats with early-stage chronic kidney disease. Kidney Int. 2011; 78:975–980
5. Gutiérrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circ., 2009; 119(19), 2545-2552.
6. Seeherunvong W, Abitbol CL, Chandar J, Rusconi P, Zilleruelo GE, Freundlich M. Fibroblast growth factor 23 and left ventricular hypertrophy in children on dialysis. Pediatr Nephrol, 2012; 27, 2129-2136.
7. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. J. Pediatr., 2002; 141(2), 191-197.
8. Borzych D, Bakkaloglu SA, Zaritsky J, Suarez A, Wong W, Ranchin B, et al. Defining left ventricular hypertrophy in children on peritoneal dialysis. Clin J Am Soc Nephrol, 2011; 6(8), 1934.
9. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J. Am. Soc. Echocardiogr., 2009; 22(6), 709-714.
10. Bakkaloglu SA, Borzych D, Ha IS, Serdaroglu E, Büscher R, Salas P, et al. Cardiac geometry in children receiving chronic peritoneal dialysis: findings from the International Pediatric Peritoneal Dialysis Network (IPPN) registry. Clin J Am Soc Nephrol, 2011; 6(8), 1926.
11. Mitsnefes MM, Betoko A, Schneider MF, Salusky IB, Wolf MS, Jüppner H, et al. FGF23 and left ventricular hypertrophy in children with CKD. Clin J Am Soc Nephrol, 2018; 13(1), 45.
12. Mitsnefes M, Flynn J, Cohn S, Samuels J, Blydt-Hansen T, Saland J, et al. Masked hypertension associates with left ventricular hypertrophy in children with CKD. J Am Soc Nephrol., 2010; 21(1), 137.
13. Smith K, Defilippi C, Isakova T, Gutiérrez OM, Laliberte K, Seliger S, et al. Fibroblast growth factor 23, high-sensitivity cardiac troponin, and left ventricular hypertrophy in CKD. Am J Kidney Dis, 2013; 61(1), 67-73.
14. Abdel-hady H, Khamis SS, Yassein YS, Elbarbary H, Zahir EM, Elmahmoudy AM. Fibroblast growth factor 23 as a risk factor of left ventricular hypertrophy and vascular calcification in predialysis chronic kidney disease patients. Menoufia Med. J., 2013; 26(1), 7.
15. Stevens KK, McQuarrie EP, Sands W, Hillyard DZ, Patel RK, Mark PB, et al. Fibroblast growth factor 23 predicts left ventricular mass and induces cell adhesion molecule formation. Int. J. Nephrol., 2011;2011:297070.
16. Chen S, Law CS, Grigsby CL, Olsen K, Hong TT, Zhang Y, et al. Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. Circ., 2011; 124(17), 1838-1847.
17. Ky B, Shults J, Keane MG, Sutton MSJ, Wolf M, Feldman HI, et al. FGF23 modifies the relationship between vitamin D and cardiac remodeling. Circ.: Heart Failure, 2013; 6(4), 817-824.
18. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, et al. Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. CLIN J AM SOC NEPHRO, 2006; 1(5), 1006-1015.
19. Kirkpantur A, Balci M, Gurbuz OA, Afsar B, Canbakan B, Akdemir R, et al. Serum fibroblast growth factor-23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients. Nephrol Dial Transplant, 2011; 26(4), 1346-1354.
20. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama, 2011; 305(23), 2432-2439.
21. Shimada T, Urakawa I, Isakova T, Yamazaki Y, Epstein M, Wesseling-Perry K, et al. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. J Clin Endocrinol Metab., 2010; 95(2), 578-585.
22. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. J CLIN INVEST, 2011; 121(11).

23. Shroff R, Weaver DJ, Mitsnefes MM. Cardiovascular complications in children with chronic kidney disease. Nat. Rev. Nephrol., 2011; 7(11), 642-649.