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Associations between Fibroblast Growth Factor 23 and Cardiac Characteristics in Pediatric Heart Failure

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Abstract

Background—In adults with heart failure, elevated levels of fibroblast growth factor 23 (FGF23) are associated with mortality. Data on FGF23 levels in pediatric heart failure are lacking.

Patients and Methods—We conducted a cross-sectional study of 17 healthy children (mean age, 13 years) and 20 pediatric patients with heart failure (mean age, 12 years) who underwent echocardiography and the following measurements: plasma FGF23 and parathyroid hormone (PTH); serum phosphate, creatinine and N-terminal prohormone brain natriuretic peptide (NT-proBNP). Symptom severity was assessed with the New York Heart Association (NYHA) and the Ross classification systems.

Results—Of 20 patients, 11 had dilated cardiomyopathy; 4, congenital heart disease; 3, hypertrophic cardiomyopathy; 1, a failing heart transplant; and 1, pulmonary hypertension. Mean phosphate levels in patients were within the reported reference range for healthy children. Median PTH levels were in the normal range in patients and controls. The median FGF23 level was higher in patients vs. controls (110.9 vs. 66.4 RU/ml, P=0.03) and higher in patients on diuretics vs. other patients (222.4 vs. 82.1 RU/ml, P=0.01). Levels of FGF23 and NT-proBNP were directly correlated (r=0.47, P=0.04), and patients with greater physical functional impairment had higher FGF23 levels (142.5 in those with moderate-severe limitation vs. 92.8 RU/ml in those with no limitation; P=0.05). Among patients with dilated cardiomyopathy, higher FGF23 levels were associated with a greater left ventricular end-diastolic diameter (r=0.63, P=0.04).

Conclusion—FGF23 levels are elevated in children with heart failure and are associated with diuretic use, severity of heart failure and left ventricular dilation.

Keywords

Heart Failure; Fibroblast growth factor 23; Parathyroid hormone; Diuretics N-terminal prohormone brain natriuretic peptide

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Introduction

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates mineral metabolism by promoting phosphaturia and decreasing renal production of calcitriol [1]. Dietary phosphate loading increases FGF23 levels, whereas dietary phosphate restriction has the opposite effect [2–4]. Levels of FGF23 are frequently elevated in patients with chronic kidney disease (CKD) [5]. In this setting of progressive loss of kidney function, the physiologic actions of FGF23 initially maintain normophosphatemia at the expense of calcitriol deficiency [6], but over time the levels become markedly elevated, with the highest FGF23 levels observed in patients without residual renal function and who are undergoing dialysis [7].

Given the prevalence of elevated FGF23 levels in kidney disease, there has been significant scientific interest in potential systemic effects of FGF23. Observational studies first suggested this possibility by reporting that elevated FGF23 levels were associated with increased risks of cardiovascular disease events and mortality in the general population and across the spectrum of CKD [8–11]. An independent association between left ventricular (LV) hypertrophy and FGF23 levels [12–14] led to the hypothesis that FGF23-mediated LV remodeling might be one putative mechanism for the consistently reported risk relationships. In support of this framework, serum levels of cardiac troponins and N-terminal prohormone brain natriuretic peptide (NT-proBNP) were found to correlate directly with FGF23 in various study populations, including patients with heart failure, CKD and those undergoing dialysis [15–18]. Recently, experimental studies have provided additional evidence for increased FGF23 as a potential mechanism for LV hypertrophy [19].

To date, two studies in the adult heart failure population evaluated FGF23 levels as a predictor of death [15, 16]. Comparable data in children with heart failure are not available. Therefore, we investigated FGF23 levels among pediatric heart failure patients, compared these with levels in healthy controls and evaluated the relationship of FGF23 with symptom severity, NT-proBNP and echocardiographic measures.

Patients and Methods

Study population

From June to December 2011, we studied 20 patients at the University of Miami/Jackson Memorial Hospital Pediatric Heart Failure and Transplant Clinic. All consecutive patients, aged up to 21 years, were enrolled; there were no exclusion criteria. All patients had a diagnosis of heart failure, as defined by the International Society for Heart and Lung Transplantation: Practice Guidelines for Management of Heart Failure in Children [20]. Additionally, we assayed stored blood specimens from 17 healthy children, who were frequency-matched on age, gender, race, and ethnicity, and were used as convenience sample controls. These healthy children were controls in a previously published case-control study of biomarkers of vascular dysfunction in HIV-infected children [21]. Briefly, controls did not have any chronic illness or acute infectious process and were from similar geographic and socioeconomic backgrounds as the children with heart failure. The University of Miami Institutional Review Board approved the study, and informed consent from the parent or guardian and assent from the patient (when appropriate) were obtained.

Demographic, clinical and laboratory data

Study assessments took place during follow-up clinic visits. We collected the following demographic and clinical data: age, sex, race, ethnicity, weight, cause of heart failure, functional status, and prescribed medications, including diuretics. Diagnoses of dilated and hypertrophic cardiomyopathies were based on the previously published echocardiographic

criteria used for enrollment in the Pediatric Cardiomyopathy Registry [22]. Functional status was established by the New York Heart Association (NYHA) class for children older than 5 years and by the Ross classification for younger children [23]. The Ross classification assigns children to four different classes of heart failure severity based on feeding history, growth parameters, and physical findings.

Blood samples were collected during routine blood draws to avoid additional venipuncture. The samples were then centrifuged, aliquoted and stored at −80 degrees C until batched assays were performed. Plasma c-terminal FGF23 levels were measured by ELISA (Immutopics, San Clemente, CA; CV<5%), and plasma intact PTH was measured using a chemiluminescent immunoassay (Roche Diagnostics, Indianapolis, IN; CV <3%). Serum NT-proBNP was measured using the Elecsys 2010 System (Roche Diagnostics, Indianapolis, IN). The clinical laboratory using standard procedures performed routine laboratory testing of blood, including renal function. Estimated glomerular filtration rate (eGFR) in ml/min/1.73m^2 was determined using an established formula of eGFR = 0.41 × height (centimeters) / serum creatinine (mg/dl) [24]. Fractional excretion of mineral (phosphate, FePi; calcium, FeCa) was calculated from spot urine collections as: (urine mineral × serum creatinine × 100)/(serum mineral × urine creatinine). The laboratory's reference ranges were 2.5 – 4.5 mg/dl for serum phosphate, 8.4 – 10.2 mg/dl for serum calcium, and 15 – 65 pg/ml for PTH. In accordance with previously published data [25], levels of NT-proBNP ≥ 150 pg/mL in infants younger than 1 year, or ≥ 100 pg/mL in children age 1 year or older, were considered abnormal. Due to limited volume of stored plasma from healthy controls, these samples were only assayed for FGF23 and PTH.

Echocardiography

All pediatric heart failure patients underwent transthoracic echocardiography using a commercially available system (Acuson Sequoia Ultrasound System C512, Acuson, Mountain View, CA). The images were recorded digitally and subsequently reviewed by two experienced pediatric cardiologists unaware of the serum tests results. M-mode tracing was obtained in the parasternal short-axis view at the level of the papillary muscles of the LV, and LV end-systolic and end-diastolic diameters were measured. To obtain normative values for echocardiographic measures, we used previously published data from 580 healthy patients aged 0 to 40 years [26, 27]. Using methods described elsewhere [28], we used the estimated means and standard deviations from regression equations to calculate Z scores for LV end-systolic diameter, LV end-diastolic diameter, septal wall thicknesses, LV posterior wall thicknesses, and LV mass relative to body surface area and Z scores for LV fractional shortening relative to age in our sample. LV ejection fraction was calculated in the apical 2- and 4-chamber views using Simpson's apical biplane method, as recommended by the American Society of Echocardiography [29]. LV mass was calculated by M-mode using the Devereux formula [30].

Statistical analysis

Demographic, clinical and laboratory values are reported as descriptive statistics. When possible, we compared values between patients and controls using t-tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. Spearman correlation coefficients were used to assess correlations. Linear regression modeling was performed to adjust for eGFR as a potential confounder. The distributions of FGF23, PTH, and NT-proBNP were right-skewed, requiring natural log (ln)-transformation. Since the etiology of heart failure was heterogeneous in our pediatric patients, we restricted analyses of associations of FGF23 with echocardiographic measures only to children with dilated cardiomyopathy. Analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). All statistical tests were two-sided, and P values <0.05 were considered significant.

Results

Patient characteristics

We studied 20 patients (mean age 12 ± 6 years) with heart failure and 17 healthy controls (mean age 13.4 ± 3 years, Table 1). Among the patients, 11 had dilated cardiomyopathy; the remaining etiologies included congenital heart disease (single ventricle, n=2; tetralogy of Fallot, n=1; dextro-transposition of great arteries, n=1), hypertrophic cardiomyopathy (n=3), failing heart transplant (n=1), and pulmonary hypertension (n=1). Loop diuretics were prescribed to 9 patients, and 8 (40%) were NYHA or Ross functional class II or higher (Table 1). Aside for lower frequency of girls in the diuretics-treated group, there were no significant differences in demographic and clinical characteristics between the two patient groups (Table 2). Per the matched study design, the distribution of demographic characteristics, including age, sex, race, and ethnicity, did not vary significantly between the patients and controls (Table 1).

Associations between baseline factors and FGF23 levels

There was no significant association between age, gender, race or ethnicity and FGF23 levels in our study population. Mean serum phosphate levels in the patients were within the reported reference range for healthy children [31]. Median PTH levels were in the normal range in patients and controls (Table 1). In contrast, the median FGF23 level was 110.9 RU/ml (interquartile range [IQR] 78.4 – 187.1), which is markedly higher than the median levels of 30 – 70 RU/ml reported in other studies of healthy children of comparable age [32, 33]. Among our patients, FGF23 levels were almost double that of in controls (110.9 vs. 66.4 RU/ml; P=0.03, Table 1), and levels were higher in patients receiving diuretics than in those who were not (222.4 [IQR 133.2 – 587.9] vs. 82.1 [IQR 53.2 – 118.3] RU/ml; P=0.01, Figure 1, Table 2). In contrast, the difference in FGFG23 levels between diuretics-untreated patients and healthy controls was not significant (82.1 [IQR 53.2 – 118.3] vs. 66.4 [IQR 59.1 – 92.7] RU/ml; P=0.49, Figure 1).

Among patients, FGF23 and NT-proBNP levels were directly correlated (r=0.47, P=0.04, Figure 2). Patients with a NYHA or Ross functional class of II or greater had higher FGF23 levels than those with class I (142.5 [IQR 112.5 – 487.4] vs. 92.8 [IQR 54.6 – 122.1] RU/ml; P=0.05; Figure 3). Both the association with NT-proBNP and with functional class was independent of eGFR, which was not a significant predictor of FGF23 concentrations (Table 3). In contrast, PTH was associated with FGF23 levels (r=0.67; P=0.001) but not with serum phosphate (r=0.40; P=0.08).

Correlations between FGF23 levels and echocardiographic measurements

The echocardiographic findings in the 11 patients with dilated cardiomyopathy, of whom 3 were assessed to be in functional class of II or greater and 4 were on diuretics, are presented in Table 4. In these patients, there was also no significant association between eGFR and FGF23 levels (r=−0.37; P =0.26), but FGF23 levels correlated with echocardiographic indicators of abnormal cardiac structure (Table 5). Higher FGF23 levels correlated with a greater LV end-diastolic diameter (r=0.63; P=0.04) and with a larger LV mass, although the latter association did not reach significance (r=0.61; P =0.06). Levels of NT-proBNP were inversely correlated with LV ejection fraction (r=–0.61; P=0.046), but not with the LV end-diastolic diameter (r=0.57; P=0.07; Table 5). In contrast, eGFR, serum phosphate and PTH levels were not significantly associated with any of the echocardiographic measures (data not shown). Finally, in a model that included both FGF23 and eGFR, neither variable was a significant predictor of LV end-diastolic diameter.

Discussion

The first new finding of our study is the demonstration of nearly 2-fold higher FGF23 levels in the pediatric heart failure population compared to healthy controls. We further show a significant relationship between FGF23, heart failure symptom severity and echocardiographic measures of abnormal cardiac structure. Additionally, FGF23 levels correlated directly with NT-pro-BNP levels. Patients with more symptomatic heart failure, as evidenced by treatment with diuretics and advanced heart failure dysfunctional class, had higher FGF23 levels. These data suggest that FGF23 levels might predict clinical status in heart failure. Elevated FGF23 in this setting might also indicate that hemodynamic consequences of heart failure led to increased FGF23 prior to occult changes in kidney function. Further studies are needed to investigate the role of FGF23 in heart failure.

Our findings suggest that heart failure may be another common medical condition in which levels of FGF23 are elevated. Further, correlates of FGF23 levels in this population may differ from those in the healthy pediatric population [33], as our data on the univariate FGF23 predictors in the two study groups seem to indicate. While cross-sectional design and residual confounding by kidney function limit our inferences, prior experimental and longitudinal observations support the possibility of a link between FGF23 levels and cardiac structure [14, 19, 34]. Higher FGF23 levels associate with greater risk of prevalent and incident LV hypertrophy [14, 19, 34], and FGF23 exerts hypertrophic effects on the myocardium in animal models [19].

FGF23 may also have detrimental effects on the vasculature, though the data on this mechanism of systemic FGF23 toxicity are less consistent. A large study of patients with CKD stages 2–4 reported no significant association following multivariable adjustment between elevated FGF23 levels and calcification of the coronary arteries or thoracic aorta [35]. In contrast, FGF23 levels were significantly higher in children with Kawasaki disease compared to healthy controls, and elevated levels independently predicted coronary artery damage [36].

Among the pediatric heart failure patients, we observed that FGF23 levels correlated with NT- proBNP levels, a finding that is in agreement with the prior report of similar relationship in the adult heart failure population [15, 16]. The consistent link between FGF23 and NT-proBNP, an established marker of cardiac wall stress [37, 38], supports the hypothesis that FGF23 may have direct effects on the myocardium. This framework is also supported by recent observations in patients with kidney disease of associations of FGF23 with serum cardiac troponin levels [17, 18], which are also released into circulation in settings of cardiac damage [39].

In contrast to one adult study [15], we found that FGF23 levels were significantly higher in those patients treated with diuretics and in those with higher NYHA or Ross functional class. These findings need to be confirmed in prospective studies. However, when evaluated in concert with a large body of evidence from longitudinal studies across multiple populations [8–10], our data support the hypothesis that FGF23 measurements in the heart failure population might have prognostic utility.

The mechanisms for elevated FGF23 levels in heart failure are not known. One possibility is that impaired kidney function in the setting of hemodynamic compromise might lead to a rise in levels. While we did not detect an association between eGFR and FGF23 in our patients, eGFR may not accurately capture kidney function in heart failure. Given that greater diuresis might result in decreased renal perfusion, our observation of significantly higher FGF23 levels among patients treated with diuretics vs. untreated patients supports the possibility of subtle loss of kidney function contributing to elevated FGF23 levels.

Phosphate homeostasis is another factor that is important in FGF23 regulation. In our small study, we were not able to detect a significant association between serum phosphate and FGF23 levels, though prior large studies found a direct correlation between these two parameters [32, 40]. Alternatively, increased production in the bone or impaired post-translational modification and processing may result in elevated FGF23. Finally, the contribution of other organs, such as the heart itself, to circulating FGF23 levels remains undefined. Identifying which of these mechanisms of FGF23 elevation is important in heart failure will require further studies.

Limitations of this study include the cross-sectional design, small sample size that impeded multivariate adjustment and limited availability of data in healthy controls. Additionally, the heterogeneity of patients by cause of heart failure further limited our ability to evaluate the relationship between FGF23 and echocardiographic measures. Despite frequency matching, the percentage of blacks in the control group was higher than in patients. Although this difference was not significant, and race was not a significant determinant of FGF23 levels in our study population, racial variability in FGF23 levels in children should be investigated further. Finally, we were not able to assess associations with vitamin D, which is known to influence FGF23 levels [41] and may also have effects on cardiac structure and function [42].

The ability of FGF23 to predict future clinical events in adults has been consistently demonstrated [8–11]. Our data now raise the possibility that FGF23 levels may also have a prognostic role in pediatric patients with heart failure and add justification to recent calls for novel biomarker development in this population [43]. Whether this prognostic utility of FGF23 measurements will be realized in this setting is unknown, and additional data are needed to confirm the direct effects of increased FGF23 on the myocardium and to establish its effects on other organs. These important questions warrant future investigation in prospective and experimental studies.

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References

1. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res. 2004; 19:429–435. [PubMed: 15040831]
2. Ferrari SL, Bonjour JP, Rizzoli R. Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. J Clin Endocrinol Metab. 2005; 90:1519–1524. [PubMed: 15613425]
3. Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. J Clin Endocrinol Metab. 2006; 91:3144–3149. [PubMed: 16735491]
4. Burnett SM, Gunawardene SC, Bringhurst FR, Juppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. J Bone Miner Res. 2006; 21:1187–1196. [PubMed: 16869716]
5. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. Kidney Int. 2012; 82:737–747. [PubMed: 22622492]
6. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Juppner H, Wolf M. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol. 2005; 16:2205–2215. [PubMed: 15917335]

7. Isakova T, Xie H, Barchi-Chung A, Vargas G, Sowden N, Houston J, Wahl P, Lundquist A, Epstein M, Smith K, Contreras G, Ortega L, Lenz O, Briones P, Egbert P, Ikizler TA, Jueppner H, Wolf M. Fibroblast growth factor 23 in patients undergoing peritoneal dialysis. Clin J Am Soc Nephrol. 2011; 6:2688–2695. [PubMed: 21903990]
8. Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M, Shlipak MG, Whooley MA, Ix JH. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. Ann Intern Med. 2010; 152:640–648. [PubMed: 20479029]
9. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutierrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. 2011; 305:2432–2439. [PubMed: 21673295]
10. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, Chonchol M. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol. 2011; 22:1913–1922. [PubMed: 21903574]
11. Arnlov J, Carlsson AC, Sundstrom J, Ingelsson E, Larsson A, Lind L, Larsson TE. Serum FGF23 and Risk of Cardiovascular Events in Relation to Mineral Metabolism and Cardiovascular Pathology. Clin J Am Soc Nephrol. 2013; 8:781–786. [PubMed: 23335040]
12. Isakova T, Gutierrez OM, Wolf M. A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. Kidney Int. 2009; 76:705–716. [PubMed: 19606082]
13. Hsu HJ, Wu MS. Fibroblast growth factor 23: a possible cause of left ventricular hypertrophy in hemodialysis patients. Am J Med Sci. 2009; 337:116–122. [PubMed: 19214027]
14. 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; 27:212902136.
15. Plischke M, Neuhold S, Adlbrecht C, Bielesz B, Shayganfar S, Bieglmayer C, Szekeres T, Horl WH, Strunk G, Vavken P, Pacher R, Hulsmann M. Inorganic phosphate and FGF-23 predict outcome in stable systolic heart failure. Eur J Clin Invest. 2012; 42:649–656. [PubMed: 22150123]
16. Gruson D, Lepoutre T, Ketelslegers JM, Cumps J, Ahn SA, Rousseau MF. C-terminal FGF23 is a strong predictor of survival in systolic heart failure. Peptides. 2012; 37:258–262. [PubMed: 22902597]
17. Smith K, deFilippi C, Isakova T, Gutierrez OM, Laliberte K, Seliger S, Kelley W, Duh SH, Hise M, Christenson R, Wolf M, Januzzi J. Fibroblast growth factor 23, high-sensitivity cardiac troponin, and left ventricular hypertrophy in CKD. Am J Kidney Dis. 2013; 61:67–73. [PubMed: 22883134]
18. Holden RM, Beseau D, Booth SL, Adams MA, Garland JS, Morton RA, Collier CP, Foley RN. FGF-23 is associated with cardiac troponin T and mortality in hemodialysis patients. Hemodial Int. 2012; 16:53–58. [PubMed: 22099949]
19. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutierrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro OM, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011; 121:4393–4408. [PubMed: 21985788]
20. Rosenthal D, Chrisant MR, Edens E, Mahony L, Canter C, Colan S, Dubin A, Lamour J, Ross R, Shaddy R, Addonizio L, Beerman L, Berger S, Bernstein D, Blume E, Boucek M, Checchia P, Dipchand A, Drummond-Webb J, Fricker J, Friedman R, Hallowell S, Jaquiss R, Mital S, Pahl E, Pearce FB, Rhodes L, Rotondo K, Rusconi P, Scheel J, Pal Singh T, Towbin J. International Society for Heart and Lung Transplantation: Practice guidelines for management of heart failure in children. J Heart Lung Transplant. 2004; 23:1313–1333. [PubMed: 15607659]
21. Miller TL, Somarriba G, Orav EJ, Mendez AJ, Neri D, Schaefer N, Forster L, Goldberg R, Scott GB, Lipshultz SE. Biomarkers of vascular dysfunction in children infected with human immunodeficiency virus-1. J Acquir Immune Defic Syndr. 2010; 55:182–188. [PubMed: 20531209]

22. Grenier MA, Osganian SK, Cox GF, Towbin JA, Colan SD, Lurie PR, Sleeper LA, Orav EJ, Lipshultz SE. Design and implementation of the North American Pediatric Cardiomyopathy Registry. Am Heart J. 2000; 139:S86–95. [PubMed: 10650321]
23. Ross RD, Daniels SR, Schwartz DC, Hannon DW, Shukla R, Kaplan S. Plasma norepinephrine levels in infants and children with congestive heart failure. Am J Cardiol. 1987; 59:911–914. [PubMed: 3825955]
24. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20:629–637. [PubMed: 19158356]
25. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, Colan SD, Neuberg DS, Dahlberg SE, Henkel JM, Asselin BL, Athale UH, Clavell LA, Laverdiere C, Michon B, Schorin MA, Sallan SE. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J Clin Oncol. 2012; 30:1042–1049. [PubMed: 22370326]
26. Colan SD, Parness IA, Spevak PJ, Sanders SP. Developmental modulation of myocardial mechanics: age- and growth-related alterations in afterload and contractility. J Am Coll Cardiol. 1992; 19:619–629. [PubMed: 1538019]
27. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. J Appl Physiol. 2005; 99:445–457. [PubMed: 15557009]
28. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, Lai WW, Moodie DS, McIntosh K, Schluchter MD, Colan SD. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P^2C^2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P^2C^2 HIV) Study Group. Circulation. 1998; 97:1246–1256. [PubMed: 9570194]
29. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989; 2:358–367. [PubMed: 2698218]
30. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986; 57:450–458. [PubMed: 2936235]
31. Mitchell DM, Juppner H. Regulation of calcium homeostasis and bone metabolism in the fetus and neonate. Curr Opin Endocrinol Diabetes Obes. 2010; 17:25–30. [PubMed: 19952739]
32. Bacchetta J, Cochat P, Salusky IB, Wesseling-Perry K. Uric acid and IGF1 as possible determinants of FGF23 metabolism in children with normal renal function. Pediatr Nephrol. 2012; 27:1131–1138. [PubMed: 22311343]
33. Fischer DC, Mischek A, Wolf S, Rahn A, Salweski B, Kundt G, Haffner D. Paediatric reference values for the C-terminal fragment of fibroblast-growth factor-23, sclerostin, bone-specific alkaline phosphatase and isoform 5b of tartrate-resistant acid phosphatase. Ann Clin Biochem. 2012; 49:546–553. [PubMed: 22984195]
34. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, Sarwar A, Hoffmann U, Coglianese E, Christenson R, Wang TJ, deFilippi C, Wolf M. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009; 119:2545–2552. [PubMed: 19414634]
35. Scialla JJ, Ling Lau W, Reilly MP, Isakova T, Hsueh-Ying Y, Crouthamel MH, Chavkin NW, Rahman M, Wahl P, Amaral AP, Hamano T, Master SR, Nessel L, Chai B, Xie D, Kallem RR, Chen J, Lash J, Kusek J, Budoff M, Giachelli CM, Wolf M. for the Chronic Renal Insufficiency Cohort Study. Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. Kidney Int. 201310.1038/ki.2013.3
36. Masi L, Franceschelli F, Leoncini G, Gozzini A, Rigante D, La Torre F, Matucci-Cerinic M, Brandi ML, Falcini F. Can fibroblast growth factor (FGF)-23 circulating levels suggest coronary artery abnormalities in children with Kawasaki disease? Clin Exp Rheumatol. 2013; 31:149–153. [PubMed: 23324126]

37. Ratnasamy C, Kinnamon DD, Lipshultz SE, Rusconi P. Associations between neurohormonal and inflammatory activation and heart failure in children. Am Heart J. 2008; 155:527–533. [PubMed: 18294492]

38. Rusconi PG, Ludwig DA, Ratnasamy C, Mas R, Harmon WG, Colan SD, Lipshultz SE. Serial measurements of serum NT-proBNP as markers of left ventricular systolic function and remodeling in children with heart failure. Am Heart J. 2010; 160:776–783. [PubMed: 20934575]

39. Lipshultz SE, Somers MJ, Lipsitz SR, Colan SD, Jabs K, Rifai N. Serum cardiac troponin and subclinical cardiac status in pediatric chronic renal failure. Pediatrics. 2003; 112:79–86. [PubMed: 12837871]

40. van Husen M, Fischer AK, Lehnhardt A, Klaassen I, Moller K, Muller-Wiefel DE, Kemper MJ. Fibroblast growth factor 23 and bone metabolism in children with chronic kidney disease. Kidney Int. 2010; 78:200–206. [PubMed: 20407479]

41. Isakova T, Xie H, Barchi-Chung A, Smith K, Sowden N, Epstein M, Collerone G, Keating L, Juppner H, Wolf M. Daily variability in mineral metabolites in CKD and effects of dietary calcium and calcitriol. Clin J Am Soc Nephrol. 2012; 7:820–828. [PubMed: 22383746]

42. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, Bhan I, Agarwal R, Zoccali C, Wanner C, Lloyd-Jones D, Cannata J, Thompson BT, Andress D, Zhang W, Packham D, Singh B, Zehnder D, Shah A, Pachika A, Manning WJ, Solomon SD. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA. 2012; 307:674–684. [PubMed: 22337679]

43. Kantor PF, Rusconi P, Lipshultz S, Mital S, Wilkinson JD, Burch M. Current applications and future needs for biomarkers in pediatric cardiomyopathy and heart failure: summary from the second international conference on pediatric cardiomyopathy. Prog Pediatr Cardiol. 2011; 32:11–14. [PubMed: 21909230]

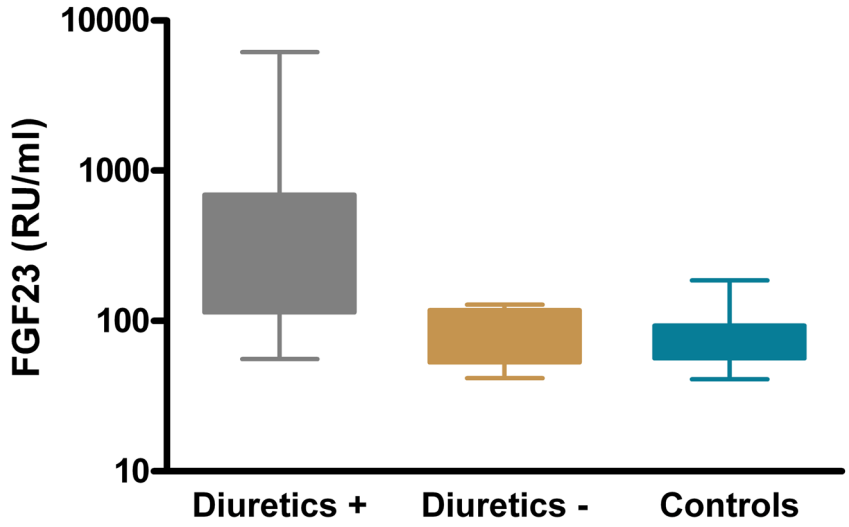

Figure 1. Median fibroblast growth factor 23 (FGF23) levels in healthy children and children with heart failure, treated with and without diuretics

Box plots represent median (interquartile range) of FGF23 by group. FGF23 levels were almost double that of in controls (110.9 vs. 66.4 RU/ml; P=0.03), and levels were higher in patients receiving diuretics than in those who were not (222.4 [IQR 133.2 – 587.9] vs. 82.1 [IQR 53.2 – 118.3] RU/ml; P=0.01).

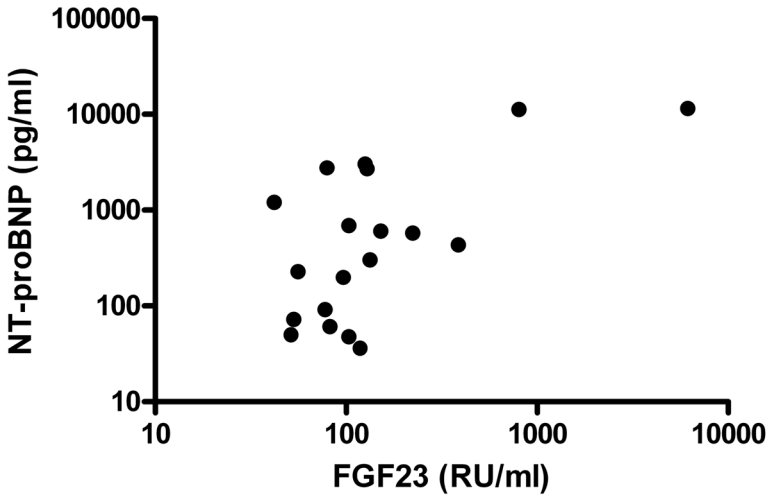

Figure 2. Correlation between NT-proBNP and fibroblast growth factor (FGF23) levels in children with heart failure

FGF23 and NT-proBNP levels were directly correlated in children with heart failure (r=0.47, P=0.04).

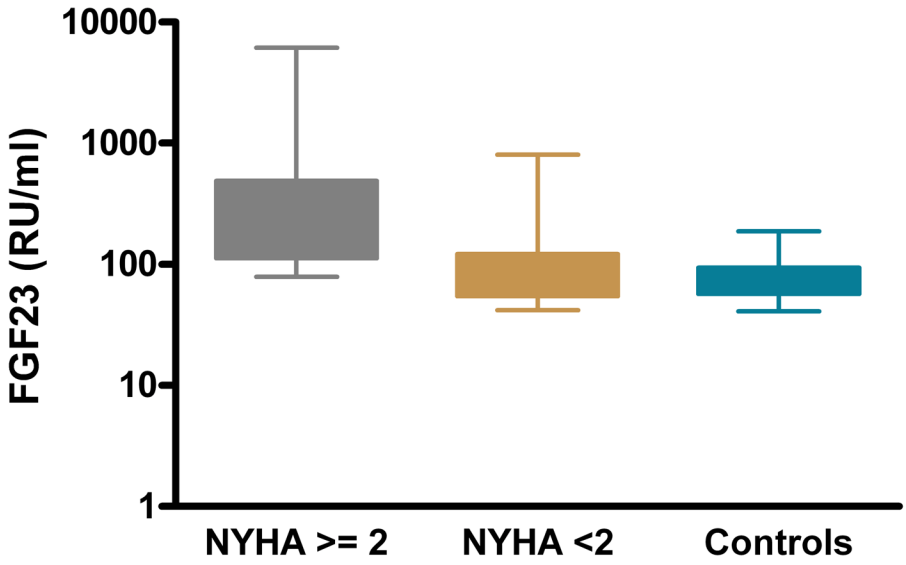

Figure 3. Median fibroblast growth factor (FGF23) concentrations in 17 healthy children and 20 children with heart failure, by functional class

Box plots represent median (interquartile range) of FGF23 by NYHA or Ross functional class. Patients with a NYHA or Ross functional class of II or greater had higher FGF23 levels than those with class I (142.5 [IQR 112.5 – 487.4] vs. 92.8 [IQR 54.6 – 122.1] RU/ml; P=0.05).

Table 1

Characteristics of children with heart failure and healthy, matched controls

	Children with heart failure (n=20)	Healthy control children (n=17)	P value
Age, mean (SD), y	12 (6)	13 (3)	0.30
Girls, n	12	11	0.77
Black, n	6	10	0.10
Hispanic, n	10	12	0.20
Weight Z score, median (25%–75%)	0.50 (−0.65 – 1.57)	0.78 (0.37 – 1.48)	0.40
Height Z score, median (25%–75%)	29 (8 – 66)	61 (21 – 73)	0.19
eGFR, mean (SD), mL/min/1.73 m^2	109.4 (56)	--	--
Creatinine, mean (SD), mg/dL	0.7 (0.3)	--	--
Calcium, mean (SD), mg/dL	9.8 (0.4)	--	--
FeCa, median (25%–75%), %	0.7 (0.2 – 0.8)	--	--
Phosphate, mean (SD), mg/dL	4.6 (0.9)	--	--
FePi, median (25%–75%), %	6.3 (4.6 –12.5)	--	--
PTH, median (25%–75%), pg/mL	41.2 (29.2 – 50.5)	34.3 (30.7 – 45.3)	0.46
FGF23, median (25%–75%), RU/mL	110.9 (78.4 – 187.1)	66.4 (59.1 – 92.7)	0.03
NT-proBNP, median (25%–75%), ng/mL	435.7 (72.4 – 2704)	--	--
Diagnosis, n			
Dilated cardiomyopathy	11	--	--
Congenital heart disease	4	--	--
Hypertrophic cardiomyopathy	3	--	--
Failing heart transplant	1	--	--
Pulmonary hypertension	1	--	--
NYHA or Ross * class, n		--	--
I	12	--	--
II	7	--	--
III	1	--	--
IV	0	--	--

eGFR, estimated glomerular filtration rate; FeCa, fractional excretion of calcium; FePi, fractional excretion of phosphate; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23, RU, reference units; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association.

* One child aged < 5 years old was staged with Ross classification (class II).

Table 2

Characteristics of children with heart failure according to diuretic treatment status

	Diuretics + (N=9)	Diuretics − (N=11)	P value
Age, mean (SD), y	9 ± 6.4	13.8 ± 4.7	0.07
Girls, n	3	9	0.03
Black, n	3	3	0.77
Hispanic, n	4	6	0.65
Weight Z score, median (25%–75%)	−0.28 (−1.71 – 1.65)	0.52 (−0.15 – 0.96)	0.54
Height Z score, median (25%–75%)	8 (4 – 68)	51 (21 – 64)	0.35
eGFR, mean (SD), mL/min/1.73 m^2	122 ± 78	99 ± 28	0.4
Creatinine, mean (SD), mg/dL	0.68 ± 0.25	0.63 ± 0.45	0.39
Calcium, mean (SD), mg/dL	9.7 ± 0.3	9.7 ± 0.4	0.83
FeCa, median (25%–75%), %	0.73 (0.08 – 2.27)	0.73 (0.47 – 0.8)	0.9
Phosphate, mean (SD), mg/dL	4.8 ± 1.0	4.3 ± 0.7	0.2
FePi, median (25%–75%), %	9.86 (3.57 – 15.48)	5.57 (4.62 – 11.16)	0.47
PTH, median (25%–75%), pg/mL	49.9 (40.8 – 57.3)	39.9 (27.0 – 41.6)	0.24
FGF23, median (25%–75%), RU/mL	222.4 (133.2 – 587.9)	82.1(53.2 – 118.3)	0.01
NT-proBNP, median (25%–75%), ng/mL	576 (303 – 999)	91 (50 – 2704)	0.28
Diagnosis, n			
Dilated cardiomyopathy	4	7	
Congenital heart disease	4	0	
Hypertrophic cardiomyopathy	0	3	0.05
Failing heart transplant	0	1	
Pulmonary hypertension	1	0	
NYHA or Ross * class, n			
I	3	9	
II	5	2	0.08
III	1	0	
IV	0	0	

eGFR, estimated glomerular filtration rate; FeCa, fractional excretion of calcium; FePi, fractional excretion of phosphate; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23, RU, reference units; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association.

* One child aged < 5 years old was staged with Ross classification (class II).

Table 3

Univariate correlations between FGF23 levels and clinical variables by heart failure status

	Children with heart failure (n=20)		Healthy control children (n=17)	
	r	P Value	r	P Value
Age (years)	− 0.18	0.46	0.29	0.26
Weight Z score	− 0.38	0.12	− 0.20	0.43
Height Z score	− 0.18	0.47	− 0.04	0.88
Creatinine (mg/dl)	− 0.04	0.88	--	--
eGFR (ml/min/1.73 m^2)	− 0.08	0.74	--	--
Calcium (mg/dl)	− 0.01	0.97	--	--
Phosphate (mg/dl)	0.40	0.08	--	--
FeCa (%)	0.17	0.49	--	--
FePi (%)	0.20	0.44	--	--
PTH (pg/ml)	0.67	0.001	0.08	0.77
NT-proBNP (ng/mL)	0.47	0.04	--	--

eGFR, estimated glomerular filtration rate; FePi, fractional excretion of phosphate; FeCa, fractional excretion of calcium; PTH, parathyroid hormone; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

Table 4

Echocardiographic measures in 11 children with dilated cardiomyopathy.

Echocardiographic Measures (Age- or BSA-adjusted Z scores for all except left ventricular ejection fraction)	Distribution	N with values outside 2 SD of normal mean	P Value
Left ventricular ejection fraction, mean (SD)	46.7 ± 12.8	--	<0.001
Left ventricular fractional shortening, median (25%–75%)	−3.7 (−6.3 – −3.0)	9	<0.001
Left ventricular wall thickness, median (25%–75%)	−1.1 (−2.6 – 0.04)	7	0.07
Septal thickness, median (25%–75%)	−1.9 (−2.3 – 0.2)	6	0.01
Left ventricular mass, median (25%–75%)	1.1 (−0.8 – 2.8)	7	0.14
Left ventricular end-systolic diameter, median (25%–75%)	4.0 (2.5 – 5.2)	9	0.001
Left ventricular end-diastolic diameter, median (25%–75%)	3.2 (1.8 – 4.5)	8	0.004

P values are for testing significance of mean Z scores being different from zero.

Table 5

Univariate correlations of echocardiographic measures with FGF23 and NT-proBNP levels in 11 children with dilated cardiomyopathy.

Echocardiographic Measures (Age- or BSA-adjusted Z scores, except for ejection fraction)	FGF23		NT-proBNP	
	r	P Value	r	P Value
Left ventricular ejection fraction	−0.49	0.12	−0.61	0.046
Left ventricular fractional shortening	−0.53	0.12	−0.53	0.12
Left ventricular wall thickness	0.59	0.06	0.02	0.96
Septal thickness	0.50	0.12	0.15	0.67
Left ventricular mass	0.61	0.06	0.45	0.19
Left ventricular end-systolic diameter	0.60	0.05	0.59	0.06
Left ventricular end-diastolic diameter	0.63	0.04	0.57	0.07

FGF-23, fibroblast growth factor-23; BSA, body surface area