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Aortic dilatation in children with mild to moderate chronic kidney disease

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Abstract

Children with mild to moderate chronic kidney disease are at an increased risk for cardiovascular sequelae, the leading cause of death in children with end stage renal disease. We aimed to establish the prevalence of aortic dilatation, a newly recognized cardiovascular sequelae of renal disease, within a cohort of pediatric patients with mild to moderate kidney disease.

A total of 501 children enrolled in the Chronic Kidney Disease in Children study contributed imaging data between April 2011 and February 2015. Aortic dilatation was defined as a dimension exceeding a z-score of 2 at any of three locations: aortic root, sinotubular junction or the ascending aorta.

Thirty children (6%) were identified to have aortic dilatation in at least one of the three locations. Multivariate analysis demonstrated an increased odds ratio for the presence of aortic dilatation associated with the following variables: high diastolic blood pressure z-scores, low weight z-score, and low body mass index z-score. Presense of protein energy wasting (modified definition, OR: 2.41, 95%CI: 1.23, 4.70) was the strongest independent predictor of aortic dilatation.

In conclusion, aortic dilatation does occur early in the course of chronic kidney disease and associates with markers of poor nutrition. Future studies should continue to evaluate these risk factors longitudinally as the kidney disease progresses.

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Disclosures

None of the authors have a conflict of interest or any disclosures to report.

Keywords

Chronic kidney disease; aortic dilatation; cardiovascular disease; protein energy wasting; malnutrition

Background

Chronic kidney disease (CKD) is a progressive life-long condition that is associated with significant morbidity and mortality. Cardiovascular disease is the leading cause of death in children with end-stage renal disease (ESRD)[1, 2]. We have recently reported that children on maintenance dialysis and after kidney transplantation have dilatation of the proximal aortic dimensions, a previously unrecognized sequelae of ESRD[3]. Dilatation of aortic dimensions can be a precursor to aortic dissection and has been reported in association with other forms of kidney disease in adults [4]. Progressive aortic dilatation is a known precursor to aortic dissection as evidenced by more aggressive aortopathies such as Marfan syndrome, Loeys Dietz syndrome and other connective tissue disorders. Aortic dissection can cause significant morbidity and mortality, especially in the context of hypertension[5]. One of the factors associated with aortic dilatation in our prior study was low body mass index (BMI) suggesting that malnutrition might play a role in this abnormality.

We sought to expand upon this work and assess the extent to which aortic dilatation was present in children with mild to moderate kidney disease and enrolled in the Chronic Kidney Disease in Children (CKiD) prospective cohort study. The CKiD study as a longitudinal cohort study, is uniquely positioned to examine aortic dilatation since detailed phenotypic data on disease progression and cardiac structure are available. Based on previous publications [2], we also evaluated the association between the protein energy wasting (PEW) phenotype as a marker of poor growth and nutrition and aortic dilatation. Understanding aortic dilatation in this population of children with CKD prior to ESRD can have a potential impact on recommendations for serial imaging surveillance to monitor for cardiac disease progression.

Methods

Study population

The CKiD study is a longitudinal cohort study designed to investigate the natural and treated history of CKD in children. A total of 891 children were enrolled with an underlying glomerular or non-glomerular CKD diagnosis with clinical data collected at annual visits. Echocardiography data was collected every two years, starting at the second study visit. A total of 501 children contributed echocardiography data to assess aortic dimensions for the present study. It should be noted that for this retrospective data collection, the sample was selected based on availability of echo images that were recorded by CD and high quality (thus studies conducted from 2006–2010 were not included) and some funding considerations. The primary outcomes were aortic root z-scores, sinotubular junction z-scores and ascending aorta z-scores. All analyses were based on the echocardiography data at which aortic dimension metrics were measured from April 2011 through February 2015,

which includes repeated measures within-individuals. Specifically, with baseline defined as the first study, the data were distributed at visit 2 (48%; 1 year after study enrollment), visit 4 (8%; 3 years after enrollment), visit 6 (35%; 5 years after enrollment) and visit 8 (9%; 7 years after enrollment). This study was approved by the CKiD steering committee and was conducted within the parameters set forth by the National Institute of Health (NIH). Informed consent was obtained from all participating members.

Echocardiography

Echocardiographic images were obtained from the different CKiD sites and retrospectively analyzed at the core imaging lab at Cincinnati Children's Hospital Medical Center. Measurements of the primary outcome of aortic dilatation were performed by two research sonographers utilizing the inner edge to inner edge technique at end-systole (see Figure.1). All measurements were performed according to the most recent guidelines by the American Society of Echocardiography (ASE)[6]. The z-scores for aortic dimensions were calculated using regression equations from Boston Children's Hospital echocardiography laboratory utilizing the Haycock formula for body surface area (BSA) calculation[7, 8]. The primary outcome of dilatation of the aorta was defined as a z-score of >2 (97.7th percentile) at any of either the aortic root, the sinotubular junction or the ascending aorta. Calculation of the indexed left ventricular mass (LVMi) was performed by dividing by the patient's height in meters^{2.7}[9]. All measurements were obtained in triplicate and averaged. Inter and intra observer variability for these basic measurements in our laboratory are <5% (internal data).

Variables

The following variables were included and analyzed relative to the primary outcome variable: Age, sex and race; years with kidney disease and years with glomerular kidney disease; BMI; systolic/diastolic blood pressure (SBP/DBP), left ventricular mass index (LVMI). Left ventricular hypertrophy was defined by left ventricular mass indexed to height (in m^{2.7}) being greater than or equal to age- and sex-specific 95th percentiles (**REF**). Obesity was defined as age- and sex-specific BMI being greater than or equal to the 95th percentile. Abnormally high total cholesterol, triglycerides and LDL were defined as being greater than or equal to the age- and sex-specific 95th percentiles. Likewise, abnormally low HDL was defined as being less than or equal to the age- and sex-specific 5th percentile (**REF**). Laboratory parameters included estimated glomerular filtration rate (eGFR); proteinuria (defined as the ratio of urine protein to urine creatinine in mg/mg); hemoglobin, phosphate, calcium, calcium phosphate (Ca-P) product; total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) cholesterol, triglycerides. Blood pressure (BP) was measured three times at each annual visit by calibrated Mabis Medic aneroid sphygmomanometer, with at least 30 seconds between measurements. For data analysis, the mean summarized these three measurements and were converted to z-scores and percentiles adjusted for age, gender and height [10]. Estimated GFR was determined by the CKiD equation based on serum cystatin c, creatinine and blood urea nitrogen [11].

The presence of a pediatric CKD protein energy wasting (PEW) syndrome and its components were also evaluated. PEW was based on the following domains: abnormal biochemistry (total cholesterol < 100 mg/dL; serum albumin < 3.8g/dL; serum transferrin <

140mg/dL; or CRP > 3mg/L), reduced body mass (BMI < 5th percentile adjusted for age and gender at entry; or a 10 decrease in BMI percentile between two annual visits from an initial BMI < 80th percentile), reduced muscle mass (mid upper arm circumference [MUAC] < 5th percentile adjusted for age, sex and height; or a 10 decrease in MUAC percentile between two annual visits), decreased appetite (self-reported fair, poor or very poor appetite in the week preceding the study visit, as a surrogate for dietary protein intake), and poor growth (height < 3rd percentile adjusted for age and sex, or poor growth velocity defined as a 10 decrease in height percentile between two annual visits). Following the definitions described by Abraham et al. [12], we investigated 1) a standard PEW definition of any positive test in at least 3 categories excluding the poor growth domain and 2) a modified PEW definition requiring any positive test in at least 3 categories including the poor growth domain.

Statistical Analysis

Clinical and demographic variables were compared by the presence of aortic dilatation. Wilcoxon rank sum for continuous variables and Fisher's exact test for categorical variables were used to investigate differences at the $p < 0.05$ level at the first available visit (i.e., baseline). Univariate and multivariate logistic regression models were used to assess the association of BP z-scores, body size z-scores, CKD severity and PEW syndrome with aortic dilatation as the outcome. CKD severity was measured by eGFR and the presence of low hemoglobin. For continuous variables, the coefficients of the independent variables was scaled to standard deviation (SD) units and were interpreted as the relative odds for a one SD change in the exposure. Multivariate models included as covariates age, years since CKD onset, use of antihypertensive therapy, use of growth hormone therapy and low hemoglobin. All covariates were selected *a priori* in the regression models presented in Table 5. We considered aortic dimensions to be fairly stable since they are variables of cardiac remodeling in response to chronic disease. Therefore, for the panel of independent variables (SBP, DBP, weight, height, BMI, GFR, hemoglobin, protein energy wasting), we sought to adjust for markers related to aortic dimensions (age), duration or burden of chronic kidney disease (years with kidney disease, anemia), and therapies that are directly related to cardiac health (antihypertensive therapy) and cardiac growth/development (growth hormone therapy). These are all factors that would be associated with the panel of independent variables we were interested in, and were therefore included them covariates.

Linear regression models were fit with aortic z-score as the outcomes (aortic root, aortic junction and aortic ascending z-score) in separate models, with generalized estimating equations (GEE) to account for repeated measurements. The independent variables of interest included markers of cardiovascular health (systolic and diastolic blood pressure z-scores based on the normal population), markers of kidney disease severity (estimated GFR in the log scale, presence of low hemoglobin), and markers of body size (height, weight and BMI z-scores based on the normal population). For continuous variables, the associations were described as the difference in aortic z-score associated with a one standard deviation change in the independent variable. Specifically, a one standard deviation increase in SBP and DBP z-scores, and a one standard deviation decrease in estimated GFR (in the log scale), height, weight and BMI z-scores; similarly, for binary variables (i.e., low

hemoglobin), we described the mean difference in aortic z-score between the groups with and without the independent variable (the latter being the reference group). Covariates included in the multivariate models were age, years with kidney disease, antihypertensive therapy use, growth hormone therapy use and low hemoglobin. All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

Results

A total of 501 CKiD children had measured aortic variables based on echocardiography scans. Of these, 6.0% (30 children) were identified as having abnormally high aortic root, aortic ST junction or ascending aortic z-scores (defined as z-scores > 2). These 501 participants contributed a total of 668 person-visits, with 336 children contributing one visit, 163 contributing two person-visits and 2 contributing three person-visits. In addition to the 30 children identified with aortic dilatation at their first visit, an additional 13 study-visits were classified as having aortic dilatation. Of the 43 person-visits identified with aortic dilatation, 41 were contributed by unique participants. Therefore, the total number of participants identified as having aortic dilatation was 41, but of these, 30 had prevalent aortic dilatation, 9 had incident aortic dilatation and 2 had persistent aortic dilatation over two visits.

Of the 30 patients with dilatation, 7 had a high aortic root z-score only, 8 had a high ST junction z-score only and 4 had a high ascending aortic z-score; 5 had a high root and ST junction z-score, 1 had a high ST junction and ascending aortic z-score and 5 had the presence of all three high z-scores. Comparison of demographic, clinical, and echocardiographic characteristics between children with and without aortic dilatation is shown in tables 1–3. Those with aortic dilatation were more likely to be boys ($p=0.003$), have lower height percentile ($p=0.07$), have lighter weight percentile ($p=0.005$) and have lower BMI percentile ($p=0.003$). Estimated GFR was lower among those with aortic dilatation ($p=0.037$), and proteinuria was higher at borderline significant levels ($p=0.068$), although the proportion with nephrotic range of proteinuria was similar. Children with aortic dilatation were more likely to be anemic ($p=0.042$). SBP and DBP percentiles were higher among those with aortic dilatation, although the effect was stronger for DBP percentiles. BP categories of elevated BP did not differ between the two groups, and proportions receiving antihypertensive therapy were also similar. LVMi and LVH were higher among those with aortic dilatation, although these differences were not statistically significant.

Because children with aortic dilatation had significantly lower weight and BMI, we then examined the association of aortic dilatation with PEW syndrome as marker of malnutrition. For components of PEW syndrome, children with aortic dilatation in general had an increased prevalence of biochemical abnormalities, BMI growth failure, reduced muscle mass, poor appetite and height growth failure, although in the baseline univariate comparison these differences were not significant (Table.4). Those with aortic dilatation had a higher number of abnormal PEW categories overall ($p=0.027$) in terms of number of positive tests, regardless of domain; and had a higher prevalence of PEW either using the modified (33% vs. 14%, $p=0.007$) or standard definition (17% vs. 7%, $p=0.061$).

Table 5 presents the results from univariate analysis and multivariate models to determine the association between pertinent variables and aortic dilatation. Univariately, higher DBP z-scores, lower weight z-score, lower BMI z-score and decreased eGFR were associated with increased odds of aortic dilatation. When adjusting for age, duration of CKD in years, antihypertensive therapy, growth hormone therapy and low hemoglobin, the inferences and effects were largely unchanged for all variables. Presence of PEW using modified definition was significantly associated with aortic dilatation in both univariate and adjusted analyses (adjusted OR: 2.41, 95%CI: 1.23, 4.70).

Additional analyses were performed to assess the associations of individual aortic outcomes: the aortic root, the sinotubular junction or the ascending aorta (Figure 2). For all aortic z-score outcomes, there was no association with SBP z-scores, eGFR or height z-scores. DBP z-score was not significantly associated with aortic ascending z-score (+0.04, 95%CI: -0.11, 0.19), but was associated with aortic root and junction z-score: a one SD increase in DBP was associated with a higher aortic root (+0.14, 95%CI: 0.03, 0.25) and junction z-scores (+0.14, 95%CI: 0.01, 0.27). Lower weight and BMI z-scores were associated with higher levels of the three aortic z-score outcomes. Lastly, lower HGB was related to higher aortic root z-score, but this relationship was borderline significant (+0.25, 95%CI: -0.004, +0.50, $p=0.053$).

Discussion

The prevalence of aortic dilatation in this study was higher than would be expected for the general population. Assuming a healthy population, one would expect about 2.3% of the children to have aortic z-scores > 2 . The true prevalence of the individual aortic segments has not been reported in pediatrics to our knowledge. We chose to include the proximal aortic dimensions as the literature historically has not differentiated between them when reporting aortopathy. In our population, we found a total prevalence of about 6% when including all three segments. This finding suggests that relatively mild CKD already manifests with aortic abnormalities, although the clinical impact of these mild abnormalities is not clear.

Aortic dilatation has been described in pediatric primary uncontrolled hypertension with a frequency of 2.8% which is slightly higher than in general pediatric population[13]. In our study, children with aortic dilatation also had a higher BP. However, this alone cannot explain the relatively higher prevalence of aortic dilatation in CKD population since only 20% of these children had uncontrolled HTN.

As kidney disease progresses to ESRD, the prevalence of aortic dilatation increases. In a study by Kaddurah et al [2] of children on maintenance dialysis and after kidney transplantation, the prevalence of aortic dilatation was 31%. In their study, children with aortic dilatation had higher BP, lower BMI, and 23% were malnourished. In our study of children with milder CKD, we also found significant association of lower BMI with aortic dilatation. In addition, we demonstrated that children with aortic dilatation were 2.4 times more likely to have PEW. Because PEW is a marker of malnutrition, poor growth and nutrition appear to be good predictors of aortic dilatation. While our study was not designed

to show causal relationship between malnutrition and aortic dilatation, the association is evident and can be used as an indicator of increased risk, requiring more frequent management.

This analysis highlighted the linear relationship of selected variables with aortic z-scores. These results also demonstrate a higher relative odds of aortopathy (z-scores > 2) across a continuous spectrum of aortic z-scores. Additionally, this analysis identified DBP as a risk factor for higher aortic root and junction z-scores, but not ascending-score. The reason for the association between DBP and aortic dilatation is not immediately clear. It is known that significant aortic insufficiency, which typically results in a wide pulse pressure and lower diastolic blood pressures, can be associated with aortic dilatation secondary to annular dilatation and associated valve dysfunction, however none of the patients had significant aortic insufficiency and actually had higher diastolic blood pressures. A higher DBP in the patients with aortic dilatation may suggest a higher DBP load, suggestive of subtle subclinical hypertension leading to cardiac sequelae. Metrics of smaller body size (weight and BMI z-scores) were consistently associated with higher aortopathy z-scores, after adjusting for covariates. Aortic dilatation was not associated with LVMi, one of the more important parameters of cardiac disease in the chronic kidney disease population. It is possible that the mild degree of dilatation in these patients coupled with the duration of dilatation (unavailable data) may be the explanation for the absence of a correlation. That is, the longer and more severe the aortic dilatation, the greater the expected impact on the heart.

There were several limitations to this study to consider in interpreting these results. This was a large pediatric study with over 500 children within the CKiD population. However, the frequency of aortic dilatation was quite low and in fact was much lower than seen in children with renal replacement therapy [2]. As such, it is difficult to make wide spread conclusions regarding associations with such small outcome numbers. Another limitation is the fact that aortic dimensions were normalized to body surface area, a marker of growth. Hence, inferences regarding associations with growth and nutrition must be interpreted with caution. Historically, short or underweight individuals will tend to appear to have greater z-score values. In a cohort such as the CKiD data, future studies should focus on longitudinal data within the same patients and perform analyses regarding rate of progression or change and how it relates to cardiovascular risk factors. We found that boys were more likely to have higher aortic z-scores which are sex-specific. Due to the small numbers of affected participants, we did not perform additional analyses to examine the effect of any sex differences. Additionally, the study was a retrospective cross sectional study utilizing data already acquired as part of other studies. We were therefore limited to the images available with no way to improve image quality or acquisition. Despite these limitations, understanding the onset of cardiovascular risk factors as kidney function deteriorates is important and the data demonstrates that some associations exist that would benefit from more study. We included dilatation at three aortic sites as equal reflections of abnormal pathology, however, we do not yet fully understand the mechanism for why certain areas of the proximal aorta dilate, while others do not. The answer is likely a combination involving valve anatomy, abnormal vessel architecture, cardiac output and systemic vascular resistance.

In summary, aortic dilatation is a cardiovascular abnormality detected in pediatric patients with mild to moderate kidney dysfunction. Markers of poor nutrition are associated with a higher prevalence of aortic dilatation. Aortic dilatation appears to accompany other cardiovascular manifestations as kidney disease progresses, and the clinician needs to be attentive to these clues as precursors to more advanced cardiac involvement, especially if other signs such as depressed function are not yet present. It has been repeatedly demonstrated that the leading causes of death in children with ESRD are cardiovascular in origin. The etiology is likely multifactorial with deterioration in kidney function and suboptimal nutrition affecting body homeostasis and cardiac muscle function. Future studies should seek to track these changes longitudinally as the disease process progresses.

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Figure 1.
Inner edge to inner edge technique at end-systole for assessment of the aortic root.

Figure 2.

Unadjusted and adjusted association of cardiovascular, CKD severity and body size variables with aortic root, ST junction and ascending z-scores. Associations are interpreted as the change in aortic z-scores (standard deviation) associated with a one standard deviation change in continuous variables, or the presence of binary variables compared to the absence (for example, the difference in aortic z-score comparing those with low hemoglobin to those with normal hemoglobin). Associations are described by unadjusted (○) and adjusted (●) analyses with 95% confidence intervals. Adjusted analyses controlled for age, years with kidney disease, antihypertensive therapy, growth hormone therapy and low hemoglobin. Significant adjusted estimates are denoted by *.

Table 1.

Demographic characteristics at baseline of children with mild to moderate chronic kidney disease, by aortic dilatation status.

	No aortic dilatation N= 471	Aortic dilatation N= 30	p-value
Age at first visit, years	13.89 [9.98, 16.86] (N= 471)	13.49 [9.3, 17.42] (N= 30)	0.722
Boys	60.7% (286)	86.7% (26)	0.003
Black race	21% (99)	20% (6)	1.000
Age at chronic kidney disease onset, years	0 [0, 2.5] (N= 471)	0 [0, 0] (N= 30)	0.179
Years with chronic kidney disease	10.87 [6.76, 14.94] (N= 471)	10.25 [6.98, 17.42] (N= 30)	0.384
Glomerular chronic kidney disease	28.5% (134)	30% (9)	0.837
Height (cm)	154.65 [135.45, 166.9] (N= 468)	154.1 [124, 163.1] (N= 30)	0.381
Height percentile	35.53 [14.15, 62.83] (N= 462)	23.52 [4.33, 49.56] (N= 30)	0.071
Weight (kg)	49.55 [32.05, 67.25] (N= 468)	43.05 [24.4, 61.8] (N= 30)	0.079
Weight percentile	55.72 [24.16, 87.07] (N= 440)	27.96 [7.67, 61.33] (N= 25)	0.005
Body Mass Index (kg/m ²)	20.2 [17.1, 24.4] (N= 467)	18.05 [15.9, 21.7] (N= 30)	0.010
Body Mass Index percentile	65.64 [35.72, 89.64] (N= 439)	36.67 [13.49, 65.2] (N= 25)	0.003
Obese	14.6% (64)	0% (0)	0.035

Table 2.

Clinical characteristics at baseline of children with mild to moderate chronic kidney disease, by aortic dilatation status.

Variable	No aortic dilatation N= 471	Aortic dilatation N= 30	P-value
Estimated glomerular filtration rate (ml/min/1.73m ²)	56.7 [40.13, 70.04] (N= 470)	44.86 [29.71, 64.5] (N= 30)	0.037
Protein to creatinine ratio (mg/ mg)	0.26 [0.09, 0.85] (N= 457)	0.68 [0.11, 1.5] (N= 30)	0.068
Nephrotic range proteinuria > 2 mg/mg	11.4% (52)	10% (3)	1.000
Hemoglobin (g/dL)	12.9 [11.8, 13.9] (N= 469)	12.2 [11.5, 13.7] (N= 30)	0.236
Anemia^a	30.9% (145)	50.0% (15)	0.042
Calcium (mg/dl)	9.4 [9.1, 9.6] (N= 470)	9.35 [9.1, 9.7] (N= 30)	0.745
Phosphate (mg/dl)	4.4 [3.9, 4.8] (N= 470)	4.65 [3.9, 5] (N= 30)	0.086
Hyperphosphatemia	5.7% (27)	3.3% (1)	1.000
Calcium × phosphate (mg ² /dL ²)	40.42 [36.1, 45.12] (N= 470)	45.06 [35.1, 48.36] (N= 30)	0.060
High calcium × phosphate	2.6% (12)	0% (0)	1.000
Total cholesterol (mg/dL)	165 [143, 192] (N= 464)	166 [140, 192] (N= 30)	0.935
High total cholesterol	20.1% (86)	24% (6)	0.613
High density lipoprotein cholesterol (mg/dL)	52.5 [44, 62] (N= 464)	53 [40, 67] (N= 30)	0.659
Low High density lipoprotein cholesterol	6.6% (28)	8% (2)	0.678
Low density lipoprotein cholesterol (mg/dL)	87 [71.5, 108] (N= 464)	88 [71, 110] (N= 30)	0.786
High low density lipoprotein cholesterol	8.9% (38)	4% (1)	0.712
Triglycerides (mg/dL)	98 [70.5, 142.5] (N= 464)	98 [72, 134] (N= 30)	0.972
High triglycerides	38.2% (163)	48% (12)	0.399
Systolic blood pressure (mmHg)	107 [99, 117] (N= 464)	108.5 [103, 120] (N= 30)	0.345
Systolic blood pressure percentile ^b	57 [29.5, 82.5] (N= 388)	69.5 [52.5, 84] (N= 24)	0.102
Diastolic blood pressure (mmHg)	66 [59, 73] (N= 464)	70.5 [63, 79] (N= 30)	0.007
Diastolic blood pressure percentile^b	62 [34.5, 86] (N= 388)	88.5 [76.5, 95] (N= 24)	<.001
Blood pressure category ^b			0.172
Normal blood pressure	68.1% (314)	53.3% (16)	
Elevated blood pressure	13.7% (63)	16.7% (5)	
Stage 1 Hypertension	15.8% (73)	23.3% (7)	
Stage 2 Hypertension	2.4% (11)	6.7% (2)	
Any anti-hypertensive therapy	63.8% (299)	70% (21)	0.560
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker therapy	56.7% (266)	60% (18)	0.850
Growth hormone therapy	7.5% (35)	6.7% (2)	1.000

^a Anemia defined as low hemoglobin or receiving erythropoietin stimulating agent therapy.

^b Blood pressure percentiles and categories defined by 2017 Clinical Practice Guidelines.

Table 3.

Echocardiographic characteristics at baseline of children with mild to moderate chronic kidney disease, by aortic dilatation status

Variable	No aortic dilatation N= 471	Aortic dilatation N= 30	p-value
Left ventricular mass index, g/m ^{2.7}	26.33 [22.46, 31.2] (N= 458)	29.49 [22.46, 33.45] (N= 30)	0.201
Left ventricular hypertrophy	4.8% (22)	10% (3)	0.193
Relative wall thickness	0.31 [0.28, 0.35] (N= 460)	0.33 [0.26, 0.36] (N= 30)	0.861
Aortic root dimension (cm)	2.39 [2.11, 2.68] (N= 384)	2.88 [2.48, 3.58] (N= 30)	<.001
Aortic ST junction dimension (cm)	1.92 [1.69, 2.16] (N= 365)	2.41 [2.07, 2.78] (N= 29)	<.001
Ascending aorta dimension (cm)	2.07 [1.79, 2.36] (N= 271)	2.67 [2.17, 3] (N= 23)	<.001
Aortic root z-score	-0.33 [-0.96, 0.28] (N= 381)	2.15 [1.08, 2.78] (N= 30)	<.001
Aortic ST junction z-score	-0.61 [-1.34, 0.18] (N= 362)	2.28 [1.31, 3.23] (N= 29)	<.001
Ascending aorta z-score	-0.6 [-1.42, 0.09] (N= 269)	1.68 [0.96, 2.18] (N= 23)	<.001

Table 4.

Malnutritional characteristics at baseline of children with chronic kidney disease, by aortic dilatation status.

Variable	No aortic dilatation N= 471	Aortic dilatation N= 30	pvalue
Low total cholesterol	1.5% (7)	3.3% (1)	0.395
Low serum albumin	5.5% (26)	6.7% (2)	0.682
Low transferrin	0.4% (1)	0% (0)	1.000
High c-reactive protein	15.5% (68)	20.8% (5)	0.562
<i>Any biochemical abnormality PEW</i>	20.2% (95)	26.7% (8)	0.361
<i>Reduced body mass PEW</i>	33.1% (156)	36.7% (11)	0.693
<i>Reduced muscle mass PEW</i>	33.8% (149)	46.7% (14)	0.167
<i>Decreased appetite PEW</i>	13.6% (63)	20% (6)	0.288
<i>Poor growth PEW</i>	30.8% (145)	46.7% (14)	0.103
<i>PEW counts</i>			0.027
PEW count = 0	25.7% (121)	20% (6)	
PEW count = 1	35.7% (168)	30% (9)	
PEW count = 2	25.1% (118)	16.7% (5)	
PEW count = 3	11.3% (53)	20% (6)	
PEW count = 4	2.1% (10)	13.3% (4)	
PEW count = 5	0.2% (1)	0% (0)	
Standard PEW definition ^a	6.8% (32)	16.7% (5)	0.061
Modified PEW definition^b	13.6% (64)	33.3% (10)	0.007

PEW = protein energy wasting

^aStandard PEW definition based on four domains: abnormal biochemistry, reduced body mass, reduced muscle mass, and decreased appetite.

^bModified PEW definition based on five domains: abnormal biochemistry, reduced body mass, reduced muscle mass, decreased appetite and poor growth.

Table 5.

Univariate and multivariate results from repeated measures logistic regression to estimate associations of biomarkers with the presence of aortic dilatation.

	Univariate OR (95%CI)	Multivariate ^a OR (95%CI)
Per 1 SD increase in systolic blood pressure (z-score)	1.16 (0.85, 1.57)	1.08 (0.79, 1.46)
Per 1 SD increase in diastolic blood pressure (z-score)	2.08 (1.39, 3.10)	1.98 (1.34, 2.92)
Per 1 SD decrease in weight (z-score)	1.51 (1.21, 1.87)	1.48 (1.21, 1.82)
Per 1 SD decrease in height (z-score)	1.28 (0.95, 1.72)	1.24 (0.91, 1.69)
Per 1 SD decrease in body mass index (z-score)	1.65 (1.30, 2.09)	1.69 (1.31, 2.17)
Per 1 SD decrease in estimated glomerular filtration rate (log scale)	1.35 (1.003, 1.83)	1.31 (0.93, 1.86)
Low hemoglobin vs. normal hemoglobin	1.74 (0.92, 3.29)	1.77 (0.90, 3.45)
2 positive counts of standard PEW ^b vs. < 2 positive counts of standard PEW	1.99 (0.80, 4.96)	1.88 (0.77, 4.56)
3 positive counts of modified PEW ^c vs. < 3 positive counts of modified PEW	2.57 (1.29, 5.11)	2.41 (1.23, 4.70)

SD = standard deviation, PEW = protein energy wasting

^a Adjusting for age, years with CKD, antihypertensive therapy, growth hormone therapy and low hemoglobin.

^b Standard PEW definition based on four domains: abnormal biochemistry, reduced body mass, reduced muscle mass, and decreased appetite.

^c Modified PEW definition based on five domains: abnormal biochemistry, reduced body mass, reduced muscle mass, decreased appetite and poor growth.