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ORIGINAL ARTICLE

Clinical Risk Factors For Kidney Tubule Biomarker Abnormalities Among Hypertensive Adults With Reduced eGFR in the SPRINT Trial

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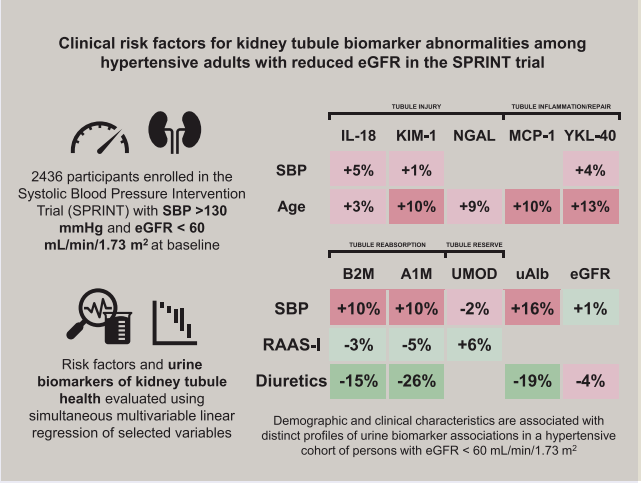
BACKGROUND
Urine biomarkers of kidney tubule health may distinguish aspects of kidney damage that cannot be captured by current glomerular measures. Associations of clinical risk factors with specific kidney tubule biomarkers have not been evaluated in detail.

METHODS
We performed a cross-sectional study in the Systolic Blood Pressure Intervention Trial among 2,436 participants with a baseline estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. Associations between demographic and clinical characteristics with urine biomarkers of kidney tubule health were evaluated using simultaneous multivariable linear regression of selected variables.

RESULTS
Each standard deviation higher age (9 years) was associated with 13% higher levels of chitinase-3-like protein-1 (YKL-40), indicating higher levels of tubulointerstitial inflammation and repair. Men had 31% higher levels of alpha-1 microglobulin and 16% higher levels of beta-2 microglobulin, reflecting worse tubule resorptive function. Black race was associated with significantly higher levels of neutrophil gelatinase-associated lipocalin (12%) and lower kidney injury molecule-1 (26%) and uromodulin (22%). Each standard deviation (SD) higher systolic blood pressure (SBP) (16 mmHg) was associated with 10% higher beta-2 microglobulin and 10% higher alpha-1 microglobulin, reflecting lower tubule resorptive function.

CONCLUSIONS
Clinical and demographic characteristics, such as race, sex, and elevated SBP, are associated with unique profiles of tubular damage, which could reflect under-recognized patterns of kidney tubule disease among persons with decreased eGFR.

GRAPHICAL ABSTRACT



Keywords: biomarkers; blood pressure; chronic; cross-sectional studies; hypertension; kidney tubules; renal insufficiency.

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The estimated prevalence of chronic kidney disease (CKD) is 13% in the United States, and hundreds of millions are estimated to be affected worldwide.[1,2] Without effective prevention and treatment of CKD, it will become an even greater burden on healthcare systems. Although the risk factors for CKD have been well-defined, the specific damage that each risk factor exerts on kidney health has not been delineated and methods for monitoring their specific effects are limited.

Currently, CKD is defined and staged by glomerular function using the estimated glomerular filtration rate (eGFR) from creatinine and/or cystatin C, and glomerular damage, assessed by the urine albumin-to-creatinine ratio (ACR).[3] However, a large body of evidence suggests that tubular function and injury, which are poorly reflected by eGFR and albuminuria, are important risk factors for progressive CKD.[4–6, 5]Furthermore, urine biomarkers associated with kidney tubular health have been shown to have pathophysiological and epidemiological associations with kidney and cardiovascular outcomes, independent of eGFR, ACR, or other risk factors.[7–9] This has been demonstrated in prior studies among participants in the Systolic Blood Pressure Intervention Trial (SPRINT) with eGFR < 60 ml/min/1.73 m^2[10–13] and other studies.[14,15]

If specific risk factors are associated with unique patterns of tubular biomarkers, then the diagnosis of CKD could be enhanced by distinguishing different patterns of kidney disease. They could also identify mechanisms of injury which could be targeted by strategies to distinguish and detect kidney disease earlier in people at risk. We, therefore, evaluated whether known risk factors for CKD incidence and progression had specific associations with urine biomarkers of kidney tubule damage and dysfunction in patients with eGFR < 60 ml/min/1.73m^2 from the SPRINT trial.

METHODS

Participants

The design and outcomes of the SPRINT trial have been described previously.[16] Briefly, SPRINT was a randomized clinical trial in which 9,361 adults aged > 50 years in the United States and Puerto Rico were randomized to antihypertensive treatment with a standard (< 140 mm Hg) or an intensive (<120 mm Hg) systolic blood pressure (SBP) target.[16] Participants had SBP greater than 130 mm Hg and increased cardiovascular risk at baseline. Persons with diabetes, prior stroke, or proteinuria > 1g/day were excluded. In our study, 2,436 SPRINT participants with baseline eGFR <60 ml/min/1.73 m^2 based on the 2012 combined creatinine and cystatin C CKD-EPI equation were included.[17] Institutional Review Boards of all participating institutions approved the study.

Urine biomarkers

Urine specimens were collected from participants at randomization and stored at −80° C until measurement. Eight urine biomarkers were used for this study: interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), chinase-3-like protein-1 (YKL-40), beta-2 microglobulin (B2M), alpha-1 microglobulin (A1M) and uromodulin (UMOD). We also evaluated urine albumin, which was measured by the parent SPRINT study. These biomarkers have been shown to reflect tubular cell injury (IL-18, KIM-1, and NGAL),[18–20] tubulointerstitial inflammation and repair (MCP-1 and YKL-40),[21,22] proximal tubular resorptive capacity (A1M and B2M),[23,24] tubular reserve via protein production in the Loop of Henle (UMOD),[25] and glomerular injury (albumin). Urine creatinine was also measured, and urine biomarker concentrations were adjusted for the concentration of urine creatinine in regression models to control for differences in urine tonicity in all analyses. Nearly all biomarkers were measured in duplicate by assays on a multiplex platform (Meso Scale Diagnostics, Rockville, MD) at the Laboratory for Clinical Biochemistry Research at the University of Vermont; urine A1M was measured in singlicate using a BNII nephelometer (Siemens). When measured in duplicate, measurements were averaged to improve precision.

Clinical characteristics

In this trial of persons without diabetes, we chose characteristics that were accessible and likely to be associated with CKD incidence and progression. Clinical and demographic data were collected by interview and exam at baseline. Risk factors and clinical characteristics that were analyzed in this study included: age, sex, self-reported race (black vs. non-black), smoking status (current versus past or never), SBP, body-mass index (BMI), prevalent heart failure, prevalent atherosclerotic cardiovascular disease (CVD), use of renin-angiotensin-aldosterone system (RAAS) inhibitors, and use of diuretics.

Analysis

Demographic and clinical characteristics of participants were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and *N* (%) for categorical variables. Urine biomarkers and urine creatinine were log-transformed [ln(biomarker)] to normalize the biomarker distributions.

Associations between CKD risk factors and urine biomarkers were initially evaluated using linear regression adjusted only for urine creatinine. Then, to assess the associations between all CKD risk factors and all urine biomarkers in combination simultaneously, we performed multivariable linear regression including all clinical and demographic characteristics as predictors of each urine biomarker. Finally, we estimated associations using the multivariable sparse group least absolute shrinkage and selection operator (MSG-LASSO) method for variable selection.[26] This method is appropriate for settings involving both multiple predictors and multiple outcomes and is able to produce a sparse solution highlighting the most influential predictors of simultaneously analyzed outcomes while removing less influential variables and groups. We reported

standardized regression coefficients as percentages to facilitate comparison of effect sizes, such that estimates would represent expected changes in a biomarker as a percentage per increment change (1 SD for continuous variables) in the predictor. Urine creatinine was included as a predictor in each regression model and the MSG-Lasso analysis to account for changes in biomarker concentration related to urine tonicity.

With ten risk factors and nine kidney biomarkers, these analyses generated numerous pairwise comparisons. In our presentation and interpretations, we focused on the relative magnitude of the risk factor-biomarker associations rather than their statistical significance. We did not adjust for multiple comparisons because each association does not reflect a unique hypothesis; rather, these analyses had a global hypothesis that each potential risk factor for kidney disease would have a distinct pattern of association with kidney tubule health.

Because SBP was the primary target for the SPRINT intervention, we explored its association with urine biomarkers in greater detail. For the three biomarkers that appeared most associated with SBP, we constructed adjusted spline models to depict the association across the range of SBP values at study entry. Splines were created from an ordinary least squares model using restricted cubic splines with knots placed at the quartiles of SBP.

Penalized regression was performed using the *MSG-Lasso* package for R version 3.6.2. All other statistical analyses were performed with SPSS 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and Stata 16.1 (StataCorp. 2019. Statistical Software: Release 16.1. College Station, TX: Stata Corporation).

RESULTS

At baseline, the study population had a mean age of 73 (SD 9) years, 40% were female and 26% were Black. The mean SBP was 140 (SD 16) mm Hg, eGFR was 46 (SD 10) ml/min/1.73m^2, and median urine ACR was 15 (IQR 7-48) mg/g. Baseline prevalence of cardiovascular disease and heart failure were 25% and 6%, respectively; 62% were on renin-angiotensin system inhibitors, and 55% were taking diuretics (**Table 1**). Urine biomarker levels are summarized in **Table 1**; results of univariate analyses are depicted in **Supplementary Figure S1** and results of multiple linear regression are depicted in **Supplementary Figure S2**.

In multivariable analysis utilizing MSG-Lasso, older age was associated with tubule injury, as well as tubulointerstitial inflammation and repair. The strongest association was with YKL-40, where each SD (9 years) older age was associated with 13% higher YKL-40. Weaker but directionally consistent associations were seen with higher KIM-1 (10%), MCP-1 (10%), and NGAL (9%) (Figure 1).

Relative to women, men had higher urine A1M (31%) and B2M (16%) reflecting worse tubule resorptive function. Associations between male sex and tubule injury and repair revealed lower IL-18 (−21%), NGAL (-41%), and YKL-40 (−27%). In addition to the tubule biomarker associations, the male sex was associated with higher urine albumin concentrations (11%).

Black race was associated with several urine biomarkers representing both more and less tubule injury, urine NGAL was 12% higher, whereas KIM-1 was 26% lower than white participants. Black race was also associated with decreased UMOD (−22%), suggesting lower tubular reserve (Figure 1).

In a multivariable analysis using MSG-Lasso, each SD higher SBP at baseline (16 mm Hg) was associated with higher urine levels of A1M (10%) and B2M (10%), suggesting lower tubular resorptive function; and lower levels of UMOD (−2%), reflecting lower tubular reserve (Figure 1). When the association of SBP with levels of A1M, B2M, and urine albumin was graphically depicted using spline functions (Figure 2), we observed that associations appeared steeper and more linear for the markers of proximal tubule dysfunction (A1M and B2M) than for urine albumin.

Atherosclerotic cardiovascular disease was associated with higher levels of urine KIM-1 (8%) and NGAL (8%) reflecting higher levels of tubular injury. Heart failure was associated with lower levels of UMOD (−9%), suggesting lower tubular reserve, and higher A1M (6%), suggesting decreased tubular resorption (Figure 1).

Smoking was associated with higher levels of urine KIM-1 (12%), NGAL (7%), MCP-1 (3%), and A1M (7%), indicating an association with worse tubule health across multiple domains, including tubular injury, tubulointerstitial inflammation and repair, and tubular resorptive function (Figure 1).

Diuretic use was associated with lower concentrations of B2M −15%), A1M (−26%), and urine albumin (−19%). RAAS inhibitors had associations with higher IL-18 (10%), NGAL (16%), and YKL-40 (11%) (Figure 1).

DISCUSSION

Evaluating hypertensive trial participants with an eGFR <60 ml/min/1.73 m^2 and without diabetes, we identified several unique, independent associations between specific clinical characteristics and urine biomarkers representative of various kidney tubule health dimensions. For example, older age, black race, and elevated blood pressure were each associated with unique profiles of tubular damage, which may reflect different mechanisms and patterns of CKD among persons with decreased eGFR. This indicates that tubule biomarker patterns may offer unique insights into phenotypes of kidney health that are not obtainable through the current clinical measures, eGFR, and albuminuria.

Our analysis found that the black race was associated with a urine biomarker profile with different levels of tubular injury biomarkers and lower levels of the tubular reserve. Black Americans are at an increased risk of end-stage kidney disease compared with white Americans,[27,28] and this could be due to socioeconomic, clinical, and genetic risk factors, including apolipoprotein L1 (*APOL1*) genotype.[29–31] *APOL1* has been strongly linked with glomerular injury and albuminuria,[32,33] though high-risk *APOL1* genotype showed no significant association with tubule injury biomarkers IL-18 and NGAL in prior studies.[34] Furthermore, Black persons with low-risk *APOL1* genotypes still have an elevated risk of CKD compared to White persons.[35] Our findings suggest that tubular injury and reserve may explain some of the

Table 1. Sociodemographic and clinical characteristics of SPRINT participants with eGFR <60 ml/min/1.73m^2 at baseline (N = 2,436)

Characteristic	*n*(%) or mean (SD)
Age, years	73 (9)
Female	983 (40)
Race/ethnicity	
White	1,611 (66)
Black	623 (26)
Hispanic	164 (7)
Other	38 (2)
Smoking	
Current	1,105 (45)
Past	1,119 (46)
Never	212 (9)
Systolic BP, mmHg	140 (16)
Diastolic BP, mmHg	74 (12)
No. of antihypertensive meds	
0	101 (4)
1	545 (22)
2	881 (36)
3	698 (29)
≥ 4	211 (9)
RAAS-I use	1,516 (62)
Diuretic use	1,332 (55)
CVD	613 (25)
Heart failure	152 (6)
BMI, kg/m^2	29.5 (5.9)
HDL cholesterol, mg/dl	52 (14)
LDL cholesterol, mg/dl	106 (34)
Total cholesterol, mg/dl	184 (41)
Serum creatinine, mg/dl	1.42 (0.40)
eGFR	46 (10)
UACR, mg/g*	15 (7, 48)
IL-18, pg/mll	31 (16, 57)
KIM-1, pg/ml	850 (387, 1,598)
MCP-1, pg/ml	181 (90, 328)
YKL-40, pg/ml	543 (214, 1,243)
B2m, ng/ml	97 (34, 319)
A1m, mg/ml	13 (7, 25)
Uromodulin, mg/ml	6,520 (4,256, 9,928)
NGAL, ng/ml	28 (15, 59)
Urine albumin, mg/dl	16 (8, 52)

Abbreviations: SPRINT, Systolic Blood Pressure Intervention Trial; CKD, chronic kidney disease; SD, standard deviation; BP, blood pressure; RAAS-I, renin-angiotensin-aldosterone system inhibitors; CVD, cardiovascular disease; BMI, body-mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; IL-18: interleukin-18; KIM-1: kidney injury marker-1; MCP-1: monocyte chemoattractant protein-1, YKL-40: chitinase-3-like protein-1; NGAL: neutrophil gelatinase-associated lipocalin; A1m, alpha-1 microglobulin; B2m, beta-2 microglobulin.

*Urine biomarkers summarized as median (25th percentile, 75th percentile).

excess risks of kidney disease in Black populations that are not conferred by *APOL1* genotype or the other clinical risk factors evaluated in our analysis. Further research is necessary to explore the underlying causes and the significance of our findings regarding black race and urine biomarkers.

Prevalent heart failure was associated with significantly lower urine uromodulin levels in our study, indicating lower tubular reserve. This could be explained, in part, by prior findings which associated lower uromodulin levels with a higher risk of incident cardiovascular events, including acute decompensated heart failure.[13] A prior study had associated heart failure with tubule injury, demonstrated by higher KIM-1, but those findings were not replicated in our study.[36]

Several other associations were intriguing and warrant confirmation. We found that older age was associated with several biomarkers indicating worse tubule health, which confirms that tubule damage accelerates with age, independent of eGFR, and may be a key mechanism for age-related CKD.[37] Similar findings were previously identified in a study that utilized biopsy specimens.[4] Tubule's health profile differed by sex, but associations were mixed. Men had higher levels of urine A1M and B2M, markers of worse tubule resorptive capacity, whereas levels of several other tubular markers of injury—IL-18, YKL-40, and NGAL—were lower in men, suggesting these domains could reflect both underlying similarities and differences in the mechanisms underlying CKD pathophysiology in men and women.[18–20]

Among modifiable risk factors, current smoking had consistent associations suggesting worse tubule health across three categories of tubule biomarkers—injury, inflammation/repair, and resorptive function. Epidemiological studies have identified smoking as a risk factor for CKD as defined by decreased eGFR and end-stage outcomes; however, its associations with albuminuria and, consequently, glomerular injury are less consistent.[38] Our findings suggest that tubular injury may be a key mechanism relating to smoking and incident CKD.

Higher SBP was not only associated with greater albuminuria but also had distinct associations with worse tubule resorption. In fact, the associations of SBP with urine A1M and B2M appeared more linear than the corresponding association with urine albumin. These associations between higher SBP and higher urine albumin, A1M, and B2M, all molecules filtered through the glomerulus, parallel observations from another study where intensive blood pressure lowering was associated with similar changes in urine biomarkers levels.[39] The similarity of these associations of blood pressure lowering and diuretic use with lower levels of the same biomarkers suggests a proposed mechanism. We believe that hemodynamic-mediated decreases in glomerular filtration coupled with preserved or improved tubular resorptive function are causing the lower urine concentrations of filtered biomarkers in participants with lower SBP or diuretic use.[39] Further investigation would be needed to confirm this hypothesis and to reconcile these findings with the comparatively more modest associations between the use of ACE inhibitors or ARBs and these biomarkers.

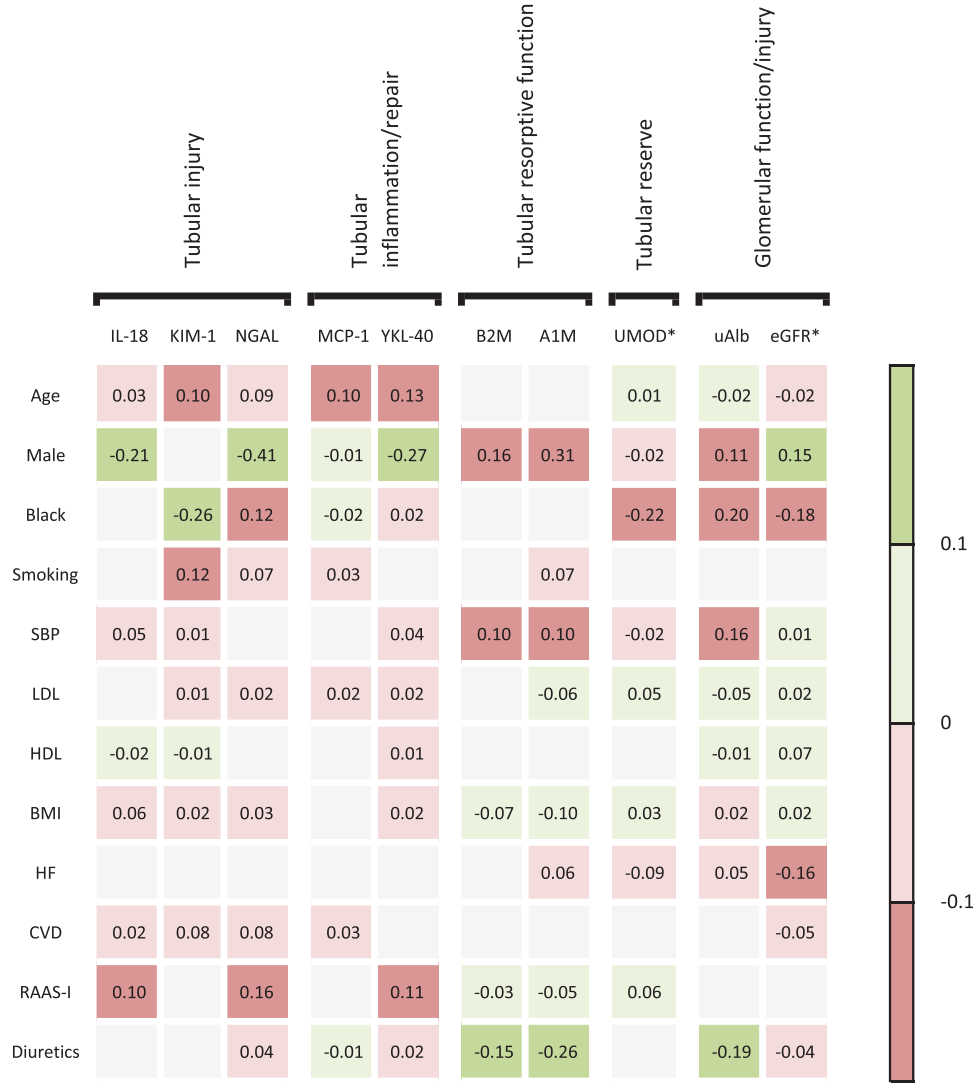

Figure 1. Simultaneous associations of clinical and demographic risk factors with urine biomarkers and eGFR among SPRINT participants with eGFR <60 ml/min/1.73 m^2 at enrollment. Estimates from a simultaneous multivariate linear regression of urine biomarker levels using characteristics selected by MSG-LASSO. Numbers depict standardized beta coefficients for estimates of urine biomarkers per increment change in clinical or demographic characteristics (1 SD for continuous variables). Cells are colored according to the scheme depicted on the right. Coefficients with *P*-values < 0.05 and characteristic-biomarker pairs not selected by MSG-LASSO are omitted and depicted as blank squares. *Color scheme is reversed for UMOD and eGFR due to clinically favorable implications of higher values, in contrast to the remaining urine biomarkers. Abbreviations: eGFR, estimated glomerular filtration rate; SPRINT, systolic blood pressure intervention trial; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein-1; YKL-40, chitinase-3-like protein-1, B2M, beta-2 microglobulin; A1M, alpha-1 microglobulin; UMOD, uromodulin; uAlb, urine albumin; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body-mass index; HF, heart failure; CVD, cardiovascular disease; RAAS-I, renin-angiotensin-aldosterone system inhibitors.

This study has important limitations. SPRINT excluded persons with diabetes and proteinuria >1g/day, which limits the generalizability of our findings. Second, our analysis was cross-sectional and does not provide information on longitudinal relationships between clinical risk factors and changes in kidney tubule health; eGFR <60 ml/min/1.73 m^2 may be a product of the associations of risk factors with the urine biomarker patterns observed in our study, and we are unable to determine whether the observed associations differ among persons with eGFR above 60 ml/min/1.73 m^2. Nonetheless, prior work has demonstrated the relationship between these biomarkers and both incident CVD and CKD progression within SPRINT.[11–13,40,41] Although we adjusted for multiple risk factors of kidney disease, the possibility of residual confounding from unmeasured factors remains. Additional studies will be needed to address these limitations.

The study also has important strengths. We studied a large sample of well-characterized participants with eGFR <60 ml/min/1.73 m^2. The evaluation of 9 biomarkers in parallel allows for a comparison of strengths of association

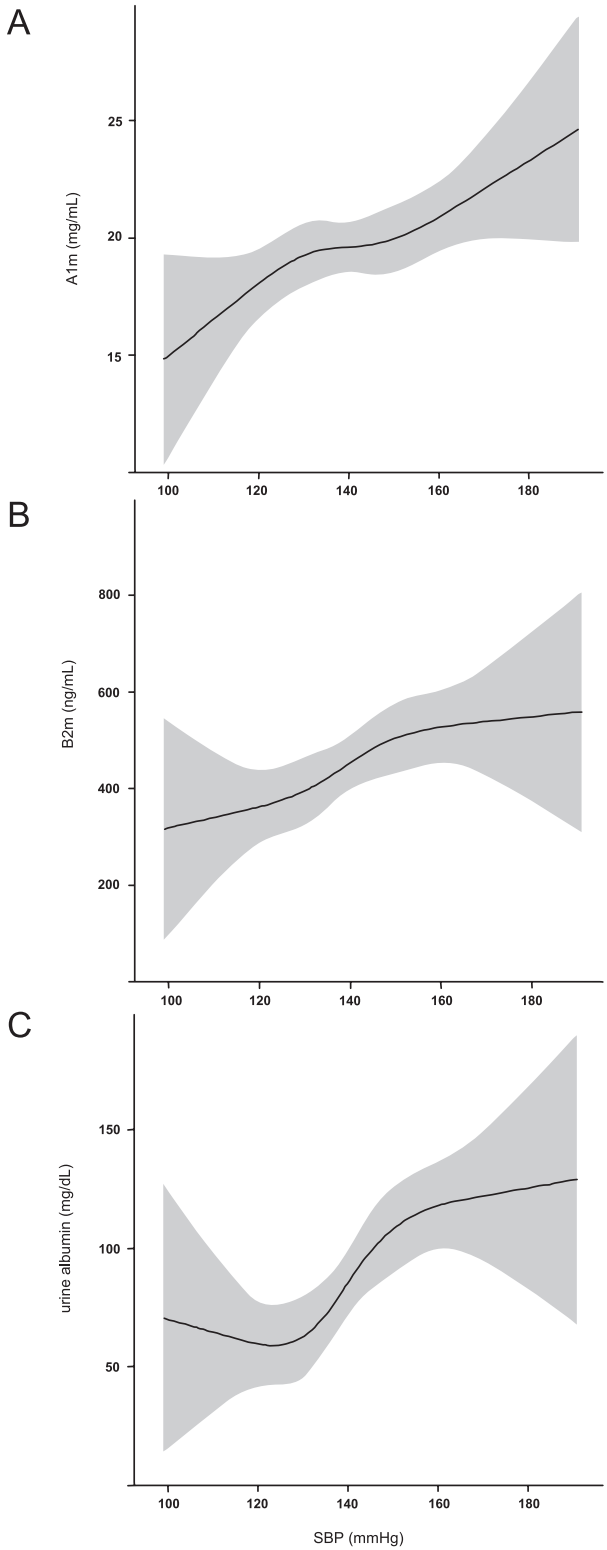

Figure 2. Select urine biomarker concentrations and baseline systolic blood pressure among SPRINT participants with eGFR <60 ml/min/1.73 m^2 at study enrollment. Splines depicting urine alpha-1 microglobulin (A), beta-2 microglobulin (B) and albumin (C) levels based on an ordinary least squares model using restricted cubic splines with knots placed at the quartiles of SBP. Abbreviations: SPRINT, Systolic Blood Pressure Intervention Trial; A1m, alpha-1 microglobulin; B2m, beta-2 microglobulin; SBP, systolic blood pressure.

and insights into unique patterns of tubule damage and dysfunction that would not be possible with a smaller set of biomarkers. The prior evaluations of these biomarkers in SPRINT are another strength, as these biomarkers have established relationships with subsequent risk for multiple endpoints, demonstrating their clinical relevance. Although individual associations between specific risk factors and biomarkers warrant replication, our overall finding is robust that traditional CKD risk factors have strong associations with worse kidney tubule health that are distinct from the risk factors' associations with eGFR and albuminuria.

In summary, among participants with relatively similar levels of kidney function and albuminuria, there are often strikingly different profiles of kidney tubule disease when using expanded measures of tubule health. These distinct associations of demographic and clinical characteristics with markers of kidney tubule health contrast with the current clinical paradigm of assessing kidney health almost exclusively by glomerular function and injury. The tubular injury that is reflected by the novel urine biomarkers analyzed in our study may represent an opportunity for earlier detection and better characterization of CKD, its causes and its consequences.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DATA AVAILABILITY

Data from the trial used in this study is available upon request through the NHLBI BioLINCC repository.

DISCLOSURES

MME and MGS receive research funding from Bayer, Inc. MME has received an honorarium from Boehringer-Ingelheim, Inc. MGS reports honoraria from Bayer, Inc., Boehringer-Ingelheim, and AstraZeneca, and previously served as a consultant to Cricket Health and Intercept Pharmaceuticals. MGS previously served as an advisor to and held stock in TAI Diagnostics. JHI holds an investigator-initiated research grant from Baxter International Inc. CAP receives salary and stock options from and serves as the Chief Medical Officer for Cricket Health, Inc. PSG receives speaking fees from Otsuka, Inc.

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