Urinary Angiotensinogen: A Promising Biomarker of AKI Progression in Acute Decompensated Heart Failure: What Does It Mean?

Jan Wysocki and Daniel Batlle

Several biomarkers that may precede increases in serum creatinine, the clinical marker of GFR, have been proposed for early detection of AKI. A kinetic GFR formula (1) is, in our opinion, a sensitive tool to recognize AKI early and more precisely estimate the decline and recovery of kidney function. Although early recognition of the fall in GFR is critical, some biomarkers may provide insights on AKI progression that the GFR itself cannot provide. AKI biomarkers include neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), IL-18, cystatin C, and liver–type fatty acid binding protein (2–6). In addition, the product of concentration of two markers of G1 cell cycle arrest, tissue inhibitor of metalloproteinases-2 and IGF binding protein 7, is viewed as a promising AKI biomarker.

AKI is a frequent complication of acute decompensated heart failure and associated with worse clinical outcomes. In this issue of the *Clinical Journal of the American Society of Nephrology*, Chen et al. (7) report the results of a prospective study examining the potential utility of urinary angiotensinogen (uAGT) in combination with three of the aforementioned kidney injury biomarkers (NGAL, IL-18, and KIM-1) in predicting AKI progression. All biomarkers were measured at the time of initial AKI diagnosis (*i.e.*, on the first day that the serum creatinine first crossed the Kidney Disease–Improving Global Outcomes stage 1 or 2 threshold). The primary outcome was defined as AKI progression defined by worsening of AKI stage (50 patients). The secondary outcome was AKI progression with subsequent death (18 patients.). In the adjusted model, patients with the highest tertile of uAGT had 10.8-fold higher risk of AKI progression compared with those with the lowest uAGT tertile. Increased urinary NGAL was associated with 4.7-fold odds of AKI progression, whereas increased urinary IL-18 revealed a 3.6-fold risk. In the adjusted analysis, NGAL, IL-18, and KIM-1, when added to the clinical model, improved the risk classification for the outcomes (*i.e.*, AKI progression and AKI progression with death). Of note, uAGT outperformed the other three biomarkers. This study is also important, because it confirms previous observations that uAGT is increased in the setting of AKI and can predict its progression to higher stages or death after cardiac surgery (8,9) or in acute decompensated heart failure (10).

The possible pathophysiologic significance of increased uAGT in AKI in general and in developing AKI in the setting of acute decompensated heart failure deserves comment. Maintenance of blood volume, vascular tone, and hemodynamic stability depends on a set of fine-tuned interactions between the heart and the kidney (11). Combined renal and cardiac disease invokes a number of hemodynamic and neurohormonal forces that synergistically worsen kidney function (11). The term cardiorenal syndrome is increasingly used to reflect this combined organ involvement (12). One of the main neurohormonal forces at play in acute decompensated heart failure is the activation of the renin–angiotensin system (RAS) (11,12). The increase in uAGT in AKI is of interest, because it likely reflects local activation of the RAS within the kidney. Studies in animal models of AKI provide evidence in support of the concept that activation of the kidney RAS contributes to the pathogenesis of AKI (13–16).

In the setting of acute decompensated heart failure, activation of the RAS systemically likely antedates any additional intrarenal RAS activation as AKI develops. An increase in circulating renin, the rate-limiting step for angiotensinogen (AGT) cleavage and formation of angiotensin I, is usually needed to initiate the activation of the RAS leading to circulating angiotensin II overactivity (17,18). An increase in plasma AGT, by contrast, is not necessary, because this protein is abundant in plasma and therefore, not a limiting step in RAS activation. At the local kidney level, however, uAGT is three to four orders of magnitude lower than in the circulation. In this context, an increase in kidney AGT could trigger RAS activation by providing the substrate for downstream formation of angiotensin peptides. AGT is a 453-amino acid-long protein with 10 N-terminal amino acids (1–10) that are cleavable by renin, resulting in the formation of angiotensin I or angiotensin III (1–10). Angiotensin III (1–10), in turn, is further converted to the angiotensin II (1–8) by angiotensin-converting enzyme (ACE) and non-ACE enzymes and exerts its potent biologic effects.

But why is uAGT increased in AKI? And is circulating plasma AGT altered as well? The answer to the latter question is likely no, because this protein is very
abundant in plasma, and moreover, the levels do not fall, even when a large supply of exogenous ACE2, an efficient angiotensin II–metabolizing enzyme (19), is provided to produce a large turnover of angiotensin peptides, which are all derived from AGT as the parent compound. Whether circulating plasma AGT is a source of uAGT or primarily kidney derived has been debated without a definitive answer. Kobori et al. (18) have proposed that the source of uAGT is intrarenal. In nondiseased kidneys, circulating AGT should not pass into the urine in any appreciable amounts owing to its molecular size, 65 kD (17). Moreover, efficient tubular reabsorption or degradation of any filtered AGT could prevent it from appearing in the urine. The fact that AGT is detectable in urines from humans and animals without kidney disease supports the view that uAGT originates primarily from local kidney sources (17,20). Moreover, kidney angiotensin II levels are much higher than those detected in the circulation. One of the possible mechanisms of increased intrarenal angiotensin II could be transcriptional upregulation of AGT mRNA in the proximal tubule (21). However, studies in mice have shown that circulation-derived AGT can activate kidney RAS when the glomerular filtration barrier is altered (22). In a transgenic mouse model of podocyte-selective injury, increased renal angiotensin II content and markedly increased both tubular AGT and uAGT proteins were attributed to increased glomerular passage of circulating AGT. This occurred without an increase in renal renin activity. These studies clearly supported the dependency of kidney angiotensin II generation on filtered AGT. But what about in a minimally proteinuric state such as AKI, where glomerular permeability is not markedly altered? Here, even if only small amounts of AGT are filtered, an increase in uAGT may occur if this protein is not reabsorbed or metabolized efficiently by a damaged proximal tubule. In this scenario, AGT could be classified as a biomarker of tubular injury similar to NGAL or KIM-1.

Whether in AKI, the increases in uAGT reflect intrarenal AGT formation, increased glomerular passage, or impaired tubular reabsorption is currently unknown, but all possibilities are plausible and nonexclusive of each other. Albumin, which has a comparable molecular mass with AGT (67 versus 65 kD), is generally believed to be completely plasma derived. A comparison of the urinary albumin and AGT levels would shed light on the degree of uAGT that is plasma derived as well (23). In a non-AKI setting, studies that have evaluated these two proteins in urine in humans found a positive and linear correlation (24). In patients with AKI in the setting of acute decompensated heart failure, elevation of uAGT was observed both with and without preexisting CKD, but the levels were significantly higher in patients with prior CKD. Of note, uAOG was an independent predictor of AKI even after adjusting for urinary albumin (10). This would support the view that, in AKI, the increases in uAGT may be independent from circulating AGT and caused by intrarenal formation.

Regardless of its origin, an increase in uAGT likely reflects kidney RAS activation. A natural question to ask is whether pharmacologic RAS blockade could have some unexpected beneficial role in AKI if the RAS is overactive. After ischemia-reperfusion (I/R) injury in rats, a model of AKI, angiotensin II levels are increased (25), whereas the levels of its counterbalancing peptide, angiotensin 1–7, are decreased (26). Deficiency of ACE2, an enzyme that converts angiotensin II to angiotensin 1–7 and is abundantly expressed in the kidney, has been shown to worsen I/R kidney injury in mice, suggesting that this enzyme may have a protective effect in AKI (27) and other forms of kidney disease (28). Patients with AKI likely have a substantial inflammatory response (8), in part, caused by angiotensin II. Of note, in rodents exposed to renal I/R injury, RAS blockade using an ACE inhibitor or an angiotensin II type 1 receptor antagonist ameliorated inflammation within the kidney and alleviated the severity of AKI (13,14). This is not to say, of course, that blocking the proinflammatory and therefore, deleterious effects of RAS activation will overcome the generally considered beneficial hemodynamic actions of angiotensin II that help maintain systemic BP and attenuate the fall in GFR that occurs in AKI associated with decompensated heart failure.

It is common clinical practice for RAS blocking agents to be temporarily placed on hold as soon as kidney function deteriorates in the setting of acute decompensated heart failure. There may be in the horizon, however, ways to deal with RAS overactivity in AKI that could be effective and hopefully safe, such as the use of AGT antisense (29) or enhancing the degradation of angiotensin II to favor the formation of angiotensin 1–7. Either recombinant ACE2 or administering angiotensin 1–7, an anti-inflammatory RAS peptide, may be a newer approach to counteract some of the undesirable effects of RAS overactivity in a way that could be designed to be easily titratable in the hospital setting. For now, an increase in uAGT may be considered one of the most promising biomarkers of AKI progression associated with acute decompensated heart failure.

Acknowledgments
This work was supported by National Institute of Diabetes and Digestive Kidney Diseases grant R01DK104785 and a gift to Northwestern University by the Joseph and Bessie Feinberg Foundation.

Disclosures
None.

References


Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Urinary Biomarkers at the Time of AKI Diagnosis as Predictors of Progression of AKI among Patients with Acute Cardiorenal Syndrome,” on pages 1536–1544.