

Urine Albumin-to-Creatinine Ratio: What's in a Number?

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The evaluation of urinary protein is a cornerstone for the diagnosis and treatment of kidney disease. Quantification of proteinuria is used to inform fundamental clinical decisions, such as whether to refer to a nephrologist, perform a kidney biopsy, or initiate therapy. Furthermore, minute interindividual differences in proteinuria associate with future risks for heart disease, kidney failure, and cancer in general population studies.^{1–3} These findings motivate optimal and consistent methods to quantify proteinuria in the clinical setting.

In this issue of *JASN*, Heerspink *et al.*⁴ compare, among 701 participants in the Reduction In Endpoints in Noninsulin Dependent Diabetes Mellitus with the Angiotensin-II Antagonist Losartan (RENAAL) trial, four standard methods for measuring urine protein: 24-hour urine protein excretion, 24-hour urine albumin excretion, first morning void spot urine albumin concentration, and first morning void spot urine albumin-to-creatinine ratio (ACR). Unlike most previous studies, which related spot urine albumin or urine protein measurements to the gold standard, 24-hour urine collection, the study by Heerspink *et al.*⁴ addresses which of the four methods most strongly associates with the clinical outcome of renal progression, defined by a doubling of serum creatinine or the development of ESRD. In general, all four methods were strongly associated with renal progression; however, associations for spot urine ACR were modestly stronger than those for the other urine protein measurements, and the superiority of urine ACR was consistent across subgroups defined by gender, race, and age. Urine protein measurements were performed concurrently using uniform collection procedures and were tested in relation to a validated, clinically relevant kidney end point. The study is the first to demonstrate that urine ACR, which is commonly used in clinical practice, not only correlates with 24-hour

urine protein but also is clinically relevant for predicting progression.

The urine ACR is calculated by dividing the urine albumin concentration by the urine creatinine concentration to account for differences in urine volume and more closely approximate the gold standard, 24-hour urine albumin excretion⁵; first morning ACRs seem more reliable than random samples.⁶ How, then, can urine ACR predict renal progression more strongly than the gold standard, 24-hour urine collection? The added value of urine ACR must come from its denominator—urine creatinine. Two recent studies demonstrated that lower urine creatinine concentrations associate with cardiovascular disease events and mortality.^{7,8} Heerspink *et al.*⁴ also observe that lower urine creatinine concentration (or 24-hour urine creatinine excretion) independently associates with renal progression. They suggest a lower urine creatinine concentration reflects muscle wasting or poor overall health. As a result, a single number, the urine ACR, actually captures two disease processes simultaneously—albuminuria and muscle wasting—and reflects the combined contribution of both processes. This phenomenon highlights a general problem of using ratios in clinical medicine, including even the definition of normal; highest quartile ACRs within the current definition of normal range, for example, predicts incident hypertension.⁹ Combining multiple patient characteristics into a single equation can improve prediction but will obscure interpretation of the combined variable. For example, Kt/V, the standard measure of dialysis adequacy, combines information regarding dialysis duration with that of body size and composition, complicating the meaning of this measurement.¹⁰

What are the implications of this study for clinical practice? Urinary protein is quantified for the diagnosis, staging, monitoring, and prognosis of a wide range of kidney diseases. These purposes require accurate, unbiased, and repeatable estimates of urine albumin excretion that can predict clinical outcomes. Excellent correlations of urine ACR with 24-hour urine albumin excretion have been the subject of many previous reports.¹¹ First morning urine ACR also compares favorably with 24-hour urine albumin excretion in terms of within-person variability, perhaps as a result of inaccuracies in 24-hour urine collections⁶ and for the moment seems less complicated than predicting incident disease from urine proteomic screens.^{12,13} The study by Heerspink *et al.*⁴ completes the picture for urine ACR by demonstrating strong associations with a relevant kidney disease outcome. Given data from this study and the considerable patient effort required for a 24-hour urine collection, we agree with the authors that the first morning ACR is in general the logical choice for quantifying proteinuria in clinical practice. The study by Heerspink *et al.*⁴ was restricted to individuals who have type 2

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diabetes and macroalbuminuria; therefore, future work is needed to confirm these findings in other populations.

The results of this study also have implications for clinical research. First, urine ACR represents more than simply proteinuria, and associations of urine ACR with disease outcomes should be interpreted in the context of dual contributions of urine albumin excretion and urine creatinine. Second, this study joins those of Ix and Oterdoom to beg the questions, “Why is low urine creatinine excretion associated with adverse kidney and cardiovascular disease outcomes independent of standard measures of body composition?” “Does a low urine creatinine concentration reflect low muscle mass, low muscle quality, or both?” “Is a low urine creatinine concentration a modifiable therapeutic target?”

In summary, Heerspink *et al.*⁴ confirm the clinical utility of the first morning urine ACR. In doing so, they shed light on important issues related to each of its components: Optimal measurement of urine albumin excretion and the underappreciated importance of urine creatinine.

DISCLOSURES

None.

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See related article, “Comparison of Different Measures of Urinary Protein Excretion for Prediction of Renal Events,” on pages ●●●–●●●.