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Relationship of Kidney Tubule Biomarkers with Cognition among Community-Living Elders in the Health ABC Study

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Key Points

- Higher baseline urinary neutrophil gelatinase-associated lipocalin was associated with worse cognitive scores at baseline.
- Lower concentrations of baseline serum bicarbonate (higher is better) were associated with lower cognitive scores at baseline.
- We found no associations with urine markers with longitudinal changes in cognition.

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Previous work has shown associations between kidney dysfunction and impaired cognition (1, 2). However, most studies have used eGFR and albumin-creatinine ratio, markers of glomerular dysfunction and injury, respectively, to evaluate these associations. Possible mechanisms that underlie the kidney-brain axis include vulnerability to microvascular injury caused by hypertension, hypoxia from dysregulated cerebral blood flow, and chronic inflammation and endothelial dysfunction (3, 4). These pathways may influence kidney tubule health, which is not captured by eGFR and albumin-creatinine ratio.

Kidney tubules are critical for a myriad of functions, and tubule atrophy and fibrosis have been detected on kidney biopsy specimens, even in the presence of normal eGFR (5). Abnormalities of the kidney tubules, assessed by urine biomarkers, have been shown in the Systolic Blood Pressure Intervention Trial to be strongly associated with cardiovascular disease, kidney function decline, risk of AKI, and different domains of cognitive function (6, 7). Similarly, kidney tubule biomarkers have been associated with heart failure, cardiovascular disease, and mortality in the Health, Aging and Body Composition (HABC) Study (8, 9). However, these markers have not yet been evaluated with cognitive function in cross-section or with longitudinal cognitive decline. Thus, we evaluated the associations of five urinary markers and one serum marker of kidney tubule health with baseline and repeated measures of cognitive function over time among older adults in the HABC Study.

HABC is a prospective cohort study of 3075 community-dwelling Black and White adults, aged 70–79 at baseline, recruited from two sites in Memphis, Tennessee and Pittsburgh, Pennsylvania. The HABC Study was approved by the institutional review boards of the clinical sites (University of Tennessee Health Science Center, Memphis, and University of Pittsburgh) and the coordinating center (University of California, San Francisco) (10). For analysis with urinary biomarkers (α-1 microglobulin, kidney injury molecule-1 [α1M], interleukin-18 [IL-18], uromodulin [Umod], and neutrophil gelatinase-associated lipocalin [NGAL]), we evaluated 502 participants, selected at random at baseline, from the entire HABC Study (11). Urine markers were transformed on the $\log_2$ scale. Serum bicarbonate ($sHCO_3$) from arterialized venous blood gas was available for all participants who attended the 3-year clinic visit ($n=2287$); thus, we leveraged this larger sample for this marker of kidney tubule acid/base regulation. Cognitive function was defined using the Modified Mini Mental State examination (3MSE), which measures global cognitive function, administered at baseline and years 3, 5, 8, 10, and 11. We also evaluated the Digit Symbol Substitution Test (DSST), which measures executive functioning, administered at baseline and years 5, 8, 10, and 11. Higher scores in both measures indicate better cognitive functioning.

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Table 1. Baseline characteristics

Characteristic	Urine Biomarker Subcohort (n=502)	Serum Bicarbonate Subcohort (n=2287)
Age (yr), mean±SD	73.6±2.8	75.6±2.8
Female sex, *n* (%)	243 (48)	1163 (51)
Black race, *n* (%)	195 (39)	869 (38)
Greater than HS diploma, *n* (%)	214 (43)	1016 (45)
Current smoker, *n* (%)	39 (8)	175 (8)
Depression score (range 0-30), mean±SD	3.2±3.5	4.4±4.1
BMI (kg/m^2), mean±SD	27.2±4.4	27.3±4.8
eGFR (ml/min per 1.73 m^2), mean±SD	71.3±15.8	82.1±18.3
ACR (mg/g), mean±SD	39.4±125.6	34.4±119.9
Systolic BP (mm Hg), mean±SD	134.3±20.7	135.3±20.4
Diastolic BP (mm Hg), mean±SD	70.3±11.4	71.5±11.0
Diabetes, *n* (%)	134 (27)	602 (26)
3MSE (range 0–100), mean±SD	90.7±7.0	90.0±8.7
DSST (range 0–90), mean±SD	36.4±14.0	34.8±14.4

Baseline for urine biomarker subcohort was year 1; baseline for serum bicarbonate subcohort was year 3. HS, high school; BMI, body mass index; ACR, urine albumin-creatinine ratio; 3MSE, Modified Mini Mental State examination; DSST, Digit Symbol Substitution Test.

We used simple linear regression for cross-sectional analyses, linear mixed models with random slopes and random intercepts, and included the biomarker by year interactions to assess change in cognition over time. Models were adjusted for urine creatinine, age, sex, race (Black versus White), educational attainment, study site, body mass index (kg/m^2), smoking status (current versus former versus nonsmoker), alcohol use, depression scale (defined using the Center for Epidemiologic Studies Depression Scale ten-item version), diabetes, systolic BP, use of antihypertension medication, history of stroke, eGFR (ml/min per 1.73 m^2; according to the 2012 Chronic Kidney Disease Epidemiology Collaboration combined creatinine and cystatin C estimating equation [12]), and urine albumin. Analyses with $sHCO_3$ were additionally adjusted for spirometry (horizontal dry rolling seal spirometer). Both sets of analyses followed participants for cognitive decline for up to 11 (urine biomarkers) or 9 ($sHCO_3$) years. For all analyses, statistical significance was defined as $P<0.05$.

Characteristics were similar between cohorts (Table 1). None of the urinary biomarkers were associated with 3MSE at baseline, however, higher urine NGAL was associated with a 0.41 lower (95% CI, −0.81 to -0.01) DSST score ($P=0.04$). Among a larger number of participants in the $sHCO_3$ cohort ($N=2287$), higher concentrations of $sHCO_3$ (higher is better) were associated with a 0.22 (95% CI, 0.07 to 0.37) greater 3MSE score ($P=0.005$) at baseline, but not with DSST (β, 0.26; 95% CI, −0.02 to 0.54; Table 2). We found that higher baseline $sHCO_3$ was associated with a 0.03 (95% CI, −0.06 to −0.01) points/yr ($P=0.02$) decrease

Table 2. Associations of biomarkers of kidney tubule health and with cognitive function at baseline and over time in community-living older adults

	β Coefficient per Two-Fold Higher (95% Confidence Interval)			
	Modified Mini Mental State Examination		Digit Symbol Substitution Test	
Biomarker	Cross-Sectional	Longitudinal	Cross-Sectional	Longitudinal
Urine biomarker subcohort (n=502)				
α1M, mg/dl	0.10 (−0.72 to 0.92)	−0.05 (−0.20 to 0.11)	−0.89 (−2.61 to 0.84)	−0.03 (−0.18 to 0.12)
KIM-1, pg/dl	−0.10 (−0.59 to 0.40)	−0.03 (−0.10 to 0.04)	−0.24 (−1.25 to 0.76)	0.05 (−0.03 to 0.13)
IL-18, pg/dl	−0.08 (−0.53 to 0.36)	−0.03 (−0.10 to 0.04)	−0.41 (−1.30 to 0.47)	−0.33 (−1.22 to 0.56)
Umod, ng/ml	0.35 (−0.16 to 0.86)	0.03 (−0.08 to 0.13)	0.48 (−0.55 to 1.50)	0.37 (−0.66 to 1.40)
NGAL, ng/ml	0.03 (−0.17 to 0.22)	−0.02 (−0.05 to 0.01)	−0.41 (−0.81 to −0.01)[a]	−0.43 (−0.83 to −0.03)
Serum bicarbonate subcohort (n=2287)				
$sHCO_3$, mmol/L	0.22 (0.07 to 0.37)[b]	−0.03 (−0.06 to −0.01)[a]	0.26 (-0.03 to 0.54)	−0.03 (−0.08 to 0.03)

Models adjusted for urine creatinine, age (years), sex, race (Black versus White/other), educational attainment, study site location, body mass index (kg/m^2), smoking status, drinking status, depression scale, diabetes, systolic BP, antihypertension medication, history of stroke, eGFR, and urine albumin. $sHCO_3$ models were additionally adjusted for spirometry (horizontal dry rolling seal spirometer). α1M, α-1 microglobulin; KIM-1, kidney injury molecule-1; Umod, uromodulin; NGAL, neutrophil gelatinase-associated lipocalin; $sHCO_3$, serum bicarbonate.

[a]$P<0.05$.

[b]$P<0.01$.

in 3MSE scores over follow-up. We found no associations with urine markers and longitudinal changes in cognition (Table 2).

In our study of well-functioning, community-dwelling older adults, we found that higher NGAL, a marker of kidney tubule injury, was associated with worse DSST scores, a test of attention and processing speed. However, this was unique to NGAL and not seen with other markers of tubule cell injury. We also found that higher (better) $sHCO_3$, a marker of kidney tubule acid/base homeostasis, was associated with higher 3MSE (a test of global cognitive function) scores at baseline. These associations were independent of glomerular markers of kidney function (eGFR and urine albumin). Contrary to our expectation, we did not observe any significant associations of urine markers with change in cognitive scores over time. Although we did find a longitudinal association with $sHCO_3$ and 3MSE, the effect was small and in the unexpected direction.

Our study has several strengths and limitations. Strengths include a large study of community-dwelling, older adults with a wide range of kidney function, and the availability of longitudinal measures of cognition over time. Limitations include the relatively small sample size for analyses with urine biomarkers, and the few individuals with established CKD. Furthermore, when accounting for multiple comparisons using Bonferroni corrections ($0.05/24=0.002$), none of the observed P values meet the critical value for significance.

In conclusion, we found modest associations between NGAL and DSST at baseline, $sHCO_3$ and 3MSE at baseline, and $sHCO_3$ and decreases in 3MSE scores over time. These associations suggest the potential for kidney tubule injury and acid/base dysregulation to share a common pathology with reduced cognition. However, in addition to the small effect sizes, conclusions should be considered in the context of multiple comparisons and interpreted with caution. Furthermore, because none of the urine biomarkers were associated with longitudinal cognitive decline, the temporal relationship of these associations is uncertain, and should be evaluated in future studies.

Disclosures

D. Drew reports having ownership interest in Ginkgo Bioworks; serving on the editorial board member for *Kidney Medicine*; and having other interests in, or relationships with, National Kidney Foundation. L. Fried reports serving on data safety monitoring boards for Akebia/Fibrogen and 3D Communications; having ownership interest, *via* stock, in Archer Daniels Midland, ATT, Kroger, Procter & Gamble, and Walmart; receiving research funding from AstraZeneca; and having consultancy agreements with Bayer, CSL Behring, and Novo Nordisk. J.H. Ix reports having consultancy agreements with Akebia, AstraZeneca, and Sanifit; serving in an advisory or leadership role for AlphaYoung; and receiving research funding from Baxter International. D.E. Rifkin reports serving on the American Board of Internal Medicine Nephrology Exam Committee, and on the editorial board of *American Journal of Kidney Diseases* (feature editor). M.J. Sarnak reports having consultancy agreements with Akebia (on the steering committee of a trial; funds come to the Division of Nephrology) and Cardurian; having ownership interest in Lilly *via* spouse (spouse is an employee); and receiving research funding from the National Institutes of Health. M.G. Shlipak reports serving in an advisory or leadership role for *American Journal of Kidney Disease*, *Circulation*, *and JASN*; receiving honoraria from AstraZeneca, Bayer, and Boehringer Ingelheim; receiving research funding from Bayer Pharmaceuticals; having consultancy agreements with Cricket Health and Intercept Pharmaceuticals; serving as a board member for the Northern California Institute for Research and Education; and having ownership interest in TAI Diagnostics. All remaining authors have nothing to disclose.

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Author Contributions

L.M. Miller was responsible for formal analysis; L.M. Miller and J.H. Ix wrote the original draft; M.J. Sarnak was responsible for data curation and funding acquisition; J.H. Ix provided supervision; and all authors conceptualized the study and reviewed and edited the manuscript.

Data Sharing Statement

Previously published data from Selamet *et al.* (11) were used for this study.

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