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Ix, Joachim

Shlipak, Michael

Gutiérrez, Orlando

et al.

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Associations of urine biomarkers of kidney tubule health with incident hypertension and longitudinal blood pressure change in middle-aged adults: the CARDIA Study

Muhammad B. Khan, MD[1], **Rebecca Scherzer, PhD**[3], **Cora E. Lewis, MD**[2], **Rakesh Malhotra, MD**[4], **Joachim H. Ix, MD**[4], **Michael G. Shlipak, MD**[3,5], **Orlando M. Gutiérrez, MD**[1,2]

[1]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

[2]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL

[3]Department of Kidney Health Research Collaborative, San Francisco Veterans Affairs Health Care System and University of California, San Francisco, San Francisco, CA

[4]Division of Nephrology-Hypertension, University of California, San Diego and Nephrology Section Veterans Affairs San Diego Healthcare System, San Diego, CA

[5]Department of Medicine, San Francisco Veterans Affairs Health Care System, San Francisco, CA

Abstract

Background: Urine biomarkers of kidney tubule injury associate with incident hypertension in older adults with comorbidities, but less is known about these associations in younger adults.

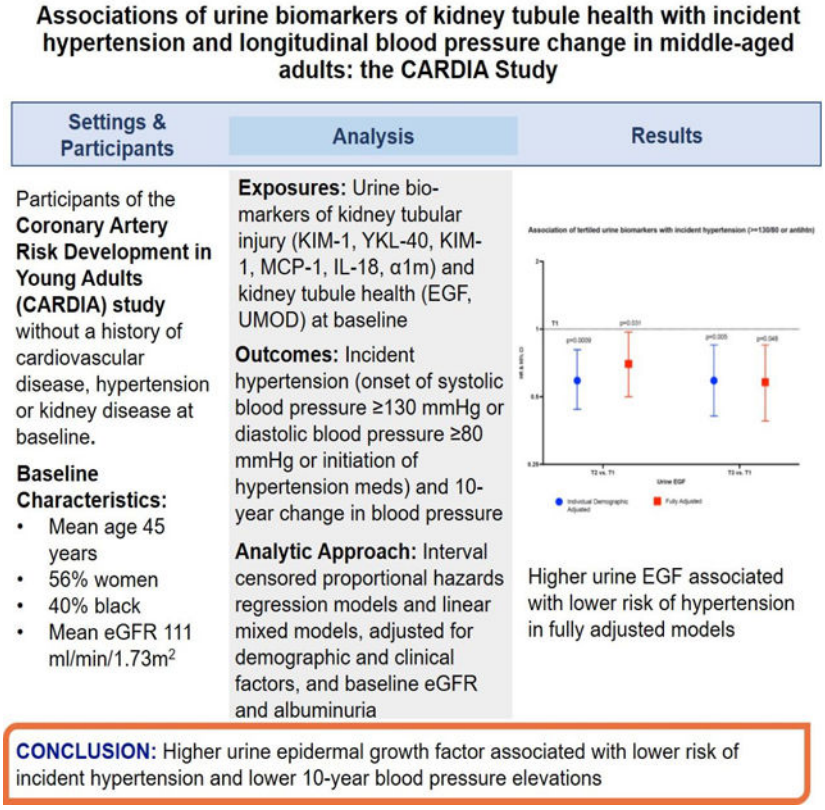
Methods: In 1,170 participants of the Coronary Artery Risk Development in Young Adults (CARDIA) study (mean age 45, 40% Black, 56% women) without hypertension, cardiovascular or kidney disease at baseline, we examined associations of urine monocyte chemoattractant protein-1, alpha-1-microglobulin, kidney injury molecule-1, epidermal growth factor, interleukin-18, chitinase-3-like protein 1, and uromodulin with incident hypertension (onset of systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg or initiation of hypertension meds) and longitudinal blood pressure change in models adjusted for hypertension risk factors, estimated glomerular filtration rate and albuminuria.

Results: After a median 9.9 years (IQR 5.9–10.2), 376 participants developed incident hypertension. In demographic-adjusted analyses, higher tertiles of epidermal growth factor associated with lower risk of incident hypertension in both Black and White participants. After multivariable adjustment, the risk of incident hypertension remained lower in tertile 2 (HR=0.70; 95%CI: 0.50–0.97) and tertile 3 (0.58; 0.39–0.85) of epidermal growth factor vs. tertile 1. In fully-adjusted models, participants in epidermal growth factor tertile 3 had smaller 10-year increases in systolic (−3.4 mmHg; 95%CI −6.1,−0.7) and diastolic blood pressure (−2.6 mmHg; 95%CI −4.6,−0.6) than tertile 1. Other biomarkers showed inconsistent associations with incident hypertension and blood pressure change.

Corresponding Author: Orlando M. Gutiérrez, MD, MMSc, University of Alabama at Birmingham, THT 647, 1720 2nd AVE S, Birmingham, AL 35294, phone: 205-996-2736 fax: 205-996-6650, ogutierrez@uabmc.edu.

Conclusion: In middle-aged adults without hypertension, cardiovascular, or kidney disease, higher urine epidermal growth factor associated with lower risk of incident hypertension and lower 10-year blood pressure elevations.

Graphical Abstract



Keywords

hypertension; health disparities; blood pressure; kidney disease; biomarker

INTRODUCTION

Hypertension (HTN) is a common condition that markedly increases the risk of cardiovascular disease events and death.[1,2] Prevention of HTN is essential for improving cardiovascular outcomes in the general population. This is particularly true for Black adults, who have a disproportionately high prevalence of HTN that manifests earlier in life, on average, and accounts for a substantial fraction of their greater risk of myocardial infarction, heart failure and stroke relative to White adults.[3–5]

Kidney tubules play a major role in regulating blood pressure.[6] Tubular atrophy and interstitial fibrosis disrupt numerous biological processes related to blood pressure control, including solute transport and hormonal regulation of circulating volume, all of which contribute to the onset of HTN.[7–10] In support of this, we showed that urine markers of tubular injury and dysfunction associate with greater incidence of HTN among a small

cohort of middle-aged, HIV-uninfected women, but not among HIV-infected women.[11,12] We also reported that Black individuals have worse markers of tubular injury and dysfunction than White individuals,[13] suggesting that a greater burden of kidney tubular injury in Black adults may partially underlie racial disparities in development of HTN.

A limitation of prior studies was that they focused on older adults with established comorbidities and relatively limited racial diversity. It is therefore unclear how biomarkers of tubular injury and dysfunction manifest in younger, healthier adults, and whether they are associated with incident HTN, longitudinal changes in blood pressure and racial disparities in these outcomes. Therefore, in middle-aged participants of the Coronary Artery Risk Development in Young Adults (CARDIA) Study who were free of HTN, cardiovascular disease and kidney disease at baseline, we hypothesized that higher urine biomarkers of kidney tubular injury or dysfunction (monocyte chemoattractant protein-1 [MCP-1], kidney injury molecule-1 [KIM-1], interleukin-18 [IL-18], chitinase-3-like protein 1 [YKL-40] and alpha-1-microglobulin [α1m]) would be associated with greater risk of incident hypertension and a greater 10-year rise in blood pressure, whereas higher urine biomarkers of kidney tubule health (epidermal growth factor [EGF] and uromodulin [UMOD]) would be associated with lower risk of incident HTN and a lower 10-year rise in blood pressure. In addition, we hypothesized that Black individuals would have higher urine biomarkers of kidney tubule injury and dysfunction than White individuals, and that this would partially mediate the higher risk of incident HTN in Black as compared to White CARDIA participants.

METHODS

Data and Material Disclosure Statement

Requests for access to the data for this study can be made at cardia.dopm.uab.edu. Data used in this manuscript can be made available on request to the CARDIA Coordinating Center.

Study Population

The CARDIA study is a prospective cohort study of 5,115 healthy Black and White adults aged 18 to 30 years recruited from 4 field centers (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) from 1985 to 1986. There have been 8 follow-up examinations completed since the baseline examination, spanning 30 years of follow-up. The overall design and objectives of the CARDIA study have been presented in detail elsewhere.[14,15] A total of 3,547 of the original 5,115 participants attended the year 20 examination, which was considered baseline for the current study. We excluded participants with prevalent HTN, defined as taking antihypertensive medications, or having a systolic blood pressure (BP) ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg at the year 20 visit (n=1269). We further excluded those with cardiovascular disease (history of heart failure, myocardial infarction, coronary revascularization, angina, stroke, transient ischemic attack or peripheral vascular disease, n=251), those missing follow-up BP values (n=124), and those without adequate urine samples for biomarker measurement (n=733), leaving a total of 1,170 participants in the final analytic sample.

Primary exposures

The primary exposures were urine concentrations of EGF, YKL-40, KIM-1, MCP-1, IL-18, UMOD, and α1m measured in spot urine samples collected at the year 20 examination. All biomarkers were measured in the University of Alabama at Birmingham-University of California, San Diego O'Brien Center for Acute Kidney Injury Research Bioanalytical Core[16] after a single freeze-thaw using multiplex assays on the Meso Scale Discovery (MSD) platform, except for α1m which was measured using an enzyme-linked immunosorbent assay (Abcam ab108884). Overall inter- and intra-assay coefficients of variation were 1.2–5.6% and 3.1–13.5%, respectively. Each biomarker was measured in duplicate for each sample and results were averaged to improve precision. Laboratory personnel who were making measurements were blinded to clinical outcomes. The median concentrations (interquartile range) of each biomarker overall and by tertile are depicted in Table S1.

Outcomes

The primary study outcome was the development of incident HTN at the year 25 or 30 examinations. Blood pressure was measured at each exam using Omron HEM907XL sphygmomanometers per a standardized protocol (3 blood pressure readings taken after sitting in a quiet room for 5 minutes). The second and third readings were averaged to give the final result at each examination visit. Incident HTN was defined as the first study examination at which the participant had systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg or initiated BP medications as per most recent 2017 guidelines.[17] As an exploratory outcome, we defined incident HTN as the first study examination at which the participant had systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or initiated BP medications. As a secondary analysis, we additionally modelled continuous, longitudinal trajectories of SBP and DBP using measures from the year 20, 25, and 30 exams.

Covariates

The following covariates were obtained from the year 20 exam: age, race, sex, smoking status, diabetes, lipids, body mass index (BMI), physical activity, education, and income. Age, sex, race, education level, income and smoking status were self-reported by participants. Standardized height and weight measurements were used to calculate BMI. Physical activity was determined through a questionnaire and reported as exercise units[18,19]. High-density lipoprotein cholesterol (HDL-C) was determined by precipitation with dextran sulfate-magnesium chloride[20] and total cholesterol and triglycerides were determined enzymatically[21]. Low density lipoprotein cholesterol (LDL-C) was derived by the Friedewald equation[22]. Diabetes was defined as a fasting glucose ≥ 126 mg/dL or taking a medication for diabetes. Cystatin C was measured at the year 20 examination by nephelometry using the N Latex cystatin C kit (Dade Behring, now Siemens, Munich, Germany) at the University of Minnesota. Cystatin C values were calibrated to reference values by inflating by 12% prior to calculating eGFR[23]. Urine albumin and urine creatinine were measured in spot urine samples using nephelometry and the Jaffé method, respectively. Urine albumin to creatinine ratios (ACR) were expressed as mg/g.

Statistical Analysis

We examined demographic and clinical characteristics overall and stratified by race (Black and White), comparing characteristics by race with the chi-square and Wilcoxon rank-sum tests for categorical and continuous variables, respectively.

We evaluated associations of race with each urine biomarker using the SAS SYSLIN procedure for seemingly unrelated regression (SUR), using log-transformed biomarker concentrations as the dependent variables to correct for right-skew.[24] The SUR model examines correlations among the errors in different equations to optimize efficiency of the regression estimates while enabling potentially different predictors for each dependent variable. Biomarkers were standardized to the same scale (mean 0, standard deviation [SD] 1) prior to analysis. Models were sequentially adjusted for age, sex, race, and urine creatinine to account for differences in urine tonicity (Model 1); and smoking, diabetes, baseline systolic BP, baseline diastolic BP, HDL-C, LDL-C, triglycerides, BMI, physical activity, education, income, urine albumin and eGFR (Model 2). We additionally compared biomarker concentrations indexed to urine creatinine in descriptive analyses to assess whether concentrations differed by race.

We next modelled associations of urine biomarker concentrations with incident HTN. Because the exact date of developing HTN was unknown, we used interval-censored proportional hazards regression models.[25] We modeled the scaled biomarkers as continuous, linear predictors (per 1-SD higher) and also categorized into tertiles, setting the lowest as the reference value and also testing for linear trend. As described above, models were constructed in stages, with adjustment for urine creatinine to account for urine tonicity in all models. Additionally, we tested biomarker-by-race interactions to determine whether urine biomarker associations differed among Black versus White participants. We also evaluated whether urine biomarkers were mediators of the association between race and incident HTN using the SAS Causalmed procedure, which implements the regression approach of VanderWeele.[26] The outcome model was analyzed using a binary distribution with logit link function, while each mediator model (race -> log(biomarker)) assumed a normal distribution with identity link function.

Finally, we investigated the association of biomarkers with BP changes over time with linear mixed models, using random intercepts and slopes to account for intra-individual correlations. These models included biomarker-by-time interactions to determine whether biomarker concentrations were associated with differential increases in BP over time. Models controlled for traditional kidney disease risk factors and sociodemographic characteristics, as described above, as well as covariate by time interactions. We further tested three-way interactions of each biomarker by race and time (biomarker *x* race *x* time) to determine whether urine biomarker associations with BP changes differed by race. Additionally, we generated least squares mean estimates of systolic and diastolic BP at exam years 20 (baseline), 25 and 30 within tertiles of each biomarker in fully adjusted models. Although our study involved multiple biomarkers, we did not include formal adjustments for multiple comparisons as our hypotheses are biologically coherent meaning that results should be mutually reinforcing, rather than a series of independent tests. Therefore, formal multiple comparisons adjustments would not be appropriate.[27–29]

All analyses were performed using SAS (Version 9.4, Cary, NC) and p-values < 0.05 were considered statistically significant for all analyses including interaction terms.

RESULTS

Study population

Baseline characteristics of the study population overall and stratified by race are depicted in Table 1. The median age overall was 45 years (interquartile range [IQR] 42,48), 56% were female, 40% black, and the median eGFR was 111 (IQR 104,117) ml/min per 1.73m^2. As compared to White participants, Black participants were on average younger, more likely to be current smokers, have lower income, educational achievement, and physical activity, and had higher BP, BMI, and eGFR.

Comparisons of urine biomarker concentrations by race

Differences in urine biomarker concentrations by race are depicted in Table 2. Urine concentrations of EGF, KIM-1, IL-18, UMOD and α1m were significantly lower in Black as compared to White participants in models adjusted for age, sex, and urine creatinine, while there was little difference in levels of YKL-40 or MCP-1. With the exception of UMOD, each of these biomarkers remained significantly lower in Black compared to White participants after further adjustment for smoking, diabetes, systolic BP, diastolic BP, lipids, BMI, physical activity, education, income, eGFR and urine albumin.

Associations of urine biomarkers with incident HTN

During a median 9.9 years of follow up (IQR 5.9–10.2), 216/463 (47%) Black participants and 160/707 (23%) White participants developed hypertension. The event rate of HTN decreased across increasing tertiles of EGF, from 5.7 per 100 person-years in Tertile 1 to 2.6 in Tertile 3 (Table 3). In analyses adjusted for demographics and urine creatinine, higher tertiles of EGF were each associated with lower risk of incident HTN (*P*-value for linear trend 0.003). In the fully-adjusted model, the risk of incident HTN remained significantly lower in the second tertile (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.50,0.97) and in the third tertile (HR 0.58, 95%CI 0.39,0.85) of EGF as compared to the first tertile of EGF (*P*-value for linear trend 0.02). When modeled continuously, the direction of the association of EGF with incident HTN was similar but the association did not reach statistical significance in any model. Associations of urine EGF with incident HTN did not differ by race whether EGF was examined in tertiles or on a continuous scale ($P_{interaction}$ > 0.10 for all comparisons, Table S2, Figure 1). The results were similar in sensitivity analyses using a more stringent definition of incident hypertension (BP ≥140/90 or initiation of BP medications, Tables S3 and S4, and Figure S1). There were no statistically significant associations of any of the other biomarkers of tubular injury or dysfunction with incident HTN in any model (Table 3). Higher urine albumin was associated with greater risk of incident HTN when modeled as a continuous variable in the demographic- and creatinine-adjusted model (HR=1.24, 95%CI 1.09,1.42) but was attenuated in the fully adjusted model (HR=1.14, 95%CI 0.99,1.31).

The risk of incident HTN was nearly two-fold greater in Black vs. White participants (HR 1.97, 95%CI 1.52,2.56) in a model adjusted for age, sex, urine creatinine, smoking, diabetes, baseline BP, lipids, BMI, exercise, education, income, urine albumin and eGFR. This risk was minimally attenuated after further adjustment for EGF (HR=1.89, 95%CI 1.43,2.49) and showed no attenuation after adjustment for other biomarkers. A formal test of mediation showed that EGF mediated 3.8% of the residual Black-White difference in HTN risk.

Associations of urine biomarkers with BP change

After 10 years of follow-up, systolic BP and diastolic BP increased by an average of 9.6 mmHg (95%CI 4.3,6.0) and 5.6 mmHg (95%CI 4.7,6.6), respectively, in Black adults; and by an average of 5.1 mmHg (95%CI 4.3,6.0) and 3.6 mmHg (95%CI 2.9,4.2), respectively, in White adults. Table 4 depicts associations of urine biomarkers with 10-year BP changes. As compared to the lowest tertile of EGF, the highest tertile of EGF associated with a 3.5 mmHg smaller increase in systolic BP over 10 years (95%CI −6.1, −0.9) in the demographic- and urine creatinine-adjusted model (*P*-value for linear trend 0.02), with minimal attenuation in the fully adjusted model (*P*-value for linear trend 0.04). These associations did not show statistically significant differences by race (Table S5 and Figure S2, $P_{\text{interaction}} > 0.10$ for all comparisons). When EGF was examined on a continuous scale, there was no significant association of urine EGF with 10-year change in BP in any model. The middle tertile of IL-18 was associated with a greater rise in systolic BP over 10 years in the demographic- and creatinine-adjusted model (2.43 mmHg, 95%CI 0.54,4.32) and in the fully adjusted model (2.53 mmHg, 95%CI 0.59,4.48); but there was no association of IL-18 with systolic BP change when IL-18 was examined on a continuous scale.

When examining diastolic BP change, results were similar, with the 2nd and 3rd tertiles of EGF being associated with smaller increases in diastolic BP over 10 years in the fully adjusted models, relative to the lowest tertile of EGF. Higher urine albumin was associated with a lesser 10-year rise in diastolic BP when examined as a continuous variable in the model that adjusted for demographic variables and urine creatinine, but the association was no longer statistically significant in the fully adjusted model, or when urine albumin was examined in tertiles in any model. No other urine biomarker was associated with 10-year change in diastolic BP in any model.

DISCUSSION

In this prospective cohort study of middle-aged adults free of HTN, cardiovascular disease and kidney disease at baseline, higher tertiles of urine EGF were associated with lower risk of incident HTN, and lesser 10-year mean rises in systolic and diastolic BP, independent of classic risk factors for HTN, urine albumin and eGFR. The associations did not appreciably differ by race. Although urine EGF was lower in Black as compared to White participants, EGF mediated only a small fraction of the risk of incident HTN in Black vs. White participants. Collectively, these results indicate that urine EGF could provide new insights into mechanisms underlying the development of hypertension that are not captured by more traditional measures of kidney health like eGFR and albuminuria.

EGF is a 53-amino acid polypeptide that is produced in multiple tissues including the kidney, where it is expressed in the loop of Henle and the distal convoluted tubule.[30] EGF regulates cellular metabolism, glomerular hemodynamics, and cell growth in the kidney by binding to the extracellular domain of the EGF receptor.[31] These actions play a critical role in promoting kidney repair, as evidenced by data showing that EGF aids tubular injury recovery by up-regulating regenerative pathways.[32] EGF may also play an important role in regulating vascular smooth muscle function.[33] Because of the important role of EGF in repairing kidney tubule damage, urine concentrations of EGF may be a marker of tubule reparative capacity.[34] Thus, unlike most urine biomarkers, higher urine EGF is considered a protective factor, correlating with lower markers of tubular damage such as interstitial fibrosis and tubular atrophy,[35] and lower risk of incident CKD and rapid kidney function decline.[36]

Kidney tubules play an important role in regulating BP, but few studies examined whether urine EGF, an established biomarker of tubular health, associates with risk of HTN or other BP parameters. In a cross-sectional study of men and women living with HIV (mean age 48), higher urine EGF concentrations were associated with lower prevalence of hypertension in unadjusted analysis, though the association was no longer significant after adjustment for other risk factors including eGFR.[12] In a prospective cohort of women living with HIV participating in the Women's Interagency Health Study (mean age 45), higher systolic BP rise was associated with a greater reduction in urine EGF concentrations over time.[37] The novelty of the current study is that we examined a relatively healthy cohort of middle-aged adults without HTN, cardiovascular disease and kidney disease at baseline and show that higher urine EGF is independently associated with lower risk of incident HTN and lower rise in systolic and diastolic BP over 10 years. Moreover, urine EGF was the only one of seven biomarkers of kidney tubule injury consistently associated with risk of incident HTN, and was more strongly associated than urine albumin as a measure of glomerular injury. Thus, although these results need to be confirmed in separate cohorts, they suggest that urine EGF is linked to pathophysiologic processes underlying the development of HTN, such as repair pathways up-regulated in response to tubular injury, providing insights into the origins of HTN in healthy adults.

We previously reported that Black individuals with diabetes and chronic kidney disease had greater evidence of kidney tubule injury and dysfunction than their White counterparts,[13] leading us to hypothesize that a higher burden of tubular injury in Black individuals may partly account for Black-White differences in HTN risk. We found that urine EGF concentrations were lower in Black than in White participants of the current study, consistent with what has been reported before. Despite these differences, our analysis found that urine EGF mediated only a small fraction of the higher risk of HTN in Black vs. White adults, suggesting that differences in kidney tubule reparative capacity may play a relatively minor role in racial disparities in HTN risk.

No urine biomarker of tubule injury or dysfunction other than EGF was associated with HTN risk and longitudinal change in BP. This may suggest that kidney tubule damage in general may not play a critical role in the etiology of HTN in middle-aged Black and White adults, but rather certain aspects of kidney tubule repair linked to EGF excretion in the urine.

Nonetheless, by design we studied a relatively healthy subset of individuals who were free of HTN and other established cardiovascular and kidney disease risk factors at baseline. It may be that we would have observed an association of other biomarkers of kidney injury and dysfunction with incident HTN if we had examined a sicker cohort of individuals at higher risk for HTN.

Our study had a number of limitations. Since this was an observational study, we cannot infer any causal associations between higher urine EGF and lower risk of incident HTN or lower 10-year rise in blood pressure. CARDIA participants only included Black and White adults, precluding us from drawing conclusions in other racial/ethnic groups. We measured urine biomarkers at only one time-point, so we could not determine the relationship of longitudinal changes in the biomarkers with BP changes over time. Our study also had key strengths such as its utilization of a large, well-characterized cohort of community-dwelling adults with available samples for measurement of urine biomarkers, and the measurement of all biomarkers in the same laboratory with detailed quality-controlled measures.

In conclusion, among seven urine biomarkers of kidney tubular health, higher urine EGF was uniquely associated with lower risk of incident HTN and a lesser rise in systolic and diastolic BP over 10 years in relatively healthy middle-aged adults. While Black individuals have lower EGF than White individuals on average, this explained only a modest degree of racial differences in HTN incidence. These results provide new insights into the potential role of kidney tubular injury repair mechanisms in BP regulation in community-living individuals without prevalent HTN, kidney or cardiovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NON-STANDARD ABBREVIATIONS

HTN	hypertension

MCP-1	monocyte chemoattractant protein-1
KIM-1	kidney injury molecule-1
IL-18	interleukin-18
YKL-40	chitinase-3-like protein 1
α1m	alpha-1-microglobulin
EGF	epidermal growth factor
UMOD	uromodulin
CARDIA	Coronary Artery Risk Development in Young Adults
BP	blood pressure
eGFR	estimated glomerular filtration rate

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Perspectives:

Hypertension is common and associated with greater risk of cardiovascular disease events and death, making prevention of hypertension a key public health priority. Kidney tubules play an important role in regulating blood pressure, yet little is known about whether biomarkers of kidney tubular health associate with future risk of hypertension. The results of this study suggest that kidney tubular repair mechanisms linked to epidermal growth factor may play a role in the development of hypertension which may point to novel therapeutic pathways for preventing hypertension in adults.

NOVELTY AND RELEVANCE

What is new?

Higher urine concentrations of epidermal growth factor were independently associated with lower risk of the development of hypertension and lesser 10-year rise in systolic and diastolic blood pressure in community-dwelling, middle-aged adults free of hypertension, cardiovascular disease and kidney disease at baseline.

What is Relevant?

Kidney tubules play a major role in regulating blood pressure, but little is known about whether biomarkers of tubular injury and dysfunction are associated with incident hypertension, longitudinal changes in blood pressure or racial disparities in these outcomes, particularly in middle-aged adults.

Clinical/Pathophysiological Implications:

Urine epidermal growth factor is a biomarker of kidney tubule regenerative capacity, with higher concentrations equating with greater kidney tubule health. These results suggest that kidney tubular repair pathways linked to epidermal growth factor may play a role in the future development of hypertension and longitudinal change in blood pressure.

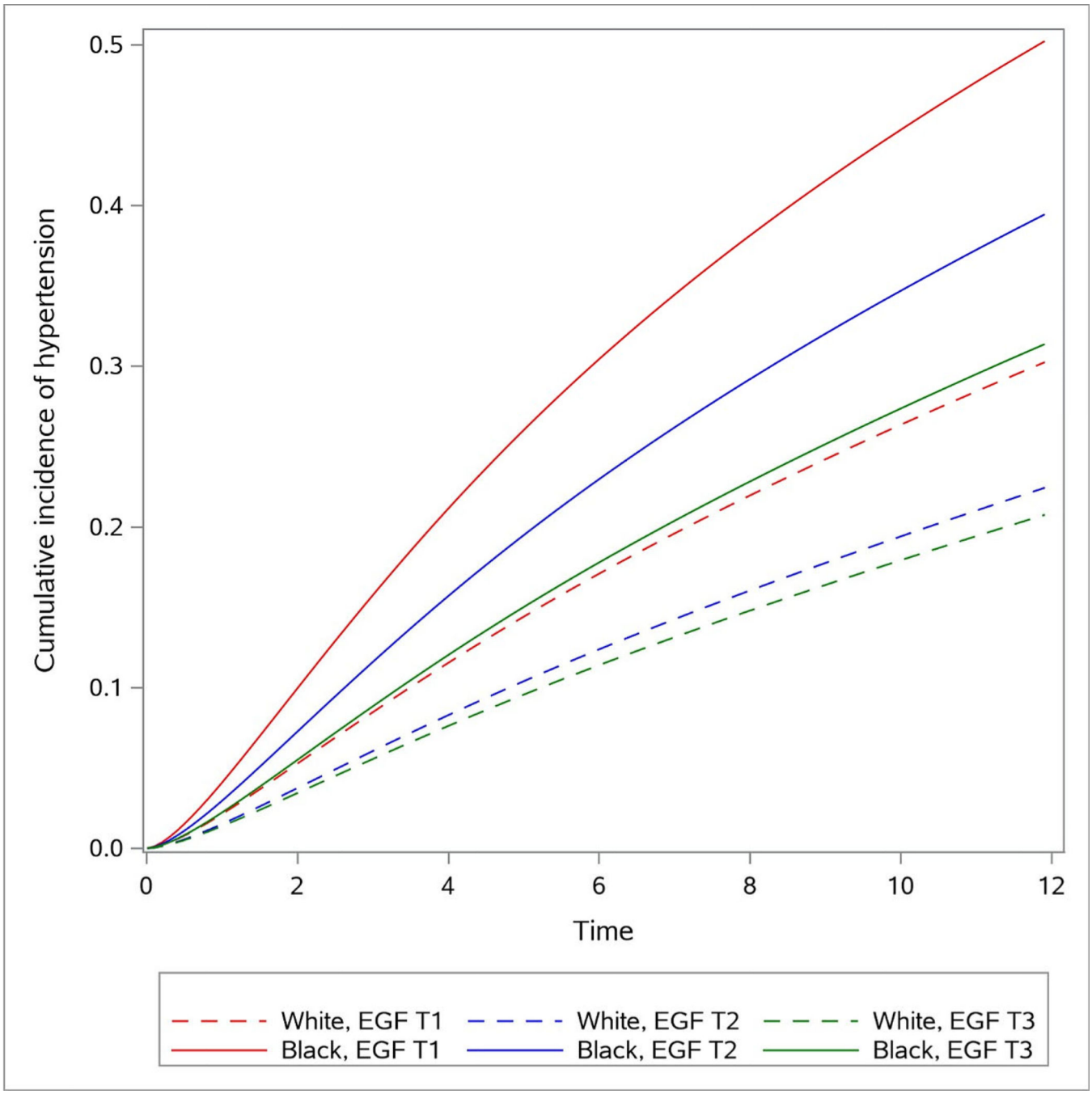

Figure 1.

Cumulative incidence of hypertension (≥130/80 or use of anti-hypertensive medications) by tertiles of urine epidermal growth factor, stratified by race. Estimates are from interval-censored proportional hazards regression models. Models are adjusted for age, sex, urine creatinine, smoking, diabetes, systolic blood pressure, diastolic blood pressure, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, body mass index, exercise, education, income, urine albumin, and estimated glomerular filtration rate.

Table 1.

Demographic and clinical characteristics of study participants overall and stratified by race at baseline *

Parameter	Overall	Black	White
	N=1170	N=463	N=707
Age	45 (42, 48)	43 (40, 47)	46 (43, 48)
Female	656 (56%)	264 (57%)	392 (55%)
Smoking status			
Current	188 (16%)	101 (22%)	87 (12%)
Past	227 (20%)	53 (12%)	174 (25%)
Never	743 (64%)	304 (66%)	439 (63%)
Diabetes	54 (5%)	26 (6%)	28 (4%)
Systolic BP, mmHg	109 (103, 116)	111 (105, 117)	108 (102, 115)
Diastolic BP, mmHg	67 (61, 72)	68 (64, 73)	66 (60, 71)
LDL-c, mg/dL	107 (86, 128)	107 (86, 131)	108 (86, 127)
HDL-c, mg/dL	53 (43, 64)	53 (44, 64)	52 (43, 64)
Triglycerides, mg/dL	81 (58, 120)	75 (55, 106)	86 (60, 130)
Body mass index, kg/m^2	27 (24, 30)	28 (25, 33)	26 (23, 29)
Physical activity intensity score	315 (148, 543)	276 (111, 477)	354 (187, 578)
Annual household income			
<$50,000/year	364 (31%)	216 (47%)	148 (21%)
$50–99,000/year	416 (36%)	167 (37%)	249 (36%)
≥$100,000/year	376 (33%)	74 (16%)	302 (43%)
Education			
≤ High school graduate	244 (21%)	151 (33%)	93 (13%)
College	622 (53%)	263 (57%)	359 (51%)
Graduate School	304 (26%)	49 (11%)	255 (36%)
eGFR, mL/min/1.73m^2	111 (104, 117)	113 (106, 119)	110 (103, 116)
Urine ACR, mg/g	4.1 (2.8, 6.0)	4.2 (2.8, 6.6)	4.0 (2.8, 5.6)

* CARDIA Year 20 examination

Data displayed are n (%) or median (interquartile range).

Abbreviations: BP, blood pressure; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; eGFRcys, estimated glomerular filtration rate (cystatin C); ACR, albumin-to-creatinine ratio

Table 2.

Differences in urine biomarker concentrations comparing Black to White participants

Biomarker	Model 1	Model 2
	Standardized Estimate (95%CI)	Standardized Estimate (95%CI)
EGF	**−0.38 (−0.44, −0.32)**	**−0.40 (−0.47, −0.33)**
YKL-40	−0.017 (−0.13, 0.095)	−0.071 (−0.20, 0.060)
KIM-1	**−0.47 (−0.55, −0.38)**	**−0.53 (−0.62, −0.43)**
MCP-1	−0.013 (−0.094, 0.067)	−0.037 (−0.13, 0.056)
IL-18	**−0.20 (−0.29, −0.11)**	**−0.28 (−0.38, −0.17)**
UMOD	**−0.12 (−0.24, −0.0012)**	−0.13 (−0.27, 0.010)
α1m	**−0.20 (−0.29, −0.10)**	**−0.19 (−0.31, −0.078)**

Bolded values indicate statistically significant results

Models estimate average standard deviation difference in urine biomarker concentrations in Black as compared to White participants.

Abbreviations: EGF, epidermal growth factor; YKL-40, chitinase-3-like protein 1; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant protein 1; IL-18, interleukin 18; UMOD, uromodulin; α1m, α1-microglobulin

Model 1 adjusts for age, sex, race, and urine creatinine

Model 2 adjusts for Model 1 + smoking, diabetes, systolic blood pressure, diastolic blood pressure, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, body mass index, exercise, education, income, urine albumin and estimated glomerular filtration rate

Table 3.

Associations of urine biomarkers with incident hypertension, defined as onset of systolic BP ≥130 or diastolic BP≥80 mmHg or initiation of blood pressure medication

Biomarker (range)	n	Event rate* (95%CI)	Model 1 HR (95%CI)	Model 2 HR (95%CI)
EGF, pg/ml				
Per 1 SD higher	1170	3.7 (3.3, 4.0)	0.87 (0.71, 1.06)	0.89 (0.72, 1.10)
T1 (135–8670)	390	5.7 (4.7, 6.9)	1.00 (ref)	1.00 (ref)
T2 (8670–16762)	390	3.0 (2.5, 3.6)	**0.59 (0.44, 0.81)**	**0.70 (0.50, 0.97)**
T3 (16771–96947)	390	2.6 (2.1, 3.3)	**0.59 (0.41, 0.85)** †	**0.58 (0.39, 0.85)** ‡
YKL-40, pg/ml				
Per 1 SD higher	1170	3.7 (3.3, 4.0)	0.98 (0.88, 1.10)	0.99 (0.88, 1.11)
T1 (0.5–158)	390	3.7 (3.1, 4.5)	1.00 (ref)	1.00 (ref)
T2 (159–408)	390	3.9 (3.3, 4.6)	1.09 (0.84, 1.42)	1.22 (0.92, 1.60)
T3 (409–7336)	390	3.3 (2.7, 4.0)	0.86 (0.64, 1.14)	0.94 (0.70, 1.27)
KIM-1, pg/ml				
Per 1 SD higher	1170	3.7 (3.3, 4.0)	1.10 (0.94, 1.29)	1.03 (0.87, 1.22)
T1 (0.5–199)	390	4.3 (3.5, 5.3)	1.00 (ref)	1.00 (ref)
T2 (199–538)	390	3.6 (3.0, 4.3)	1.00 (0.74, 1.35)	0.98 (0.72, 1.33)
T3 (539–4665)	390	3.0 (2.4, 3.7)	0.99 (0.70, 1.40)	0.92 (0.64, 1.32)
MCP-1, pg/ml				
Per 1 SD higher	1170	3.7 (3.3, 4.0)	1.09 (0.93, 1.29)	1.10 (0.91, 1.32)
T1 (0.5–81)	390	3.8 (3.1, 4.8)	1.00 (ref)	1.00 (ref)
T2 (82–174)	390	3.4 (2.9, 4.1)	0.90 (0.66, 1.23)	0.75 (0.54, 1.04)
T3 (175–4744)	390	3.6 (2.9, 4.4)	0.92 (0.65, 1.30)	0.88 (0.61, 1.28)
IL-18, pg/ml				
Per 1 SD higher	1170	3.7 (3.3, 4.0)	1.15 (0.99, 1.33)	1.02 (0.88, 1.18)
T1 (0.2–23)	390	3.3 (2.7, 4.1)	1.00 (ref)	1.00 (ref)
T2 (24–53)	391	3.9 (3.3, 4.6)	1.33 (0.99, 1.79)	1.20 (0.89, 1.63)
T3 (53–1509)	389	3.6 (3.0, 4.4)	1.34 (0.96, 1.88)	1.04 (0.73, 1.48)
UMOD, ng/ml				
Per 1 SD higher	1170	3.7 (3.3, 4.0)	0.93 (0.84, 1.02)	0.96 (0.85, 1.07)
T1 (1–58936)	390	3.9 (3.2, 4.6)	1.00 (ref)	1.00 (ref)
T2 (58935–111112)	390	3.9 (3.3, 4.6)	1.10 (0.85, 1.42)	1.16 (0.89, 1.52)
T3 (111249–796474)	390	3.1 (2.6, 3.8)	0.90 (0.68, 1.19)	0.97 (0.72, 1.30)
α1m, ng/mL				

Biomarker (range)	n	Event rate* (95%CI)	Model 1 HR (95%CI)	Model 2 HR (95%CI)
Per 1 SD higher	1170	3.7 (3.3, 4.0)	0.99 (0.87, 1.14)	0.91 (0.79, 1.04)
T1 (0.4–1699)	390	3.9 (3.2, 4.7)	1.00 (ref)	1.00 (ref)
T2 (1706–4339)	390	3.5 (2.9, 4.2)	0.97 (0.73, 1.28)	0.91 (0.67, 1.22)
T3 (4342–45506)	390	3.4 (2.8, 4.2)	0.94 (0.69, 1.27)	0.88 (0.63, 1.22)
Albumin, mg/dL				
Per 1 SD higher	1162	3.7 (3.3, 4.0)	**1.24 (1.09, 1.42)**	1.14 (0.99, 1.31)
T1(0.05–0.33)	386	3.5 (2.8, 4.3)	1.00 (ref)	1.00 (ref)
T2(0.34–0.76)	389	3.2 (2.6, 3.8)	0.95 (0.70,1.31)	0.94 (0.68, 1.30)
T3(0.76–45)	387	4.3 (3.5, 5.2)	1.26 (0.90,1.76)	1.09 (0.77, 1.54)

*Per 100 person-years of follow-up

†*P*-value for linear trend 0.003;

‡*P*-value for linear trend 0.02

Bolded values indicate statistically significant results

Abbreviations: IQR, interquartile range; 95%CI, 95% confidence interval; SD, standard deviation; EGF, epidermal growth factor; YKL-40, chitinase-3-like protein 1; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant protein 1; IL-18, interleukin 18; UMOD, uromodulin; α1m, α1-microglobulin; T1, T2, T3—tertile 1, tertile 2, tertile 3

Model 1 adjusts for age, sex, race, and urine creatinine

Model 2 adjusts for Model 1 + smoking, diabetes, systolic blood pressure, diastolic blood pressure, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, body mass index, exercise, education, income, urine albumin, and estimated glomerular filtration rate

Table 4.

Associations of urine biomarkers with 10-year systolic and diastolic blood pressure changes

		Δ Systolic Blood Pressure, mmHg		Δ Diastolic Blood Pressure, mmHg	
Biomarker (range)	**n**	**Model 1 Estimate (95%CI)**	**Model 2 Estimate (95%CI)**	**Model 1 Estimate (95%CI)**	**Model 2 Estimate (95%CI)**
EGF, pg/mL					
Per 1 SD higher	1170	−0.72 (−2.05, 0.60)	−0.70 (−2.11, 0.70)	−0.69 (−1.70, 0.31)	−0.83 (−1.86, 0.20)
T1 (135–8670)	390	ref	ref	ref	ref
T2 (8670–16762)	390	−1.38 (−3.50, 0.74)	−1.50 (−3.72, 0.71)	−1.30 (−2.87, 0.26)	**−1.98 (−3.60, −0.36)**
T3 (16771–96947)	390	**−3.52 (−6.11,−0.92)** *	**−3.40 (−6.13,−0.68)** **	−1.86 (−3.77,0.06) †	**−2.59 (−4.59,−0.60)** ‡
YKL-40, pg/mL					
Per 1 SD higher	1170	−0.14 (−0.92, 0.64)	−0.03 (−0.85, 0.80)	−0.14 (−0.68, 0.41)	−0.07 (−0.62, 0.49)
T1 (0.5–158)	390	ref	ref	ref	ref
T2 (159–408)	390	0.94 (−0.80, 2.68)	0.99 (−0.81, 2.79)	0.32 (−0.97, 1.60)	0.30 (−1.02, 1.61)
T3 (409–7336)	390	−0.67 (−2.53, 1.19)	−0.43 (−2.35, 1.48)	−0.19 (−1.57, 1.18)	−0.26 (−1.66,1.14)
KIM-1, pg/mL					
Per 1 SD higher	1170	0.50 (−0.65, 1.65)	0.35 (−0.83, 1.54)	−0.15 (−0.95, 0.66)	−0.14 (−0.97,0.68)
T1 (0.5–199)	390	ref	ref	ref	ref
T2 (199–538)	390	1.16 (−0.82, 3.14)	0.84 (−1.21, 2.90)	0.58 (−0.88, 2.04)	0.59 (−0.91, 2.09)
T3 (539–4665)	390	0.50 (−1.84, 2.85)	0.37 (−2.07, 2.80)	0.00 (−1.73, 1.73)	0.07 (−1.72, 1.85)
MCP-1, pg/mL					
Per 1 SD higher	1170	0.38 (−0.67, 1.43)	0.05 (−1.05, 1.14)	0.18 (−0.59, 0.95)	−0.09 (−0.86,0.68)
T1 (0.5–81)	390	ref	ref	ref	ref
T2 (82–174)	390	−0.67 (−2.71, 1.36)	−1.03 (−3.16, 1.10)	−0.38 (−1.88, 1.12)	−0.60 (−2.16,0.95)
T3 (175–4744)	390	−1.77 (−4.12, 0.59)	−2.23 (−4.73, 0.26)	−0.71 (−2.45, 1.02)	−1.22 (−3.05,0.60)
IL-18, pg/mL					
Per 1 SD higher	1170	0.09 (−0.78, 0.97)	0.18 (−0.77, 1.13)	−0.41 (−1.03, 0.21)	−0.13 (−0.77,0.52)
T1 (0.2–23)	390	ref	ref	ref	ref
T2 (24–53)	391	**2.43 (0.54, 4.32)**	**2.53 (0.59, 4.48)**	0.33 (−1.06, 1.72)	0.44 (−0.99, 1.87)
T3 (53–1509)	389	0.11 (−2.05, 2.27)	0.21 (−2.07, 2.49)	−1.53 (−3.13, 0.06)	−0.99 (−2.66,0.69)
UMOD, ng/mL					
Per 1 SD higher	1170	−0.24 (−0.89, 0.41)	−0.29 (−0.99, 0.41)	−0.15 (−0.65, 0.35)	−0.33 (−0.84,0.19)
T1 (1–58936)	390	ref	ref	ref	ref
T2 (58935–111112)	390	−0.47 (−2.18, 1.25)	−0.62 (−2.39, 1.14)	−0.28 (−1.55, 0.99)	−0.64 (−1.93,0.65)
T3 (111249–796474)	390	−1.53 (−3.37, 0.31)	−1.88 (−3.80, 0.03)	−0.35 (−1.71, 1.01)	−0.95 (−2.35,0.45)
α1m, ng/mL					

		Δ Systolic Blood Pressure, mmHg		Δ Diastolic Blood Pressure, mmHg	
Biomarker (range)	**n**	**Model 1 Estimate (95%CI)**	**Model 2 Estimate (95%CI)**	**Model 1 Estimate (95%CI)**	**Model 2 Estimate (95%CI)**
Per 1 SD higher	1170	−0.13 (−0.99, 0.73)	−0.29 (−1.16, 0.58)	−0.19 (−0.80, 0.41)	−0.26 (−0.85,0.33)
T1 (0.4–1699)	390	ref	ref	ref	ref
T2 (1706–4339)	390	−0.94 (−2.77, 0.90)	−0.91 (−2.80, 0.99)	−0.83 (−2.19, 0.52)	−0.99 (−2.37,0.40)
T3 (4342–45506)	390	−1.28 (−3.33, 0.78)	−1.51 (−3.66, 0.63)	−1.00 (−2.51, 0.52)	−1.14 (−2.71,0.43)
Albumin, mg/dL					
Per 1 SD higher	1162	−0.56 (−1.54, 0.43)	−0.57 (−1.61, 0.46)	**−0.79 (−1.53, −0.04)**	−0.74 (−1.48,0.00)
T1 (0.05–0.33)	386	ref	ref	ref	ref
T2 (0.34–0.76)	389	−0.11 (−2.11, 1.89)	0.25 (−1.81, 2.32)	0.33 (−1.15, 1.80)	0.35 (−1.16, 1.86)
T3 (0.76–45)	387	−0.39 (−2.62, 1.84)	−0.20 (−2.53, 2.12)	−0.63 (−2.28, 1.01)	0.69 (−2.39, 1.01)

[*] *P*-value for linear trend 0.02;

[**] *P*-value for linear trend 0.04.

[†] *P*-value for linear trend 0.15;

[‡] *P*-value for linear trend 0.03.

Bolded values indicate statistically significant results

Abbreviations: 95%CI, 95% confidence interval; SD, standard deviation; EGF, epidermal growth factor; YKL-40, chitinase-3-like protein 1; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant protein 1; IL-18, interleukin 18; UMOD, uromodulin; α1m, α1-microglobulin; T1, T2, T3—tertile 1, tertile 2, tertile 3

Model 1 adjusts for study time, age, sex, race, and urine creatinine

Model 2 adjusts for Model 1 + smoking, diabetes, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, body mass index, exercise, education, income, urine albumin (except for model in which urine albumin is the primary exposure), and estimated glomerular filtration rate