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Fibroblast Growth Factor-23 in Obese, Normotensive Adolescents is Associated with Adverse Cardiac Structure

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Abstract

Objectives—Fibroblast growth factor-23 (FGF23) is a biomarker for cardiovascular (CV) disease. Obesity may promote FGF23 production in the absence of chronic kidney disease (CKD). We sought to determine among normotensive African American adolescents, whether FGF23 levels are higher in obese compared with normal weight African American adolescents; and to determine the relationship of FGF23 with markers of cardiac structure and insulin resistance.

Study design—Cross-sectional data were obtained from a cohort of 130 normotensive, African American adolescents aged 13-18 years old without CKD; 74 were obese; 56 were normal weight. Plasma C-terminal FGF23, fasting glucose and insulin, and hsCRP were measured; participants underwent M-mode echocardiography.

Results—FGF23 was skewed and approximately normally distributed after natural log transformation (logFGF23). FGF23 levels were higher in obese versus normal weight participants (geometric mean 43 vs. 23 RU/mL, $p < 0.01$). FGF23 values were significantly higher in participants with eccentric or concentric cardiac hypertrophy compared with those without hypertrophy ($p < 0.01$). LogFGF23 directly correlated with BMI, BMI z-score, waist

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circumference, fasting insulin levels, and HOMA scores. Regression models adjusted for age, sex, and hsCRP suggest that each 10% increase in FGF23 is associated with 1.31 unit increase in LVM ($p<0.01$), 0.29 unit increase in LVMI ($p<0.01$), and 0.01 unit increase in left atrial dimension indexed to height ($p=0.02$).

Conclusions—In this sample of obese African American adolescents, FGF23 blood levels were associated with abnormal cardiac structure. We postulate that FGF23 may be an early marker of cardiac injury in obese but otherwise healthy African American adolescents.

Keywords

obesity; left ventricular mass; FGF23; adolescence; African American

Fibroblast growth factor-23 (FGF23) is a biomarker for cardiovascular disease, demonstrated first in adults with chronic kidney disease (CKD). (1) Secreted by osteocytes and osteoblasts from bone, FGF23 was discovered for its primary hormonal endocrine actions to increase kidney phosphate excretion, decrease active vitamin D production, and increase active vitamin D catabolism. (2) More recently the non-classical actions of FGF23 on the cardiovascular system have been studied. Most strikingly, in CKD at all stages, blood levels of FGF23 are one of the strongest known indicators of cardiovascular events and are independently and positively associated with increasing left ventricular mass index (LVMI). (3) The relationship with LVMI has now been demonstrated in older individuals, but without CKD, (4) suggesting that FGF23 may be a cardiovascular (CV) risk factor in adults, regardless of kidney function. Although an association of obesity with cardiac mass has been described in adolescents, (5) there is limited information on FGF23 and its associations with cardiovascular risk factors such as obesity and cardiac mass in childhood.

Experimental studies have demonstrated that leptin increases FGF23. (6) Because leptin is uniformly increased in both obese adults (7) and obese adolescents, (8) we reasoned that we would find elevated blood levels of FGF23 in childhood obesity and in the absence of CKD. In a previous study we sought to determine if there was an interaction of high BP (prehypertension) with obesity (BMI 95th percentile) on target organ damage, in particular LVM, in African American adolescents. Our results did not detect statistically significant interaction, but did identify independent effects of obesity and high BP on LVMI. Moreover, we detected left ventricular hypertrophy (LVH) in 24% of obese normotensive adolescents. (5) Therefore, for this study we hypothesized that FGF23 elevation would be associated with abnormal cardiac structure. Our objectives were to determine whether otherwise healthy, normotensive, obese African American adolescents without CKD have elevated FGF23 levels in blood compared with normal weight African American adolescents. We sought to determine if the elevation in FGF23 blood levels was associated with cardiac mass and/or structure. Lastly, we sought to determine if FGF23 levels were related to an estimate of insulin resistance.

Methods

Healthy African American adolescents aged 13-18 years were recruited and enrolled in Philadelphia, PA and Wilmington DE, between 2009 and 2011, through primary care

practices in the Departments of Family Medicine and Pediatrics at Thomas Jefferson University and from community primary care practices, as previously published.(5) Exclusion criteria included known secondary hypertension, diabetes, chronic kidney disease, cardiovascular disease, autoimmune disease, thyroid disease, sickle cell disease, eating disorders, and use of corticosteroids. For the current study, cross-sectional data were obtained from a subset of the original cohort which included all normotensive subjects. For this study we included cases of normotensive adolescents who had frozen stored samples available for FGF23 assay. The cases were approximately balanced by age and sex. The study included 130 African American adolescents, age 13-18 years, with normal kidney function (normal creatinine and eGFR by Schwartz) and absent proteinuria (urinary albumin excretion less than 20 mg/gram of creatinine on a timed overnight collection). Among the 74 normotensive obese participants in this study, with a body mass index (BMI) 95th percentile for age and sex, 20 (27%) had left ventricular hypertrophy, defined as LVMI 95th percentile based on sex-specific normative LVMI data published by Khoury et al.(9) Among the 56 normal weight (BMI < 85th percentile) normotensive participants, with similar age, LVMI was normal in all. The study protocol was approved by the Institutional Review Boards of Thomas Jefferson University and the Ann & Robert H. Lurie Children's Hospital of Chicago. Written informed consent was obtained from a parent of each participant and assent was obtained from the adolescent participant. Participants who were 18 years of age signed their own consent form.

Demographic data, anthropometric measurements (height, weight, and waist circumference) and blood pressures were obtained. BMI was calculated as weight (kg) divided by height squared (m²), and obesity was defined as BMI 95th percentile according to the Centers for Disease Control and Prevention criteria for children (<http://www.cdc.gov/obesity/childhood/defining.html>), which are derived from population-standardized BMI Z-scores based on age, sex, and BMI. All blood pressure measurements in this study were obtained by research staff trained in pediatric blood pressure measurement methodology; measurements were obtained by auscultation with an aneroid device following a 10-minute rest period. During blood pressure measurement the subject was seated with back supported, feet flat on the floor, and the arm on which blood pressure was measured was supported at heart level. The average of 3 successive measurements on 2 separate visits was used as the blood pressure value for each participant to determine that they had normal blood pressure (data not shown).

Glucose (glucose oxidase technique, YS model 27; Glucostat, Yellow Springs, Ohio) and insulin (solid phase radioimmunoassay, Coat-a-Count; Diagnostic Products Corp, Los Angeles, California) were measured after overnight fasting. Insulin resistance was estimated using the homeostasis model assessment (HOMA) of insulin resistance.(10) Plasma C-terminal FGF23 (Immunotopics International, San Clemente, CA), adiponectin (R&D Systems, Minneapolis, Minnesota), and high sensitivity C Reactive Protein (hsCRP) (R&D Systems, Minneapolis, Minnesota) were measured from plasma samples stored at -80°C until assay.

All participants underwent M-mode echocardiography by a single, trained technician. Measurements of the left atrial diameter, left ventricular (LV) internal dimension, interventricular septal thickness, and posterior wall thickness during diastole were made

according to methods established by the American Society of Echocardiography.(11) Left ventricular mass (LVM) was calculated from measurement of the LV using the equation $LVM (g) = 0.81(1.04 [\text{interventricular septal thickness} + \text{posterior wall thickness} + \text{LV end diastolic internal dimension}])^3 - (\text{LV end diastolic internal dimension})^3 + 0.06$.(12) LVM was indexed to height raised to the 2.7 power.(9) Left atrial diameter was measured indexed to height (LADI=LAD/height in meters). Tissue Doppler analysis of the lateral MV annulus and the septal annulus was performed and values from sequential beats were averaged. Diastolic time interval (DTI) ratio = E/Ea was calculated as a marker of diastolic function.

Statistical analyses

Statistical analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL) and SAS version 9.3 (SAS Institute, Cary, NC). FGF23 data were positively skewed and were summarized in LVMI and LV relative wall thickness subgroups with geometric means and the first and third quartiles of the data. FGF23 was approximately normally distributed after natural log transformation (logFGF23). Medians were calculated and presented as box plot summaries of the data. Measures of correlation with logFGF23 were performed using the Pearson Product Moment Correlation (ρ). A two sided t-test was used to compare group means. Ordinary least squares regression was employed for multivariate analyses of linear associations (slopes, denoted by β) between logFGF23 and continuous variables. The significance level for all tests was set in advance at $\alpha = 0.05$.

Results

The obese and normal weight subgroups in this cohort of 130 adolescents were similar in terms of age and sex. The BMI, BMI z-score, and measures of LVM were higher in the obese subgroup (Table I). Creatinine was similar between the 2 subgroups and eGFR, calculated by the Schwartz formula,(13) was normal in the entire group ($>100 \text{ ml/min/1.73m}^2$). However, the blood levels of FGF23 were higher in the obese versus the normal weight African American adolescents ($p<0.01$; Figure 1).

We examined associations of FGF23 with cardiac structure in the entire study sample and detected significant associations with both LVM and LVMI. Increasing FGF23 may relate to increasing values of LVM, but is not statistically significantly in these data ($\rho=0.17$, $p=0.054$; Figure 2, A). However, increasing FGF23 was associated with increasing values of LVMI ($\rho=0.26$, $p<0.01$; Figure 2, B). Left atrial diameter indexed to height (LADI) also increased with increasing FGF23 in the entire sample of both obese and normal weight study participants ($\rho=0.22$, $p=0.01$; Figure 3 available at www.jpeds.com), and in the obese subgroup, FGF23 values above their median value of 43 RU/mL were associated with a higher DTI ratio ($p=0.04$; Figure 4 available at www.jpeds.com). Further, FGF23 levels were significantly higher among those participants with eccentric or concentric LVH compared with those with normal LVMI and LV geometry ($p=0.02$; Table II). For those without LVH, the geometric mean FGF23 was 31.5 RU/mL, while for those with LVH, the geometric mean FGF23 was 42.0 RU/mL ($p<0.01$). In multivariate analyses, when adjusting for age, sex, and hsCRP, logFGF23 was a statistically significant predictor of LVM, LVMI, and LADI ($\beta=13.7$, $p<0.01$; $\beta=3.0$, $p<0.01$; $\beta=0.10$, $p=0.02$, respectively). These results

suggest that each 10% increase in FGF23 relates to a 1.31 unit increase in LVM expected values, a 0.29 unit increase in LVMI expected values, and a 0.01 unit increase in LADI expected values.

For the entire study sample, logFGF23 directly correlated with both fasting insulin levels ($\rho=0.34$, $p<0.01$) and HOMA scores ($\rho=0.34$, $p<0.01$). Additionally, logFGF23 was significantly inversely correlated with adiponectin ($\rho=-0.21$, $p=0.01$) and directly correlated with hsCRP ($\rho=0.26$, $p=0.01$). LogFGF23 correlated with measures of adiposity, including BMI ($\rho=0.50$, $p<0.01$), BMI z-score ($\rho=0.53$, $p<0.01$), and waist circumference ($\rho=0.47$, $p<0.01$). Neither creatinine nor eGFR was significantly correlated with FGF23 values in this population.

Discussion

Based on the consistent observation of higher blood pressure levels among obese children, it has been assumed that the cardiovascular burden of childhood obesity is largely related to systemic hypertension. However, this traditional risk factor does not account for the entire burden of cardiovascular disease, as there is not a direct linear relationship of left ventricular hypertrophy with severity of hypertension in adolescents.(14) While previous work has noted the relationship between obesity and increased LVMI,(5, 15) and additionally, other work has established a relationship between BMI and concentric and eccentric left ventricular remodeling among healthy adolescents,(16) the novel findings in our current study confirm the relationship between obesity and cardiac structure and suggest that FGF23 is a possible mediator for these relationships. Importantly, we demonstrated that the association of obesity and elevated blood levels of FGF23 were present even in the absence of hypertension.

Previous studies in adults have linked FGF23 blood levels with left ventricular structure, cardiovascular events, and mortality in adults with or without CKD.(1, 3, 4, 17) This relationship in adults has persisted, even when adjusted for mineral metabolism abnormalities and subclinical cardiovascular damage.(18) Groundwork for the causal relationship between FGF23 and cardiovascular disease has been demonstrated by the recent experimental work of Faul et al, in which FGF23 exposure in-vitro caused direct myocardial cell hypertrophy and where repetitive FGF23 injections led to the development of left ventricular hypertrophy.(19) Confirmation of these experimental findings was not uniformly reproduced by another group.(20) However, FGF23 blood levels in humans have been linked to broader disease states of the left ventricle, including atrial fibrillation and LV dysfunction, as well as heart failure.(21, 22) Therefore, we hypothesize that the elevated FGF23 blood levels in the obese adolescents in our study and their association with higher cardiac mass may reflect activation of an FGF23-mediated pathway that, with long term exposure, may lead to altered cardiac structure.

Obesity is commonly observed among children and adolescents with primary hypertension. In a previous study on African American adolescents with and without prehypertension, and that included normotensive obese and non-obese African American participants, we detected significant associations of prehypertension and obesity with LVH that were both

independent and additive.(5) Recent studies on childhood primary hypertension that examined LVMI describe consistent associations of obesity with LVH.(23-25) Moreover, a race effect is also reported. Hanevold et al reported that LVH was more prevalent among Hispanic and African American children with hypertension compared with Caucasians with hypertension. In other reports limited to children with primary hypertension, LVH was more prevalent among African American children than non-African American children, (24, 25) and as reported by Pruette et al, BMI and race were independently associated with LVH.(25) In addition to the reports on children with hypertension, Crowley et al examined secular changes in LVMI based on echocardiogram data from 2 large samples of healthy children; one period was prior to the obesity epidemic and the other period was following the obesity epidemic. (26) The authors report that in both periods the determinants of LVMI were BMI z-score, younger age, male sex, and African American race. Together, these reports suggest that race, in particular African American ethnicity, may contribute to abnormal cardiac geometry under the influence of hypertension.

Our study population was exclusively African American, and therefore, the significant associations of FGF23 and LVH in our sample of African American adolescents may not be generalizable to other races or ethnic groups. Alternatively, the findings in our study could provide some insights into racial disparity in CV disease observed among African Americans. In fact, one small study reported a 2.6-fold elevation in FGF23 levels in healthy adult African Americans compared with Caucasians despite a statistically higher creatinine clearance and with no difference in phosphorus or vitamin D levels.(27) Although the small numbers did not provide sufficient power to detect a statistical difference, importantly, the BMI was the same between the two groups.

Further studies of FGF23 in other race and ethnic groups with and without obesity will be necessary to determine if the associations of FGF23 with LVH detected in our study are generalizable to other race groups. However, a recent study suggests that obesity alone may confer higher FGF23 levels; for example, elevated FGF23 levels have been documented in obese versus non-obese Caucasian adults, although cardiac structure was not studied.(28)

We recognize that the current cross-sectional study does not establish causality between FGF23 and increased cardiac mass or structure. Our data demonstrate that FGF23 levels are significantly associated with obesity in normotensive African American adolescents. However, we do not have a sufficient sample size to conduct the necessary statistical modeling to prove or disprove that the association of FGF23 with LVH is independent of obesity, especially if FGF23 elevations are a consequence of obesity. However the findings in our study and reports in adults do suggest biologic plausibility for a role of FGF23 in the associations of BMI and LVMI.

Because clustering of cardiometabolic risk factors in adolescence is predictive of adult health status,(29) prospective studies could determine if FGF23 levels in adolescents are independently related to cardiac hypertrophy in young adulthood. If proven to be a predictor of CV outcomes FGF23 could be a novel biomarker to identify CV disease at an earlier time point than heretofore available. Because FGF23 elevations predict progressive loss of

glomerular filtration, (30) it is possible that FGF23 may be an early marker for participants who may progress to CKD, also a known complication of obesity.

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List of Abbreviations

FGF23	Fibroblast Growth Factor-23
CKD	Chronic kidney disease
BMI	Body mass index
HOMA	Homeostasis model assessment
hsCRP	Highly sensitive C-reactive protein
SD	Standard deviation
GM	Geometric mean
Q1	1 st quartile
Q3	3 rd quartile

References

1. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. *Kidney Int.* Oct.2012 82:737–47. [PubMed: 22622492]
2. Larsson TE. The role of FGF-23 in CKD-MBD and cardiovascular disease: friend or foe? *Nephrol Dial Transplant.* May.2010 25:1376–81. [PubMed: 20124546]
3. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collierone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation.* May 19.2009 119:2545–52. [PubMed: 19414634]
4. Mirza MA, Larsson A, Melhus H, Lind L, Larsson TE. Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis.* Dec.2009 207:546–51. [PubMed: 19524924]
5. Falkner B, DeLoach S, Keith SW, Gidding SS. High risk blood pressure and obesity increase the risk for left ventricular hypertrophy in African-American adolescents. *J Pediatr.* Jan.2013 162:94–100. [PubMed: 22817908]
6. Tsuji K, Maeda T, Kawane T, Matsunuma A, Horiuchi N. Leptin stimulates fibroblast growth factor 23 expression in bone and suppresses renal 1 α ,25-dihydroxyvitamin D3 synthesis in leptin-deficient mice. *J Bone Miner Res.* Aug.2010 25:1711–23. [PubMed: 20200981]
7. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med.* Feb 1.1996 334:292–5. [PubMed: 8532024]
8. Sanches PL, de Mello MT, Elias N, Fonseca FA, Campos RM, Carnier J, et al. Hyperleptinemia: Implications on the Inflammatory State and Vascular Protection in Obese Adolescents Submitted to an Interdisciplinary Therapy. *Inflammation.* Aug 9.2013
9. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr.* Jun.2009 22:709–14. [PubMed: 19423289]

10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. Jul.1985 28:412–9. [PubMed: 3899825]
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. Dec.2005 18:1440–63. [PubMed: 16376782]
12. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. Feb 15.1986 57:450–8. [PubMed: 2936235]
13. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. Mar.2009 20:629–37. [PubMed: 19158356]
14. Brady TM, Fivush B, Flynn JT, Parekh R. Ability of blood pressure to predict left ventricular hypertrophy in children with primary hypertension. *J Pediatr*. Jan.2008 152:73–8. e1. [PubMed: 18154904]
15. Batalli-Kepuska A, Bajraktari G, Zejnullahu M, Azemi M, Shala M, Batalli A, et al. Abnormal systolic and diastolic myocardial function in obese asymptomatic adolescents. *Int J Cardiol*. Feb 14.2013
16. H, Hietalampi; K, Pahlkala; E, Jokinen; T, Ronnema; JS, Viikari; H, Niinikoski, et al. Left ventricular mass and geometry in adolescence: early childhood determinants. *Hypertension*. Nov. 2012 60:1266–72. [PubMed: 22987921]
17. Arnlov J, Carlsson AC, Sundstrom J, Ingelsson E, Larsson A, Lind L, et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. *Kidney Int*. Jan.2013 83:160–6. [PubMed: 22951890]
18. Arnlov J, Carlsson AC, Sundstrom J, Ingelsson E, Larsson A, Lind L, et al. Serum FGF23 and risk of cardiovascular events in relation to mineral metabolism and cardiovascular pathology. *Clin J Am Soc Nephrol*. May.2013 8:781–6. [PubMed: 23335040]
19. Faul C, Amaral AP, Oskoue B, Hu MC, Sloan A, Isakova T. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. Nov 1.2011 121:4393–408. [PubMed: 21985788]
20. Shalhoub V, Shatzen EM, Ward SC, Davis J, Stevens J, Bi V, et al. FGF23 neutralization improves chronic kidney disease-associated hyperparathyroidism yet increases mortality. *J Clin Invest*. Jul 2.2012 122:2543–53. [PubMed: 22728934]
21. Seiler S, Cremers B, Rebling NM, Hornof F, Jeken J, Kersting S, et al. The phosphatonin fibroblast growth factor 23 links calcium-phosphate metabolism with left-ventricular dysfunction and atrial fibrillation. *Eur Heart J*. Nov.2011 32:2688–96. [PubMed: 21733911]
22. di Giuseppe R, Buijsse B, Hirche F, Wirth J, Arregui M, Westphal S, et al. Plasma Fibroblast Growth Factor 23, Parathyroid Hormone, 25-HydroxyvitaminD3 and risk of Heart Failure: a prospective, case-cohort study. *J Clin Endocrinol Metab*. Jan 1.2013 jc20132963.
23. Hanevold C, Waller J, Daniels S, Portman R, Sorof J. The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. *Pediatrics*. Feb.2004 113:328–33. [PubMed: 14754945]
24. Brady TM, Fivush B, Parekh RS, Flynn JT. Racial differences among children with primary hypertension. *Pediatrics*. Nov.2010 126:931–7. [PubMed: 20956429]
25. Pruetten CS, Fivush BA, Flynn JT, Brady TM. Effects of obesity and race on left ventricular geometry in hypertensive children. *Pediatr Nephrol*. Oct.2013 28:2015–22. [PubMed: 23703719]
26. Crowley DI, Khoury PR, Urbina EM, Ippisch HM, Kimball TR. Cardiovascular impact of the pediatric obesity epidemic: higher left ventricular mass is related to higher body mass index. *J Pediatr*. May.2011 158:709–14. e1. [PubMed: 21147488]

27. Gutierrez OM, Isakova T, Smith K, Epstein M, Patel N, Wolf M. Racial differences in postprandial mineral ion handling in health and in chronic kidney disease. *Nephrol Dial Transplant*. Dec.2010 25:3970–7. [PubMed: 20530498]
28. Grethen E, Hill KM, Jones R, Cacucci BM, Gupta CE, Acton A, et al. Serum leptin, parathyroid hormone, 1,25-dihydroxyvitamin D, fibroblast growth factor 23, bone alkaline phosphatase, and sclerostin relationships in obesity. *J Clin Endocrinol Metab*. May.2012 97:1655–62. [PubMed: 22362819]
29. Okosun IS, Seale JP, Boltri JM, Davis-Smith M. Trends and clustering of cardiometabolic risk factors in American adolescents from 1999 to 2008. *J Adolesc Health*. Feb.2012 50:132–9. [PubMed: 22265108]
30. Lundberg S, Qureshi AR, Olivecrona S, Gunnarsson I, Jacobson SH, Larsson TE. FGF23, albuminuria, and disease progression in patients with chronic IgA nephropathy. *Clin J Am Soc Nephrol*. May.2012 7:727–34. [PubMed: 22383747]

Figure 1.

The blood levels of FGF23 are higher in obese vs. non-obese AA adolescents ($p < 0.01$). Shown are the boxplots of the data with median values depicted by bold lines, 1st and 3rd quartiles outlined by the boxes, whiskers delineating the spread, and outliers of 95th percentile values and beyond denoted as open circles and asterisks, respectively. Blood levels of FGF23 in the study sample.

Figure 2.

Higher FGF23 may relate to higher LVM, but not statistically significantly in these data (Fig 2A, $\rho=0.17$, $p=0.05$). Higher FGF23 was significantly associated with higher LVMI (Fig 2B, $\rho=0.26$, $p<0.01$). Shown are the boxplots of the data with median values depicted by bold lines, 1st and 3rd quartiles outlined by the boxes, whiskers delineating the spread, and outliers of 95th percentile values and beyond denoted as open circles. Relationships of increasing FGF23 quartiles with LVM and LVMI.

Figure 3.

LADI increased in participants with higher FGF23 values ($\rho=0.22$, $p=0.01$). FGF23 is grouped according to quartiles. Shown are the boxplots of the data with median values depicted by bold lines, 1st and 3rd quartiles outlined by the boxes, whiskers delineating the spread, and outliers of 95th percentile values and beyond denoted as open circles. Left Atrial Diameter Index (LADI) as a function of FGF23 quartiles.

Figure 4.

DTI Ratio was higher in the obese participants with FGF23 values greater than or equal to 43 RU/mL ($p=0.04$). Shown are the boxplots of the data with median values depicted by bold lines, 1st and 3rd quartiles outlined by the boxes and outliers of 95th percentile values and beyond denoted as circles.

Diastolic Time Interval (DTI) Ratio as a function of a median split of FGF23 among the obese subgroup.

Table 1

Selected characteristics of the study sample.

	Obese n=74	Normal Weight n=56	p-value
Age , years, mean (SD)	15.9 (1.7)	16.0 (1.8)	0.66
Females , n (%)	47 (64)	25 (45)	0.04
BMI (kg/m ²), mean (SD)	34.3 (5.8)	20.6 (1.9)	<0.01
BMI z-score , mean (SD)	2.1 (0.3)	0.0 (0.7)	<0.01
Creatinine (mg/dL), GM [Q1, Q2] [‡]	0.8 [0.7, 0.9]	0.7 [0.6, 0.9]	0.31
hsCRP (mg/dL), GM [Q1, Q2] [‡]	1.4 [0.6, 3.7]	0.4 [0.2, 0.8]	<0.01
LVM (g), mean (SD)	143 (37.0)	112 (22.0)	<0.01
LVMI (g/m ^{2.7}), mean (SD)	35.2 (7.0)	28.0 (4.5)	<0.01
FGF23 (RU/mL), GM [Q1, Q2] [‡]	43.4 [32, 58]	22.9 [17, 31]	<0.01

[‡]Geometric mean with [first quartile, third quartile] presented.

Table 2

FGF23 by LVMI subgrouping and LV geometry.

	No LVH		LVH		p-value [‡]
	Normal (n=96)	Concentric Remodeling (n=18)	Eccentric LVH (n=14)	Concentric LVH (n=6)	
FGF23 (RU/ml) [‡]	32.1 [22, 48]	28.6 [21, 43]	41.0 [26, 60]	44.2 [34, 62]	0.02

[‡] FGF23 was compared in adolescents without LVH (those with normal LVMI and LV geometry; geometric mean FGF23 = 32.1) to those with LVH (eccentric or concentric LVH; geometric mean FGF23 = 42.0, p=0.02).

[‡] Geometric means with [first quartile, third quartile] presented.