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

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Objectives Fibroblast growth factor-23 (FGF23) is a biomarker for cardiovascular disease. Obesity may promote FGF23 production in the absence of chronic kidney disease. We sought to determine among normotensive African American adolescents whether FGF23 levels are greater in obese compared with normal-weight 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 ages 13-18 years without chronic kidney disease; 74 were obese; 56 were normal weight. Plasma C-terminal FGF23, fasting glucose and insulin, and high-sensitivity C-reactive protein were measured; participants underwent M-mode echocardiography.

Results FGF23 was skewed and approximately normally distributed after natural log transformation (logFGF23). FGF23 levels were greater in obese vs normal-weight participants (geometric mean 43 vs 23 RU/mL, $P < .01$). FGF23 values were significantly greater in participants with eccentric or concentric cardiac hypertrophy compared with those without hypertrophy $P < .01$). LogFGF23 directly correlated with body mass index, body mass index z-score, waist circumference, fasting insulin levels, and homeostasis model assessment scores. Regression models adjusted for age, sex, and high-sensitivity C-reactive protein suggest that each 10% increase in FGF23 is associated with a 1.31 unit increase in left ventricular mass ($P < .01$), a 0.29-unit increase in left ventricular mass index ($P < .01$), and a 0.01-unit increase in left atrial dimension indexed to height ($P = .02$).

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. *(J Pediatr 2014;165:738-43)*.

Fibroblast growth factor-23 (FGF23) is a biomarker for cardiovascular (CV) 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 nonclassical actions of FGF23 on the CV system have been studied. Most strikingly, in CKD at all stages, blood levels of FGF23 are one of the strongest known indicators of CV 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 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 CV 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 increased blood levels of FGF23 in childhood obesity and in the absence of CKD. In a previous study we sought to determine whether there was an interaction of high blood pressure (BP) (prehypertension) with obesity (body mass index [BMI] ≥95th percentile) on target organ damage, in particular left ventricular mass (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 an increase in FGF23 would be associated with abnormal cardiac structure. Our objectives were to determine

BMI	Body mass index	hsCRP	High-sensitivity C-reactive protein
BP	Blood pressure	LADI	Left atrial diameter indexed to height
CKD	Chronic kidney disease	LV	Left ventricular
CV	Cardiovascular	LVH	Left ventricular hypertrophy
DTI	Diastolic time interval	LVM	Left ventricular mass
eGFR	Estimated glomerular filtration rate	LVMI	Left ventricular mass index
FGF23	Fibroblast growth factor-23		

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whether otherwise-healthy, normotensive, obese African American adolescents without CKD have increased FGF23 levels in the blood compared with normal-weight African American adolescents. We sought to determine whether the increase in FGF23 blood levels was associated with cardiac mass and/or structure. Finally, we sought to determine whether FGF23 levels were related to an estimate of insulin resistance.

Methods

Healthy African American adolescents ages 13-18 years were recruited and enrolled in Philadelphia, Pennsylvania, and Wilmington, Delaware, 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, CKD, CV disease, autoimmune disease, thyroid disease, sickle cell disease, eating disorders, and the use of corticosteroids.

For the current study, cross-sectional data were obtained from a normotensive subset of the original cohort. 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, ages 13-18 years, with normal kidney function (normal creatinine and estimated glomerular filtration rate [eGFR] by Schwartz et al[13]) and absent proteinuria (urinary albumin excretion <20 mg/g of creatinine on a timed overnight collection). Among the 74 normotensive obese participants in this study, with a BMI ≥95th percentile for age and sex, 20 (27%) had LVH, 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 BPs were obtained. BMI was calculated as weight (kg) divided by height squared (m^2), 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 BP measurements in this study were obtained by research staff trained in pediatric BP measurement methodology; measurements were obtained by auscultation with an aneroid device following a 10-minute rest period. During BP measurement, the subject was seated with back supported, feet flat on the floor, and the arm on which BP was measured was supported at heart level. The average of 3 successive measurements on 2 separate visits was used as the BP value for each participant to determine that they had normal BP (data not shown).

Glucose (glucose oxidase technique; Glucostat, YS model 27; Yellow Springs Instruments, 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 of insulin resistance.[10] Plasma C-terminal FGF23 (Immunotopics International, San Clemente, California), 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] LVM was calculated from measurement of the LV using the equation LVM (g) = 0.81 (1.04 [interventricular septal thickness + posterior wall thickness + LV end diastolic internal dimension])^3 − (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 = left atrial diameter/height in meters). Tissue Doppler analysis of the lateral mitral valve 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, Illinois) and SAS version 9.3 (SAS Institute, Cary, North Carolina). 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 2-sided t test was used to compare group means. Ordinary least squares regression was used 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 greater in the obese