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ORIGINAL RESEARCH

High Fibroblast Growth Factor 23 as a Biomarker for Severe Cardiac Impairment in Children with Chronic Kidney Disease: A Single Tertiary Center Study

Retno Palupi-Baroto[1]
Kristia Hermawan[1]
Indah Kartika Murni[1]
Tiara Nurlitasari[1]
Yuli Prihastuti[1]
Debora Roselita Karo Sekali[2]
Cahyani Gita Ambarsari[2]

[1]Department of Child Health, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [2]Department of Child Health, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Introduction: Left ventricular hypertrophy (LVH) is the most common cardiac abnormality in chronic kidney disease (CKD). Changes in cardiac geometry and functions may occur in an early stage and worsen as CKD progresses. Recently, the role of fibroblast growth factor 23 (FGF23) is being highlighted and investigated in CKD-related cardiomyopathy. However, only a few studies have reviewed the utilization of FGF23 as a diagnostic biomarker in the pediatric CKD population.

Purpose: This study aimed to identify the role of FGF23 as a biomarker in assessing cardiac changes in children with CKD.

Patients and Methods: We conducted a cross-sectional study that involved children aged 2 to 18 years old with CKD stages 2 to 5D in Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The level of FGF23 was measured using an immunometric enzyme-linked immunosorbent assay. LVMI, RWT, and left ventricular ejection fraction (LVEF) were assessed with echocardiography. Receiver-operating characteristic (ROC) analyses were conducted to assess the diagnostic performance of FGF23 in detecting LVH with impaired contractility.

Results: A total of 43 children with CKD stages 2 to 5D were included, among whom the prevalence of LVH diagnosis was 95.35%. The area under the curve (AUC) of FGF23 to assess LVH and systolic dysfunction was 0.82 (95% CI 0.62–1.0), and the optimal cutoff point was 1413 RU/mL (sensitivity 80%, specificity 78.95%). The median concentration of FGF23 increased with the decreasing eGFR and the increasing LVMI although the systolic and diastolic functions were preserved.

Conclusion: FGF23 might be used as an early biomarker to detect cardiac changes in pediatric CKD patients, particularly for LVH and impaired systolic function among children with CKD stage 2 and higher.

Keywords: FGF23, left ventricular hypertrophy, ventricular ejection fraction, end-stage kidney disease, dialysis

Introduction

Cardiovascular disease (CVD) is the leading cause of death in children with chronic kidney disease (CKD). Studies reported that 40–50% of all deaths were due to cardiovascular causes, and especially high among those receiving hemodialysis or peritoneal dialysis.[1] Cardiac-related death in the dialysis population was caused by cardiac arrest, congestive heart failure, cardiomyopathy, acute myocardial infarction, and pericarditis.[1]

Correspondence: Retno Palupi-Baroto
Jl. Farmako Sekip Utara, Yogyakarta, 55281
Tel +6281284934038
Fax +62274 581 876
Email retno.palupibaroto@ugm.ac.id

Changes in cardiac geometry and functions may occur in an early stage and worsen as CKD progresses. Left ventricular hypertrophy (LVH) is the most prevalent cardiac abnormality in CKD-related cardiomyopathy.[1] As many as 17–50% of pediatric patients with CKD stages 2–4 developed LVH, and the number was greater in the pediatric dialysis population (30–92%).[1,2] Impaired systolic and diastolic functions have also been observed in pediatric CKD.[3,4]

Fibroblast growth factor 23 (FGF23) is a glycoprotein produced by osteocytes and osteoblasts.[5] Under physiological circumstances, it functions as a mineral metabolism regulator in the kidneys and bones. Studies have revealed that the FGF23 level increased as the glomerular filtration rate (GFR) declined[6] and elevated before the levels of parathyroid hormone (PTH) and phosphate started to rise.[7] Recently, the role of FGF23 in the development of CVD is being highlighted and investigated. However, only a few studies have reviewed the utilization of FGF23 as a parameter in the pediatric CKD population. Mitsnefes et al[8] showed that plasma concentration of FGF23 above 170 RU/mL was an independent LVH predictor in children with estimated GFR (eGFR) ≥45 mL/min per 1.73 m^2. A recent prospective cohort study found that high FGF23 was borderline associated with high left ventricular mass index (LVMI) ($\beta = 1.8$, $p = 0.06$) in children with CKD and strongly associated with impaired diastolic function over time ($\beta = -0.43$, $p = 0.01$).[9] Limited studies on FGF23 in pediatric CKD and its role as a biomarker of CVD warrant further investigation.

The objective of this study was to investigate FGF23 as a biomarker to assess CVD in pediatric CKD. To the best of our knowledge, this is among the first study using FGF23 as a diagnostic marker to assess CVD in children with CKD.

Materials and Methods

Participants

This cross-sectional study involved children with CKD stages 2 to 5D in Dr. Sardjito General Hospital, Yogyakarta, Indonesia, a regional referral hospital for Yogyakarta and southern Central Java, from November 2018 to March 2019. Eligible subjects aged 2 to 18 years were diagnosed with CKD based on Kidney Disease Improving Global Outcomes (KDIGO) 2012.[10] Subjects with congenital heart diseases, acquired heart diseases (eg, rheumatic heart disease, Kawasaki disease, and myocarditis), or malignancy of the kidneys were excluded.

The research was conducted in ethical accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Dr. Sardjito General Hospital Institutional Review Board and the Medical and Health Research Ethics Committee Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada (KE/FK/251/EC/2018). All patients' caregivers were provided with written informed consent. Complete demographic and clinical data were obtained by the doctors during an outpatient visit or hospital admission.

Echocardiographic Assessment

Echocardiography was done by a pediatric cardiologist who was masked to any patient-specific clinical information. Echocardiography was done using USG Phillips Affiniti 70®. Criteria for LVH in this study was determined based on an increase of LVMI and relative wall thickness (RWT). Left ventricular mass index (LVMI) was determined by the following formula: left ventricle mass (LVM)/body surface area (g/m^2). Left ventricular mass (LVM) was calculated by 0.8 ×(1.04 ([left ventricular end-diastolic (LVED) + posterior wall thickness (PW) + interventricular septum (IVS)]^3 − LVED) + 0.6 g. Relative wall thickness (RWT) was calculated by 2 × PW/LVED.[11] Systolic function was measured by deriving left ventricular ejection fraction (LVEF) as calculated by ((end diastolic diameter-end systolic diameter)/end diastolic diameter) x 100.[12] Diastolic function was described by transmitral flow velocity ratio (MV E/A).[3]

LVMI, RWT, and LVEF were defined based on age and sex-specific reference percentiles by Diaz et al[12]. High LVMI was defined as LVMI ≥95th percentiles according to age and sex. High RWT was defined as RWT ≥95th percentiles according to age and sex.[12] Reduced LVEF was defined as LVEF <5th percentiles. Left ventricular geometry was classified as normal (normal LVMI, normal RWT), concentric remodeling (normal LVMI, high RWT), eccentric LVH (high LVMI, normal RWT), and concentric LVH (high LVMI, high RWT).[13] Severe cardiac impairment was defined with LVH and reduced systolic function.

Assays

Venous blood samples were collected in ethylene diamine tetra-acetic (EDTA)-containing vacutainers. Enzyme-linked immunosorbent assay (ELISA), quantitative sandwich enzyme immunoassay, was done to measure the level

of FGF23. A specific FGF23 carboxyl-terminal (C-terminal), from Immutopics Inc., San Clemente, CA 92673, USA, was determined using immunometric enzyme assay with the measurement instruments Microplate Reader Biorad 680 (Bio-rad Laboratories Inc, CA, USA) and software Microplate Manager version 5.2.1 (Bio-rad Laboratories Inc., CA, USA). The final values of FGF23 were derived from the average of two replicates from each sample.

Clinical and Laboratory Parameters

The etiologies of CKD were categorized as glomerular disease (nephrotic syndrome, glomerulonephritis, lupus nephritis, and diabetic nephropathy), structural (obstructive uropathy, kidney aplasia/hypoplasia/dysplasia, and reflux nephropathy), and others (polycystic kidney disease [PKD] and nephrocalcinosis). eGFR was calculated with the revised Schwartz Formula 36.5 × L/Cr; GFR was expressed in mL/min per 1.73 m^2 body surface area. L represents body length in centimeters, and Cr represents serum creatinine concentration in μmol/L. We recruited children with CKD stages 2 to 5D based on KDIGO staging recommendation as follows: stage 2 (eGFR = 60–89 mL/min per 1.73 m^2), stage 3a (eGFR = 45–59 mL/min per 1.73 m^2), stage 3b (eGFR = 30–44 mL/min per 1.73 m^2), stage 4 (eGFR = 15–29 mL/min per 1.73 m^2), stage 5 (eGFR <15 mL/min per 1.73 m^2), and stage 5D (eGFR <15 mL/min per 1.73 m^2 who underwent long-term hemodialysis or peritoneal dialysis).[10] Hemoglobin, uric acid, calcium, phosphate, PTHlevels were taken from medical records at the same time when FGF23 and echocardiography was performed.

Statistical Analysis

Data were presented as a percentage for categorical variables, mean ± standard deviation (SD) for normally distributed data, and median (interquartile range) for non-normally distributed data. Univariate comparisons were analyzed by univariate logistic regression. Log transformation was performed in the case of abnormality distributed variables. P-values less than 0.05 ($p < 0.05$) were considered statistically significant.

The receiver operating characteristic (ROC) curve was used to determine the area under curve (AUC) for identifying the presence of LVH with impaired contractility. The ROC was also used to review the presence of impaired systolic function. The optimal cutoff value of FGF23 was defined as the cutoff obtaining the highest total of sensitivity and specificity. All statistical analyses were performed using the STATA version 14.0 software.

Results

Forty-three children with CKD stages 2 to 5D were included in the study. The median age when FGF23 was tested was 12.89 (IQR 9.26–15.63) years. Almost 90% of the subjects were in advanced CKD.

Table 1 summarizes the baseline characteristics of patients in the study. The primary diagnoses of CKD were glomerular diseases (22/43, 51.16%), congenital anomalies of the kidney and urinary tract (CAKUT) (17/43, 39.53%), and others (4/43, 9.3%). The glomerular diseases included nephrotic syndrome (13/43, 27.91%), lupus nephritis (2/43, 4.65%), diabetic nephropathy (1/43, 2.33%), and other glomerulonephritis (7/43, 16.28%). CAKUT disorders included kidney aplasia/hypoplasia/dysplasia (9/43, 20.93%), obstructive uropathy (7/43, 16.28%), and reflux nephropathy (1/43, 2.33%). Others consisted of PKD (3/43, 6.98%) and bilateral nephrocalcinosis (1/43, 2.33%).

Table 1 Baseline Characteristics of Subjects

Variables	Subjects (n = 43)
Gender	
Female, number (%)	22 (51.16)
Age (years), median (IQR)	12.89 (9.26–15.63)
CKD stages	
Stage 2	2 (4.65)
Stage 3a	4 (9.30)
Stage 3b	6 (13.95)
Stage 4	5 (11.63)
Stage 5ND	6 (13.95)
Stage 5D	20 (46.51)
Hypertension, number (%)	19 (44.19)
Anemia, number (%)	33 (76.74)
LVH, number (%)	41 (95.35)
Eccentric LVH, number (%)	37 (86.05)
Concentric LVH, number (%)	4 (9.3)
Impaired LVEF, number (%)	5 (11.63)
Impaired diastolic function, number (%)	5 (11.63)
FGF23 (RU/mL), median (IQR)	742.02 (264.88–1493.2)

Notes: CKD stages referred to the CKD status at the time of echocardiography and FGF23 were checked.

Abbreviations: IQR, interquartile range; CKD, chronic kidney disease; stage 5ND, stage 5 non dialysis; stage 5D, stage 5 dialysis; LVH, left ventricle hypertrophy; LVEF, left ventricle ejection fraction; FGF23, fibroblast growth factor 23.

Table 2 FGF23, LVMI, RWT, and Systolic and Diastolic Function by CKD Stage

CKD Stage	FGF23, RU/mL	LVMI, g/m^{2,7}	LVEF (%)	RWT	MV E/A
2	125.03 (42.56–207.5)	53.79 (52.38–55.2)	72.55 (68.90–76.20)	0.26 (0.21–0.32)	1.31 (1.05–1.57)
3	328.88 (221.58–461.69)	54 (46.06–63.98)	70 (64–73.39)	0.24 (0.21–0.27)	1.47 (1.11–1.92)
4	1008.86 (869.9–1050.22)	70.86 (63.53–80.76)	69 (68.90–74.20)	0.26 (0.23–0.27)	1.22 (1.08–1.76)
5*	1182.88 (538.93–5153.06)	85.50 (54.94–148.31)	67.3 (63.20–72.90)	0.26 (0.23–0.32)	1.46 (1.11–1.75)
5D**	1350.13 (583.91–6037.90)	115.27 (55.84–151.11)	69 (62.5–73.6)	0.26 (0.23–0.32)	1.37 (1.11–1.69)

Notes: Data are stated in median (interquartile range). *: CKD stage 5 non-dialysis and with dialysis. **5D: CKD stage 5 with dialysis.
Abbreviations: FGF23, fibroblast growth factor 23; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; RWT, relative wall thickness; MV E/A, transmitral flow velocity ratio.

Plasma FGF23, LVH, Systolic and Diastolic Functions, and CKD Progression

Table 2 shows the median values of LVMI, RWT, LVEF, and MV E/A in children with CKD stages 2 to 5D. The median concentration of FGF23 substantially increased in the higher stage of CKD. As kidney functions deteriorated, the median values of LVMI increased, but systolic and diastolic functions remained preserved. Figure 1 shows that the median values of FGF23 increased significantly in patients with LVH and impaired systolic function ($p = 0.03$).

Plasma FGF23 as a Biomarker for CVD in Pediatric CKD

The associations of FGF23, eGFR, hypertension, hemoglobin level, bone mineral biomarkers, and severe cardiac impairment are shown in Table 3. Univariate logistic regression showed that FGF23 was associated with LVH and systolic dysfunction (OR 2.82 (95% CI 1.11–7.15), p-value 0.03), whereas other variables did not show any association. The ROC for plasma FGF23 as a biomarker for LVH with impaired systolic is displayed in Figure 2. The AUC of FGF23 as a biomarker for low LVEF was 0.82 (95% CI 0.62–1.00). The optimal cutoff point was 1413 RU/mL. When this was used as a cutoff to define reduced ejection fraction, sensitivity and specificity were 80% and 78.95%, respectively.

Discussion

Cardiovascular disease is one of the most common complications occurring in children with CKD. The incidence and severity of CVD become more significant in patients who receive long-term dialysis. A recently published study from the pediatric kidney transplantation centers in Indonesia reported that all patients had hypertension and 42% of patients had cardiomyopathy before the kidney transplantation and the longest dialysis duration before the transplantation was 72 months.[14] About 86.05% of patients in our study had LVH with eccentric type. The eccentric LVH shows the addition of serial cardiac sarcomere and is associated with volume overload, causing thickening of the cardiac wall and enlargement of the left ventricular space.[15,16] Compared to previous studies reporting the number of patients with LVH in the pediatric CKD population, our current study displays a greater prevalence. Two significant CKD-related comorbidities that occurred in our study subjects, namely hypertension (44.19%) and anemia (76.74%), likely contributed to this. The Chronic Kidney Disease in Children (CKiD) study 2012 reported the prevalence of hypertension was 54% and the prevalence of anemia was 45% in children with CKD.[17] Studies involving the pediatric CKD population show that most of the patients suffered from anemia and hypertension.[15,18] Furthermore, the majority of the pediatric CKD cases received multiple blood transfusions before hemodialysis initiation, implying that severe anemia is commonly found in children with severe CKD in Indonesia.[19] Another important point to consider is that 55.81% of our study population were at CKD stage 5D which has greater risks for having long-term hypertension and anemia, and thus, this also resulted in a significant number of severe cardiac impairments.[1]

The role of FGF23 as an early biomarker for LVH has been proposed by prior publications both in children[8] and adults.[20,21] Mitsnefes et al[8] suggested the upper tertile of FGF23 level in children with CKD was 170 RU/mL, while our study displayed remarkably high FGF23 values that have started to increase as early as CKD stage 2. Compared to the study by Mitsnefes et al[8] which suggested that LVH occurred in pediatric CKD patients with FGF23 level ≥100 RU/mL, our study identified one LVH

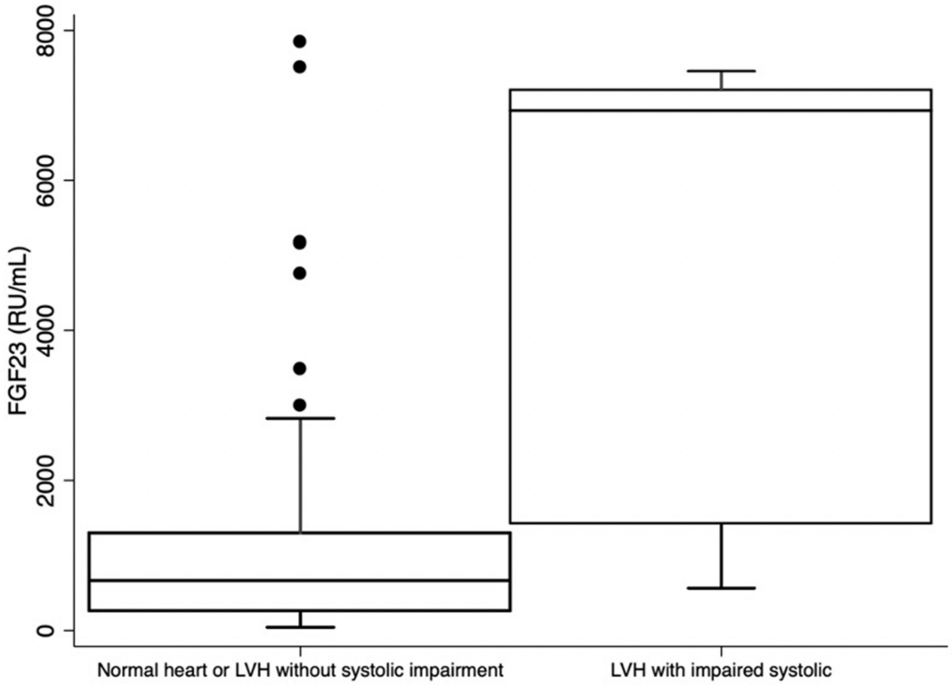

Figure 1 Plasma FGF23 and cardiac changes.
Note: data are presented in median (interquartile range)
Abbreviations: FGF23, fibroblast growth factor 23; LVH, left ventricular hypertrophy.

case with an FGF23 level as low as 42 RU/mL who had CKD for 30 months without hypertension and anemia as comorbidities. The remarkably high values of FGF23 were also observed in an Indonesian study comprised of adult patients with CKD on hemodialysis (median 6737 rU/mL; range 958–10723).[23] The level of FGF23 might be associated with dietary phosphate intake and fractional excretion of phosphate depending on areas in a given population.[24] Our results raised a question as to whether the level of FGF23 in children with CKD could be influenced by local dietary habits containing high phosphate.

As far as we are aware, this is one of the first studies using FGF23 to assess LVH with impaired contractility in children with CKD. Our findings indicated FGF23 is a good biomarker to determine the presence of LVH with systolic dysfunction (AUC 0.82; 95% CI 0.62–1.00). One cross-sectional study by

Table 3 Severe Cardiac Impairment Associated with FGF23, eGFR, Hypertension, Hemoglobin and Bone-Mineral Disease Markers

Variables	Univariate Logistic Regression	p-value
	OR (95% CI)	
Log FGF23 (per increase in 1 unit)	2.82 (1.11–7.15)	0.03
Log eGFR (per increase in 1 unit)	0.23 (0.04–1.33)	0.10
Hypertension (normotension is reference)	2.61 (0.27–25.65)	0.41
Hemoglobin (per increase in 1 g/dL)	0.81 (0.55–1.12)	0.29
Log phosphate (per increase in 1 unit)	1.12 (0.08–16.03	0.93
Log uric acid (per increase in 1 unit)†	1.62 (0.21–12.15)	0.64
Parathyroid hormone (per increase in 1 pg/mL)**	1.00 (0.99–1.01)	0.46

Notes: † Uric acid levels performed in 38 subjects. ** Parathyroid hormone performed in 19 subjects.
Abbreviations: FGF23, fibroblast growth factor 23; eGFR, estimated glomerular filtration rate.

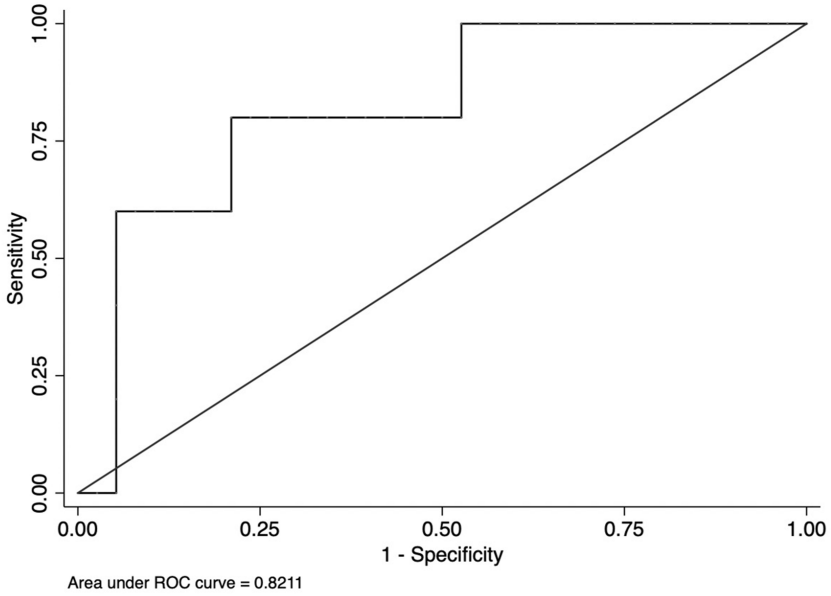

Figure 2 Receiver operating curve (ROC) plasma FGF23 for assessing LVH and impaired systolic function.

Nielsen et al[21] in adults with end-stage kidney disease also concluded that higher FGF23 levels were associated with lower cardiac function. LVH can evolve into a maladaptive form and show a continuous process of cardiac remodeling resulting in myocyte death, decreased capillary density, and increased myocardial fibrosis. In this phase, the patients present with arrhythmias, diastolic dysfunction, and systolic dysfunction, which ultimately leads to congestive heart disease. The exact pathological mechanism of how FGF23 correlates with reduced LVEF has not been elucidated. Our study suggests that FGF23 could be used as an early biomarker to detect changes in patients with severe cardiac impairment. Mitsnefes et al[8] and Seeherunvong et al[22] reported strong correlations between FGF23 and LVMI. The large cohort by Mitsnefes et al[8] included 587 children in CKD stages 2 to 4 with a longer CKD duration of 5 to 13 years. A retrospective study by Seeherunvong et al[22] involved 26 pediatric patients on long-term hemodialysis, and thus, hypertension contributed to the increased LVMI as a common comorbidity in CKD.

The present study found the median concentration of FGF23 increased with the deterioration of kidney function, together with an increase in the LVMI, while the systolic and diastolic functions were preserved (Table 2). This holds a significant point because most children with CKD do not have multiple comorbidities that may affect the cardiac function as adults do, namely pre-existing vascular diseases, cardiac diseases, or diabetes.

This study has some strengths. Both acquisition and interpretation of the echocardiography were done blinded by one cardiologist. This is also the first study that assessed the role of FGF23 in LVH with impaired contractility in children with CKD. This study has some limitations. Firstly, although we acknowledge that cFGF23 has high intra-individual variation thereby lowering its sensitivity for diagnostic purpose,[24] we used cFGF23 rather than intact FGF23 as a parameter due to the unavailability of intact FGF23 assay in our country. Secondly, the number of subjects was small, being completed in a single tertiary center. In addition, the pediatric dialysis unit has not been extensively accessible in Indonesia. Indonesia is the world's largest island country with a large population, and its referral system is complex; thus, many patients either had deteriorated before admission[25] or had not been documented. We believe the magnitude of CKD progression toward FGF23 can be more significant if the sample size was greater.

Conclusion

FGF23 might be used as an early biomarker to detect cardiac changes in pediatric CKD patients, particularly for LVH and impaired systolic function among children with CKD stage 2 and higher.

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Disclosure

The authors report no conflicts of interest in this work.

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