Original Article

Association of Kidney Function and Early Kidney Injury With Incident Hypertension in HIV-Infected Women

Simon B. Ascher, Rebecca Scherzer, Carmen A. Peralta, Phyllis C. Tien, Carl Grunfeld, Michelle M. Estrella, Alison Abraham, Deborah R. Gustafson, Marek Nowicki, Anjali Sharma, Mardge H. Cohen, Anthony W. Butch, Mary A. Young, Michael R. Bennett, Michael G. Shlipak

Abstract—Subclinical kidney disease is associated with developing hypertension in the general population, but data are lacking among HIV-infected people. We examined associations of kidney function and injury with incident hypertension in 823 HIV-infected and 267 HIV-uninfected women in the Women's Interagency HIV Study, a multicenter, prospective cohort of HIV-infected and uninfected women in the United States. Baseline kidney biomarkers included estimated glomerular filtration rate using cystatin C, urine albumin-to-creatinine ratio, and 7 urine biomarkers of tubular injury: α-1-microglobulin, interleukin-18, kidney injury molecule-1, neutrophil gelatinase–associated lipocalin, liver fatty acid–binding protein, N-acetyl-β-D-glucosaminidase, and α1-acid-glycoprotein. We used multivariable Poisson regression to evaluate associations of kidney biomarkers with incident hypertension, defined as 2 consecutive visits of antihypertensive medication use. During a median follow-up of 9.6 years, 288 HIV-infected women (35%) developed hypertension. Among the HIV-infected women, higher urine albumin-to-creatinine ratio was independently associated with incident hypertension (relative risk =1.13 per urine albumin-to-creatinine ratio doubling, 95% confidence interval, 1.07–1.20), as was lower estimated glomerular filtration rate (relative risk =1.10 per 10 mL/min/1.73 m^2 lower estimated glomerular filtration rate; 95% confidence interval, 1.04–1.17). No tubular injury and dysfunction biomarkers were independently associated with incident hypertension in HIV-infected women. In contrast, among the HIV-uninfected women, urine albumin-to-creatinine ratio was not associated with incident hypertension, whereas higher urine interleukin-18, α1-acid-glycoprotein, and N-acetyl-β-D-glucosaminidase levels were significantly associated with incident hypertension. These findings suggest that early glomerular injury and kidney dysfunction may be involved in the pathogenesis of hypertension in HIV-infected people. The associations of tubular markers with hypertension in HIV-uninfected women should be validated in other studies. (***Hypertension*. 2017;69:00-00. DOI: 10.1161/HYPERTENSIONAHA.116.08258.)**

● **Online Data Supplement**

Key Words: albuminuria ■ glomerular filtration rate ■ HIV ■ hypertension ■ kidney disease

With the success of combination antiretroviral therapy, people with HIV infection have dramatically increased life expectancies and face an increasing burden of age-related comorbidities, including cardiovascular disease.[1,2] Hypertension in HIV-infected individuals is common, with prevalence estimates ranging from 13% to 45%,[3–7] and associated with a 2-fold increased risk of acute myocardial infarction.[8] Despite these observations, our understanding of risk factors for hypertension in the HIV-infected population is limited.[9–12]

The kidneys play a central role in blood pressure regulation.[13] Reduced kidney function is common among HIV-infected individuals, with prevalence estimates of chronic kidney disease ranging from 7% to 32%.[14–17] Compared with uninfected individuals, HIV-infected individuals have a 3-fold increased risk of developing end-stage renal disease and have significantly higher cystatin C levels, an endogenous marker of filtration.[18–20] Although several cross-sectional studies show that chronic kidney disease is highly prevalent among HIV-infected individuals with hypertension,[17,21] to our knowledge, there are no studies in the HIV population that have evaluated whether reduced kidney function is associated with the development of hypertension.

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From the Kidney Health Research Collaborative, Department of Medicine, San Francisco VA Medical Center (S.B.A., R.S., C.A.P., P.C.T., C.G., M.G.S.) and Department of Epidemiology and Biostatistics (C.A.P., P.C.T., C.G., M.G.S.), University of California, San Francisco; Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD (M.M.E., A.A.); Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY (D.R.G.); Department of Medicine, University of Southern California, Los Angeles (M.N.); Department of Medicine, Albert Einstein College of Medicine, Bronx, NY (A.S.); Department of Medicine, Stroger Hospital and Rush University, Chicago, IL (M.H.C.); Department of Pathology and Laboratory Medicine, UCLA Health System, Los Angeles, CA (A.W.B.); Georgetown University Medical Center, Washington, DC (M.A.Y.); and Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, OH (M.R.B.).

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Correspondence to Michael G. Shlipak, Department of Epidemiology and Biostatistics, University of California, San Francisco, 4150 Clement St (111A1), San Francisco, CA 94121. E-mail michael.shlipak@ucsf.edu

Substantial kidney injury occurs subclinically—before a measurable reduction in kidney function—and is independently associated with hypertension among HIV-uninfected people.[22,23] The most common measure of kidney injury is urinary albumin concentration, which reflects endothelial and hemodynamic changes within the glomerulus. HIV-infected individuals have a 5-fold higher prevalence of microalbuminuria compared with uninfected individuals, and higher urinary albumin levels among HIV-infected individuals are associated with subsequent kidney function decline.[24,25] Glomerular injury leading to the development of hypertension may explain the strong association between albuminuria and cardiovascular disease in HIV-infected individuals.[26] Higher urinary albumin levels may also reflect widespread inflammation, which could be a particularly important mechanism of hypertension in HIV-infected individuals because of HIV-associated chronic immune system activation.[27,28]

Tubulointerstitial injury may also play an important role in the pathophysiology of hypertension. Several experimental studies have shown that tubulointerstitial injury may lead to hypertension through abnormal tubuloglomerular feedback and impaired sodium handling.[22,29] The proximal tubules are known to be a site of the latent HIV reservoir, and we have recently shown that several tubular injury markers are not only elevated in HIV-infected individuals compared with HIV-uninfected individuals but also associated with longitudinal decline in kidney function.[25,30,31] To our knowledge, no epidemiological studies in any population have evaluated the association of biomarkers for tubular dysfunction and injury with the development of hypertension.

In this study, we investigated whether markers of kidney function, glomerular injury, and tubular dysfunction and injury are associated with incident hypertension in a large cohort of HIV-infected and HIV-uninfected women. We evaluated kidney function with estimated glomerular filtration rate (eGFR) by cystatin C, glomerular injury with the urinary albumin-to-creatinine ratio (ACR), and tubular dysfunction and injury with 7 urine biomarkers: α-1-microglobulin (α1m), interleukin-18 (IL-18), kidney injury marker-1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), liver fatty acid–binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG), and α1-acid-glycoprotein (AAG).

Methods

Study Design

The WIHS (Women's Interagency HIV Study) study design and methods have been described previously.[32] In brief, 3766 women (2791 HIV-infected and 975 uninfected women) of similar backgrounds were enrolled in 1994 to 1995 (n=2623) and in 2001 to 2002 (n=1143) from 6 sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington). The WIHS HIV Kidney Aging study was designed as a nested cohort study to investigate the onset of kidney disease in the setting of HIV. Between October 1999 and March 2000, 1197 women (908 HIV-infected and 289 HIV-uninfected women) had baseline urine and serum specimens collected. This study included the HIV-infected and HIV-uninfected women with available urine and serum specimens collected during this time interval. We excluded from our analysis women with prevalent hypertension at the time of specimen collection, defined as the use of antihypertensive medication at ≥2 consecutive visits before and including the nested study baseline visit. We also excluded participants without any follow-up blood pressure measurement after the baseline visit. Follow-up started at the nested study baseline visit and was truncated at 10 years.

WIHS was approved by the institutional review boards of all participating institutions, and informed consent was obtained from all study participants. This study of kidney injury was also approved by the Committee on Human Research of the University of California, San Francisco.

Predictors

We evaluated eGFR, ACR, and 7 urine markers of tubular injury: IL-18, KIM-1, NGAL, NAG, AAG, α1m, and L-FABP. We calculated eGFR using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation.[33] Cystatin C was measured by a particle-enhanced immunoturbidimetric assay (Gentian). All urinary biomarkers were measured at the Cincinnati Children's Hospital Medical Center Biomarker Laboratory (for details on urine biomarker measurements, see the online-only Data Supplement).

We analyzed urine biomarkers as continuous variables (log-transformed because of their right-skewed distribution) and categorical variables divided into tertiles. We additionally analyzed ACR as a dichotomous variable using the clinically meaningful cut point (ACR ≤30 versus >30 mg/g). We analyzed eGFR as a continuous variable, in tertiles, and dichotomized (eGFR ≤60 versus >60 mL/min/1.73 m^2).

Outcomes

Our primary outcome was incident hypertension, which we defined as use of an antihypertensive medication at 2 consecutive visits. Our secondary outcome was incident hypertension defined as presence of at least 2 of the following 3 conditions at 2 consecutive visits: (1) systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, (2) use of an antihypertensive medication, or (3) self-reported history of hypertension. WIHS-trained personnel assessed blood pressure and medication use during each semiannual WIHS examination. After the participant sat for at least 5 minutes, 3 blood pressure measurements were obtained from the right arm using a DINAMAP 1846 SX automated oscillometric device (Critikon, Inc, Tampa, FL). Blood pressure measurements at each visit were averaged across the 3 readings.

Covariates

Demographics, traditional hypertension risk factors, and HIV-related characteristics were collected at each examination and analyzed as time-varying covariates. The following covariates were included in all models for the HIV-infected group: hepatitis C virus infection (confirmed by detectable hepatitis C virus RNA after a positive hepatitis C virus antibody result), current CD4 lymphocyte count, current HIV viral load, and current highly active antiretroviral therapy use. Hepatitis C virus infection was included in all models for the HIV-uninfected group. Tubular biomarker models also included urine creatinine to account for variations in urine concentration. We tested the following demographic characteristics and traditional hypertension risk factors as candidate covariates in all multivariable models: age; race/ethnicity; diabetes mellitus (defined using confirmatory criteria for fasting glucose ≥126 mg/dL, self-reported diabetes mellitus, self-reported diabetes mellitus medication use, or hemoglobin A1c ≥6.5%), insulin resistance estimated using the homeostasis model assessment score defined as (insulin×glucose)/405, cigarette smoking status (current, former, and never), menopause status, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, serum albumin, body mass index, waist circumference, current stimulant use, and alcohol use (none, light, moderate, and heavy). We tested the following HIV-related characteristics as candidate covariates in the HIV-infected group: nadir CD4 lymphocyte count, history of AIDS diagnosis, current nucleoside reverse transcriptase inhibitor use, current non-nucleoside reverse transcriptase inhibitor use, and current protease inhibitor use.

Statistical Analysis

We performed all analyses separately in the HIV-infected and HIV-uninfected groups. We compared demographic and baseline clinical characteristics by ACR level (ACR ≤30 versus >30 mg/g). We used Poisson regression with a robust variance estimator to model the associations of each kidney biomarker with our primary and secondary definitions of hypertension. For covariate selection, we used Bayesian model averaging and retained variables in our final models with posterior probabilities >35%.[34]

We evaluated kidney biomarker associations both individually (without adjusting for other biomarkers) and after adjustment for ACR and eGFR. We performed interaction testing to evaluate whether associations of ACR and eGFR with incident hypertension varied by age, race, and diabetes mellitus. We also combined the HIV-infected and HIV-uninfected participants into one study population and performed interaction testing to evaluate whether associations of each kidney biomarker with incident hypertension varied by HIV status. We conducted a sensitivity analysis excluding patients with diabetes mellitus to evaluate whether kidney biomarker associations with incident hypertension were modified by diabetes mellitus.

Bayesian model averaging was performed using the BMA package for the R statistical computing language (R Development Core Team, Vienna, Austria). All other analyses were performed using the SAS system, version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Of the 1197 women in WIHS with available urine samples collected in the nested study, we excluded 85 out of 908 HIV-infected women (9.4%) and 22 out of 289 HIV-uninfected women (7.6%) with prevalent hypertension. The remaining 823 HIV-infected and 267 HIV-uninfected women represented our study population. All subjects had at least 2 follow-up blood pressure measurements (median: 19; interquartile range, 14–19).

Among the HIV-infected women, the mean age at baseline was 40 years; 59% had a baseline systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg. HIV-infected participants with higher ACR at baseline were more often of black race and menopausal, had lower high-density lipoprotein, higher triglycerides, higher HIV viral load, and lower eGFR (Table 1). During a median follow-up of 9.6 years (interquartile range, 9.3–9.9), 288 out of 823 HIV-infected women (35%) and 98 out of 267 HIV-uninfected women (37%) developed hypertension. In unadjusted analyses, lower eGFR and higher α1m, IL-18, L-FABP, NAG, and AAG concentrations were associated with increased risk of incident hypertension in both HIV-infected and HIV-uninfected women, whereas higher ACR were associated with increased risk of incident hypertension only in HIV-infected women (Figures 1 and 2).

After adjusting for traditional and HIV-related hypertension risk factors in the HIV-infected group, the highest tertile of ACR remained associated with an 80% increased risk of incident hypertension, relative to the lowest tertile (Table 2). ACR >30 mg/g was associated with a 73% increased risk of incident hypertension compared with an ACR ≤30 mg/g. The association of higher ACR with incident hypertension showed little attenuation after adjusting for eGFR.

Lower eGFR was also associated with incident hypertension in HIV-infected participants after controlling for traditional and HIV-related hypertension factors. Each 10 mL/min/1.73 m^2 decrement in baseline eGFR was associated with a 12% increased risk of incident hypertension, whereas the lowest eGFR tertile was associated with a 73% increased risk of developing hypertension compared with the highest eGFR tertile.

In HIV-uninfected women, ACR had minimal association with hypertension after multivariate adjustment including eGFR (Table 3). The test for HIV by ACR interaction was marginally significant (P=0.08). By contrast, lower eGFR was associated with increased risk of incident hypertension in HIV-uninfected women after multivariate adjustment including ACR.

Higher α1m, IL-18, L-FABP, NAG, and AAG levels in HIV-infected women showed modest associations with incident hypertension after multivariate adjustment, but after adjustment for ACR and eGFR, these associations were no longer statistically significant (Table 2). KIM-1 seemed to be associated with a decreased risk of hypertension after multivariate adjustment for ACR and eGFR. Among HIV-uninfected women, higher α1m, IL-18, NAG, and AAG levels were associated with incident hypertension after multivariate adjustment (Table 3). After adjustment for ACR and eGFR, associations of IL-18, NAG, and AAG remained statistically significant. Tests for interaction by HIV status for each tubular injury biomarker were not statistically significant (all interaction P values >0.20).

Results were similar in analyses using the secondary outcome definition for hypertension in HIV-infected women (Table S1 in the online-only Data Supplement) and HIV-uninfected women (Table S2). Associations of ACR and eGFR with incident hypertension did not seem to vary by age or race (all interaction P values >0.20). As a sensitivity analysis, we examined associations of kidney biomarkers with incident hypertension in nondiabetic HIV-infected participants (n=645). Although the association of ACR with risk of hypertension did not vary by diabetes mellitus status (test for diabetes mellitus by ACR interaction: P=0.53), the association of low eGFR with incident hypertension seemed to be stronger in nondiabetics (test for diabetes mellitus by eGFR interaction: P=0.0086). Specifically, each 10 mL/min/1.73 m^2 decrement in eGFR was associated with a 17% increased risk of hypertension (95% confidence interval, 1.08–1.26) in the fully adjusted analysis. In addition, the lowest eGFR tertile was associated with a 99% increased risk of incident hypertension compared with the highest eGFR tertile (95% confidence interval, 1.32–2.99), and eGFR≤60 mL/min/1.73 m^2 was associated with a 51% increased risk of hypertension (95% confidence interval, 0.93–2.46). In the HIV-infected population, tubular markers had no significant associations with hypertension among nondiabetics in fully adjusted models.

Discussion

Early identification of HIV-infected individuals at risk for hypertension is important because HIV infection is associated with a higher risk of cardiovascular disease and because of the growing burden of chronic diseases in the aging HIV population.[1,2] In this cohort study, we found that higher ACR and lower eGFR were independently associated with a greater risk of incident hypertension in HIV-infected women, even after adjustment for traditional and HIV-related hypertension risk factors. Counter to our hypothesis, biomarkers for tubular dysfunction and injury had at most weak associations with incident hypertension in HIV-infected women, which were attenuated after adjustment for ACR and eGFR. In a similar group of HIV-uninfected women,

Table 1. Study Population Baseline Characteristics by ACR

Demographics	HIV-Infected Women			HIV-Uninfected Women		
	ACR ≤30 mg/g (n=670)	ACR >30 mg/g (n=153)	*P* Value	ACR ≤30 mg/g (n=247)	ACR >30 mg/g (n=20)	*P* Value
Age, y	40 (36–45)	41 (36–46)	0.10	39 (33–44)	42 (37–46)	0.19
Race						
Black	358 (53)	101 (66)	0.01	148 (60)	12 (60)	0.57
White	144 (21)	21 (14)		30 (12)	1 (5)	
Other	168 (25)	31 (20)		69 (28)	7 (35)	
Menopause	122 (18)	41 (27)	0.02	26 (11)	2 (11)	0.99
Current smoking	336 (50)	79 (52)	0.52	139 (57)	14 (74)	0.33
Diabetes mellitus	139 (21)	39 (25)	0.20	59 (24)	10 (53)	<0.01
HOMA-IR	2.8 (2.0–4.1)	3.4 (2.4–5.6)	<0.01	2.7 (1.9–4.2)	3.7 (2.2–6.5)	0.10
Systolic blood pressure, mm Hg	115 (107–122)	121 (111–130)	<0.01	117 (110–127)	124 (114–133)	0.15
Diastolic blood pressure, mm Hg	72 (67–77)	77 (71–82)	<0.01	73 (67–80)	76 (67–81)	0.46
LDL cholesterol, mg/dL	101 (87–113)	103 (89–118)	0.06	106 (93–120)	108 (100–115)	0.90
HDL cholesterol, mg/dL	49 (43–54)	46 (41–53)	0.02	53 (47–59)	51 (46–59)	0.63
TG, mg/dL	137 (114–168)	156 (125–189)	<0.01	129 (101–155)	124 (97–160)	0.86
BMI, kg/m^2	26 (23–30)	27 (23–31)	0.92	29 (24–34)	33 (25–37)	0.27
Waist circumference, cm	87 (79–97)	88 (79–102)	0.44	92 (80–100)	96 (79–109)	0.27
Active hepatitis C	204 (30)	48 (31)	0.83	52 (21)	3 (16)	0.57
Current stimulant use	76 (11)	12 (8)	0.21	41 (17)	5 (26)	0.29
eGFR, mL/min/1.73 m^2	92 (78–106)	81 (66–96)	<0.01	103 (91–117)	102 (88–108)	0.46
HAART use	398 (59)	86 (56)	0.47			
NRTI use	453 (68)	93 (61)	0.11			
NNRTI use	181 (27)	47 (31)	0.36			
PI use	287 (43)	58 (38)	0.27			
Current CD4	391 (246–555)	384 (168–624)	0.58			
Nadir CD4	222 (122–337)	212 (97–339)	0.46			
History of AIDS	353 (53)	82 (54)	0.84			
HIV viral load						
≤80	203 (30)	41 (27)	<0.01			
81–1999	162 (24)	22 (15)				
2000–9999	115 (17)	24 (16)				
>10 000	187 (28)	63 (42)				

Data are presented as median (interquartile range) or n (%). ACR indicates albumin-creatinine ratio; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOMA-IR, insulin resistance; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; and TG, triglyceride.

lower eGFR and higher levels of several tubular injury biomarkers were associated with greater risk of incident hypertension, but we observed no association with higher ACR. To our knowledge, this is the first study to evaluate associations of kidney function and multiple markers of kidney injury with the development of hypertension in an HIV-infected cohort.

There are multiple studies in non-HIV populations that have reported associations between higher urinary albumin excretion and an increased risk of incident hypertension.[35–39] Meanwhile, a cohort study of middle-aged, ethnically diverse men and women without clinically apparent cardiovascular disease found that lower eGFR, but not albuminuria, was associated with incident hypertension.[23] Urinary albumin excretion represents glomerular injury, and there is growing evidence suggesting that subclinical renal microvascular injury may lead to the development of hypertension.[22] The association between higher ACR and incident hypertension in the HIV-infected group may reflect HIV-associated systemic endothelial dysfunction and arterial inflammation that produce glomerular injury and also lead to hypertension.[27,28] Because few HIV-uninfected

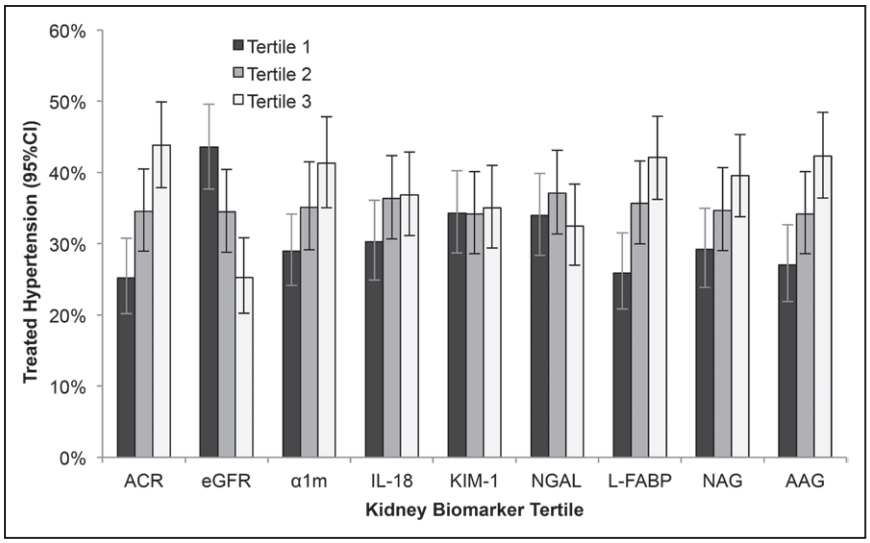

Figure 1. Incident hypertension by tertile of kidney biomarkers in HIV-infected women. In unadjusted analysis, the lowest tertile of estimated glomerular filtration rate (eGFR) using cystatin C was associated with increased risk of incident hypertension compared with the highest tertile, and the highest tertiles of urine albumin-to-creatinine ratio (ACR), α-1-microglobulin (α1m), interleukin-18 (IL-18), liver fatty acid–binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG), and α1-acid-glycoprotein (AAG) concentrations were associated with increased risk of incident hypertension compared with the lowest tertiles.

participants had an ACR >30 mg/g, our study may have been underpowered to detect an association between higher ACR and incident hypertension in the HIV-uninfected group.

Our finding of an association between kidney dysfunction and incident hypertension in both the HIV-infected and HIV-uninfected groups is similar to reports from the limited number of studies in non-HIV populations.[23,39,40] Reduced kidney function may represent several mechanisms involved in the pathogenesis of hypertension, including congenitally reduced nephron numbers, impaired sodium handling, salt sensitivity, and vasoconstriction from activated sympathetic and renin–angiotensin systems.[41] Higher levels of inflammation among HIV-infected individuals may also underlay the association of subclinical kidney disease and hypertension because elevated inflammatory markers are associated with kidney dysfunction in the HIV-infected population and with incident hypertension in the general population.[42,43]

To our knowledge, this is the first study in any population to evaluate associations of biomarkers for tubular injury and dysfunction with risk of incident hypertension. In the HIV-infected group, the weak associations across all tubular injury markers and the attenuation after including ACR and eGFR suggest that tubulointerstitial injury plays a smaller role in the development of hypertension compared with glomerular injury and kidney dysfunction. Although higher levels of IL-18, NAG, and AAG were associated with hypertension in the HIV-uninfected group, interaction testing by HIV status was not statistically significant. We hypothesized that higher concentrations of α1m, IL-18, L-FABP, KIM-1, and NAG would be associated with hypertension because they represent injury specific to the proximal tubule, which is responsible for the majority of water and sodium reabsorption.[44] The weak associations in the HIV-infected group may be because HIV-related kidney injury and inflammation are more pronounced in the glomerulus compared with the tubulointerstitium. Alternatively, our study may not have adequately captured tubulointerstitial injury occurring before or after the baseline measurements. Unexpectedly, KIM-1 was associated with decreased risk of developing hypertension in the HIV-infected group, although in models without adjustment for urine creatinine there was no association between KIM-1 or any of the tubular markers and incident hypertension. This finding requires confirmation in other cohorts.

Strengths of our study include the use of a multicenter and racially and ethnically diverse cohort representative of US HIV-infected women with a mean follow-up period of 10

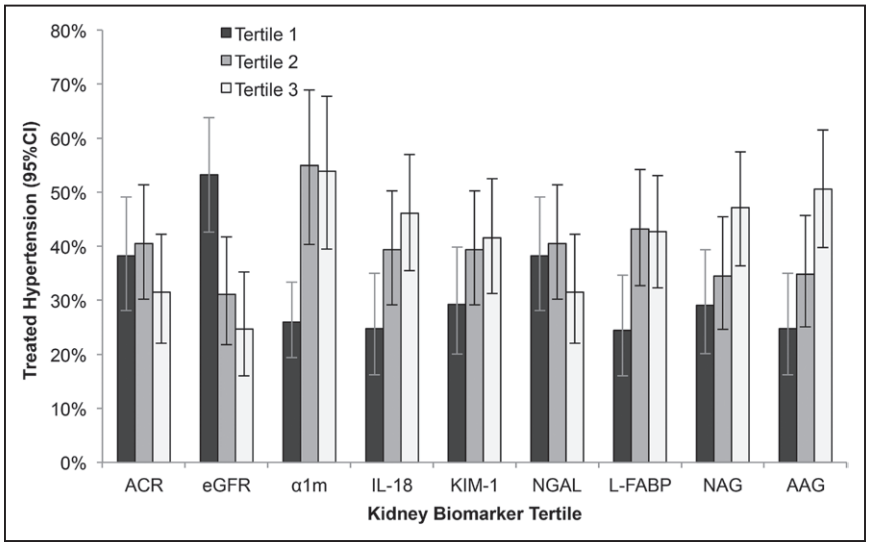

Figure 2. Incident hypertension by tertile of kidney biomarkers in HIV-uninfected women. In unadjusted analysis, the lowest tertile of estimated glomerular filtration rate (eGFR) using cystatin C was associated with increased risk of incident hypertension compared with the highest tertile, and the highest tertiles of α-1-microglobulin (α1m), interleukin-18 (IL-18), liver fatty acid–binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG), and α1-acid-glycoprotein (AAG) concentrations were associated with increased risk of incident hypertension compared with the lowest tertiles.

Table 2. Association of Kidney Biomarkers With Risk of Incident Hypertension in HIV-Infected Women

		Unadjusted	Multivariable Adjusted	
Biomarker	Participants (n)	RR (95% CI)	Individual Markers, RR (95% CI)*	Individual Markers+ACR+eGFR, RR (95% CI)†
ACR				
Continuous	823	1.18 (1.12–1.25)	1.15 (1.08–1.22)	1.13 (1.07–1.20)
T1: <6.9 mg/g	274	Reference	Reference	Reference
T2: 6.9–15 mg/g	275	1.43 (1.05–1.96)	1.48 (1.08–2.02)	1.49 (1.09–2.04)
T3: >15 mg/g	274	2.11 (1.57–2.84)	1.80 (1.33–2.43)	1.72 (1.27–2.33)
≤30 mg/g	670	Reference	Reference	Reference
>30 mg/g	153	2.00 (1.54–2.61)	1.73 (1.32–2.26)	1.68 (1.28–2.21)
eGFR				
Continuous‡	823	1.16 (1.10–1.22)	1.12 (1.06–1.19)	1.10 (1.04–1.17)
T1: <81 mL/min/1.73 m^2	280	2.13 (1.59–2.86)	1.73 (1.26–2.38)	1.65 (1.20–2.28)
T2: 81–99 mL/min/1.73 m^2	270	1.43 (1.05–1.96)	1.32 (0.96–1.81)	1.33 (0.97–1.83)
T3: >99 mL/min/1.73 m^2	273	Reference	Reference	Reference
≤60 mL/min/1.73 m^2	69	1.85 (1.28–2.67)	1.48 (1.00–2.18)	1.32 (0.89–1.96)
>60 mL/min/1.73 m^2	754	Reference	Reference	Reference
α1m				
Continuous	823	1.19 (1.08–1.30)	1.14 (1.03–1.26)	0.98 (0.87–1.10)
T1§	339	Reference	Reference	Reference
T2	242	1.20 (0.89–1.62)	1.08 (0.80–1.46)	0.98 (0.72–1.32)
T3	242	1.55 (1.15–2.10)	1.22 (0.90–1.66)	0.95 (0.69–1.32)
IL-18				
Continuous	823	1.09 (0.98–1.21)	1.11 (0.99–1.24)	1.05 (0.94–1.18)
T1	274	Reference	Reference	Reference
T2	275	1.17 (0.85–1.59)	1.19 (0.87–1.63)	1.13 (0.82–1.55)
T3	274	1.15 (0.82–1.63)	1.27 (0.89–1.80)	1.15 (0.80–1.64)
KIM-1				
Continuous	823	1.03 (0.93–1.14)	1.00 (0.89–1.12)	0.90 (0.80–1.01)
T1	274	Reference	Reference	Reference
T2	275	0.83 (0.61–1.14)	0.70 (0.50–0.97)	0.68 (0.49–0.94)
T3	274	0.86 (0.61–1.19)	0.78 (0.55–1.12)	0.69 (0.48–0.98)
NGAL				
Continuous	823	1.01 (0.94–1.10)	1.01 (0.94–1.10)	0.96 (0.89–1.04)
T1	274	Reference	Reference	Reference
T2	275	1.03 (0.77–1.37)	1.03 (0.77–1.38)	1.03 (0.77–1.38)
T3	274	0.87 (0.64–1.19)	0.90 (0.66–1.22)	0.81 (0.59–1.11)
L-FABP				
Continuous	823	1.11 (1.05–1.17)	1.06 (1.00–1.13)	1.02 (0.97–1.08)
T1	274	Reference	Reference	Reference
T2	275	1.32 (0.96–1.83)	1.14 (0.82–1.57)	1.12 (0.81–1.55)
T3	274	1.77 (1.27–2.47)	1.38 (0.98–1.94)	1.23 (0.87–1.75)
NAG				
Continuous	823	1.22 (1.09–1.35)	1.14 (1.02–1.27)	0.97 (0.86–1.10)

(*Continued*)

Table 2. Continued

		Unadjusted	Multivariable Adjusted	
T1	274	Reference	Reference	Reference
T2	271	1.13 (0.81–1.57)	0.99 (0.71–1.39)	0.92 (0.65–1.29)
T3	278	1.45 (1.01–2.06)	1.19 (0.83–1.72)	0.92 (0.63–1.36)
AAG				
Continuous	823	1.17 (1.10–1.24)	1.13 (1.06–1.20)	1.03 (0.96–1.11)
T1	274	Reference	Reference	Reference
T2	275	1.31 (0.96–1.79)	1.17 (0.85–1.61)	1.10 (0.80–1.52)
T3	274	1.78 (1.31–2.41)	1.46 (1.07–2.00)	1.10 (0.78–1.54)

AAG indicates α1-acid-glycoprotein; ACR, albumin-to-creatinine ratio; α1m, α-1-microglobulin; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate by cystatin C; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HOMA-IR, insulin resistance; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid–binding protein; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase–associated lipocalin; NRTI, nucleoside reverse transcriptase inhibitor; RR, relative risk; and T, tertile.

*Adjusted for age, race/ethnicity, DM, HOMA-IR, stimulant use, current CD4 lymphocyte count, current HIV viral load, NRTI, HAART, and HCV. Tubular markers also adjusted for urine creatinine. Biomarkers included individually, not simultaneously.

†Adjusted for age, race/ethnicity, DM, HOMA-IR, stimulant use, current CD4 lymphocyte count, current HIV viral load, NRTI, HAART, HCV, ACR, and eGFR. Tubular markers also adjusted for urine creatinine.

‡Continuous eGFR is modeled per 10 mL/min/1.73 m^2 decrease. All other continuous predictors are modeled per doubling.

§All below detectable.

years and a frequently measured outcome. We had the ability to adjust for multiple traditional and HIV-related hypertension risk factors and to simultaneously assess multiple kidney injury biomarkers. We were also able to perform our analysis in a similar group of HIV-uninfected women. Our study also has several limitations. First, urinary albumin was quantified from a single spot urine sample instead of multiple samples or a 24-hour urine collection. However, despite the variations in ACR influenced by diet, muscle mass, and time of day, ACR has been shown to be an accurate estimator of albuminuria, and its use is supported by national guidelines.[45] ACR may have nondifferentially overestimated albuminuria because of lower muscle mass in HIV-infected women leading to lower urinary creatinine levels. Second, blood pressure was measured at biannual WIHS clinic visits instead of with ambulatory blood pressure monitoring, which may lead to nondifferential outcome misclassification related to masked hypertension or white-coat hypertension, and may not capture hypertension diagnosed and treated between visits.[46] Third, antihypertensive medications may have been prescribed to diabetic participants with albuminuria but without hypertension. However, ACR associations did not substantially differ in our sensitivity analysis excluding diabetic participants. Fourth, because of the bidirectional association between kidney dysfunction and hypertension, our results could reflect hypertension not captured at baseline. However, we used data from up to 5 years before the baseline visit to exclude prevalent hypertension. Fifth, our observational study may not have accounted for all potential confounders given the numerous risk factors for hypertension and kidney injury. For example, we lacked data on exposure to nephrotoxic medications such as NSAIDs. Finally, our results may not be generalizable to HIV-infected men.

Perspectives

We report independent associations of ACR and eGFR with incident hypertension in a large, diverse cohort of HIV-infected women, and independent associations of eGFR and several tubular injury biomarkers with incident hypertension in a similar group of HIV-uninfected women. Our findings suggest that early glomerular injury and kidney dysfunction may be involved in the pathogenesis of hypertension in HIV and may help explain their associations with cardiovascular disease in HIV-infected individuals.[26] Additional studies are needed to evaluate whether HIV-associated inflammation plays a role in kidney injury and hypertension and to corroborate whether ACR and eGFR could be used for targeting HIV-infected individuals at risk of hypertension. The associations of several tubular injury biomarkers with incident hypertension in HIV-uninfected women should be validated in other studies.

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Table 3. Association of Kidney Biomarkers With Risk of Incident Hypertension in HIV-Uninfected Women

		Unadjusted	Multivariable Adjusted	
Biomarker	Participants (n)	RR (95% CI)	Individual Markers, RR (95% CI)*	Individual Markers+ACR+eGFR, RR (95% CI)†
ACR				
Continuous	267	1.04 (0.88–1.23)	0.98 (0.84–1.13)	0.97 (0.84–1.11)
T1: <6.1 mg/g	89	Reference	Reference	Reference
T2: 6.1–10 mg/g	89	1.09 (0.69–1.75)	1.11 (0.69–1.78)	1.10 (0.68–1.76)
T3: >10 mg/g	89	0.92 (0.56–1.52)	0.96 (0.58–1.61)	1.00 (0.60–1.68)
≤30 mg/g	247	Reference	Reference	Reference
>30 mg/g	20	1.63 (0.82–3.23)	1.01 (0.50–2.04)	0.98 (0.48–1.98)
eGFR				
Continuous‡	267	1.32 (1.19–1.47)	1.18 (1.06–1.32)	1.18 (1.06–1.32)
T1: <96 mL/min/1.73 m^2	92	2.65 (1.59–4.42)	1.89 (1.09–3.27)	1.87 (1.08–3.25)
T2: 96–112 mL/min/1.73 m^2	90	1.44 (0.82–2.54)	1.27 (0.71–2.26)	1.25 (0.70–2.24)
T3: >112 mL/min/1.73 m^2	85	Reference	Reference	Reference
≤90 mL/min/1.73 m^2	63	2.49 (1.66–3.74)	1.81 (1.16–2.83)	1.81 (1.16–2.83)
>90 mL/min/1.73 m^2	204	Reference	Reference	Reference
α1m				
Continuous	267	1.37 (1.08–1.74)	1.07 (0.83–1.37)	1.03 (0.77–1.36)
T1§	164	Reference	Reference	Reference
T2	51	2.38 (1.47–3.87)	1.99 (1.21–3.26)	1.94 (1.16–3.23)
T3	52	2.45 (1.47–4.08)	1.65 (0.96–2.83)	1.51 (0.87–2.64)
IL-18				
Continuous	267	1.25 (1.06–1.47)	1.18 (1.00–1.41)	1.16 (0.97–1.38)
T1	89	Reference	Reference	Reference
T2	89	2.07 (1.18–3.62)	1.78 (1.00–3.16)	1.80 (1.00–3.24)
T3	89	2.43 (1.33–4.45)	2.11 (1.10–4.03)	2.28 (1.17–4.46)
KIM-1				
Continuous	267	1.21 (0.99–1.49)	1.19 (0.96–1.48)	1.17 (0.94–1.45)
T1	89	Reference	Reference	Reference
T2	89	1.41 (0.79–2.52)	1.25 (0.68–2.29)	1.33 (0.72–2.44)
T3	89	1.77 (0.96–3.26)	1.42 (0.73–2.80)	1.50 (0.75–3.02)
NGAL				
Continuous	267	0.93 (0.80–1.07)	1.04 (0.90–1.21)	1.04 (0.89–1.21)
T1	89	Reference	Reference	Reference
T2	89	1.12 (0.69–1.83)	1.20 (0.72–1.99)	1.17 (0.71–1.95)
T3	89	0.84 (0.48–1.46)	1.19 (0.68–2.08)	1.20 (0.68–2.11)
L-FABP				
Continuous	267	1.15 (1.02–1.29)	1.05 (0.94–1.18)	1.04 (0.92–1.16)
T1	90	Reference	Reference	Reference
T2	88	2.04 (1.16–3.58)	1.91 (1.09–3.36)	1.80 (1.02–3.18)
T3	89	1.96 (1.05–3.67)	1.52 (0.80–2.89)	1.45 (0.76–2.78)
NAG				
Continuous	267	1.48 (1.20–1.82)	1.31 (1.05–1.63)	1.31 (1.05–1.64)

(*Continued*)

Table 3. Continued

		Unadjusted	Multivariable Adjusted	
T1	93	Reference	Reference	Reference
T2	87	1.31 (0.74–2.31)	1.44 (0.81–2.57)	1.57 (0.87–2.82)
T3	87	2.25 (1.22–4.15)	2.16 (1.16–4.03)	2.35 (1.23–4.47)
AAG				
Continuous	267	1.22 (1.08–1.37)	1.08 (0.96–1.21)	1.09 (0.96–1.24)
T1	89	Reference	Reference	Reference
T2	89	1.37 (0.79–2.39)	1.22 (0.69–2.17)	1.24 (0.70–2.21)
T3	89	2.45 (1.44–4.18)	1.87 (1.08–3.23)	1.82 (1.04–3.17)

AAG indicates α1-acid-glycoprotein; ACR, albumin-to-creatinine ratio; α1m, α-1-microglobulin; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate by cystatin C; HCV, hepatitis C virus; HOMA-IR, insulin resistance; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid–binding protein; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase–associated lipocalin; RR, relative risk; and T, tertile.

*Adjusted for age, race/ethnicity, DM, HOMA-IR, stimulant use, and HCV. Tubular markers also adjusted for urine creatinine. Biomarkers included individually, not simultaneously.

†Adjusted for age, race/ethnicity, DM, HOMA-IR, stimulant use, HCV, ACR, and eGFR. Tubular markers also adjusted for urine creatinine.

‡Continuous eGFR is modeled per 10 mL/min/1.73 m^2 decrease. All other continuous predictors are modeled per doubling.

§All below detectable.

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Novelty and Significance

What Is New?

- This is the first study to evaluate associations of kidney function and multiple markers of kidney injury with the development of hypertension in an HIV-infected cohort.
- Among HIV-infected women, biomarkers of kidney dysfunction and glomerular injury were independently associated with an increased risk of developing hypertension, whereas biomarkers of kidney tubular injury and dysfunction showed no associations.
- In contrast, in a similar group of HIV-uninfected women, biomarkers of kidney dysfunction and kidney tubular injury and dysfunction were associated with an increased risk of developing hypertension, whereas glomerular injury showed no association.

What Is Relevant?

- Our findings should help inform the pathogenesis of hypertension and the relationship between kidney disease and cardiovascular disease in both HIV-infected and HIV-uninfected people.
- Our findings could be used for targeting HIV-infected people at risk of hypertension.

Summary

Biomarkers of glomerular injury and kidney dysfunction are associated with incident hypertension in a large, diverse cohort of HIV-infected women. Our study suggests that subclinical kidney disease may be involved in the pathogenesis of hypertension in HIV.