Prevalence and Correlates of Multiple Cardiovascular Risk Factors in Children with Chronic Kidney Disease

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Summary

Background and objectives Although prevalence of traditional cardiovascular risk factors (CVRF) has been described in children with CKD, the frequency with which these CVRF occur concomitantly and the clinical characteristics associated with multiple CVRF are unknown. This study determined the prevalence and characteristics of multiple CVRF in children in the Chronic Kidney Disease in Children study.

Design, setting, participants, & measurements Using cross-sectional data from first follow-up visits, we determined the prevalence of four CVRF: hypertension (casual BP >95th percentile or self-reported hypertension with concurrent use of anti-hypertensive medication), dyslipidemia (triglycerides >130 mg/dl, HDL <40 mg/dl, non-HDL >160 mg/dl, or use of lipid-lowering medication), obesity (BMI >95th percentile), and abnormal glucose metabolism (fasting glucose >110 mg/dl, insulin >20 µIU/ml, or HOMA-IR >2.20, >3.61, or >3.64 for those at Tanner stage 1, 2 to 3, or 4 to 5, respectively) in 250 children (median age 12.2 years, 74% Caucasian, median iohexol-based GFR 45.2 ml/min per 1.73 m2).

Results Forty-six percent had hypertension, 44% had dyslipidemia, 15% were obese, and 21% had abnormal glucose metabolism. Thirty-nine percent, 22%, and 13% had one, two, and three or more CVRF, respectively. In multivariate ordinal logistic regression analysis, glomerular disease and nephrotic-range proteinuria were associated with 1.96 (95% confidence interval, 1.04 to 3.72) and 2.04 (95% confidence interval, 0.94 to 4.43) higher odds of having more CVRF, respectively.

Conclusions We found high prevalence of multiple CVRF in children with mild to moderate CKD. Children with glomerular disease may be at higher risk for future cardiovascular events.


Introduction

In adults, chronic kidney disease (CKD) is associated with increased risk for cardiovascular disease (CVD). CVD is the leading cause of death in patients with ESRD, accounting for nearly 50% of deaths (1,2). The data are more alarming for young CKD patients, as CVD-specific mortality rates in children and young adults with ESRD have increased over the last two decades (3) and are approximately 1000 times higher than in comparably aged populations without CKD (4). It is likely that the coexistence of highly prevalent traditional (5–15) and uremia-related (16–19) cardiovascular risk factors (CVRF) contribute to this population’s unique susceptibility to CVD.

Coexistence of multiple traditional CVRF is common among adults with ESRD, with up to 70% of incident dialysis patients having at least three CVRF (20). However, the etiology of CKD in children is different than in adults; congenital abnormalities of the urinary tract account for most cases of pediatric CKD, whereas hypertensive and diabetic nephropathy, the leading causes of CKD in adults, are quite rare in children. Despite this difference in etiology, up to 21% of children have multiple CVRF at time of transplant, with 40% of patients affected at 1 year post transplant (21). There are few published data regarding prevalence and disease-specific correlates of multiple CVRF in children with earlier stages of CKD.

In 2005, the National Institutes of Health established the Chronic Kidney Disease in Children (CKiD) study (22). Identification of the prevalence and evolution of traditional and novel CVD risk factors in children with CKD are among the study’s primary aims. The goals of this ancillary study were to determine the cross-sectional prevalence of four traditional CVRF, namely hypertension, dyslipidemia, obesity, and abnormal glucose metabolism, and to determine patient characteristics associated with the presence of multiple CVRF.

Materials and Methods

Study Design and Population

From April 2005 through September 2009, CKiD enrolled a total of 586 children with mild to moderate CKD into a multicenter, prospective cohort study at
48 North American pediatric nephrology centers (22). Briefly, eligible children were between the ages of 1 and 16 years and had an estimated GFR between 30 and 90 ml/min per 1.73 m². At the first annual follow-up study visit, the CKiD study used the plasma disappearance of iohexol to calculate a GFR (23) and also determined an estimated GFR using published equations (24). The CKiD study design and conduct were approved by an external advisory committee appointed by the National Institutes of Health and by the review boards at each participating center. Each participating family provided informed consent.

This report presents data from the first annual follow-up visit, because this was the first CKiD visit in which lipids, glucose, and insulin (measured at even-numbered visits) were collected concurrently with BP and weight (measured at all visits); this visit will be referred to as the index visit. As of July 2010, 507 (87%) of 586 participants had completed their index visit and had data to define both hypertension and obesity. In cases where data on hypertension and/or obesity were missing at the index visit (n = 38), data from the baseline visit were used to classify individuals as hypertensive and/or obese. Of these 507 participants, 35 were known not to be fasting (by parent/patient report) at the index visit and were excluded. Of the remaining 472 participants, 460 (97%) had lipid data available to define dyslipidemia. Of these 460, 254 (55%) also had insulin data available to define abnormal glucose metabolism. Our final study population was limited to the 250 (98%) participants who had complete data on all CKD-related exposures of interest and covariates (described below).

**Primary Outcomes**

**Hypertension.** Casual BP was determined as the mean of three independent BP measurements (5). BP was obtained by auscultation using an aneroid sphygmomanometer (Mabis MedicKit 5; Mabis Healthcare, Waukegan, IL). The CKiD Clinical Coordinating Centers provided all of the participating sites with identical equipment, as well as standardized training and certification in BP measurement, with annual recertification and central equipment calibration. Age-gender-height-specific systolic and diastolic BP percentiles were calculated according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High BP in Children and Adolescents (25). Participants were classified as hypertensive if either the systolic or diastolic BP measurement was >95th age-gender-height-specific percentile or if the participant reported hypertension in the year before the index visit and was currently using anti-hypertensive medication.

**Dyslipidemia.** Fasting lipid levels were measured in a central laboratory (15). Dyslipidemia was defined by the presence of at least one of: hypertriglyceridemia (triglycerides >130 mg/dl), low HDL cholesterol (<40 mg/dl), elevated non-HDL cholesterol (>160 mg/dl), or use of lipid-lowering medication(s).

**Obesity.** Height and weight were each determined as the mean of two independent measurements. These average measurements were used to calculate body mass index (weight [kg]/height squared [m²]). Obesity was defined as a body mass index (BMI) > age-gender-specific 95th percentile as defined by 2000 Centers for Disease Control growth charts (26).

**Abnormal Glucose Metabolism.** Fasting glucose levels were measured in a central laboratory. Fasting insulin levels were determined utilizing the Human Insulin ELISA (Millipore, Billerica, MA, EZHI-14K, intra-assay coefficient of variation = 5.96 ± 1.17% and interassay = 10.3 ± 0.9%). All of the insulin assays were carried out in the Touchstone Diabetes Center at The University of Texas Southwestern Medical Center, Dallas, using samples from the CKiD Biologic Repository. Abnormal glucose metabolism was defined as the presence of at least one of the following: fasting hyperglycemia (glucose >110 mg/dl), hyperinsulinemia (serum insulin >20 μU/ml), or elevated homeostasis model assessment of insulin resistance (HOMA-IR = [Insulin (μU/ml) × glucose (mg/dl)]/405; threshold values of >2.20, >3.61, or >3.64 for those at Tanner stage 1, 2 to 3, or 4 to 5, respectively, were used) (27).

**Statistical Analyses**

Continuous characteristics were summarized using the median and interquartile range; categorical characteristics were summarized using percentages. A Cochran-Mantel-Haenszel test was used to assess the significance of the ordinal association between age-gender-specific BMI percentile (≤85th percentile, >85th to ≤95th percentile, and >95th percentile) and the number of CVRF (0,1,2,3) excluding obesity. In addition, the significance of the relationship between BMI percentile, hypertension, dyslipidemia, and abnormal glucose metabolism status was assessed using three separate Cochran-Mantel-Haenszel tests.

Primary exposures of interest were current GFR level, annual percentage change in GFR from baseline to index visit, etiology of CKD (glomerular disease versus other), and presence of nephrotic range proteinuria (urine protein to creatinine ratio >2). Covariates included age, gender, and race (self-report). Univariate and multivariate ordinal logistic regression models were used to quantify the degree of association that each of these primary exposures and covariates had with the number of CVRF. Because of the small number of participants who satisfied criteria for all four CVRF, we combined those with either three or four risk factors into one group, which resulted in an ordinal outcome with a total of four values (0, 1, 2, and 3 to 4). The summary measure of association between exposure and outcome is the odds ratio (OR), i.e., odds of a more severe outcome in the exposed group divided by the odds of a more severe outcome in the unexposed group. The proportional odds assumption was not violated in any of the univariate or multivariate ordinal logistic regression models.

**Results**

**Cohort Characteristics**

Clinical and demographic characteristics are shown in Table 1. The majority of patients were male (56%) and Caucasian (74%) with a median age of 12.2 years, and 78% had CKD of a nonglomerular origin (congenital abnormalities of the urinary tract, inherited cystic diseases, Wilms’ tumor, and metabolic disorders). Median BMI percentile was 62.6. Median fasting glucose was 90 mg/dl, with
Table 1. Study population characteristics at the index visit (n = 250)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (IQR) or % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>age-gender-height-specific systolic blood pressure percentile</td>
<td>60.1 (28.9 to 83.4)</td>
</tr>
<tr>
<td>age-gender-height-specific diastolic blood pressure percentile</td>
<td>61.0 (38.1 to 84.9)</td>
</tr>
<tr>
<td>self-report of hypertension in the previous year current use of anti-hypertensive medications triglycerides, mg/dl</td>
<td>106 (74 to 141)</td>
</tr>
<tr>
<td>HDL, cholesterol, mg/dl</td>
<td>48 (41 to 55)</td>
</tr>
<tr>
<td>non-HDL cholesterol, mg/dl</td>
<td>126 (107 to 144)</td>
</tr>
<tr>
<td>age-gender-specific body mass index percentile</td>
<td>62.6 (34.5 to 89.5)</td>
</tr>
<tr>
<td>fasting glucose, mg/dl</td>
<td>90 (84 to 96)</td>
</tr>
<tr>
<td>insulin, micromolars/ml</td>
<td>7.6 (4.3 to 12.1)</td>
</tr>
<tr>
<td>homeostasis model assessment</td>
<td>1.7 (1.0 to 2.8)</td>
</tr>
<tr>
<td>Primary exposures</td>
<td></td>
</tr>
<tr>
<td>GFR, ml/min per 1.73 m² b</td>
<td>45.2 (34.6 to 58.2)</td>
</tr>
<tr>
<td>annual percentage change in GFR</td>
<td>-1% (-12% to 9%)</td>
</tr>
<tr>
<td>urine protein to creatinine ratio &gt;2.0</td>
<td>12% (29)</td>
</tr>
<tr>
<td>glomerular etiology of CKD percentage of life with CKD</td>
<td>22% (54)</td>
</tr>
<tr>
<td>glomerular etiology of CKD percentage of nonglomerular etiology of CKD</td>
<td>31% (20% to 51%)</td>
</tr>
<tr>
<td>nonglomerular etiology of CKD</td>
<td>99% (68% to 100%)</td>
</tr>
<tr>
<td>Demographics and clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>age, years</td>
<td>12.2 (8.9 to 15.6)</td>
</tr>
<tr>
<td>male</td>
<td>56% (141)</td>
</tr>
<tr>
<td>race</td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>74% (184)</td>
</tr>
<tr>
<td>African American</td>
<td>12% (31)</td>
</tr>
<tr>
<td>other/mixed</td>
<td>14% (35)</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.3 (4.1 to 4.5)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>0.3 (0.05 to 1.47)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; CKD, chronic kidney disease.

*Insulin (micromoles/ml) x glucose (mg/dl))/405.

**GFR, n = 233 (93%) directly measured by iohexol plasma disappearance; n = 17 (7%) based on estimating equation.

[(GFR at index visit – GFR at baseline visit)/GFR at baseline visit]/(date of index visit – date of baseline visit); n = 242 (97%) baseline GFR directly measured by ioheox plasma disappearance; n = 8 (3%) baseline GFR based on estimating equation.

*C-reactive protein data were not available for 28 (11%) of the 250 participants.

Prevalence of CVRF

The distribution of CVRF and frequency at which each potential combination of CVRF occurred are detailed in Table 2. Briefly, hypertension (n = 114, 46%) and dyslipidemia (n = 110, 44%) were the most prevalent CVRF, followed by abnormal glucose metabolism (n = 53, 21%) and obesity (n = 37, 15%). Among the 110 children with dyslipidemia, hypertriglyceridemia was more frequent (n = 83; 33% of entire study population) than either low HDL (n = 43; 17%) or elevated non-HDL (n = 38; 15%) cholesterol, whereas elevated HOMA-IR was the measure by which 48 of the 53 children were deemed to have abnormal glucose metabolism. Sixty-four study participants (26%) had no CVRF, and 97 (39%) had only one CVRF. Over one-third of participants had multiple CVRF: 56 (22%) had two, 27 (11%) had three, and six (2%) had four CVRF.

There was a significant relationship between body habitus and both the number of other CVRF present and the prevalence of each of the other CVRF assessed. Overweight (BMI >85th to ≤95th percentile) and obese (BMI >95th percentile) study participants were more likely (P<0.001) to have a greater number of CVRF (Figure 1), and demonstrated higher frequencies of hypertension (P<0.001), dyslipidemia (P<0.001), and abnormal glucose metabolism (P<0.001) than lean participants (BMI ≤85th percentile) (Figure 2). However, even lean participants had relatively high rates of the other CVRF, with 20% having two other CVRF and 2% having all three of the other CVRF (Figure 1). Abnormal glucose metabolism was highly prevalent among overweight (44%) and obese participants (46%), but it was also present in 12% of lean individuals (Figure 2).

Correlates of Multiple CVRF

Univariate and multivariate ordinal logistic regression analyses were performed with the number of risk factors (zero, one, two, or three or more) as the outcome and exposures and covariates included as described previously. In univariate analyses, glomerular disease and nephrotic-range proteinuria were significantly associated with having a greater number of CVRF (Table 3). Specifically, 62% of those with nephrotic-range proteinuria had at least two CVRF, versus 32% of those with a urine protein to creatinine ratio ≤2.0. Likewise, 44% (versus 37%), 24% (versus 22%), and 24% (versus 10%) of those with glomerular CKD (versus those with nonglomerular CKD) had one, two, or three or more CVRF, respectively. In multivariate analysis, the presence of nephrotic-range proteinuria and glomerular etiology of CKD was associated with 2.04 (95% confidence interval [CI], 0.94 to 4.43) and 1.96 (95% CI, 1.04 to 3.72) higher odds of having a greater number of CVRF, respectively.

Given the association between CVRF and glomerular disease, we analyzed the relationship between glucocorticoid use and presence of multiple CVRF. Children with glomerular disease were more likely to report glucocorticoid use than those with nonglomerular etiology of CKD (24% [n = 13] versus 1% [n = 2]). In univariate analysis, glucocorticoid exposure was associated with an increased number of CVRF. However, when included in multivariate

median fasting insulin of 7.6 μU/ml and median of HOMA-IR 1.7. There were no statistically significant demographic or clinical differences between the studied subset and the remainder of the CKiD cohort (data not shown).
analysis, that association was insignificant, and there was minimal attenuation of the association between the presence of multiple CVRF and glomerular disease (data not shown). Because calcineurin inhibitors were grouped into a general “immunosuppressive medication” category, complete information on relevant medication exposure was not available, so we elected not to include medication exposures in our final multivariate model shown in Table 3. Because the association between proteinuria and multiple CVRF did not reach statistical significance, we questioned whether this was related to confounding by inclusion of etiology of CKD in the model. To further clarify the relationship between CVRF and proteinuria, we performed a subgroup analysis of the 196 children (16 with urine protein to creatinine ratio <1000 mg/dl) with nonglomerular CKD. In this analysis, the association of proteinuria with CVRF persisted, with univariate OR of 3.31 (95% CI, 1.30 to 8.46) and multivariate OR of 2.99 (95% CI, 1.11 to 8.07); the model includes all factors in Table 3 except etiology of CKD.

Discussion

Our results demonstrate that accumulation of CVRF begins well before children with CKD reach ESRD. Over
one-third of the cohort had two or more CVRF; 13% had three or more. Even lean patients had high prevalence of multiple CVRF, with nearly one-quarter having two or three CVRF. Overweight (BMI >85th to ≤95th percentile) participants had very high prevalence of multiple CVRF, similar to rates in obese (BMI >95th percentile) children without kidney disease (28). This pattern differentiates the population of children with CKD from healthy children, in whom the coexistence of multiple CVRF is extremely infrequent, and restricted to those who are obese (28). In the Bogalusa Heart Study (29), an increased number of CVRF was associated with the extent of fatty streaks in the aorta and coronary arteries in young people without CKD. Thus, the results of this study suggest that children with CKD are at higher risk for development of early atherosclerosis and premature CVD as a result of early accumulation of multiple CVRF.

This study demonstrates high prevalence of abnormal glucose metabolism, with 21% of the cohort affected. The majority of these patients were neither hyperglycemic nor hyperinsulinemic, but rather had increased HOMA-IR, a marker of insulin resistance. Normative values for HOMA-IR in childhood and adolescence remain controversial and are based on cross-sectional studies, with no long-term data available to suggest a threshold value above which risk for CVD in adulthood increases. Therefore, to be consistent with other CVRF definitions, we chose to use HOMA-IR values that represent 95th percentiles (by Tanner stage) among healthy children (27). There exist other proposed definitions of “normal” HOMA-IR in children and adolescents; however, most of the normative data published are studies of adolescents only (with no Tanner staging noted). Because our cohort includes both young children and teenagers with delayed puberty and because it is known that there is a peak of insulin resistance during puberty, we considered it more appropriate to utilize normative data on the basis of Tanner stage rather than to apply a single “normal” value across the entire study population.

Neither measurement of insulin nor calculation of HOMA-IR is a routine feature of clinical practice in this population; therefore, our results suggest that this important CVRF may be underappreciated clinically. Because increased HOMA-IR is emerging as an independent risk factor for the development of CKD in adults (30), there is also potential for insulin resistance to emerge as a risk factor for progression among children with pre-existing CKD. Longitudinal follow-up is needed to elucidate whether abnormal glucose metabolism is persistent and its role in the development of CVD and progression of CKD.

The high prevalence of multiple CVRF including abnormal glucose metabolism in this cohort raises important questions about whether multiple CVRF in CKD should be considered as an entity distinct from the so-called “metabolic syndrome.” Traditionally, the presence of central adiposity is held to be a primary driving force in the development of insulin resistance and the metabolic syndrome, with some definitions of the metabolic syndrome requiring the presence of either obesity or increased waist circumference to make the diagnosis. The presence of multiple CVRF among lean patients suggests that multiple CVRF in CKD may be a different entity altogether, with development driven primarily by factors other than obesity. These may include type of CKD diagnosis, degree of kidney dysfunction, specific medication exposures, and derangements in other metabolic factors (e.g., adipokine levels). It could also be speculated that this population’s uniquely high prevalence of multiple CVRF is related to nondisease-specific factors, such as family history of CVD or CVD risk factors. Family history of hypertension, dyslipidemia, heart attack, and/or stroke is nearly universal in this cohort, present in 93% of the 191 patients in whom data were available. Initially, this appears higher than the 39% prevalence of positive family history reported in the general adolescent population (31). However, our definition of positive family history is more inclusive, and there is potential for recall bias among parents of children with chronic disease, both potentially exaggerating the difference between the two populations. Inclusion of family history of CVD as a variable in our multivariate model did not change the inferences presented in Table 3 and was not significantly associated with having a greater number of CVRF (data not shown); however, because only 7% had a negative family history, the study’s ability to detect significant differences related to family history was quite low.

Our finding that glomerular disease and nephrotic-range proteinuria are associated with the presence of multiple CVRF is unsurprising, because these characteristics tend to associate with either disease processes or use of medications that promote development of hypertension, dyslipidemia, insulin resistance, or weight gain. Unfortunately, our ability to analyze specific medications was limited, as noted previously. However, the finding that proteinuria associated independently with an increased number of CVRF among patients with nonglomerular etiology of CKD suggests that the relationship between glo-
merular disease and CVRF is not entirely related to medications. Additionally, we did not utilize ambulatory BP monitoring (ABPM) in our hypertension definition, because requiring both complete ABPM data and insulin data at the index visit would significantly decrease the population available for study. Therefore, we may have underestimated the true prevalence of hypertension and multiple CVRF in our cohort (5). However, analysis of the subset (n = 164) of patients with both sets of data available demonstrates that this likelihood is low, because our chosen definition for hypertension is in very good agreement (κ = 0.73; 95% CI, 0.63 to 0.84) with an ABPM-based definition (mean wake or sleep systolic or diastolic BP >95th percentile) for hypertension, with 49 and 51% classified as hypertensive by the two definitions, respectively. Furthermore, white-coat hypertension is rare in the CKiD cohort (1 to 1.5%) (8), so it is unlikely that hypertension prevalence is overestimated.

Because this study is cross-sectional, we cannot draw conclusions regarding the time course over which CVRF developed with respect to the initial presentation with CKD and/or the therapies used in its treatment. Nor are we able to assess whether multiple CVRF are persistent over time or how the presence of multiple CVRF impacts progression of CKD or development of intermediate CV outcomes. Future research will utilize longitudinal data from the CKiD cohort to answer these important questions.

Conclusions
This study highlights the high prevalence of multiple CVRF in children with moderate CKD. Multivariate analysis of correlates of multiple CVRF suggests that children with glomerular disease and children with nonglomerular disease and high-grade proteinuria may be at increased risk for future cardiovascular abnormalities.

Acknowledgments
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