The kidney tubules make up the vast majority of the kidney’s cortical structure, expend most of the energy used by the kidneys, and play a central role in a variety of essential biological functions. However, chronic kidney disease (CKD) diagnosis, staging, and prognosis remain anchored to estimated glomerular filtration rate (eGFR) and albuminuria, which primarily reflect glomerular health and do not fully capture tubular pathology. Biopsy-proven interstitial fibrosis and tubular atrophy is found in nearly all forms of CKD, and its severity is strongly prognostic of kidney failure. Recent studies evaluating the clinical significance of noninvasive biomarkers reflecting tubule injury and dysfunction in individuals with CKD have further strengthened the argument that a broader assessment of kidney health—beyond eGFR and albuminuria—can provide additional information about the health of the kidney and an array of downstream adverse consequences.

A critical function of the kidney tubules is maintaining body water homeostasis through urinary dilution and concentration. Previous studies examining associations of urine osmolality, an indicator of vasopressin stimulation and urine concentrating ability, with adverse kidney outcomes have yielded conflicting results. Several large multicenter CKD cohort studies have demonstrated that lower urine osmolality is associated with faster decline in eGFR and subsequent risk of CKD progression independent of eGFR and albuminuria. In addition, an analysis of individuals with autosomal dominant polycystic kidney disease (ADPKD) and largely preserved eGFR showed that lower baseline urine osmolality was associated with faster decline in eGFR. In contrast, smaller studies of individuals with and without ADPKD reported that higher, rather than lower, urine osmolality was associated with adverse kidney outcomes.

More recently, a study of individuals with ADPKD evaluated urine-to-plasma ratio of urea ([U/P]urea)—a purported surrogate for urine concentrating ability—and found that lower [U/P]urea is strongly correlated with lower urine osmolality after an overnight fast, and is independently associated with faster decline in eGFR. In this issue of *AJKD*, Liu et al extend these findings by evaluating [U/P]urea in individuals with non-ADPKD CKD in the Chronic Renal Insufficiency Cohort (CRIC). They report that lower [U/P]urea is associated with faster decline in eGFR and greater risk of CKD progression and kidney failure, independent of eGFR and albuminuria. The study has several strengths, including the use of a large CKD cohort with a long follow-up duration and frequent and protocolized eGFR assessments, and adjustment for numerous potential confounders. In addition, and in contrast to many novel biomarkers, plasma and urine urea are widely available clinical assays, so the results can be immediately translated to the clinical setting. But what is the [U/P]urea really measuring? Specifically, does lower [U/P]urea reflect impaired tubular concentrating ability, or is it simply a marker of GFR?

It is well known that plasma urea tracks closely with GFR; as the denominator of [U/P]urea, an elevated plasma urea from reduced GFR would lead to a lower [U/P]urea. It is of no surprise that a marker correlated with GFR will be associated with decline in kidney function. Indeed, the authors report a strong positive correlation (r = 0.63) between [U/P]urea and creatinine-based eGFR in this study—this is as strong as the correlation between serum cystatin C and creatinine-based eGFR reported in prior large-scale studies. Second, in multivariate analyses in the article by Liu et al, models were adjusted for 24-hour urine urea excretion to account for protein intake. This, of course, is highly related to urine urea concentration in the denominator of [U/P]urea with kidney outcomes. In these models, [U/P]urea remains strongly associated with outcomes. Third, in unadjusted models [U/P]urea had a hazard ratio of approximately 12, which was attenuated to 3 following adjustment for eGFR. This implies significant confounding in the unadjusted model, and raises questions whether all of the confounding by GFR was captured by adjusting for a one-time assessment of eGFR, which is known to be an imprecise estimate of true GFR. This residual confounding remains possible, notwithstanding a statistically significant association of [U/P]urea with CKD progression after adjusting for eGFR. Finally, because [U/P]urea was calculated using urea measured in 24-hour urine collections, the extent to which urinary urea reflected water intake variability throughout the day versus urine concentrating ability in this study is suspect. Likely, urinary urea concentration after a timed and prolonged fast would more closely assess the kidney’s ability to maximally concentrate urine than a 24-hour specimen.

The findings of this study leave little doubt that a low [U/P]urea is associated with CKD progression, especially in those with eGFR >30 mL/min/1.73 m². However we believe several steps should be taken to more fully understand the clinical meaning of [U/P]urea before it is used in clinical practice. Calculating [U/P]urea with urinary urea concentration...
from a fasting morning sample or a more rigorous water deprivation test, evaluating the degree to which \([U/P]_{\text{urea}}\) relates to urine osmolality, and considering alternative approaches to modeling urine and plasma urea instead of use of a ratio could help address the question of whether \([U/P]_{\text{urea}}\) signifies tubular capacity for osmoregulation, a strong correlate of GFR, or perhaps both. Simple but highly informative experiments might test how \([U/P]_{\text{urea}}\) and urine osmolality at baseline might predict the kidney’s response to tolvaptan and desmopressin. Such studies may be useful to clarify the role of \([U/P]_{\text{urea}}\) in marking the kidney’s concentrating capacity above and beyond GFR. Beyond marking risk of CKD progression, such studies would have significant clinical value if a simple \([U/P]_{\text{urea}}\) biomarker could be used to identify persons with CKD particularly vulnerable to dehydration.14

In summary, the study by Liu et al reinforces the concept that a broader assessment of kidney health beyond eGFR and albuminuria can provide prognostic information about long-term kidney outcomes. Additional work is needed to more confidently ascribe tubular concentrating ability to \([U/P]_{\text{urea}}\) in individuals with common forms of CKD. Based on the findings presented by Liu et al, we believe \([U/P]_{\text{urea}}\) is likely to be confirmed by its relationship to GFR above and beyond concentrating ability. Even so, \([U/P]_{\text{urea}}\) has the potential to help transform our glomerulocentric approach to CKD care.

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**References**


