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Tubular Secretion of Creatinine and Risk of Kidney Failure: The Modification of Diet in Renal Disease (MDRD) Study

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To the Editor:

Kidney function is most commonly monitored using estimated glomerular filtration rate (eGFR) and albuminuria, which are markers of glomerular function.[1] Tubular secretion is an important nonglomerular kidney function and is critical for toxin excretion and excretion of non-filtered endogenous metabolites.[2,3] Creatinine is filtered by the glomerulus and secreted by the proximal tubule such that creatinine clearance (CL_{cr}) overestimates GFR by 10% to 20%. Whether measuring secretory function provides additional insights into kidney tubule health is uncertain. The difference between measured CL_{cr} (mCL_{cr}) and measured GFR (mGFR) represents the clearance of creatinine due to tubular secretion (TS_{cr}). To assess whether TS_{cr} could be used to assess the impact of secretion on longterm clinical outcomes, we performed a post hoc analysis of the MDRD Study.

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Supplementary Material
Supplementary File (PDF)
Item S1, Tables S1-S4

During the baseline period of the MDRD Study before randomization, mGFR was determined using ^{125}I-iothalamate and mCL_{cr} was determined using a 24-hour urine collection performed at 2 time points (Item S1).[4] Of 840 participants with mGFR data, 838 completed a baseline urine collection. For participants with mCL_{cr} and mGFR at both time points (n = 718), the average of the 2 was considered (Table S1). We evaluated the association of TS_{cr} with time to initiation of kidney replacement therapy (KRT) for kidney failure (primary outcome) and all-cause and cardiovascular disease (CVD) mortality (secondary outcomes) through December 31, 2010. We used Cox regression after adjusting for demographics, comorbid conditions, lifestyle factors, and laboratory parameters (including baseline proteinuria and mGFR). In sensitivity analyses, we calculated the slope of mGFR between the 2 prerandomization visits and adjusted for it instead of mGFR.

Mean age of 838 participants was 51.7 years and 60.5% were men. At baseline, mean mGFR, mCL_{cr}, and TS_{cr} were 33.0, 42.4, and 9.5 ± 7.3 mL/min/1.73 m^2, respectively. Compared with the highest TS_{cr} quartile, there were no statistically significant differences in age, sex, race, smoking status, or diabetes in participants with lower TS_{cr}, whereas BMI was higher across quartiles of TS_{cr} and prevalent CVD was lower (Table S2). At any level of mGFR, there was a wide distribution of TS_{cr} across participants, and TS_{cr} was positively and modestly correlated with mGFR (Fig 1).

There were 626 cases of incident KRT during a median follow-up of 6.0 (interquartile range, 3.5-11.6) years. Each 10-mL/min/1.73 m^2 higher TS_{cr} was associated with 25% lower multivariable-adjusted risk for incident KRT; the lowest quartile of TS_{cr} had 1.6-fold higher risk for incident KRT versus the top quartile ($P < 0.001$; Table 1). Results of sensitivity analysis adjusting for mGFR slope instead of mGFR were similar, showing 27% lower risk for incident KRT (HR, 0.73 [95% CI, 0.65-0.82]) per 10-mL/min/1.73 m^2 higher TS_{cr}. There was no interaction between diet randomization arm and TS_{cr} ($P > 0.05$). There were 444 cases of all-cause mortality and 202 CVD-related deaths during follow-up. Although the incidence rate of both outcomes was lower with higher quartiles of TS_{Cr}, after multivariable adjustment, TS_{Cr} was not statistically significantly associated with either outcome in multivariable-adjusted models (Tables S3 and S4).

Our findings suggest that lower secretion of creatinine may give insights about kidney health above and beyond GFR and proteinuria. Prior studies have shown that a number of small molecules are present in the plasma of dialysis patients and are excreted primarily through tubular secretion in healthy individuals.[5] Low clearance of some of these markers has also been associated with mortality risk[6] and kidney failure[7] independent of eGFR in persons with advanced chronic kidney disease (CKD). However, measurement accuracy for these metabolites is yet to be established. Our results support the same concept but evaluate a precisely measured metabolite that is well known to be secreted by the proximal tubule (creatinine). Given that tubulointerstitial fibrosis is common in nearly all forms of kidney disease [8–10] and its severity is the most reliable feature on biopsy to predict progression to kidney failure,[10] developing additional markers of tubule health is likely to refine our ability to detect and monitor global kidney health above and beyond eGFR and albuminuria.

Our study is limited by the use of only prerandomization TS_{cr}; potential measurement errors in variables used to calculate TS_{cr}; the lack of older participants and those with insulin-dependent diabetes, and the limited number of those of non-European ancestry; and the lack of detailed smoking history. Strengths include the large number of participants, long-term follow-up and large number of events, detailed ascertainment of potentially confounding variables, and concurrent availability of mGFR and mCl_{cr} at baseline (twice in most participants).

In conclusion, lower TS_{cr} is associated with risk for incident KRT independent of mGFR or proteinuria in a large cohort of persons with mild to moderate predominantly nondiabetic CKD. Future studies should further evaluate the role of tubule secretory markers, confirm their association with adverse kidney outcomes, and determine whether they may can be used for improving the dosing of drugs that are primarily excreted by secretion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PSG has received clinical trial support from Kadmon Inc and speaker fees from Otsuka. MJS serves on the steering committee for Akebia, served on an advisory board for Bayer, and is a consultant for Cardurian. JHI is principal investigator of an investigator-initiated research project from Baxter Int. The other authors declare that they have no relevant financial interests.

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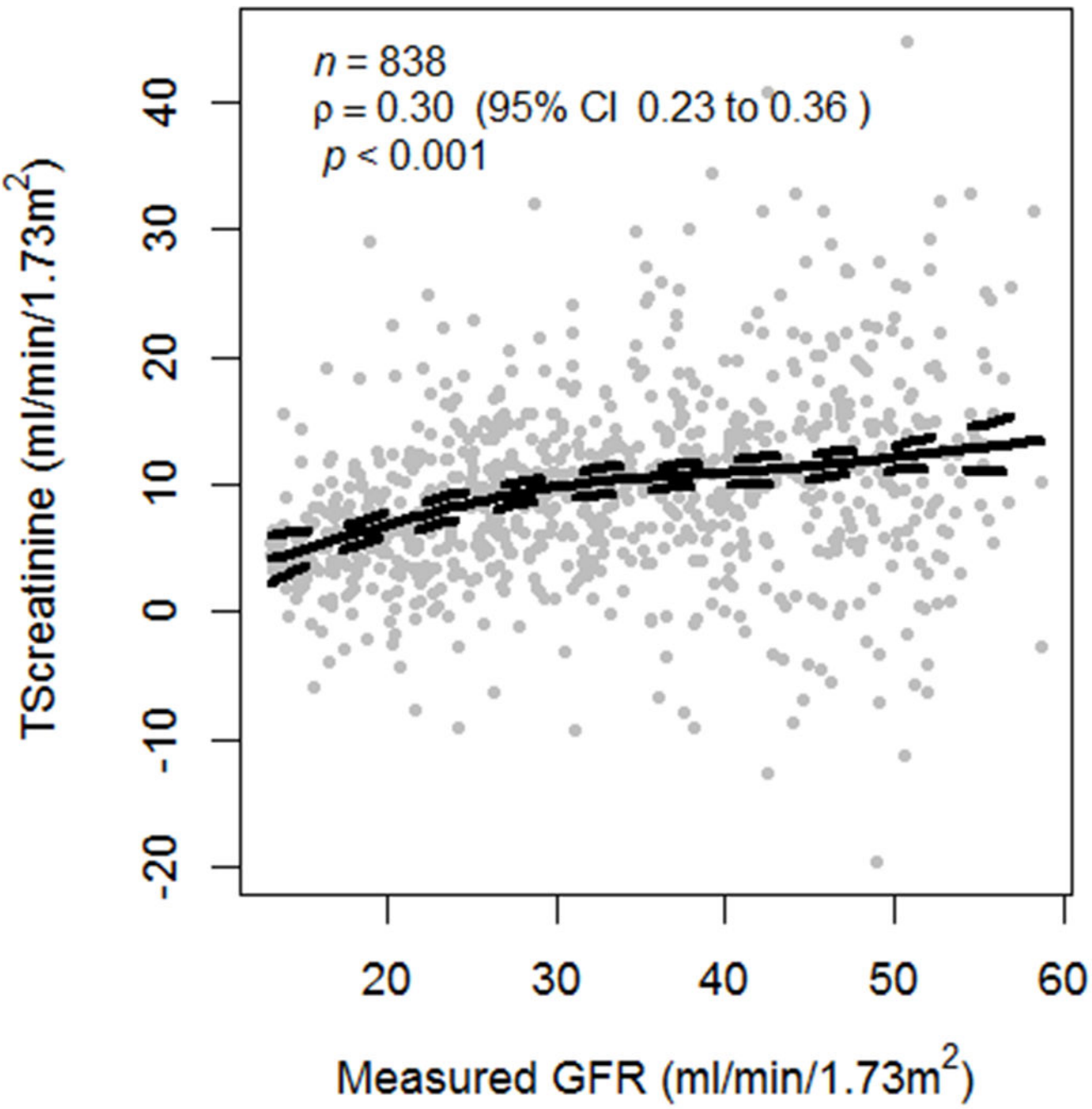

Figure 1.
Scatter plot of creatinine secretion across the spectrum of mGFR at baseline among 838 MDRD Study participants, showing a correlation (Pearson correlation = 0.3) between creatinine secretion and mGFR (*P* for significance < 0.001).

Table 1.

Association of Tubular Secretion of Creatinine With Clinical Outcomes

	No. of Patients	Incident KRT		All-Cause Mortality		CVD Mortality	
		Events	HR (95% CI)[a]	Events	HR (95% CI)	Events	HR (95% CI)
TS_{cr}, per 10 mL/min/1.73 m^2 greater	838	626	0.75 (0.67-0.85)	444	0.90 (0.78-1.04)	202	0.83 (0.67-1.02)
TS_{cr} category							
≤4.9 mL/min/1.73 m^2	209	168	1.64 (1.28-2.10)	120	1.06 (0.79-1.42)	58	1.16 (0.75-1.79)
>4.9-9.0 mL/min/1.73 m^2	210	170	1.46 (1.15-1.87)	114	1.22 (0.91-1.62)	50	1.27 (0.82-1.97)
>9.0-13.5 mL/min/1.73 m^2	210	150	1.16 (0.91-1.48)	105	0.87 (0.65-1.15)	51	0.99 (0.65-1.51)
>13.5 mL/min/1.73 m^2	209	138	1.00 (reference)	105	1.00 (reference)	43	1.00 (reference)

Abbreviation: HR, hazard ratio.

[a]Multivariable adjusted (for age, sex, race, smoking status, MDRD [Modification of Diet in Renal Disease] Study A/B, blood pressure target, protein diet randomization, cause of kidney disease, history of CVD, proteinuria, transferrin level, mean arterial pressure, lower serum high-density lipoprotein cholesterol level, and mGFR).