THE ASSOCIATION BETWEEN RENAL FUNCTION BIOMARKERS AND SUBCLINICAL CARDIOVASCULAR MEASURES IN AFRICAN CARIBBEAN FAMILIES

Background: Risk of cardiovascular disease (CVD) and mortality are increased in people with subclinical CVD. The impact of ethnicity and race on subclinical CVD is substantial. Previous studies assessed the heritability of several renal function biomarkers and their relationship with subclinical CVD among populations of European ancestries, but, to our knowledge, no such data are available in African ancestry populations.

Objective: Our aim was to investigate the relationships between renal function biomarkers and subclinical CVD among Afro-Caribbean residing on the island of Tobago.

Design and Methods: 402 participants, aged 18 to 103 years, from seven large, multi-generation pedigrees (average family size: 50); range: 19 to 96; ~3500 relative pairs) were included in this study. Subclinical cardiovascular disease (SCVD) was assessed by brachial-ankle pulse wave velocity (baPWV) and carotid intima-media thickness (IMT). Serum cystatin C, creatinine, and eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation were used to assess kidney function. The variance component approach, implemented in Sequential Oligogenic Linkage Analysis Routines (SOLAR), was used to assess heritability of these traits, and association with SCVD.

Results: Heritability of renal function biomarkers ranged from .19–.32 (all P<.001), and was highest for cystatin C (h²=.32, P<.0001). Serum cystatin C was independently associated with arterial stiffness (P=.04). This association was not found with other renal function biomarkers. No significant association between renal function and IMT was found.

Conclusion: Our data suggest that cystatin C is significantly heritable and associated with arterial stiffness among Afro-Caribbeans. (Ethn Dis. 2013;23[4]:492–498)

Key Words: Cardiovascular disease, Renal function biomarkers, Afro-Caribbeans

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States. The incidence of CVD and mortality are substantially increased for people with subclinical cardiovascular disease (SCVD) compared to those without subclinical disease.1–4 Identifying and quantifying SCVD is possible using noninvasive and sensitive methods that are being translated into clinical practice.5 B-mode ultrasound examination of the carotid arteries is the most commonly used surrogate marker of subclinical atherosclerosis as assessed by intima-media thickness (IMT). Pulse wave velocity (PWV) is an index of arterial stiffness that is now easily quantitated by measuring brachial-ankle PWV (baPWV), which measures both the central and peripheral arteries.6,7

Serum creatinine, and serum creatinine-based estimators of eGFR, Modification of Diet in Renal Disease Study (MDRD)8 and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation9 are most commonly used to assess kidney function in the clinical setting and in population studies. Serum cystatin C is an alternative to serum creatinine as a marker of kidney function. Unlike serum creatinine, which is a by-product of muscle cells and affected by many factors other than kidney disease, cystatin C is produced by all nucleated cells and is excreted into the bloodstream at a constant level without impact of age, gender, sex and muscle mass.10,11 Numerous studies have found that cystatin C levels are a more accurate predictor of glomerular filtration rate (GFR), especially in mild-to-moderate kidney disease (eGFR between the range of 60 to 90 [mL · min⁻¹ · (1.73 m²)⁻¹]),12–14 Cystatin C is also a stronger predictor of subclinical coronary atherosclerosis,15 peripheral arterial disease,16 all-cause mortality, cardiovascular morbidity, and heart failure17,18 than creatinine-based measures among populations within the normal range of renal function. The underlying mechanisms accounting for such associations are not clear but may involve insulin resistance and inflammation.19,20 The impact of ethnicity and race on subclinical CVD is substantial. African Americans have significantly lower amounts of coronary artery and carotid

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Our aim was to evaluate the heritability of renal biomarkers and assess the relationship of these markers to SCVD in an African ancestry population.
artery calcified plaque relative to Whites despite having increased carotid IMT and blood pressure. To our knowledge, no previous studies have comprehensively studied the association of renal function, assessed by both serum creatinine and cystatin C, with SCVD measurements in a population of African ancestry. Therefore, our aim was to evaluate the heritability of renal biomarkers and assess the relationship of these markers to SCVD in an African ancestry population.

**METHODS**

**Study Participants**

Our study was conducted in 402 individuals (3,535 relatives) aged 18–103 years (mean age 42 years) belonging to seven multi-generation Afro-Caribbean families (mean family size, 50 individuals) on the island of Tobago. The detailed description of study population was published in the previous study. Written informed consent was obtained from each participant, using forms and procedures approved by the Tobago Division of Health and Social Services and the University of Pittsburgh, institutional review boards.

**Assessment of SCVD**

The common carotid artery (CCA) IMT was measured using B-mode ultrasonography with an Acuson Cypress portable ultrasound machine (Siemens Medical Solutions, Malvern, PA), using semi-automated reading software (AMS system; Dr. Thomas Gustavsson, Sweden). Both the near and far walls of the distal common carotid artery were captured for one centimeter proximal to the carotid bulb. Mean IMT measures correspond to the mean IMT of two images per side across all pixels of both the near and far wall of the common carotid artery on both the right and left arteries. All images were read centrally at Ultrasound Research Laboratory (University of Pittsburgh, Pittsburgh, PA). Reproducibility analyses were conducted with an inter-sonographer intraclass correlation (ICC) and Inter-reader ICC: 0.97 and 0.99, respectively.

The baPWV measures were automatically generated using a noninvasive and automated waveform analyzer (VP1000, Omron Co., Komaki, Japan). Following standardized placement procedures, the arm cuffs were placed on bare arms or over light clothing, and the ankle cuffs were placed on bare ankles. ECG electrodes were placed on both wrists and a phonocardiogram (PCG) was placed on the left edge of the sternum. The cuffs were connected to a plethysmographic sensor that determined volume pulse waveforms and to an oscillometric pressure sensor that measured blood pressure. Brachial pulse pressure was calculated by systolic blood pressure (SBP) minus diastolic blood pressure (DBP). The baPWV was calculated as (distance between arterial sites) divided by (time between the foot of the respective waveforms). The distance measure was calculated using height-based formula. The baPWV was calculated by time-phase analysis, for the right and left sides, using waveforms of the respective brachial and ankle (tibial) arterial sites, from the following equation: (La - Lb)/time difference between the brachial and ankle waveform. An average of baPWV based on three time measurements from the both sides was used in our analyses.

**Laboratory Measurements**

Blood samples, obtained by venipuncture, and spot urine were in the morning after a 12-hour fast. Aliquots of serum and urine were frozen at −80 °C.

Serum cystatin C was measured from frozen samples using a protocol similar to the Cardiovascular Health Study (CHS). The intra-assay variation ranged from 2.0% to 2.8%, and the interassay variation ranged from 2.3% to 3.1%. The serum sample was diluted with VITROS 7% BSA, and urine sample was diluted with 1:1 reagent-grade water. Serum creatinine was quantitatively determined by the VITROS CREA Slide method, which were traceable to a Gas Chromatography Isotope Dilution Mass Spectrometry (GC/IDMS) method and National Institute of Standards and Technology (NIST) SRM#914 creatinine standard reference material. The variation between runs was 6.0%. Albumin in urine was measured using a turbidimetric procedure on the Olympus AU400 using reagents provided by Olympus America, Inc. (Center Valley, PA). The intra- and inter-assay variations were below 2.5% and 5.1%, respectively. Metabolic traits were measured in Heinz Laboratory in the University of Pittsburgh using standard protocols.

**Disease Definitions**

Hypertension was defined as diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure ≥ 140 mm Hg, or currently taking blood pressure medication. Diabetes was defined as fasting glucose level ≥ 126 mg/dl or currently taking diabetes medication. Obesity was defined as BMI ≥ 30 kg/m². The spot albumin-to-creatinine ratio (ACR) was calculated and reported in milligrams per gram. According to the American Diabetes Association (ADA) and the National Kidney Foundation, albuminuria was defined as ACR > 30 mg/g; microalbuminuria was defined as ACR between 30–299 mg/g and macroalbuminuria was defined as ACR ≥ 300 mg/g.

**Statistical Methods**

Estimated GFR was calculated using the CKD-EPI: Female: 1) serum creatinine ≤ 0.7, GFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 166*(Scr/0.7)⁻¹·³·²⁹*(0.993)⁰⁹; 2) serum creatinine > 0.7, GFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 166*(Scr/0.7)⁻¹·³·²⁹*(0.993)⁰⁹; Male: 1) serum creatinine ≤ 0.9, GFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 163*(Scr/0.9)⁻¹·⁴·¹¹*(0.993)⁰⁹; 2) serum creatinine > 0.9, GFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 163*(Scr/0.9)
The heritability, correlation and association of renal function traits and SCVD were subsequently evaluated in SOLARs. Briefly, the variance components approach involves partitioning the variance into a genetic (polygenic) component and a residual non-measured environmental component. Residual heritability was calculated as the proportion of the total phenotypic variance explained by additive genetic effects after accounting for covariates. The interactions were tested between renal biomarkers and BMI and sex. The interactions were tested between renal function measures, the mean ± SD serum cystatin C was 0.62 ± 0.19 mg/L, serum creatinine was 0.93 ± 0.23 mg/dL, and microalbumin was 2.6 ± 9.3 mg/dL.

There was no difference in the mean serum concentration of cystatin C between men and women (P=.24). Table 1 shows that higher concentrations of cystatin C were associated with older age, higher body mass index, triglycerides, fasting insulin, serum creatinine and estimated GFR. The prevalence of hypertension increased across ascending tertiles of cystatin C.

Table 2 displays the age adjusted means of SCVD measures. The mean ± SD baPWV was 14.22 ± 3.74 m/s and was somewhat higher in men than in women (14.38 ± 3.21 vs. 14.21 ± 4.03 m/s, P=.34). The mean ± SD common carotid IMT was .69 ± .15 and was numerically higher in men than women (.71 ± .16 vs .68 ± .14, P=.09). SCVD measures increased across age groups in both men and women.

RESULTS

Among the 402 participants with renal function measures, the mean ± SD serum cystatin C was 0.62 ± 0.19 mg/L, serum creatinine was 0.93 ± 0.23 mg/dL, and microalbumin was 2.6 ± 9.3 mg/dL. There was no difference in the mean serum concentration of cystatin C between men and women (P=.24). Table 1 shows that higher concentrations of cystatin C were associated with older age, higher body mass index, triglycerides, fasting insulin, serum creatinine and estimated GFR. The prevalence of hypertension increased across ascending tertiles of cystatin C.

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Heritability of Renal Biomarkers

Table 3 presents the residual heritability (h²). Serum cystatin C was 0.32 ± 0.1 (P<.0001) heritable after adjusting...
Table 2. Age-adjusted pulse wave velocity and intima-media thickness among Afro-Carribeans

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>BaPWV&lt;sup&gt;a&lt;/sup&gt; (m/s)</th>
<th>Carotid IMT&lt;sup&gt;b&lt;/sup&gt; (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall 390</td>
<td>Women 14.12±4.04</td>
</tr>
<tr>
<td></td>
<td>19 10.89±1.43</td>
<td>17 0.69±0.15</td>
</tr>
<tr>
<td></td>
<td>161 12.09±1.89</td>
<td>163 0.56±0.06</td>
</tr>
<tr>
<td></td>
<td>151 14.98±3.00</td>
<td>155 0.73±0.12</td>
</tr>
<tr>
<td></td>
<td>39 17.68±3.33</td>
<td>35 0.89±0.12</td>
</tr>
<tr>
<td></td>
<td>20 22.14±4.06</td>
<td>22 0.88±0.17</td>
</tr>
</tbody>
</table>

<sup>a</sup>BaPWV: brachial ankle pulse wave velocity, an average of left and right sides.
<sup>b</sup>Carotid IMT: carotid intima-media thickness, an average of left and right sides.

for age, sex, hypertension, triglyceride and insulin level. The serum creatinine was .28 ± .10 (P<.0001) heritable after adjusting for age, sex, anti-hypertensive treatment and serum LDL-C (all covariates had P<.01). The urinary albumin was .22 (P=.0006) heritable after simultaneously accounting for sex and systolic blood pressure. The urinary albumin to creatinine ratio was .19 (P=.0007) heritable, after adjusting for sex, glucose and systolic blood pressure.

Genetic, Environmental and Phenotypic Correlations

Table 3 also shows the genetic, environmental and phenotypic correlation between renal biomarkers and SCVD measures. The heritability of baPWV and IMT was .27 ± .1 (P=.09) and .47 ± .1 (P<.0001), respectively after adjusting for age and sex (data not shown). Cystatin C had a higher genetic correlation with baPWV (p<.297) than serum creatinine (p=.166). Furthermore, cystatin C had a greater phenotypic correlation with baPWV (p=.223) than serum creatinine (p=.116) or eGFR (p<.116) Neither the albumin creatinine ratio nor albuminuria was significantly correlated with baPWV. No significant correlations were identified between renal biomarkers and IMT.

**Association between Renal Measures and SCVD**

No significant association was observed between renal measures and carotid IMT (data not shown). Table 4 shows the association between renal measures and baPWV, adjusting for age, sex, hypertension, diabetes and BMI. The proportion of variance due to covariates was 62%. Only cystatin C was a significant predictor to baPWV (P=.04). Cystatin C explained an additional 1% of total variance in baPWV. None of the other renal function measurements was statistically significant correlates of baPWV.

**DISCUSSION**

To our knowledge, this report is the first to investigate the heritability of renal function and its relationship to SCVD among African ancestry individuals. Our findings suggest that a significant degree of variability in renal function biomarkers is explained by genetic factors, with 19%–32% of variance attributable to polygenic influences after accounting for measured environmental factors.

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influences after accounting for measured environmental factors. Several studies have reported a significant heritability of serum creatinine among hypertensive families of African descents, ranging from .17 to .45. The Framingham Offspring study reported a residual heritability of serum cystatin C and creatinine among Caucasians to be very similar as found in our study. We found suggestive evidence (LOD score > 2) for loci linked to kidney function on chromosomes 2, 3, and 4. These findings confirm and extend a familial aggregation of renal function in African ancestry individuals and justify further analyses aimed at understanding the genetic determinants of renal function among this high-risk ethnic group.

The renal biomarkers assessed, we found that serum cystatin C was independently associated with arterial stiffness (baPWV) (P=.04). This association was not found with other renal function biomarkers, and was not modified by age, sex, BMI and the presence of diabetes or hypertension. This finding was consistent with those of the Health ABC study and another study of healthy individuals with normal serum creatinine.

Furthermore, we also report a positive phenotypic correlation between baPWV and serum cystatin C, creatinine and creatinine based eGFR adjusting only age and sex. Cystatin C showed higher genetic correlation and phenotypic correlation to baPWV compared to serum creatinine. This may reflect that cystatin C was also significantly associated with pulse pressure (ρp=.148) but not serum creatinine (ρp=.059). This is the first to report genetic correlation between cystatin C and baPWV. Future studies are needed to replicate our findings.

We did not find a significant association of these renal function measures with carotid IMT. This is consistent with null findings in the Multi-Ethnic Study of Atherosclerosis (MESA) among 6,557 ethnically diverse participants (aged 45 to 84 years). Thus, despite the finding that patients with severe renal failure are reported to exhibit a significantly increased IMT, early kidney disease does not appear to be associated with increased levels of atherosclerosis in arteries in our relatively young African ancestry families.

An important and novel aspect of our study is its unique extended pedigree structure. Study participants came from the island of Tobago, located in the Southern Caribbean. Compared to African Americans, the Tobago population is a more homogeneous population of West African ancestry with only about 6% admixture. The family sizes were large, thus facilitating recruitment of extended multigenerational families and providing ample power and a unique opportunity to characterize the genetic architecture of renal function in a population of West African ancestry.

While the mechanisms underlying the relationship between renal function and arterial stiffness are not fully understood, decreased renal function may increase baPWV through insulin resistance and elevated blood pressure. Numerous clinical observations indicate

### Table 4. The association of baPWV (age, sex, diabetes and hypertension adjusted) with renal function measures

<table>
<thead>
<tr>
<th>Proportion of Variance due to Covariates</th>
<th>Base Model&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Base Model plus Serum Cystatin C</th>
<th>Base Model plus Serum Creatinine</th>
<th>Base Model plus Urinary Albumin</th>
<th>Base Model plus eGFR-CKD-EPI&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β(SE)</td>
<td>P</td>
<td>β(SE)</td>
<td>P</td>
<td>β(SE)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>.009</td>
<td>.0001</td>
<td>.008</td>
<td>.0001</td>
<td>.009</td>
</tr>
<tr>
<td>Sex</td>
<td>-.06</td>
<td>.009</td>
<td>.06</td>
<td>.01</td>
<td>.05</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>.07</td>
<td>.02</td>
<td>.02</td>
<td>.02</td>
<td>.08</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>.11</td>
<td>&lt;.0001</td>
<td>.10</td>
<td>&lt;.0001</td>
<td>.11</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>.02</td>
<td>.6</td>
<td>.02</td>
<td>.7</td>
<td>.02</td>
</tr>
<tr>
<td>Serum cystatin C (mg/l)</td>
<td>.09</td>
<td>.04</td>
<td>.09</td>
<td>.55</td>
<td>.003</td>
</tr>
<tr>
<td>Serum creatinine (mg/l)</td>
<td>.02</td>
<td>.6</td>
<td>.02</td>
<td>.7</td>
<td>.02</td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/g)</td>
<td>.003</td>
<td>.55</td>
<td>.003</td>
<td>.55</td>
<td>.003</td>
</tr>
<tr>
<td>eGFR [mL * min-1 * (1.73 m&lt;sup&gt;2&lt;/sup&gt; -1)]</td>
<td>-.002</td>
<td>.71</td>
<td>-</td>
<td>.042</td>
<td>.37</td>
</tr>
</tbody>
</table>

<sup>a</sup>The models were assessed in SOLAR: base model did not contain any renal biomarkers;<br><sup>b</sup>eGFR-CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation: Age in years; serum creatinine in mg/dL

Female: 1) serum creatinine ≤0.7, GFR [mL * min<sup>-1</sup> * (1.73 m<sup>2</sup>)<sup>-1</sup>] = 166*(Scr/0.7)<sup>-1.209</sup>(0.993)<sup>0.042</sup>;<br>2) serum creatinine >0.7, GFR [mL * min<sup>-1</sup> * (1.73 m<sup>2</sup>)<sup>-1</sup>] = 166*(Scr/0.7)<sup>-1.209</sup>(0.993)<sup>0.042</sup>;<br>
Male: 1) serum creatinine ≤0.9, GFR [mL * min<sup>-1</sup> * (1.73 m<sup>2</sup>)<sup>-1</sup>] = 163*(Scr/0.9)<sup>-1.411</sup>(0.993)<sup>0.374</sup>;<br>2) serum creatinine >0.9, GFR [mL * min<sup>-1</sup> * (1.73 m<sup>2</sup>)<sup>-1</sup>] = 163*(Scr/0.9)<sup>-1.209</sup>(0.993)<sup>0.374</sup>.

<sup>b</sup>baPWV, brachial ankle pulse wave velocity.
that end stage renal failure is associated with vascular complications such as increased stiffness of large conduit arteries and early wave reflections.43 Furthermore, vascular stiffness was significantly higher among patients with diabetic nephropathy than non-diabetic CKD patients.44 Hypertension is another basic pathophysiological mechanism of altered kidney function. It is possible that kidney damage may cause an increase in other risk factors for arterial stiffness such as hypertension, anemia or vascular calcification;45 in contrast, the increased arterial stiffness leads to increased pulse pressure, which leads to deterioration in kidney function, eventually resulting in decreased GFR. Such vicious cycles promote each other. However, the cross-sectional nature of our study does not allow us to distinguish the direction of this association.

Our study has several potential limitations. Most importantly, as mentioned already, in any cross-sectional study, the direction of the association cannot be ascertained. A longitudinal study design is needed to establish a causal relationship between these renal function biomarkers and SCVD or CVD. Secondly, GFR was not directly measured. CKD-EPI is a newly developed equation to predict GFR,9 which may be more precise and accurate than the MDRD equation that was developed among CKD patients.46 The CKD-EPI was created using a pooled analysis, comprised of more than 8,200 research participants from multiple ethnic groups and validated in an additional 3,800 participants.9 The CKD-EPI equation has lower bias compared to the MDRD equation, especially at an estimated GFR greater than 60 mL/min per 1.73 m²; but the precision remains limited. The lower bias at higher eGFR reflects the usage of a spline term for serum creatinine in CKD-EPI equation. Like the MDRD equation, the CKD-EPI equation includes age, race and sex as surrogates for non-renal function determinants of serum creatinine. It is also possible that there is residual confounding from other unmeasured factors that were not evaluated in this study. Third, the probands and family members were recruited without regard to health status, all participants were ambulatory, relatively young and healthy; thus, the association of renal function biomarkers and subclinical CVD among these healthy families, so called ‘healthy family effect,’ might have biased our findings toward the null.

**CONCLUSION**

In conclusion, our data suggest that renal function biomarkers are significantly heritable among Afro-Caribbean. In addition, serum cystatin C was independently associated with arterial stiffness ($P<.04$). The association was not found with other renal function biomarkers, and was not modified by age, sex, BMI, the presence of diabetes, or hypertension. Future studies are needed to replicate our findings, and further investigate the genetic variation underlying both traits.

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Manuscript draft: Li, Kuipers, Kuller, Wheeler, Zmuda

Statistical expertise: Li, Kuipers, Kuller, Wheeler, Zmuda

Acquisition of funding: Li, Bunker, Kuller, Miljkovic, Patrick

Administrative: Zmuda

Supervision: Bunker, Zmuda

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