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Urinary albumin to creatinine ratio as potential biomarker for cerebral microvascular disease

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Abstract

Elevated urinary albumin to creatinine ratio (ACR) and white matter hyperintensity (WMH) volume seen on brain MRI are measures of microvascular disease which may have shared susceptibility to metabolic and vascular insults. We hypothesized that elevated ACR may be useful as inexpensive biomarker to predict presence of cerebral microvascular disease. We assessed the association between ACR at study entry and subsequent WMH volume. We evaluated pulse pressure, mean arterial pressure, hypertension duration, waist circumference, fasting glucose, glomerular filtration rate (GFR) and C-reactive protein (CRP) as potential mediators and diabetes as a moderator of the association between ACR and WMH. Data were collected at study entry and at follow-up approximately 7 years later in a multi-ethnic population sample of 1281 participants (mean age=51, SD=9.5) from Dallas County. Overall, ACR differences were only marginally ($p=0.05$) associated with subsequent WMH. In mediator analysis, however, ACR differences related specifically to arterial pulsatility ($\beta=0.010$, bootstrap 95% Confidence Interval (CI): 0.002 to 0.021) and waist circumference ($\beta=-0.004$, bootstrap 95% CI: -0.011 to -0.001) were significantly associated with WMH. ACR differences related to serum glucose and CRP were not associated with WMH. ACR evaluated at the same time as WMH had a higher level of significance ($p<0.001$) indicating greater utility in predicting current cerebrovascular insults.

Keywords

Arterial pulsatility; Epidemiology; Glucose handling; Inflammation; Magnetic Resonance Imaging; Microvascular Disease; Waist Circumference; White matter disease / hyperintensities

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1. Introduction

Increasing evidence suggests that cerebral microvascular disease plays an important role in declining cognitive function with aging [1; 2] and influences progression and severity of Alzheimer's disease [3; 4]. Early detection of cerebral microvascular disease may be important to identify those who would benefit most from heightened preventive efforts at controlling vascular risk factors to lower risk of cognitive decline and dementia. Brain MRI can detect evidence of cerebral microvascular disease, such as white matter hyperintensities (WMH), but cost limits its utility as a screening procedure. Elevated urine albumin is associated with larger WMH volumes [5-7] and may be useful as an inexpensive indicator of microvascular disease in the brain.

The microvasculatures of the brain and kidneys have several shared physiologic properties that may underlie shared susceptibility to end organ disease [8; 9]. Both vasculatures are high flow, low impedance systems with end-arteriolar control of pressure resulting in heightened transmission of pulsatility to the microvasculature [8]. Diabetes is known to result in widespread endothelial dysfunction [10] and may induce microvascular disease in both systems [11]. While diabetes is well known to confer risk for renal microvascular disease, its relation to cerebral microvascular disease remains less clear; some studies show an association [12] while others have not [13]. Low grade chronic inflammation has also been linked to endothelial dysfunction in the kidneys [14-17] and the brain [18], resulting in increased urine albumin excretion [19; 20] and larger WMH volume [21]. It remains unclear which of these vascular risk factors are among the most important mediators of the association between urine albumin and WMH in a community setting.

It is important to understand the mediators of the association between urine albumin and WMH because the degree of association may differ depending on which risk factors are present. For example, increased urine albumin may have a different association with WMH in the setting of hypertension than diabetes. Our experience has suggested arterial stiffness to be the strongest indicator of WMH [22] and we hypothesized arterial pulsatility would be the primary driver of the association between ACR and WMH. We therefore investigated blood pressure, glucose handling, obesity, inflammation and glomerular filtration rate (GFR) as potential mediators and diabetes as a moderator of the association between urine ACR at study entry and WMH volume seven years later among 1281 participants in the Dallas Heart Study. Secondary analysis investigated mediators and moderators at study entry of the cross-sectional association between ACR and WMH at follow up.

2. Methods

2.1 Study population

All subjects provided written informed consent and the study was approved by the UT Southwestern Institutional Review Board. This investigation was conducted as part of the Dallas Heart Study, a longitudinal, population-based, multi-ethnic cohort study with over sampling of African-Americans to ensure approximately 50% representation [23]. The initial Dallas Heart Study included clinical evaluation and in-home blood and urine specimen collection [24]. Follow up was conducted seven years later with repeat clinical evaluation

and addition of MRI of the brain. A total of 1281 participants without a history of stroke were evaluated.

2.2 Outcome variables

The outcome measure was WMH volume (mL) assessed at follow up. WMH volume was automatically quantified from 2D Fluid Attenuation Inversion Recovery (FLAIR) and 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) brain imaging acquired during follow up evaluation using a 3T MRI system (Achieva, Philips Medical Systems). Our WMH segmentation method has been previously described [25].

2.3 Predictor variable

The primary predictor variable in the current study was urine albumin (mg) / creatinine (g) ratio (ACR) collected at study entry. Urine albumin and creatinine were measured in first morning void samples. Albumin was quantified by a turbidimetric method and creatinine by an alkaline picrate method with a Beckman Coulter analyzer (Fullerton, CA) [24]. A secondary model evaluated ACR collected during the follow up visit as a predictor.

2.4 Mediator variables

Potential mediators assessed at study entry were pulse pressure (mm Hg), mean arterial pressure (mm Hg), hypertension duration (years), glomerular filtration rate (GFR, ml/min per 1.73 m² body surface area), waist circumference (cm), CRP (mg/L), and fasting blood glucose (mg/dL). Blood pressure was measured by an automated oscillometric device (Welch Allyn Inc., Skaneateles Falls, NY, US) taking the mean value of the 3rd-5th recordings. Estimated GFR was obtained using the Modification of Diet in Renal Disease formula: $GFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ [26]. High-sensitivity CRP was measured with a Roche Tina-quant assay using a latex-enhanced immune-turbid metric method [27].

2.5 Moderator variable

Diabetes at study entry was evaluated as a moderator of the relationship between ACR and WMH both directly and through the previously mentioned mediators. Diabetes mellitus was defined by either self-report accompanied by use of anti-hyperglycemic medication, fasting serum glucose > 126 mg/dL [7.0 mmol/L], or non-fasting glucose > 200 mg/dL [11.1 mmol/L] [28].

2.6 Covariates

Covariates included total cranial volume (mL) automatically derived from brain MRI using the FMRIB Software Library (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), age at time of MRI, gender, and ethnicity.

2.7 Statistical analysis

ACR and WMH volume was log transformed to obtain more normal distributions.

Multiple Mediation Model—The multiple mediation path analytic model, as described by Preacher and Hayes [29] and Hayes [30], was used to estimate the *direct effect* of log of ACR (X) at study entry on the log of WMH (Y) at study follow up as well as the *total and specific indirect effects* of log of ACR on the log of WMH through each of the 7 mediators assessed at study entry operating in parallel (i.e., mediators operating in parallel were not causally-linked to other mediators in the model), while controlling for the demographic risk factors and total cranial volume. Secondary analysis evaluated the association between ACR assessed at follow up and WMH with these same mediators from study entry.

Moderation Mediation Model—The conditional process moderation mediation path analytic model as described in Hayes[30] was used to estimate the effect of log of ACR (X) on the log of WMH (Y) directly as well as indirectly through each of the 7 mediators, with both the *conditional direct and indirect effects* moderated by diabetic status, while controlling for the demographic risk factors and total cranial volume.

The procedures of the *PROCESS* computational SAS macro developed by Hayes [30] were used to implement the path analysis-based multiple mediation as well as the conditional moderation mediation models. All path coefficients were unstandardized and estimated using ordinary least squares regression. The *PROCESS* computational SAS macro also allowed for statistical control of aforementioned covariates. A test of the *indirect effects* was conducted by bootstrapping standard errors and confidence intervals (95% bias-corrected) from 5,000 bootstrap samples. We performed all statistical analyses using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). The level of significance for all tests was set at $\alpha=0.05$ (two-tailed).

Testing for Multicollinearity—To ascertain the presence of multicollinearity in our multiple mediation and moderation mediation models, which used ordinary least squares estimation, we examined the variance inflation factor for each of the variables in each model. The estimated variance inflation factor for the variables were all close to 1 and less than 2.18, suggesting that multicollinearity was not present or problematic for any of the variables in our regression-based path-analytic models.

3. Results

Participant characteristics are reported in Table 1.

3.1 Mediator analysis

In the primary analysis we investigated the mediators of the association between ACR at study entry and WMH at follow up. Regarding total effect, ACR obtained at study entry was weakly associated with subsequent WMH volume assessed at follow up seven years later ($\beta=0.039$, $p=0.05$). A significant association (less than $p=0.05$) was seen for ACR differences specifically mediated by pulse pressure ($\beta=0.010$, bootstrap 95% Confidence Interval (CI): 0.002 to 0.021) and waist circumference ($\beta= -0.004$, bootstrap 95% CI: -0.011 to -0.001), with no residual direct association between ACR and WMH ($p=0.2$). Evaluating path coefficients, increased ACR related to increased waist circumference was associated with decreased WMH volume. GFR CRP, mean arterial pressure, hypertension duration or

fasting serum glucose were not significant mediators (bootstrap CI contained 0) of the predictive association between ACR at study entry and subsequent WMH. The degree of association and confidence intervals are shown in Figure 1 and a diagram depicting the mediator relationships is shown in figure 2.

In the secondary analysis, we investigated mediators of the association between ACR assessed concurrently with WMH at follow-up. This cross sectional association between ACR and WMH had a greater total effect ($\beta=0.073$, $p<0.001$) and a greater direct effect ($\beta=0.069$, $p<0.001$) than that observed between ACR at study entry and subsequent WMH. The cross sectional association between ACR and WMH was also significantly mediated by pulse pressure ($\beta=0.004$ bootstrap 95% CI: 0.001 to 0.011) and waist circumference ($\beta=-0.004$ bootstrap 95% CI: -0.010 to -0.001) assessed at study entry, but this accounted for only a small part of the total association. GFR, CRP, mean arterial pressure, hypertension duration or fasting serum glucose were also not significant mediators (bootstrap CI contained 0) of this cross-sectional association between ACR and WMH.

3.2 Moderator analysis

Pulse pressure was a significant mediator of the indirect predictive association between ACR at study entry and subsequent WMH volume whether diabetes (the moderator) was present ($\beta=0.014$ bootstrap 95% CI: 0.001 to 0.039) or absent ($\beta=0.008$ bootstrap 95% CI: 0.002 to 0.020). Waist circumference mediated a negative association between ACR and subsequent WMH only when diabetes was present ($\beta=-0.010$ bootstrap 95% CI: -0.026 to -0.001), not if absent ($\beta=-0.002$, bootstrap 95% CI: -0.008 to 0.001). After adjustment, no association was seen between ACR at study entry and WMH whether diabetes was present ($\beta=-0.002$, $p=0.96$) or absent ($\beta=0.032$, $p=0.14$).

4. Discussion

In this study we examined the nature of the association between markers of microvascular disease in the brain and kidney. Pulse pressure emerged as the primary mediator of the positive association between urine ACR and brain WMH volume assessed 7 years later. Elevations in ACR related to increased pulse pressure, but not mean arterial pressure, CRP or serum glucose, were predictive of increased WMH volume. This was true whether or not diabetes was present. Waist circumference mediated a surprising negative association in those with diabetes, whereby increased ACR in the setting of increased waist circumference was actually associated with less WMH; however, this may be confounded by adjustment in our model. Overall, the association between ACR and WMH was marginal. These findings suggest that when using ACR as a marker to predict risk of brain microvascular disease the clinical context is important. Specifically, ACR likely has the most utility as a marker of WMH when it is secondary to hypertension. This highlights the importance of not viewing markers of end organ disease as pure risk factors, but rather amalgams of cumulative effects of various risk factors that may have distinct associations with the outcomes being studied. Urine albumin had a weaker association with subsequent WMH than we had anticipated. Secondary analysis was therefore performed to evaluate the relationship between ACR assessed at the same time as WMH. This showed a stronger association but importantly replicated the same mediating relationships for pulse pressure and waist circumference.

These findings support susceptibility to arterial pulsatility as the primary link between microvascular damage in the brain and kidneys.

ACR changes related to differences in serum glucose, CRP, mean arterial pressure, hypertension duration and GFR were not predictive of WMH volumes. An unexpected negative relationship was also seen whereby greater ACR related to increased waist circumference was linked to less WMH. This finding should be evaluated in the context of this multivariate mediator model which adjusts for serum glucose, CRP and hypertension which may mediate the negative effects of large waist circumference. The observed waist circumference effect represents only those not mediated through these other factors. Waist circumference is a marker for obesity. Evidence suggests a J- or U-shaped association curve for weight with extreme low values being as harmful as extreme high values [31]. The residual effect of weight after adjustment for risk factors related to obesity may therefore be dominated by the potentially harmful effects of low weight. A protective effect of increased weight beyond what is currently considered ideal has also been suggested for some outcomes [32], though this remains controversial. Future studies with a focus on the relationship between precise descriptors of body habitus, such as lean body mass and waist-hip ratio, and their effect on outcomes with attention to the role of mediators, are needed to better understand this finding.

This study has several limitations. We assessed WMH at only one point in time during the follow up study. We can infer that WMH increases with age across the population, but we cannot assess changes in WMH for individuals. Furthermore, the association between ACR and subsequent WMH was weaker than expected. As a result we conducted secondary analysis for ACR measured at the same time as WMH which more closely mirrored previously reported associations between these two markers. After accounting for the mediator effects of arterial pulsatility and waist circumference, no direct association was seen between ACR and WMH in our community study. Severe renal impairment has certainly been linked to brain insults. Renal insufficiency may lead to an increase in serum glutamate and other excitotoxic substances in the blood [33] or intracranial hemorrhage following thrombolytic treatment for stroke [34]. We do not have cognitive outcomes in our study and we therefore cannot assess whether ACR or WMH are better predictors of cognitive decline. The risk for dementia conferred by ACR and WMH may be due to an association with another factor not evaluated in this study such as disruption of the blood brain barrier [35].

In conclusion, changes in ACR related specifically to pulse pressure are the most associated with greater WMH, which confers risk for cognitive decline associated with numerous neurodegenerative diseases [3]. Changes in ACR related to baseline serum glucose and the inflammatory marker CRP were not indicative of current or future WMH. ACR was more strongly correlated with current than future WMH burden. Overall, this suggests that ACR may be most useful as a marker of current cerebral microvascular disease burden in the setting of elevated pulse pressures.

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Figure 1. Mediators of the predictive association between log of albumin to creatinine ratio and log of subsequent white matter hyperintensity volume

Note. A test of indirect effects was conducted by bootstrapping standard errors and confidence intervals (95% bias-corrected) from 5,000 bootstrap samples. β =unstandardized ordinary least squares regression coefficient. Hypertension duration=only if hypertension was present. The multiple mediation model included statistical control of covariates (demographic risk factors and total cranial volume) that were not proposed to be mediators. Statistical significance set at $\alpha=.05$. Model $R^2=0.24$

Figure 2. Direct and indirect associations between microvascular disease in kidneys and brain
 Diagram of direct association between albumin to creatinine ratio and white matter hyperintensity volume and significant associations found from mediator analysis. A. Albumin to Creatinine Ratio and brain MRI White Matter Hyperintensity volume are both measures of microvascular disease that are significantly associated, but the underlying shared risk factors responsible for this association in the community have been unclear. B. Mediator analysis shows that this association is due to an indirect effect through shared associations with hypertension and waist circumference, with no remaining direct association seen between Albumin Creatinine Ratio and White Matter Hyperintensity volume. Serum glucose and C reactive protein were not significant mediators. The dashed arrow between waist circumference and white matter hyperintensity volume indicates a significant negative correlation

Table 1**Participant Characteristics**

Variable	Study Population
(N=1,281)
Female sex	711 (56)
African American	558 (44)
Caucasian	506 (40)
Hispanic	189 (15)
Other Race	28 (2)
<i>At Study Entry</i>	
Age (years)	43.7 ± 9.6
Albumin Creatinine Ratio (mg/g)	0.3 [0.2-0.6]
Pulse Pressure (mmHg)	47.0 ± 10.6
Mean Arterial Pressure (mmHg)	94.2 ± 11.6
Waist circumference (cm)	95.5 ± 14.4
CRP (mg/L)	4.14 ± 4.82
Fasting Serum Glucose (mg/dL)	98.5 ± 34.4
GFR (ml/min per 1.73 m ² BSA)	98.3 ± 21.4
Diabetes prevalence	97 (7.6)
Hypertension prevalence	300 (23.4)
Hypertension duration ^a (years)	17.1 ± 10.7
<i>At follow up</i>	
Age (years)	50.9 ± 9.5
WMH Volume (mL)	1.47 ± 2.68
Albumin Creatinine Ratio (mg/g)	0.5 [0.2-0.9]

Note: Categorical variables are given as number (percentage) while continuous variables are reported as mean ± standard deviation or median [interquartile range].

^a Among those reporting history of hypertension.