RESEARCH LETTER
Kidney Tubular Injury Biomarkers and Secretory Function in Acute Decompensated Heart Failure

To the Editor:

The assessment of kidney function is a critical component of care for patients admitted for acute decompensated heart failure. A valid measurement of kidney function is needed to guide diuretic and other key therapies. However, serum creatinine level, the traditional marker of kidney function, does not comprehensively capture the multidimensional processes of the kidneys. Relying on changes in the serum creatinine levels in patients with acute decompensated heart failure may be problematic for several reasons: acute hemodynamic alteration during heart failure treatment violates the steady-state assumption, autoregulation within the glomerular circulation obscures intrinsic kidney injury, and the skeletal muscle mass may be reduced. Consequently, there have been conflicting observations reporting that elevations in serum creatinine be reduced. Consequently, there have been conflicting correlations among serum creatinine levels and novel biomarkers can also estimate the functional capabilities of the kidney tubules, including tubular secretion, which plays a central role in loop diuretic delivery and efficacy.

Therefore, the aim of this pilot study was to determine correlations among serum creatinine levels and novel tubular injury biomarkers, including tubular secretion, which play a central role in loop diuretic delivery and efficacy.

We obtained clinical data and biospecimens within 24 hours of admission from 61 acute decompensated heart failure admissions (58 patients) at the University of Washington. This study was approved by the University of Washington Institutional Review Board (STUDY00005006), and all participants provided informed consent for participation. We abstracted the serum creatinine and B-type natriuretic peptide levels of each patient. The biomarkers of tubular injury may increase earlier in the course of kidney injury in acute decompensated heart failure and may identify patients with intrinsic, as opposed to hemodynamic, injury with greater specificity. Novel biomarkers can also estimate the functional capabilities of the kidney tubules, including tubular secretion, which plays a central role in loop diuretic delivery and efficacy.

We measured the urine creatinine levels and following tubular injury biomarkers: neutrophil gelatinase-associated lipocalin; kidney injury molecule 1; liver fatty acid–binding protein; interleukin 18; tissue inhibitor of metalloproteinase 2 and insulin-like growth factor–binding protein 7 product; calprotectin; and N-acetyl-β-glucosaminidase. These biomarkers were indexed to urine creatinine concentrations to normalize for approximate urine concentration.

In a subset of 21 participants, we measured the markers of tubular secretion: cinnamoylglycine, isovalerylglycine, kynurenic acid, pyridoxic acid, and tiglylglycine in blood and spot urine samples. We calculated the fractional excretion of secretory biomarkers to estimate the secretory clearance normalized to the estimated glomerular filtration rate (indicated by the serum creatinine level). A lower fractional excretion suggested decreased secretory function. Pearson correlations were calculated between each kidney measure along with the admission B-type natriuretic peptide.

The mean (± standard deviation) age of the study participants was 63 ± 13 years, and 26% of the participants had nonischemic heart failure. Analysis of demographic characteristics of the study population is presented in Table 1.

Table 1. Characteristics at Admission for the Study Cohort (N=61)

| Baseline Variable | Value |
|------------------|-------|
| Age, y           | 62 (± 13) |
| Female           | 16 (26%) |
| Demographics     |       |
| White            | 44 (72%) |
| Black            | 7 (12%)  |
| Medical history  |       |
| Nonischemic heart failure† | 39 (67%) |
| Heart failure with preserved ejection fraction | 22 (36%) |
| No CKD           | 33 (54%) |
| CKD stage 1-2    | 7 (11%)  |
| CKD stage 3      | 21 (34%) |
| Diabetes         | 22 (36%) |
| Hypertension     | 35 (57%) |
| COPD             | 16 (26%) |
| Atrial fibrillation | 31 (51%) |
| Heart transplant | 3 (5%)   |
| Home medication use |     |
| ACE-I or ARB     | 35 (57%) |
| β-Blocker        | 45 (74%) |
| Calcium channel blocker | 9 (15%) |
| Vasodilator      | 15 (25%) |
| Inotrope         | 6 (10%)  |
| Aldosterone antagonist | 21 (34%) |
| Loop diuretic, mg/d | 46 (±71) |
| Thiazide         | 2 (3.3%) |
| Clinical measurements |     |
| No edema†        | 14 (24%) |
| Trace/1+ edema² | 19 (32%) |
| 2+ edema²       | 17 (29%) |
| 3+ edema²       | 9 (15%)  |
| Heart rate, beats/min | 89 (±21) |
| Systolic blood pressure, mm Hg | 121 (±25) |
| Diastolic blood pressure, mm Hg | 75 (±19) |
| Laboratory serum levels at admission |     |
| Creatinine, mg/dL | 1.4 (±0.6) |
| Serum urea nitrogen, mg/dL | 33 (±19) |
| BNP              | 1183 (±1131) |
| Admit creatinine = peak creatinine | 6 (10%) |

Note: All results are presented as mean (± standard deviation) or number (% of cohort).

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

†n=48 due to etiology of heart failure being unknown for 3 individuals.

‡n=59 due to the lack of mention of peripheral edema examination in the medical documentation.
were women (Table 1). Heart failure etiology was non-ischemic for 67% of the participants, and 36% had heart failure with preserved ejection fraction. The mean admission serum creatinine level was 1.45 ± 0.55 mg/dL, and at baseline, 44% of the participants had chronic kidney disease.

At admission, the serum creatinine levels weakly correlated with tubular injury biomarkers and were not correlated with fractional excretions (by definition, fractional excretion should be unrelated to creatinine) (Fig 1, Fig S1). The fractional excretion of secretory biomarkers generally correlated significantly with one another. The admission B-type natriuretic peptide level was not correlated with the serum creatinine level but was correlated with the injury biomarker, N-acetyl-β-glucosaminidase, and with lower fractional excretion of isovalerylglycine (r = −0.36, P = 0.049) (Fig 1).

The results of this preliminary study demonstrate that serum creatinine levels weakly correlate with biomarkers of kidney tubular injury in patients admitted for acute decompensated heart failure. Our findings expand on existing research by using a larger panel of contemporary injury biomarkers.5,6 We also noted weak correlations between the biomarkers of kidney tubular injury. Taken together, these findings suggest the possibility of unrecognized, distinct phenotypes of kidney injury.

Although the serum creatinine level generally relates to the total secretory function, wide distributions in the fractional excretion of secretory biomarkers imply that variability in tubular function exists for any given glomerular filtration rate. Additionally, there was a consistently positive correlation between secretory biomarkers, demonstrating the utility of these endogenous biomarkers to reflect tubular secretory function. These

![Fig 1. Correlation coefficients of serum creatinine level with urine biomarkers of tubular injury, secretory clearance, and BNP within 24 hours of admission for acute decompensated heart failure and that of serum creatinine level with admission serum BNP level. (N for serum creatinine and BNP = 61). Abbreviations: BNP, B-type natriuretic peptide; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; L-FABP, liver fatty acid–binding protein; NAG, N-acetyl-β-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; TIMP2*IGFBP7, tissue inhibitor of metalloproteinase 2 and insulin-like growth factor–binding protein 7 product.](image-url)
same biomarkers have been shown to correlate with the secretion of furosemide into the tubular lumen in healthy individuals. This suggests that the tubular secretory biomarkers could be relevant for tailoring diuretic strategies with greater specificity than is possible using serum creatinine level alone.

These findings are hypothesis-generating and highlight the need for larger studies of patients with acute decompensated heart failure to identify specific kidney injury phenotypes. Specifically, more research is needed to understand how filtration, tubular injury, and secretory clearance relate both to response to treatment and to clinical outcomes in patients admitted with acute decompensated heart failure.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Differences in r values with Pearson correlation between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction.

ARTICLE INFORMATION

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