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Original Investigation

Cystatin C and Cardiac Measures in Children and Adolescents With CKD

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Background: Cardiovascular disease (CVD) is highly prevalent among children with chronic kidney disease (CKD). Cystatin C is an established marker of kidney function and an emerging biomarker for CVD events. We quantified the relationship between cystatin C level and cardiac structure and function over time among children with CKD and assessed whether cystatin C level and diastolic function retained an association after accounting for kidney function.

Study Design: Prospective cohort study.

Setting & Participants: 678 children and adolescents with mild to moderate CKD enrolled in the CKD in Children (CKiD) Study with 1,228 echocardiographically obtained cardiac structure and function measurements.

Predictor: Serum cystatin C (mg/L) measured annually.

Outcomes: Cardiac structure (left ventricular mass index [$g/m^{2.7}$]) and cardiac function (shortening fraction; E/A, E′/A′, E/E′ ratios) measured every other year.

Measurements: Demographics and anthropometrics, measured glomerular filtration rate (mGFR), heart rate, blood pressure, hemoglobin *z* score, serum albumin level, and calcium-phosphorus product.

Results: Independent of time, each 1-mg/L increase in cystatin C level was independently associated with a concurrent 7.7% (95% CI, 5.3%-10.0%) increase in left ventricular mass index, a −4.7% (95% CI, −7.0% to −2.4%) change in E/A ratio, a −6.6% (95% CI, −9.0% to −4.2%) change in E′/A′ ratio, and a 2.5% (95% CI, 0.3%-4.7%) increase in E/E′ ratio. mGFR was also independently associated with E′/A′ ratio. When cystatin C level and mGFR were included in the same model, cystatin C level remained independently associated with E′/A′ ratio, whereas mGFR was not.

Limitations: 24% of the cohort was missing data for outcomes of interest or measurements; study population includes only children and adolescents with mild to moderate CKD.

Conclusions: In this study of children and adolescents with mild to moderate CKD, cystatin C level was independently associated with cardiac structure and diastolic function. Cystatin C level remained able to predict diastolic function decline via E′/A′ ratio even after adjusting for mGFR, suggesting that cystatin C level may have an independent role in CVD risk stratification among children and adolescents with CKD.

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INDEX WORDS: Biomarker; cardiovascular disease (CVD); left ventricular hypertrophy (LVH); left ventricular mass (LVM); pediatrics; children; adolescents; systolic function; cystatin C; chronic kidney disease (CKD); renal function; echocardiograph; cardiac structure; cardiac function.

Sudden cardiac death remains the most common cause of mortality among children with chronic kidney disease (CKD).[1] Children with CKD manifest a multitude of cardiovascular disease (CVD) risk factors and show early signs of heart disease, including dilated cardiomyopathy and left ventricular hypertrophy (LVH). The progression of these abnormalities to cardiac death is thought to explain the markedly decreased life spans of children with advanced CKD.[1] Although the increased CVD risk in youth with CKD has been well established,[2,3] the morbidity and mortality related to CVD has nevertheless increased over time.[4] Identifying new biomarkers or clinical characteristics that could more easily identify those at increased CVD risk would help tailor treatment efforts.

Diastolic dysfunction is one of the earliest signs of cardiac disease among children with CKD,[5] and it progresses as CKD advances.[5,6] Despite this, serum

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creatinine level has not been shown to be a reliable biomarker of diastolic dysfunction.[5,7] Cystatin C, an endogenous proteinase inhibitor widely used as a surrogate marker of kidney function, is an emerging biomarker for CVD events. Cystatin C level is associated with cardiac geometry, cardiac remodeling, and CVD outcomes in adults.[8-11] In this study, we aimed to quantify the independent relationship between cystatin C level and both cardiac structure and function over time among children and adolescents with mild to moderate CKD. We also sought to determine how well other measures of kidney function predict diastolic function and whether any independent relationship between cystatin C level and diastolic function existed after accounting for directly measured kidney function.

METHODS

Study Population

As of December 2015, a total of 891 children and adolescents (586 in April 2005 to August 2009 and 305 between February 2011 and March 2014) with mild to moderate CKD were enrolled in the CKD in Children (CKiD) Study, a multicenter prospective cohort study conducted at 49 pediatric nephrology centers across North America. The study design and conduct were approved by an observational study monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases and by the internal review boards of each participating center. Data approval numbers are as follows: data coordinating center, H.34.03.09.05.A2; East Coast Clinical Coordinating Center, 10-007880; and Midwest Clinical Coordinating Center, 11120124. Each participating family provided informed consent.

Study participants attended annual follow-up visits after their initial baseline visit. Children and adolescents were included in our analyses if they had echocardiography data from one or more visits and complete data for the exposure of interest and all covariates. There were 1,401 visits across 733 participants, with full echocardiography data that had occurred by December 2015. At 173 of these visits, the exposure of interest or at least one covariate was missing, leaving 1,228 visits from 678 children and adolescents (median follow-up, 3.0 years) in our primary analysis. The 678 participants contributed 1 to 4 visits to the analysis (334, one visit; 188, two visits; 106, three visits; and 50, four visits [Fig 1]).

Echocardiography

At even-numbered annual CKiD visits (or once every 2 years), participants undergo local standardized protocol echocardiography. Images are read centrally by a study cardiologist, for which measurements are taken in triplicate and averaged. LV mass (LVM) is obtained by American Society of Echocardiography criteria[12,13] using 2-dimensional M-mode, and LVM index (LVMi) is calculated as LVM/height$^{2.7}$, where LVM is in grams and height is in meters.[12,14] To assess systolic function, shortening fraction was obtained: [(LV end-diastolic diameter − LV end-systolic diameter)/LV end-diastolic diameter]. Pulsed-wave tissue Doppler in the apical view is used to obtain the maximal early filling (E-wave) and late diastolic filling (A-wave) velocities and the early diastolic annular (E′) and late diastolic annular (A′) velocities.[15] These measurements are then used to obtain the measures of diastolic function described next.

Primary Outcomes

LVMi was used to determine cardiac structure, with values at or greater than the age-/sex-specific 95th percentile indicative of LVH.[16] Systolic function was ascertained by shortening fraction. Values $< 25\%$ indicate abnormally low shortening fraction. Diastolic function was assessed via 3 ratios: E/A ratio (early to atrial LV filling ratio), E′/A′ ratio (early to late septal mitral annular peak velocity), and E/E′ ratio (estimate of LV filling pressure). Normal E/A and E′/A′ ratios are >1.0; lower values denote stiffer ventricular walls and diminished ability for adequate LV relaxation and fill. The E/E′ ratio is an estimate of LV filling pressures, and normal values are <8.0[15]; higher values indicate worse LV compliance.

Primary Exposure

Cystatin C was measured at each annual visit. Serum specimens were analyzed by standardized methods to produce measurements in milligrams per liter.[17] The cystatin C value taken at the time of echocardiography was used in the analyses.

Covariates

The following variables were included in all multivariable analyses: baseline age, sex, and race; average age-/sex-specific body

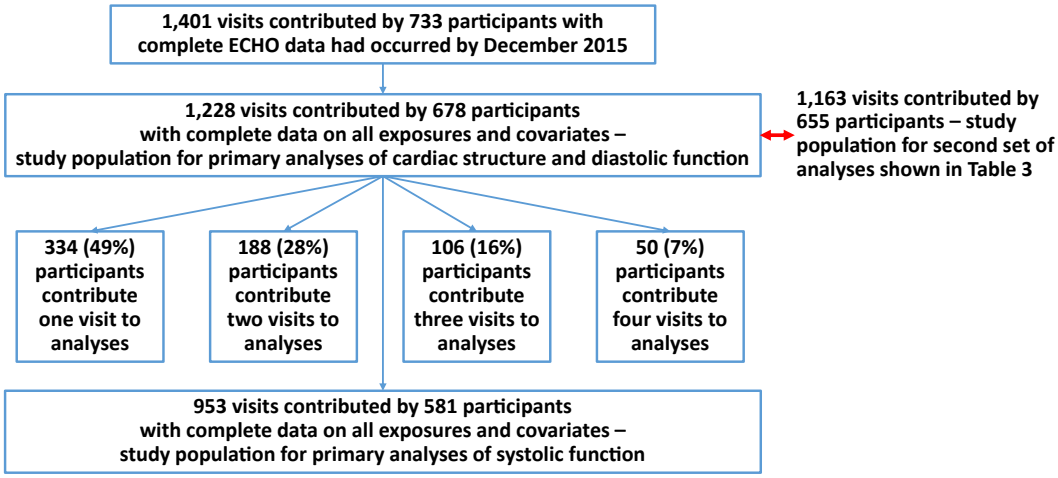

Figure 1. Flow chart outlines number of visits and number of participants contributing data to the primary and subsequent analyses. Abbreviation: ECHO, echocardiography.