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# A suPAR Biomarker for Chronic Kidney Disease

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The worldwide epidemic of chronic kidney disease — an insidious illness that manifests with asymptomatic reductions in the estimated glomerular filtration rate (eGFR) to less than 60 ml per minute per 1.73 $m^2$ of body-surface area, excessive urinary excretion of protein, or both — afflicts an estimated 600 million people.[1] Many will have progression to end-stage kidney disease and require dialysis or kidney transplantation for survival or succumb to related cardiovascular complications, even while taking antihypertensive agents and medications to lower blood glucose levels.[2,3] Chronic kidney disease shortens survival, reduces the quality of life remaining to these patients, and constitutes a "death sentence" in regions of the world where renal-replacement therapies are not available. Unfortunately, albuminuria and decreased renal function are detected only after substantial kidney injury has already occurred. Thus, there is an urgent need to identify new biomarkers that can accurately determine the risk of impending chronic kidney disease while renal function is still well preserved and there is a higher likelihood that medical interventions can slow or prevent progression.[4]

The rationale for considering the plasma concentration of soluble urokinase-type plasminogen activator receptor (suPAR) as a candidate biomarker for incipient chronic kidney disease is based on reports that elevated levels of this receptor could act as a circulating permeability factor that may be involved in initiating focal segmental glomerulosclerosis, an important cause of chronic kidney disease.[5] In this scenario, elevated levels of circulating suPAR increase glomerular permeability, leading to a cascade of events that result in focal segmental glomerulosclerosis. As they now report in the *Journal*, Hayek et al.[6] have extended that initial observation by evaluating suPAR as a new biomarker for chronic kidney disease. The research on suPAR is controversial, because several studies, using a variety of suPAR assays and involving patients with different causes of kidney disease, did not confirm an association of an elevated suPAR level with nephropathy.[7] In addition, as stated by Hayek et al., the precise mechanisms of the suPAR effect remain unknown.

The current report evaluated two disparate patient cohorts with data on progression to chronic kidney disease: the Emory Cardiovascular Biobank cohort and the Women's Interagency HIV Study cohort. Cross-sectional associations were detected between plasma suPAR concentration and baseline eGFR in the Emory cohort, along with longitudinal associations of baseline suPAR level with a decline in the eGFR and with incident chronic kidney disease in both cohorts. Importantly, effects were strongest in participants with an initially preserved eGFR, in whom plasma suPAR concentrations improved risk discrimination for subsequent chronic kidney disease as compared with conventional predictors.

Several aspects of the study warrant discussion. The study design was relatively complex; association testing was performed in the full Emory cohort, followed by repeat analyses in

random subgroups from the cohort. The study emphasized future decline in the eGFR and the development of chronic kidney disease. However, it had only semiquantitative measurement of proteinuria and lacks corresponding accurate measures of urinary protein excretion, which would be important in studying a factor that increases glomerular permeability; thus, risk discrimination may not have been able to dissect interactions between increasing albuminuria and a decline in kidney function.

Whether kidney disease per se could have elevated suPAR concentrations owing to reduced renal clearance or metabolism is uncertain. The authors posited that a reduced eGFR is unlikely to have accounted for elevated plasma suPAR levels, because high suPAR concentrations were present in 30% of study participants with a normal eGFR (≥90 ml per minute per 1.73 $m^2$). Many of the participants with high suPAR levels and a normal initial eGFR will not go on to have chronic kidney disease. Hence, provision of the positive and negative predictive values of high suPAR levels in populations without kidney disease would have been helpful, as would follow-up measurement of suPAR concentrations. Such repeat measurements might also distinguish between an association of elevated suPAR levels with acute kidney injury (a known risk factor for chronic kidney disease)[8] and plasma suPAR concentration as an independent biomarker for impending chronic kidney disease. However, the authors did try to rule out this very real possibility by using a repeat analysis strategy, which excluded patients with possible acute kidney injury. Finally, persons with acute infections or cancer were excluded, owing to the recognized effects of these conditions on suPAR concentrations; therefore, the results should not be applied to patients with such illnesses. Given the foregoing reservations, the observation that plasma suPAR concentrations, when measured with a different assay, were also significantly associated with chronic kidney disease in the Women's Interagency HIV Study provides a high level of reassurance that plasma suPAR concentration is a potential biomarker for impending or early chronic kidney disease.

Hayek and colleagues attempt to address the important challenge of detecting new biomarkers for the prediction of progression to chronic kidney disease in currently overlooked patients with the earliest stages of kidney disease, who might benefit most from health interventions. Associations with proteinuria, as well as interactive relationships among plasma suPAR concentration, proteinuria, and progression to chronic kidney disease, will require further study with more precise measurements of albuminuria. The findings by Hayek et al. should engender validation studies in additional cohorts, together with future studies to assess whether conventional and new therapies provided to patients with high suPAR levels and a preserved eGFR are effective in preventing subsequent declines in kidney function. Improving outcome is the ultimate goal for biomarker studies in major progressive diseases, and studies that show that intervention based on suPAR levels is beneficial could cement a potential relationship between suPAR and chronic kidney disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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