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The Relationship of Kidney Tubule Biomarkers with Brain Imaging in CKD Patients in SPRINT

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Key Points

- Urine biomarker concentrations reflecting kidney tubule injury and dysfunction were not associated with brain MRI measures.
- Higher eGFR was associated with lower total brain cerebral blood flow.
- This is the first evaluation of the relationship of kidney tubule biomarkers with brain imaging by MRI in patients with CKD.

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CKD is associated with stroke and small vessel brain disease, likely reflecting ischemic injury from impaired cerebral blood flow (CBF) regulation (1,2). However, eGFR and urine albumin to creatinine ratio (UACR) primarily quantify glomerular function and injury. A prior report from the Systolic Blood Pressure Intervention Trial (SPRINT) described that lower eGFR was associated with higher CBF, but not with white matter hyperintensities (3). Conversely, higher UACR was associated with white matter hyperintensities, but not CBF, suggesting that different mechanisms may contribute to each.

Biomarkers of kidney tubular function provide noninvasive measurements of kidney tubule health, offering insights beyond eGFR and UACR. Kidney tubules are critical for numerous functional processes to maintain homeostasis, and tubule atrophy and fibrosis are detectable even with normal eGFR levels. Urine tubule biomarkers are prognostic for subsequent loss of kidney function and cardiovascular disease beyond eGFR and UACR (4,5). Prior studies suggest that vascular damage to the kidney tubules may lead to fibrosis, which may have a similar pathology to cerebral vascular injury (6). Because both the kidney and brain regulate organ perfusion independent of systemic blood pressure, we hypothesized that biomarkers reflecting kidney tubule injury and dysfunction may associate with brain perfusion and ischemia.

Among SPRINT participants with CKD, markers of kidney injury and dysfunction have been associated with different domains of cognitive function (7). However, evaluating the association between measures of cerebrovascular disease that may precede subsequent cognitive decline may provide insights into the mechanisms that underlie the kidney-brain axis. Using a subgroup of SPRINT participants with CKD, we evaluated the cross-sectional association of kidney tubular biomarkers with total brain CBF, total brain volume (TBV), and abnormal white matter lesions (WML).

The trial design and outcomes are described elsewhere (8). Of the 9361 randomized participants, an ancillary study measured eight kidney tubule health biomarkers (Table 1) among 2514 individuals with eGFR <60 ml/min per 1.73 m^2 at the baseline study visit (9). Among these 2514, 211 individuals participated in a brain magnetic resonance imaging (MRI) substudy at baseline (10). All participants provided written informed consent, and Institutional Review Boards of all participating institutions approved the study.

Each urine biomarker was transformed on the $\log_2$ scale. We evaluated their associations with total brain CBF, TBV, and WMLs using linear regression adjusted for urine creatinine to account for urine concentration, type of MRI scanner, intracranial volume, age, sex, race (Black versus White/other), years of education, body mass index, history of cardiovascular disease, systolic and diastolic blood pressure, use of an angiotensin converting enzyme inhibitor or angiotensin

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Table 1. Characteristics of participants (n=211)

Characteristics	Mean (SD) or n (%)
Age, yr	72.3 (9.0)
Female sex	118 (56%)
Black race	46 (22%)
Education, yr	7.8 (2.4)
Body mass index, kg/m^2	29.6 (5.5)
History of CVD	24 (11%)
Systolic BP, mm Hg	139.8 (17.4)
Diastolic BP, mm Hg	75.2 (12.4)
Use of Angiotensin II receptor blockers	57 (27%)
Use of ACE inhibitors	74 (35%)
eGFR, ml/min per 1.73 m^2	45.9 (10.4)
Scanner	
3T GE MR750W	14 (7%)
3T Philips Achieva 3.2	69 (33%)
3T Siemens Skyra VD11B	19 (9%)
3T Siemens Tim Trio VB17	45 (21%)
3T Siemens Verio VB17	64 (30%)
Outcomes, mean (SD)	
Total brain volume, cm^3	1110.6 (115.3)
Total brain CBF, mL/100 mg/min	38.3 (12.3)
Abnormal WML volume, cm^3	2.3 (1.0)
Urine biomarkers, median (IQR)	
IL18, pg/ml	30.6 (16.4, 57.1)
KIM-1, pg/ml	848.0 (388.2, 1596.3)
NGAL, ng/ml	27.6 (14.7, 59.2)
YKL40, pg/ml	9.10 (7.7, 10.3)
MCP-1, pg/ml	180.7 (89.6, 329.1)
A1M, mg/g	13.4 (7.1, 24.95)
B2M, ng/mL	104.2 (38.8, 333.5)
Umod, ng/ml	6.5 (4.3, 9.9)
Urine albumin, mg/g	17 (8, 52)

CVD, cardiovascular disease; CBF, cerebral blood flow; WML, white matter lesions; IQR, interquartile range; IL-18, interleukin-18;KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; YKL40, chitinase-3-like protein; MCP-1, monocyte chemoattractant protein-1; B2M, β2-microglobulin; A1M, α1-microglobulin; Umod, uromodulin.

receptor blockers, eGFR, and urine albumin. We also provide the associations of eGFR and urine albumin with the MRI measures separately for the purposes of comparisons of strengths of association.

The mean age was 72.3 (±9.0) years and 56% were women. Other participant characteristics and median concentrations of biomarkers can be found in Table 1. We found no association between urine tubule biomarkers with any of the MRI measures. Generally, higher concentrations of biomarkers were associated with lower total brain CBF and smaller total brain volume by consistent directions of these associations, albeit none of them were statistically significant (Table 2). Higher eGFR was associated with a lower total brain CBF, but not TBV or abnormal WMLs. Urine albumin was not associated with any of the three brain MRI outcomes.

In our study of 211 SPRINT participants with CKD, we found that urine biomarker concentrations reflecting kidney tubule injury and dysfunction were not associated with brain MRI measures at baseline. Similar to what has been found previously in SPRINT, we found that higher eGFR was associated with lower total brain CBF (3).

Although, to our knowledge, this is the first evaluation of the relationship of kidney tubule biomarkers with brain imaging by MRI in patients with CKD, the study has important limitations. First, the lack of statistically significant associations may be due to limited statistical power. Consistent with this, although we observed the association of higher eGFR with lower CBF consistent with prior findings in the larger SPRINT sample, we failed to observe associations of urine albumin with abnormal WML. However, we can conclude that any association of kidney tubule dysfunction markers with these brain MRI findings is likely modest in strength, and weaker than with eGFR. The study is also cross-sectional, precluding evaluation of temporality.

In conclusion, among hypertensive individuals with CKD, concentrations of kidney tubule biomarkers were not associated with neuroimaging markers of cerebrovascular disease. However, given prior findings that these same biomarkers were independently associated with different domains of cognitive function and the limited sample size available here, future studies are warranted to evaluate these biomarkers in larger study samples and over time to clarify mechanisms and identify temporal patterns that may relate kidney function and cognitive decline.

Disclosures

D. Rifkin reports being a scientific advisor or member of American Journal of Kidney Diseases Editorial Board (feature editor), American Board of Internal Medicine Nephrology Exam Committee; and reports having other interests/relationships as Co-investigator, US site, Empagliflozin-KIDNEY study (pending). D.E. Weiner reports having consultancy agreements by participating in Medical Advisory Boards for Akebia (2020, 2021), Cara Therapeutics (2020), Janssen Biopharmaceuticals (2019), and Tricida (2019); reports receiving honoraria for Akebia, paid to DCI; reports receiving research funding from all compensation paid to AstraZeneca (site Principal Investigator (PI), completed 2020), CSL Behring (site PI, ongoing), Goldfinch Bio (site PI, ongoing), Janssen Biopharmaceuticals (site PI, completed 2019), Tufts MC, Dialysis Clinic, Inc. (site PI for trials contracted with Dialysis Clinic, Inc. [DCI] including Ardelyx, ongoing, and Cara Therapeutics, completed); reports receiving honoraria from the National Kidney Foundation for editorial positions at American Journal of Kidney Diseases and Kidney Medicine, Elsevier for royalties from the National Kidney Foundation's (NKF) Primer on Kidney Diseases; reports being a scientific advisor or member as Co-Editor-in-Chief, NKF Primer on Kidney Diseases, 8th Edition, Editor-in-Chief, Kidney Medicine, Medical Director of Clinical Research, Dialysis Clinic Inc., Member, American Society of Nephrology Quality and Policy Committees and American Society of Nephrology representative to Kidney Care Partners, Scientific Advisory Board, National Kidney Foundation; and reports having other interests/relationships as Chair, adjudications committee, Evaluation of Effect of TRC101 in Progression of CKD in Subjects with Metabolic Acidosis (VALOR-CKD Trial, George Institute, Clinical Research Organization [CRO], sponsored by Tricida), Member of the Data Monitoring Committee, "Feasibility of Hemodialysis with GARNET? In Chronic Hemodialysis Patients with a Bloodstream Infection" Trial (Avania CRO). J.H. Ix reports having consultancy agreements with Ardelyx, AstraZeneca, Bayer, Jnana, and Sanifit; reports receiving research funding from Baxter International; and reports being a scientific advisor or member of AlphaYoung. M. Marquine reports research funding

Table 2. Cross-sectional association between biomarkers of kidney tubule function and injury (per two-fold higher) with magnetic resonance imaging measures of brain function

	β Coefficient, 95% Confidence Interval		
Biomarker	Total Brain Cerebral Blood Flow, ml/100 mg per min	Total Brain Volume, cm^3	Abnormal White Matter Lesions, cm^3
Log_2 IL-18, pg/ml	−0.28 (−1.46 to 0.90)	−2.06 (−7.42 to 3.29)	−0.06 (−0.16 to 0.03)
Log_2 KIM-1, pg/ml	0.39 (−0.59 to 1.37)	−2.79 (−7.23 to 1.65)	−0.02 (−0.10 to 0.06)
Log_2 NGAL, ng/ml	−0.20 (−1.25 to 0.84)	−2.97 (−7.71 to 1.77)	0.03 (−0.06 to 0.12)
Log_2 YKL40, pg/ml	−0.06 (−0.84 to 0.72)	−3.16 (−6.68 to 0.36)	0.01 (−0.06 to 0.07)
Log_2 MCP-1, pg/ml	−0.03 (−1.15 to 1.09)	−3.49 (−8.56 to 1.57)	−0.01 (−0.10 to 0.09)
Log_2 A1M, mg/g	0.61 (−0.86 to 2.08)	−0.57 (−7.26 to 6.12)	−0.01 (−0.14 to 0.11)
Log_2 B2M, ng/ml	−0.19 (−0.79 to 0.42)	0.34 (−2.41 to 3.10)	0.01 (−0.04 to 0.06)
Log_2 Umod, ng/ml	1.40 (−0.23 to 3.04)	0.91 (−6.59 to 8.40)	0.06 (−0.08 to 0.19)
eGFR, ml/min per 1.73 m^2	−0.28 (−0.43 to -0.14)[a]	0.45 (−0.19 to 1.09)	−0.01 (−0.02 to 0.05)
Log_2 urine albumin, mg/g	−0.01 (−0.01 to 0.01)	0.02 (−0.01 to 0.05)	0.0002 (−0.0004 to 0.001)

Values are given as given as β coefficient (continuous analysis). Values in parentheses are 95% confidence intervals. Models adjusted for urine creatinine, type of magnetic resonance imaging scanner, intracranial volume, age, sex, race (Black versus White/other), years of education, body mass index, history of cardiovascular disease, systolic and diastolic BP, use of angiotensin receptor blockers or angiotensin converting enzyme, eGFR and urine albumin (except for models with eGFR and urine albumin as predictors). IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein-1; YKL40, chitinase-3-like protein; B2M, β2-microglobulin; A1M, α1-microglobulin; Umod, uromodulin.
[a]$P<0.001$.

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Author Contributions

J. Ix, M. Kurella Tamura, L. Miller, N. Pajewski, D. Rifkin, M. Shlipak, and D. Weiner conceptualized the study; L. Miller was responsible for the formal analysis; M. Kurella Tamura and L. Miller were responsible for the funding acquisition; M. Kurella Tamura was responsible for the data curation, investigation, methodology, and resources; J. Ix provided supervision; J. Ix, M. Kurella Tamura, L. Miller, and N. Pajewski wrote the original draft; J. Ix, M. Kurella Tamura, M. Marquine, L. Miller, N. Pajewski, D. Rifkin, M. Shlipak, and D. Weiner reviewed and edited the manuscript.

Data Sharing Statement

Previously published data were used for this study including Garimella PS, Lee AK, Ambrosius WT, et al. Markers of kidney

tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. *Eur Heart J* 40(42): 3486–3493, 2019 doi: 10.1093/eurheartj/ehz392; Nasrallah IM, Pajewski NM, Auchus AP, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA* 322(6): 524–534, 2019. Complete de-identified patient data is available at the National Heart Lung, and Blood Institute data repository https://biolincc.nhlbi.nih.gov/studies/sprint/.

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