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Proximal Tubular Secretion: A New Way to Assess for Kidney Dysfunction?

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In clinical nephrology, the estimation of kidney function is central to the assessment of patients and is used in the diagnosis, staging, and management of chronic kidney disease. Traditionally, measures of kidney function have focused on the glomerular filtration rate (GFR).[1] The GFR is estimated by the measurement of serum levels of endogenous filtration markers such as creatinine and cystatin C and the use of estimating equations such as the Chronic Kidney Disease Epidemiology Collaboration equation,[2,3] the Modification of Diet in Renal Disease study equation,[4] or the Cockroft-Gault equation[5] to derive an estimated GFR (eGFR) or estimated creatinine clearance. However, these endogenous filtration markers and associated estimating equations have several limitations. Importantly, apart from glomerular filtration, they do not directly measure other aspects of kidney function such as tubular secretion and other endocrine and metabolic functions.[6] Creatinine levels are also influenced by factors such as muscle mass, diet, medications, and chronic illness.[7] Estimating equations are derived from specific populations and on the basis of averages and can therefore be less accurate in patients who are at extremes of muscle mass and/or diet, have reduced muscle mass (e.g., from amputation), or who are from a population different to that included in the derivation studies.[7] In addition, creatinine and eGFR measures are generally not sensitive to changes in kidney function, particularly in early kidney disease.

In this study by Granda *et al.*,[8] the authors investigated the association between the proximal tubular secretion of 5 endogenous solutes and eGFR decline using patients from the Jackson Heart Study. The Jackson Heart Study is a community-based prospective study of more than 5000 African American adults aged 21 years to 84 years in Jackson, Mississippi, United States. Serum creatinine measurements were taken at baseline and at 10 years of follow-up. A random subset of 1027 patients in this cohort provided a 24-hour urine collection at baseline assessment. Using a nested case-control study design, the authors identified cases with a $\geq$25% decline in eGFR from baseline to the 10-year follow-up examination and controls with a $<$10% decline in eGFR matched by baseline eGFR, age, diabetes status, and sex. The association between the baseline clearance of 5 secretory solutes (cinnamoylglycine, isovalerylglycine, kynurenic acid, p-cresol sulfate, and xanthosine) and eGFR decline over 10 years (case status) was assessed using conditional logistic regression. A summary secretion score derived from the scaled average of the 5 secretory solutes was also derived, and its association with case status was assessed. The authors found that lower kidney clearances of secretory solutes were associated with decline in kidney function over 10 years, with every 50% lower kidney clearance of certain solutes associated with 1.4-fold to 2.2-fold greater odds of eGFR decline. These associations persisted after adjustment for baseline eGFR and albuminuria.

These results demonstrate that measurement of tubular secretory clearance can add to the current GFR-based measurements of kidney function and potentially allow the identification of kidney disease at an earlier stage than can be detected by current GFR-based methods. A strength of this study is the use of a large community-based cohort of patients and the long 10-year duration of follow-up to evaluate decline in GFR. However, with the smaller number of patients with baseline tubular secretory

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clearance who also met the definition of case or controls, matching resulted in a relatively small cohort of only 127 cases and 127 controls. The findings of this study add to previous study findings on tubular secretory clearance in patients with chronic kidney disease by the same authors.[9] In their previous study of 3416 patients with impaired kidney function from the Chronic Renal Insufficiency Cohort study, the authors found an association between tubular secretory clearance and kidney disease progression after accounting for confounders, including traditional measures of kidney function such as eGFR and albuminuria.[9] Together, these findings indicate the potential for proximal tubular secretory clearance as an additional tool in the assessment of kidney function and prognostication of kidney function decline in both patients with preserved GFR and those with impaired GFR. Further validation of these or other secreted solutes may lead to the wider use of proximal tubular clearance in the assessment and prediction of kidney function in the future.

DISCLOSURE

The authors declared no competing interests.

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