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Serum Creatinine Variability as a Novel Biomarker Predictive of Albuminuria Progression in Type 2 Diabetes Mellitus – Discovery and Validation in Two Longitudinal Cohorts

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Objective(s): The role of stability of renal function on kidney disease progression is unknown. We examined association between serum creatinine (scr) variability and albuminuria progression in Type 2 Diabetes(T2DM) and elucidated mechanism for the association.

Materials and Methods: In a discovery cohort, we identified 589 T2DM patients attending Diabetes Centre with ≥6 scr readings and no macroalbuminuria at baseline in 2002-2014. Scr variability was expressed adjusted-Cr-standard-deviation(CrSD)=SD/√[n/(n-1). We used cox-proportional hazards regression for outcome on progression (worsening across albuminuria stages), adjusting for demographics, medication, blood pressure, urinary-albumin-to-creatinine ratio (uACR), estimated glomerular filtration rate (eGFR), glycated haemoglobin(HbA1c) and cr-intrapersonal-mean (CRMEAN). We validated the association in a prospective cohort comprising 554 T2DM patients attending Diabetes Centre in 2011-2016. The Homeostatic model assessment (HOMA2)-Insulin Resistance (IR) index was obtained from HOMA Calculator. Sobel-Goodman mediation test was performed to examine extent of mediation between IR(defined by HOMA2-IR>1.8) and progression by adjusted-CrSD.

Results: Progression occurred in 31.2% of patients in discovery cohort. The progressors had higher median adjusted-CrSD than non-progressors (9.62(5.90-16.93) vs. 6.94(4.64-10.57); p<0.001) and poorer baseline eGFR, uACR and HbA1c (p<0.05). Log-transformed adjusted-CrSD was significantly associated with progression (adjusted HR 1.46(1.06-2.01); p=0.021). Similar findings were noted in validation cohort (adjusted OR 1.51 (1.09-2.09); p=0.013). CrMEAN was not associated with progression in both cohorts. Adjusted-CrSD accounted for 26% of association between IR and progression after adjustment in mediation test in validation cohort (p=0.015).

Conclusion: Higher scr variability predicted albuminuria progression, independently of intrapersonal mean. It is a potential mediator of association between IR and ACR progression.