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Original Investigation

Urinary Kidney Injury Molecule 1 (KIM-1) and Interleukin 18 (IL-18) as Risk Markers for Heart Failure in Older Adults: The Health, Aging, and Body Composition (Health ABC) Study

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Background: Kidney damage and reduced kidney function are potent risk factors for heart failure, but existing studies are limited to assessing albuminuria or estimated glomerular filtration rate (eGFR). We evaluated the associations of levels of urinary biomarkers of kidney tubular injury (interleukin 18 [IL-18] and kidney injury molecule 1 [KIM-1]) with future risk of heart failure.

Study Design: Retrospective cohort study.

Setting & Participants: 2,917 participants without heart failure in the Health, Aging, and Body Composition (Health ABC) cohort.

Predictors: Ratios of urine KIM-1, IL-18, and albumin to creatinine (KIM-1:Cr, IL-18:Cr, and ACR, respectively).

Outcomes: Incident heart failure over a median follow-up of 12 years.

Results: Median values of each marker at baseline were 812 (IQR, 497-1,235) pg/mg for KIM-1:Cr, 31 (IQR, 19-56) pg/mg for IL-18:Cr, and 8 (IQR, 5-19) mg/g for ACR. 596 persons developed heart failure during follow-up. The top quartile of KIM-1:Cr was associated with risk of incident heart failure after adjustment for baseline eGFR, heart failure risk factors, and ACR (HR, 1.32; 95% CI, 1.02-1.70) in adjusted multivariate proportional hazards models. The top quartile of IL-18:Cr also was associated with heart failure in a model adjusted for risk factors and eGFR (HR, 1.35; 95% CI, 1.05-1.73), but was attenuated by adjustment for ACR (HR, 1.15; 95% CI, 0.89-1.48). The top quartile of ACR had a stronger adjusted association with heart failure (HR, 1.96; 95% CI, 1.53-2.51).

Limitations: Generalizability to other populations is uncertain.

Conclusions: Higher urine KIM-1 concentrations were associated independently with incident heart failure risk, although the associations of higher ACR were of stronger magnitude.

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INDEX WORDS: Interleukin 18 (IL-18); kidney injury molecule 1 (KIM-1); cystatin C; heart failure; chronic kidney disease (CKD); risk marker; cardiovascular disease (CVD); albuminuria; kidney tubular injury.

Chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or urine albumin-creatinine ratio (ACR) > 30 mg/g, is a major public health problem, with 23.2 million people affected in the United States.[1] Lower eGFR is an established independent risk factor for cardiovascular disease, in particular for heart failure.[2] Albuminuria is an established marker of

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glomerular injury, and elevated ACR is associated independently with risks of CKD-related adverse outcomes, including heart failure.[3-5] Therefore, both glomerular injury and dysfunction appear pathophysiologically linked to heart failure.

Kidney tubule health is not part of the routine assessment of CKD, but may also be important in the pathogenesis of heart failure. Novel markers of kidney tubular injury have been developed that can detect and quantify early tubular damage, which in turn has been shown to predict the onset of CKD.[6-8] As a harbinger of decreased homeostatic reserve in the kidney, these markers of kidney tubule damage may predict reduced capacity to regulate volume status that would result in clinical heart failure. To gain a broader understanding of the association between early kidney disease and heart failure, we sought to evaluate and compare associations of both glomerular and tubular injury markers with incident heart failure. In a population of community-dwelling older adults, we hypothesized that both markers of kidney tubular injury (urine kidney injury molecule 1 [KIM-1] and interleukin 18 [IL-18]) and ACR would be associated independently with risk of incident heart failure.

METHODS

Design and Participants

The Health, Aging, and Body Composition (Health ABC) Study is a National Institute on Aging (NIA)-sponsored cohort study that enrolled 3,075 well-functioning men and women aged 70-79 years from 2 clinical sites in Memphis, TN, and Pittsburgh, PA. Additionally, because older adults experience the highest prevalence of CKD and heart failure, Health ABC presents a unique opportunity to study risk factors in this population because Health ABC was composed of mostly well-functioning older adults without heart failure at baseline. Participant eligibility required self-reported lack of difficulty walking a quarter mile, climbing 10 steps, and performing basic activities of daily living; the absence of life-threatening illness; and plans to remain in the geographic area for at least 3 years. Baseline examinations occurred in 1997-1998 and participants underwent a 1-day evaluation that included medical history, physical activity assessment, physical examination, and radiographic tests. Those with prevalent heart failure or missing heart failure data at baseline, without baseline cystatin C measurements, and without baseline urine samples were excluded from this study (n = 158). Prevalent heart failure at baseline was based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes as defined by the Centers for Medicare & Medicaid Services from 1995-1998, self-reported history of heart failure, and use of selected medications.[9] The results represent an average median follow-up of 12.0 (interquartile range [IQR], 7.0-13.2) years, with the last clinic visit occurring on the year-16 visit (2012-2013). The study was approved by the institutional review boards at the University of Tennessee Health Science Center and the University of Pittsburgh. In addition, the present study was approved by the University of California, San Francisco; San Francisco VA Medical Center; and Tufts University committees on human research.[10,11]

Urinary Markers

Primary predictors in this study were urine concentrations of albumin, KIM-1, and IL-18, all of which were measured concurrently from previously frozen stored urine samples and indexed by the concurrent urine creatinine concentrations (denoted as ACR, KIM-1:Cr, and IL-18:Cr, respectively). All urine biomarkers were measured at the Cincinnati Children's Hospital Medical Center Biomarker Laboratory. Albumin and creatinine were measured by immunoturbidimetry and colorimetric enzyme assay, respectively, using a Siemens Dimension Xpand plus HM clinical analyzer. The KIM-1 enzyme-linked immunosorbent assay (ELISA) was constructed using commercially available reagents (R&D Systems Inc).[12] IL-18 was measured using a commercially available ELISA kit (Medical & Biological Laboratories Co Ltd). Coefficients of variation for urine measures were albumin, 5.9%; creatinine, 4.1%; IL-18, 7.2%; and KIM-1, 5.2%.

Candidate Covariates

Other characteristics that were covariates for multivariable analyses included demographic characteristics, socioeconomic factors, and traditional risk factors for heart failure, all of which were measured at baseline. The following characteristics were included as covariates in all multivariable models: age, sex, race, education level, income, diabetes (use of hypoglycemic agents, self-report, fasting plasma glucose level $\geq$ 126 mg/dL, or oral glucose tolerance test result $\geq$ 200 mg/dL), systolic blood pressure, hypertension (self-report plus use of antihypertensive medications), fasting high- (Johnson & Johnson Vitros 950 analyzer) and low-density lipoprotein cholesterol (calculated using the Friedewald equation)[13] levels, body mass index, waist circumference, prevalent cardiovascular disease (coronary heart disease, myocardial infarction, angina, and coronary artery bypass), C-reactive protein level (measured in duplicate by ELISA kits from R&D Systems Inc),[14] current smoking (defined as current vs former or never), alcohol (defined as $\geq$1 vs $<$1 drink per day), and serum albumin level (measured by a colorimetric technique on a Johnson & Johnson Vitros 950 analyzer).[15]

An additional covariate was baseline kidney function, assessed by serum cystatin C–based GFR estimates. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C)[16] using a BNII nephelometer (Dade Behring Inc). We estimated GFR using the 2012 CKD-EPI (CKD Epidemiology Collaboration) cystatin C equation, which includes age and sex.[17]

Incident Heart Failure Outcome

During semiannual telephone interviews and annual clinical visits, participants were asked to report any hospitalization and were asked directly about interim events. Medical records from all reported overnight hospitalizations were examined. Incident heart failure was defined as the first overnight hospitalization for decompensated heart failure. Heart failure criteria required at least a diagnosis from a physician and treatment for heart failure (prescription for a diuretic agent and either digitalis or a vasodilator). Events were confirmed through medical record review by a panel of clinicians based on symptoms, signs, chest radiograph results, and echocardiography findings, as previously described.[18]

Statistical Analyses

Baseline characteristics of participants by quartiles of KIM-1:Cr, IL-18:Cr, and ACR were compared using t test or χ^2 test when appropriate. Spearman correlation coefficients were calculated among the 3 urine injury markers. To evaluate the form of association between each urine injury marker level and heart failure risk, we then used natural piecewise cubic splines and placed the specified interior knots at the quartiles of the distributions of KIM-1:Cr, IL-18:Cr, and ACR, respectively. We also dichotomized ACR at 30 mg/g because that is the clinical cutoff point.

We then used Cox proportional hazards models to investigate associations of KIM-1:Cr, IL-18:Cr, and ACR with time to