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Risk factor profile for chronic kidney disease is similar to risk factor profile for small artery disease

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Abstract

Background and method—We investigated whether chronic kidney disease detected by increased serum creatinine (S_{Cr}) or urine albumin-to-creatinine ratio (U_{ACR}) may reflect arteriosclerosis involving the kidneys. The sample consisted of 1585 members of sibships (804 non-Hispanic whites and 781 non-Hispanic blacks) in which at least two siblings had primary hypertension. We first evaluated the correlations of increased S_{Cr} and U_{ACR} with the presence of cerebral small vessel arteriosclerosis, which was determined by increased subcortical white matter hyperintensity (WMH) volume on brain magnetic resonance imaging; and with peripheral large vessel arteriosclerosis, which was determined by decreased ankle-brachial index (ABI). After age adjustment, increased S_{Cr} and U_{ACR} correlated with increased WMH volume (0.54 and 0.52, respectively) and with decreased ABI (0.50 and 0.54, respectively; all $P < 0.001$). We then used logistic regression to evaluate the dependency of each measure of disease on conventional risk factors for arteriosclerosis to assess whether the risk factors' effects were proportional across different measures of disease.

Results—Age, race, sex, hypertension, diabetes, total cholesterol, and smoking made similar overall contributions to the prediction of each measure of disease, as judged by the model C-statistics, which varied in a narrow range from 0.84 to 0.85 (all $P < 0.001$). However, the relative contributions that the modifiable risk factors, including hypertension, diabetes, total cholesterol, and smoking made to prediction of increased S_{Cr} and U_{ACR} were disproportionate to their relative contributions to prediction of decreased ABI ($P < 0.0001$).

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Conflicts of interest

There are no conflicts of interest.

Conclusion—The findings support the view that chronic kidney disease detected by increased S_{Cr} or U_{ACR} primarily reflects small vessel arteriosclerosis involving the kidneys.

Keywords

albuminuria; ankle-brachial blood pressure index; arteriosclerosis; blood pressure; glomerular filtration rate; hypertension; subcortical white matter hyperintensity

Introduction

Arteriosclerosis encompasses two patterns of disease [1]. In larger capacitance and conduit arteries, the dominant pattern is atherosclerosis (large vessel arteriosclerosis). In small arteries and arterioles, the dominant pattern is arteriolosclerosis (small vessel arteriosclerosis). As low-resistance, highly perfused organs, the kidneys are expected to be just as vulnerable to arteriosclerotic damage as the brain, heart, and peripheral arteries [2]. We hypothesized that chronic kidney disease (CKD) commonly detected by increased serum creatinine (S_{Cr}) or albumin-to-creatinine ratio (U_{ACR}) [3] primarily reflects small vessel arteriosclerosis involving the kidneys.

The first objective of this study was to assess the association of CKD detected by increased S_{Cr} or U_{ACR} with the presence of arteriosclerosis in two other target organ locations: the brain and peripheral arteries. The presence of cerebral small vessel arteriosclerosis was determined by increased subcortical white matter hyperintensity (WMH) volume on brain MRI [4], and the presence of peripheral large artery arteriosclerosis was determined by decreased ankle-brachial index (ABI), which is calculated as the ratio of ankle-to-brachial artery SBPs [5]. We expected that CKD detected by increased S_{Cr} or U_{ACR} would correlate with arteriosclerosis elsewhere. However, because CKD detected by increased S_{Cr} and U_{ACR} is more likely to reflect small than large vessel arteriosclerosis [6], we hypothesized that S_{Cr} and U_{ACR} would correlate more strongly with the WMH volume measure of small vessel disease than with the ABI measure of large vessel disease.

The second objective of this study was to assess the association of CKD detected by increased S_{Cr} or U_{ACR} with conventional risk factors for arteriosclerosis, including age, race, sex, hypertension, diabetes, total cholesterol, and smoking. We reasoned that the contribution these risk factors would make to predicting CKD would be comparable to their contributions to predicting arteriosclerosis in other target organ locations. However, because some previous studies have suggested that particular risk factors may differ in the magnitude of their impact on large versus small vessel arteriosclerosis [7], we hypothesized that the risk factor profiles for S_{Cr} and U_{ACR} would differ from their effects on the ABI measure of large vessel disease but not from their effects on the WMH volume measure of small vessel disease.

Methods

Participants

The 1585 study participants, consisting of 804 non-Hispanic white adults (485 women and 319 men) and 781 non-Hispanic black adults (538 women and 243 men), were members of sibships that enrolled in the Genetic Epidemiology Network of Arteriopathy (GENOA) study of the Family Blood Pressure Program, which began in 1995 with the overall objective to identify genetic determinants of hypertension in multiple ethnic groups [8,9]. In Rochester, Minnesota, non-Hispanic white sibships were recruited through hypertensive probands from Olmsted County [10]. In Jackson, Mississippi, African-American sibships were recruited through hypertensive probands from the Atherosclerosis Risk in Communities

cohort [11]. Sibships in which the proband was known to have a cause of secondary hypertension, including renal artery stenosis or CKD were not recruited. All available members of the recruited sibships, including normotensive siblings, were invited to an initial study visit conducted between 1996 and 2000. At a second study visit conducted between 2000 and 2004, 2721 GENOA participants underwent noninvasive renal and peripheral arterial assessments including measurements of S_{Cr} , U_{ACR} , and ABI. Of the 2721 returning participants, 1746 who had no history of stroke or neurologic disease and no implanted metal devices underwent brain MRI to determine WMH volume [12]. The median time between the second GENOA examination and the brain MRI was 11.9 months. Brain MRIs suitable for analysis were obtained in 1678 of the 1746 participants. The present sample of 1585 included all participants with analyzable brain MRIs and measurements of at least one of the other measures of CKD or ABI.

Study protocol

The study protocols were approved by the Human Studies Review Board at each institution and informed consent was obtained from all participants. A standardized questionnaire was administered to obtain personal and medical histories. Height was measured by a wall stadiometer, weight by electronic balance, and BMI was calculated in units of kg/m^2 . Blood pressure was measured with a random zero sphygmomanometer (Hawksley and Sons, West Sussex, England) and a cuff appropriate for arm size. The second and third of three readings taken from the right arm after the participant sat for at least 5 min were averaged for the analyses. The ABI was measured by examiners who had undergone standardized training at the Mayo Clinic. Following a 5-min rest, participants were evaluated in the supine position. Appropriately sized blood pressure cuffs were placed on each arm and ankle, and a Doppler ultrasonic instrument (Medisonics, Minneapolis, Minnesota, USA) was used to detect each pulse. The lower of the average ABIs from the two legs [13] was used in the analyses.

Hypertension was confirmed if a prior diagnosis and prescription antihypertensive medication were reported, or if the average SBP or DBP was at least 140 or at least 90 mmHg, respectively. Severity of hypertension was quantitated as a function of the measured blood pressure levels $[(SBP - 120)/60 + (DBP - 70)/30]$ and the number of antihypertensive medications with different pharmacologic mechanisms of action. Diabetes was diagnosed if the participant reported treatment with insulin or oral hypoglycemic agents or the fasting serum glucose concentration was at least 126 mg/dl.

Laboratory measurements

Blood was drawn after an overnight fast of at least 8 h and urine was collected on the morning of the study visit. S_{Cr} , glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride concentrations; and urine albumin, total protein, and creatinine concentrations were measured by standard methods automated on an Hitachi 911 Chemistry Analyzer (Roche Diagnostics, Indianapolis, Indiana, USA) [14,15]. Creatinine was measured using the Creatinine Plus standardized enzymatic assay (Roche Diagnostics). Urine albumin was measured by immunoturbidity using the SPQ Test System assay (DiaSorin, Stillwater, Minnesota, USA). The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation: $CKD-EPI\ eGFR = 140 \times \min(S_{Cr}/\kappa, 1)^\alpha \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if women] $\times 1.159$ [if black], where S_{Cr} is standardized S_{Cr} , κ is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of S_{Cr}/κ and 1, and max indicates the maximum of S_{Cr}/κ and 1 [16]. Brain MRI was performed at both sites on identically equipped Signa 1.5 Tesla MRI scanners (GE Medical Systems, Waukesha, Wisconsin, USA). Brain and subcortical WMH volumes were determined from axial fluid-attenuated inversion recovery images [12,17]. Scans with cortical infarctions

were excluded from the analyses to not distort WMH volume estimates. Lacunar infarctions, which reflect small vessel disease [4], were included in the WMH volume measurements.

Statistical analyses

All analyses were performed with the Statistical Analysis System (SAS, Raleigh, North Carolina, USA). Statistical significance was defined by *P* value of 0.05 or less. The WMH volume was adjusted by linear regression for brain volume [12]. Because the renal, cerebral, and peripheral arterial measurements are on different scales and their distributions are skewed, linear correlations between them were assessed by normalized rank correlation coefficients. Because the correlations may be nonlinear, we also calculated tetrachoric correlations, after identifying 'optimal' cutpoint values that distinguished between the presence versus absence of disease. To determine the optimal cutpoints, we used an algorithm that dichotomized the four outcome measures (S_{Cr} , U_{ACR} , WMH volume, and ABI) using a finite set of possible cutpoints for each, and then calculated the χ^2 statistics for all pairwise tests within each race and sex group. To maximize the intercorrelations between measures of disease in the same and across different target organ locations, the combined χ^2 statistics from the pairwise tests were compared over all possible sets of cutpoints to find the set that resulted in the largest combined χ^2 statistic. Analyses were based on S_{Cr} instead of estimated GFR values because demographic measures used in estimating GFR from S_{Cr} bias the estimated associations with risk factors [18]. Because S_{Cr} values are greater among men than women, the cutpoints for S_{Cr} were sex-specific.

Multiple variable logistic regression was used to assess dependency of each categorical measure of disease on conventional risk factors for arteriosclerosis [19]. Quantitative risk factors were normalized to facilitate comparison of the relationships across different measures of disease. A bivariate probit method was used to test for proportionality of the regression coefficients between models. Although the same set of risk factors may influence two different measures of disease, nonproportionality of the regression coefficients implies differences in the relative contributions of the different risk factors.

Results

Sample description

The 1585 study participants included 781 blacks (49%) and 1023 women (65%) with median age of 62 years (Table 1). Consistent with the recruitment scheme, most participants had hypertension (74%) and were taking blood pressure-lowering medications (69%). Twenty percent of participants were diabetic and 11% were current smokers.

Measures of disease

The cutpoint values that maximized intercorrelations among measures of disease were as follows: for presence of CKD, S_{Cr} at least 1.6 mg/dl in men and at least 1.4 mg/dl in women and U_{ACR} at least 80 mg/g; for presence of cerebral small vessel disease, WMH volume at least 40 cm³; and for presence of peripheral large vessel disease, ABI less than 0.85 (Table 2). The prevalence of disease was higher when based upon clinically recommended cutpoints (Table 2). The prevalence of CKD defined by CKD-EPI estimated GFR less than 60 ml/min per 1.73 m² was 8%, compared with 2.5% when defined by the cutpoint values used for elevated S_{Cr} . The prevalence of albuminuria defined by U_{ACR} more than 17 in men or more than 25 in women was 12%, compared with 4.4% when defined by the cutpoint value used for elevated U_{ACR} .

Correlations between different measures of disease

Linear correlations between the quantitative measures of disease in different target organ locations were weak (0.01–0.15). After adjustment for age, the only linear correlations that remained statistically significantly greater than zero were of U_{ACR} with WMH volume (0.15, $P < 0.001$) and with ABI (0.07, $P < 0.01$). In contrast, tetrachoric correlations between categorical measures of disease (presence/absence) were stronger (0.42–0.73), significantly greater than zero (all $P < 0.001$), and strengthened by age adjustment (0.47–0.79; Table 3). The strongest tetrachoric correlations were between the two measures of CKD, increased S_{Cr} and increased U_{ACR} . Otherwise, the tetrachoric correlations between measures of disease in different target organs varied only in a narrow range from 0.47 to 0.54.

Dependency on risk factors

In multivariable logistic regression models, overall ability of conventional risk factors for arteriosclerosis to predict presence of disease did not differ between S_{Cr} , U_{ACR} , WMH volume, and ABI (Table 4). The model C-statistics varied in a narrow range from 0.836 to 0.845. Each risk factor was associated with statistically significant odds ratios for elevated S_{Cr} , U_{ACR} , WMH volume, or decreased ABI. After adjusting for the nonmodifiable risk factors (age, race, and sex), the test for nonproportionality of the effects of the modifiable risk factors (hypertension severity, diabetes, total cholesterol, and smoking) indicated no significant nonproportionality between effects on the two measures of CKD ($P = 0.870$), or between effects on the WMH volume measure of cerebral small vessel arteriosclerosis versus S_{Cr} ($P = 0.08$) or versus U_{ACR} ($P = 0.06$). In contrast, the risk factors' effects on the ABI measure of large vessel arteriosclerosis were significantly nonproportional to their effects on S_{Cr} ($P < 0.00001$) and on U_{ACR} ($P < 0.00001$). This nonproportionality was a consequence of greater impact of hypertension and diabetes on S_{Cr} and U_{ACR} than on ABI, and a greater impact of smoking on ABI than on S_{Cr} and U_{ACR} (Table 4).

Discussion

A main finding of this study is that conventional measures of CKD (elevated S_{Cr} and U_{ACR}) are correlated with measures of arteriosclerosis in the brain (increased WMH volume) and peripheral arteries (decreased ABI). In addition, conventional risk factors for arteriosclerosis, including sex, age, hypertension, total cholesterol, diabetes, and smoking make similar aggregate contributions to predicting CKD as they do to predicting arteriosclerosis in other target organ locations. Together these findings support the hypothesis that CKD commonly detected by increased S_{Cr} and U_{ACR} reflects the renal manifestation of systemic arteriosclerosis [20].

Considerable other data support the conclusion that arteriosclerosis is a major contributor to kidney damage, dysfunction, and failure [6,21–29]. Increased S_{Cr} (or decreased eGFR) and albuminuria may serve as independent predictors of death and complications from CVD [30,31] precisely because they reflect arteriosclerotic damage to and dysfunction of the kidneys indicative of the extent and severity of arteriosclerosis [20]. This is analogous to other target organ measures of arteriosclerosis, including coronary artery calcium score, carotid intima-media thickness, ABI, and subcortical white matter changes, each of which improves the ability to predict CVD events beyond what is possible with conventional risk factors [5,32–35].

A previous study suggested that measures of arteriosclerosis in large versus small arteries of the lower extremities are not correlated and may associate with different risk factors and convey different risks of future CVD events [36]. Results from other studies have suggested that risk factors for arteriosclerosis may differ among target organs and between large and

small arteries [37–42]. Although our expectation was confirmed that CKD detected by increased S_{Cr} and U_{ACR} would correlate with arteriosclerosis elsewhere, our hypothesis was not confirmed that S_{Cr} and U_{ACR} would correlate more strongly with the WMH volume measure of small vessel disease than with the ABI measure of large vessel disease. Our expectation that conventional risk factors for arteriosclerosis would contribute to the prediction of CKD detected by increased S_{Cr} and U_{ACR} was confirmed. In addition, whereas the risk factors had similar aggregate effects on S_{Cr} , U_{ACR} , WMH volume, and ABI, the subset of modifiable risk factors including hypertension, diabetes, and smoking appeared to have nonproportional effects on S_{Cr} and U_{ACR} compared to their effects on ABI. This nonproportionality reflected relatively greater impact of hypertension and diabetes on S_{Cr} and U_{ACR} and relatively greater impact of smoking on ABI.

A strength of our study is the inclusion of both non-Hispanic black and white cohorts that are well characterized for risk factors and measures of subclinical arteriosclerosis in multiple target organ locations. However, because the cohorts were not randomly sampled adults from the communities, extension of inferences to groups of different ethnicities or background predispositions to arteriosclerosis must be cautious. Because the numbers of participants who met the optimal cutpoint criteria for disease in each target organ location was relatively small, the power to detect differences in the relationships with risk factors may be limited. Moreover, additional studies that simultaneously evaluate measures of both large and small vessel disease within and among multiple different target organ locations are indicated to confirm that particular risk factors differentially influence the patterns of large versus small vessel arteriosclerosis [37,42]. Finally, the S_{Cr} and U_{ACR} measures of CKD are indirect assessments of subclinical kidney dysfunction and damage. Their correlations with other indirect measures of subclinical arteriosclerosis (WMH volume and ABI) and their dependencies on CVD risk factors support but do not prove that arteriosclerosis is the shared causative pathological process.

CKD detected by measurements of S_{Cr} and U_{ACR} affects 13% of the US adult population (26 million) [43]. Arteriosclerosis is the most prevalent chronic disease and the leading cause of premature death and disability in the developed world [44]. Although most of the public health burden results from acute events involving large vessel disease (atherosclerosis), stable or slowly progressive clinical syndromes such as CKD may also develop, resulting from small vessel disease (arteriolosclerosis) within target organs. Physicians would like to be able to predict the severity of arteriosclerosis in one target organ location by measuring the severity in another. Results of the present study suggest that convenient, noninvasive measures of CKD based on S_{Cr} and U_{ACR} provide such ability.

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Abbreviations

ABI	ankle-brachial index
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology
HDL	high-density lipoprotein

S_{Cr}	serum creatinine
U_{ACR}	urine albumin-to-creatinine ratio

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Table 1Descriptive characteristics of study participants ($N = 1585$)

Characteristic	Median (interquartile range) or [N (%)]
Black race	781 (49)
Female sex	1023 (65)
Age (years)	62 (54–67)
BMI (kg/m^2)	30 (27–34)
SBP (mmHg)	131 (121–144)
DBP (mmHg)	77 (70–82)
Total cholesterol (mg/dl)	197 (173–223)
HDL-cholesterol (mg/dl)	52 (43–64)
Triglycerides (mg/dl)	117 (82–166)
Hypertension	1180 (74)
Hypertension severity index	2.7 (1.3–3.6)
Antihypertensive drug(s)	1094 (69)
Diabetes	313 (20)
Diabetes drugs, [n (%)]	252 (16)
Smoker, current	168 (11)
Smoker, past	525 (33)
Smoking, pack-years	19 (7–35)

Table entries are median (interquartile range) for quantitative traits or count (percentage) for categorical traits. HDL, high-density lipoprotein.

Table 2Measures of target organ disease in study participants ($N = 1585$)

Kidney function	Median (interquartile range) or [N (%)]
S_{Cr} (mg/dl)	0.80 (0.7–1.0)
$S_{Cr} > 1.6$ in men, > 1.4 in women, [N (%)]	39 (2.5)
CKD-EPI eGFR (ml/min per 1.73 m^2)	88 (75–101)
CKD-EPI eGFR < 60 ml/min per 1.73 m^2 [N (%)]	127 (8)
Kidney damage	
U_{ACR} (mg/g)	3.8 (2.1–8.7)
$U_{ACR} > 80$ mg/g [N (%)]	69 (4.4)
$U_{ACR} > 17$ in men, > 25 in women, [N (%)]	188 (12)
Brain injury	
WMH volume (cm^3)	6.3 (4.6–9.5)
WMH volume $> 40 \text{ cm}^3$ [N (%)]	26 (1.6)
Peripheral arterial disease	
ABI	1.07 (1.00–1.17)
ABI < 0.85 [N (%)]	72 (4.5)
ABI < 0.9 [N (%)]	105 (7)

Table entries are median (interquartile range) for quantitative traits or count (percentage) for categorical traits. ABI, ankle-brachial index; CKD-EPI, chronic kidney disease epidemiology consortium equation; eGFR, estimated glomerular filtration rate; S_{Cr} , serum creatinine; U_{ACR} , urine albumin-creatinine ratio; WMH, cerebral subcortical white matter hyperintensity determined by brain MRI.

Table 3

Correlations between different measures of target organ disease

Target organ locations	Correlation between disease measures	Correlation coefficient	
		Unadjusted	Age adjusted
Kidney	$\uparrow S_{Cr} \leftrightarrow \uparrow U_{ACR}$	0.73 [‡]	0.79 [‡]
Kidney and brain	$\uparrow S_{Cr} \leftrightarrow \uparrow WMH$ volume	0.46 [‡]	0.54 [‡]
	$\uparrow U_{ACR} \leftrightarrow \uparrow WMH$ volume	0.43 [‡]	0.52 [‡]
Kidney and peripheral arteries	$\uparrow S_{Cr} \leftrightarrow \downarrow ABI$	0.42 [‡]	0.50 [‡]
	$\uparrow U_{ACR} \leftrightarrow \downarrow ABI$	0.51 [‡]	0.54 [‡]
Brain and peripheral arteries	$\downarrow ABI \leftrightarrow \uparrow WMH$ volume	0.42 [‡]	0.47 [‡]

Numeric table entries are tetrachoric correlation coefficients based on cutpoint values for presence/absence of disease: S_{Cr} 1.6 mg/dl in men and 1.4 mg/dl in women, U_{ACR} 80 mg/g; WMH volume 40 cm³; and $ABI < 0.85$. ABI , ankle-brachial index; S_{Cr} , serum creatinine; U_{ACR} , urine albumin-creatinine ratio; WMH, white matter hyperintensity; $\uparrow$, increased; $\downarrow$, decreased; $\leftrightarrow$, correlation between disease measures. Symbols indicate statistical significance of test for correlation coefficient = 0, P value:

[‡] <0.001 – 0.0001 .

Table 4

Odds ratios from multiple variable logistic regression models

Risk factors	Kidney		Brain	Periphery
	S _{Cr} >1.6 in men, >1.4 in women	U _{ACR} >80	WMH volume >40	ABI <0.85
Age	1.8 [‡] (1.2–2.8)	1.0 (0.8–1.4)	2.1 [‡] (1.3–3.4)	2.6 [‡] (1.9–3.6)
Black race	1.9 (0.9–4.1)	5.6 [‡] (2.6–12.1)	4.0 [‡] (1.4–11.0)	2.1 [‡] (1.2–3.6)
Male sex	2.1 [*] (1.0–4.4)	1.3 (0.7–2.3)	2.5 [*] (1.1–6.2)	1.1 (0.6–1.9)
Hypertension severity	2.3 [‡] (1.6–3.5)	2.0 [‡] (1.5–2.7)	2.2 [‡] (1.4–3.6)	1.3 [*] (1.0–1.8)
Diabetes	4.3 [‡] (2.2–8.7)	4.2 [‡] (2.5–7.1)	0.9 (0.4–2.3)	1.4 (0.8–2.5)
Log (total cholesterol)	1.4 [*] (1.0–1.9)	1.5 [‡] (1.2–1.9)	1.1 (0.7–1.6)	1.4 [*] (1.0–1.7)
Log (pack-years)	1.0 (0.7–1.4)	1.0 (0.8–1.3)	1.4 (1.0–2.1)	2.3 [‡] (1.8–3.0)
# positive (C-stat):	39 (0.84)	69 (0.84)	26 (0.85)	72 (0.84)
	P value of proportionality contrast with increased S _{Cr} :	0.87	0.08	<0.0001
		P value of proportionality contrast with increased U _{ACR} :	<0.06	<0.0001
			P value of proportionality contrast with increased WMH volume:	0.05

Table entries are odds ratios (95% confidence intervals). For quantitative predictor variables, the odds ratios correspond to one-standard deviation increases in the predictor. ABI, ankle-brachial index; S_{Cr}, serum creatinine; U_{ACR}, urine albumin-creatinine ratio; WMH, white matter hyperintensity. Symbols indicate statistical significance for test of odds ratio = 1. *P* value:

^{*}, <0.05–0.01;

[‡], <0.01–0.001;

[‡], <0.001–0.0001.