Urinary Biomarkers of Kidney Tubular Damage and Risk of Cardiovascular Disease and Mortality in Elders

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Rationale & Objective: Novel urinary biomarkers have enabled earlier detection of kidney tubular damage, but their prognostic value for adverse cardiovascular outcomes is uncertain. We hypothesized that tubular damage, measured by urine α_1-microglobulin (A1M), amino-terminal propeptide of type III procollagen (PIIINP), and neutrophil gelatinase-associated lipocalin (NGAL), would be associated with higher risks for cardiovascular events and mortality among elders.

Study Design: Case-cohort study.

Setting & Participants: This study included a randomly selected subcohort (n=502), cardiovascular disease (CVD) cases (n=245), and heart failure cases (n=220) from the Health, Aging, and Body Composition (Health ABC) Study.

Predictors: Baseline urine A1M, PIIINP, and NGAL concentrations.

Outcomes: Incident CVD, heart failure, and all-cause mortality.

Analytical Approach: Cox proportional hazards models were used to evaluate biomarker associations with each outcome.

Results: At baseline, mean age was 74 years and estimated glomerular filtration rate was 73 mL/min/1.73 m^2. After adjustment for demographics, estimated glomerular filtration rate, albumin-creatinine ratio, and other cardiovascular risk factors, each doubling in biomarker concentration was associated with the following adjusted HRs for CVD: A1M, 1.51 (95% CI, 1.16-1.96); PIIINP, 1.21 (95% CI, 1.00-1.46); and NGAL, 1.12 (95% CI, 1.05-1.20). There were 248 deaths in the subcohort during a median follow-up of 12.4 years. Adjusted associations of each biomarker (HR per doubling) with all-cause mortality were: A1M, 1.29 (95% CI, 1.10-1.51); PIIINP, 1.05 (95%, 0.94-1.18); and NGAL, 1.07 (95% CI, 1.02-1.12). Biomarker concentrations did not have statistically significant associations with heart failure after multivariable adjustment.

Limitations: Urine biomarkers were measured at a single time point; no validation cohort available.

Conclusions: Kidney tubular damage is an independent risk factor for CVD and death among elders. Future studies should investigate mechanisms by which kidney tubular damage may adversely affect cardiovascular risk.

Complete author and article information provided before references.

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Chronic kidney disease (CKD) is an established risk factor for cardiovascular disease (CVD) and heart failure, but the underlying mechanisms are uncertain.[1-3] Kidney tubular function is essential for volume status regulation, acid-base homeostasis, mineral metabolism, and hormone production.[4] On kidney biopsy, the presence of kidney tubular atrophy and interstitial fibrosis are strong predictors of kidney disease progression.[5,6] However, tubular injury and dysfunction are poorly quantified by traditional measures of kidney health, including estimated glomerular filtration rate (eGFR) and albuminuria.[7]

In certain settings, urine biomarkers have been useful for the prognostication of CKD incidence and progression.[8-12] It is less clear whether they can forecast CKD complications, including cardiovascular risk and death. Urine α_1-microglobulin (A1M), amino-terminal propeptide of type III procollagen (PIIINP), and neutrophil gelatinase-associated lipocalin (NGAL) are promising markers of kidney tubular damage. In kidney biopsy series, urine A1M, PIIINP, and NGAL concentrations were reported to correlate significantly with the extent of tubulointerstitial fibrosis.[13-17] Higher urine A1M, PIIINP, and NGAL concentrations have also been shown to be independent predictors of kidney function decline.[8,11,18-20] Some studies have evaluated their prognostic value for CVD, heart failure, and mortality; however, these studies have yielded conflicting results.[10,13,14,18-22] Further, no prior study has measured these biomarkers concurrently to compare their relative strengths of association with longitudinal outcomes.

The objective of this study was to evaluate the associations of urine A1M, PIIINP, and NGAL concentrations with incident CVD, heart failure, and all-cause mortality in an ambulatory cohort of elderly individuals. We hypothesized that tubular damage, as assessed by urine biomarker concentrations, would be an independent predictor of cardiovascular outcomes and death.

Methods

Study Design and Participants

The Health, Aging, and Body Composition (Health ABC) Study is a National Institute on Aging–sponsored cohort that enrolled 3,075 well-functioning men and women aged 70 to 79 years from 2 clinical sites in Memphis, TN, and Pittsburgh, PA. Eligibility required self-reported ability to walk a quarter mile, climb 10 steps, and perform basic activities of daily living without difficulty; the absence of

life-threatening illness; and plans to remain in the geographic area for at least 3 years. Informed consent was obtained from all participants, and the study was performed in compliance with the Declaration of Helsinki. Participants underwent a baseline evaluation in 1997 to 1998 that included a medical history and physical assessment, physical examination, and radiographic tests. Follow-up occurred every 6 months by telephone or through annual visits to clinical centers.

We developed a case-cohort sample of the Health ABC Study for measurement of novel kidney injury biomarkers (Fig 1). The case-cohort design uses a subsampling technique in survival data for estimating the relative risk for disease in a cohort study without collecting data from the entire cohort. Among the entire cohort of 3,075 Health ABC participants, overall event rates for CVD, heart failure, and mortality were 2.06% per year, 1.64% per year, and 3.88% per year, respectively. From the entire cohort, 502 participants were selected as a random subcohort; within the subcohort, 248 (49%) participants died during follow-up, providing ample power for mortality analyses. Additionally, we selected at random 245 cases of CVD (50% of total CVD events) and 220 cases of heart failure (57% of total heart failure events). Among these, 97 CVD cases and 94 heart failure cases originated in the subcohort. This design provided a total of 776 individuals who underwent urine biomarker measurement.

The study was approved by the institutional review boards at the University of Tennessee Health Science Center and the University of Pittsburgh. The present study was also approved by the University of California, San Francisco; San Francisco Veterans Affairs Medical Center; and Tufts Medical Center committees on human research.

Predictors

Urine A1M, PIIINP, and NGAL were measured concurrently at the Cincinnati Children's Hospital Medical Center Laboratory from urine specimens collected at the baseline visit. All urine specimens were in continuous storage at −80°C until biomarker measurement without prior freeze-thaw. Laboratory personnel performing the biomarker assays were blinded to clinical information about participants. Urine A1M was measured using a commercially available assay (Siemens BNII nephelometer). The detectable limit of the A1M assay was 0.5 mg/dL. Urine PIIINP was measured by a commercially available enzyme-linked immunosorbent assay (ELISA; USCN Life Sciences). Urine NGAL was assayed using a human-specific commercially available ELISA (Antibody-Shop).[23] Intra- and interassay coefficients of variation for urine measurements were A1M, 4.1%/10.3%; PIIINP, <10%/<12%; and NGAL, 2.1%/9.1%.

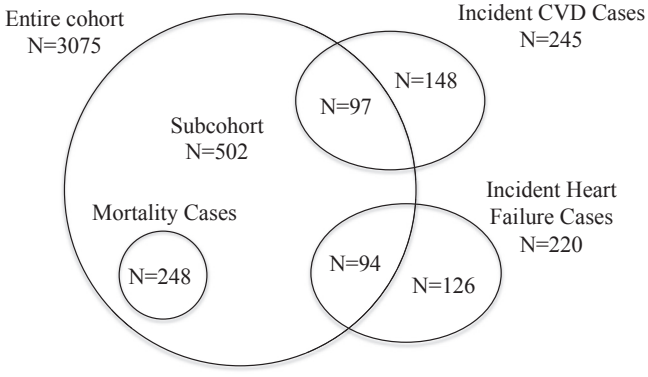

Figure 1. Sampling for the study within the Health, Aging, and Body Composition (Health ABC) cohort. Abbreviation: CVD, cardiovascular disease.

Outcomes

The outcomes were incident CVD, heart failure, and death. Follow-up was analyzed through 2011. Participants were questioned about hospitalizations for coronary heart disease (CHD), heart failure, or stroke every 6 months. When an event was reported, hospital records were collected and verified by a Health ABC Disease Adjudicator at each site. Incident CVD was defined by either the first CHD event and/or stroke after enrollment. CHD was defined as coronary death or any overnight hospitalization in an acute-care hospital for acute myocardial infarction. Incident stroke was defined as fatal and nonfatal stroke events. Incident heart failure was defined as the first overnight hospitalization for decompensated heart failure. Heart failure criteria required a diagnosis from a physician and treatment for heart failure. Deaths were ascertained by review of local obituaries, reports to the clinical centers by family members, or semiannual study contacts. Date of death was taken from the death certificate.[24]

Covariates

Covariates were assessed at baseline and included age, sex, race, clinical site, education level, current smoking (defined as current vs former or never), diabetes mellitus (defined as self-reported use of hypoglycemic agents, fasting plasma glucose > 126 mg/dL, or 2-hour oral glucose tolerance test result > 200 mg/dL), hypertension (defined as either self-report plus use of antihypertensive medications or measured systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg), prevalent heart failure, prevalent CHD (defined as myocardial infarction, angina, or coronary artery bypass), systolic blood pressure, body mass index, serum albumin concentration (measured by colorimetric assay on a Johnson & Johnson Vitros 950 analyzer),[25] C-reactive protein (CRP) concentration (measured in duplicate by ELISA kits from R&D Systems, Inc),[26] fasting high- and low-density lipoprotein cholesterol concentrations (calculated using the Friedewald equation),[27] and current statin use. Cystatin C was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C) using a BNII Nephelometer (Dade Behring, Inc). GFR was estimated using the combined CKD-EPI (CKD Epidemiology Collaboration) creatinine–cystatin C equation.[28] Urine