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Soluble urokinase receptor is a biomarker of cardiovascular disease in chronic kidney disease

Björn Meijers[1,2], Ruben Poesen[2], Kathleen Claes[1,2], Ruth Dietrich[3], Bert Bammens[1,2], Ben Sprangers[1,2], Maarten Naesens[1,2], Markus Storr[3], Dirk Kuypers[1,2] and Pieter Evenepoel[1,2]

[1]UZ Leuven, Department of Nephrology, Leuven, Belgium; [2]KU Leuven, Department of Microbiology and Immunology, Leuven, Belgium and [3]Research and Development, Gambro Dialysatoren GmbH, Hechingen, Germany

Soluble urokinase-type plasminogen activator receptor (suPAR) accumulates in patients with chronic kidney disease (CKD). In various non-CKD populations, suPAR has been proposed as a prognostic marker for mortality and cardiovascular disease. However, it is not known whether suPAR holds prognostic information in patients with mild-to-moderate CKD. In a prospective observational study of 476 patients with mild-to-moderate kidney disease, we examined multivariate associations between suPAR, overall mortality, and cardiovascular events. After a mean follow-up of 57 months, 52 patients died and 76 patients had at least one fatal or nonfatal cardiovascular event. Higher suPAR was directly and significantly associated with both overall mortality (univariate hazard ratio 5.35) and cardiovascular events (univariate hazard ratio 5.06). In multivariate analysis, suPAR remained significantly associated with cardiovascular events (full model, hazard ratio 3.05). Thus, in patients with mild-to-moderate CKD, suPAR concentrations show a clear, direct, and graded association with a higher risk for new-onset cardiovascular disease.

Kidney International (2015) **87,** 210–216; doi:10.1038/ki.2014.197; published online 4 June 2014

KEYWORDS: cardiovascular events; chronic kidney disease; urokinase

Correspondence: *Björn Meijers, UZ Leuven, Department of Nephrology, Herestraat 49, Leuven 3000, Belgium. E-mail: bjorn.meijers@uz.kuleuven.ac.be*

Received 16 December 2013; revised 26 March 2014; accepted 3 April 2014; published online 4 June 2014

Soluble urokinase-type plasminogen activator receptor (suPAR) originates from proteolytic cleavage of the urokinase-type plasminogen activator receptor (uPAR) at its glycosyl phosphatidyl inositol anchor site.[1,2] uPAR elicits a plethora of cellular responses that include cellular adhesion, differentiation, proliferation, and migration.[1] Given the role of uPAR as a versatile cellular signaling orchestrator, it is not surprising that both uPAR and suPAR have been implicated in various pathologies.

suPAR is present in low concentrations in healthy individuals, where it has a role in neutrophil trafficking and stem cell mobilization.[1] Serum concentrations are elevated in infectious diseases induced by various pathogenic species, including infection with viruses (HIV, Hanta),[3,4] mycobacteria,[5] and malaria.[6] suPAR levels are also elevated in patients with inflammatory disorders, including arthritis[7] and inflammatory bowel disease.[8] On the basis of these data, suPAR has been considered a marker of (low-grade) activation of the immune system.[9]

The observed variation in suPAR concentrations holds prognostic information. In the general population, individuals with high suPAR concentrations are at an increased risk for cardiovascular events, independent from Framingham risk factors.[10,11] In patients with non-ST elevation acute coronary syndrome, as well as in patients with ST-elevation myocardial infarction (MI), suPAR predicts all-cause mortality and recurrent MI.[12,13] A substantial number of studies reported on suPAR in critically ill patients. In these patients, suPAR correlates with markers of organ dysfunction and is a predictor of both ICU mortality and long-term mortality beyond and above severity-of-disease classification systems such as APACHE-II or SOFA.[9,14]

In the kidneys, suPAR regulates the permeability of the glomerular filtration barrier, as it is involved in a signaling pathway leading to podocyte injury, podocyte effacement, and proteinuria.[2,15] We recently demonstrated that in patients with chronic kidney disease (CKD), but without focal segmental glomerulosclerosis (FSGS), the glomerular filtration rate is a strong independent determinant of suPAR.[16,17] Not unexpectedly, we and others noted very high concentrations of suPAR in patients with advanced CKD.[16–18]

Given that suPAR is a prognostic marker in various non-CKD populations and given the significant accumulation in patients at reduced glomerular filtration rate, we questioned whether suPAR is of clinical relevance in CKD. We therefore studied associations between suPAR and clinical outcomes in the Leuven mild-to-moderate CKD cohort.

RESULTS

Patients and demographics

We measured suPAR in patients at different stages of CKD included in the Leuven mild-to-moderate CKD cohort. As there is still some controversy over whether patients with FSGS have higher concentrations of suPAR, we excluded patients ($n = 13$) with biopsy-proven FSGS. The study cohort thus consisted of 476 patients (Figure 1), with a median age of 64 years. There were slightly more men ($n = 260$, 54.6%) than women ($n = 216$, 45.4%). Baseline demographics and biochemical measurements are summarized in Table 1.

When looking for determinants of serum suPAR concentrations using Spearman rank analyses, we found known positive associations with age, female sex, presence of diabetes, and the c-reactive protein (CRP), and known negative associations with serum albumin and the estimated glomerular filtration rate (eGFR) (Table 2). When looking at the conventional cardiovascular risk factors, higher suPAR was associated with higher age, higher blood pressure, and diabetes mellitus ($P < 0.0001$ for all), but with lower serum cholesterol ($P = 0.0004$). There was no relationship with current smoking. Patients with a past history of cardiovascular event had significantly higher suPAR concentrations ($P < 0.0001$) as compared with those without a previous cardiovascular event.

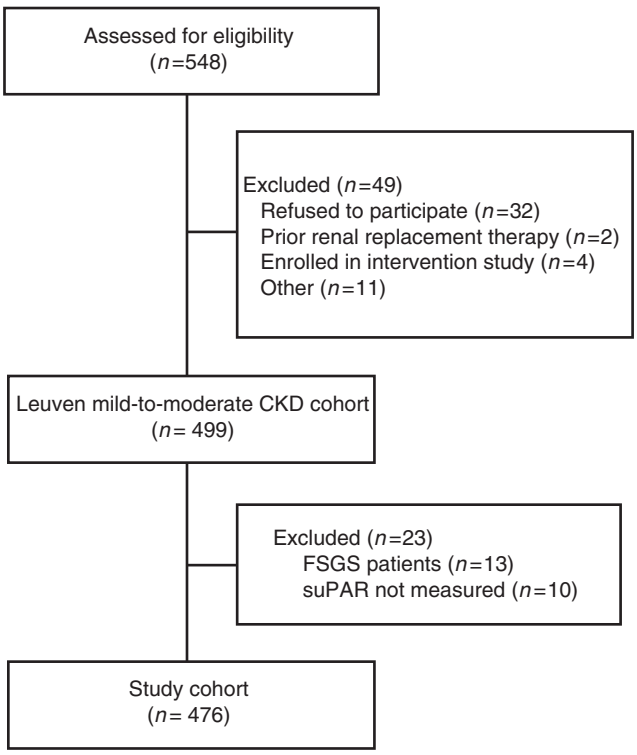

Figure 1 | Patient enrollment during the study period. CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; suPAR, soluble urokinase-type plasminogen activator receptor.

suPAR and mortality

We analyzed associations between suPAR and overall mortality, with a mean follow-up of 57 (standard deviation 2.7) months. During the study period, 52 patients died, 17 (32.7%) because of cardiovascular death (cause of death, Supplementary Table S1 online). The survival curve (Figure 2) for tertiles of suPAR demonstrated a clear association between suPAR and overall mortality ($P < 0.0001$). In univariate Cox proportional hazards analysis, high suPAR was directly associated with mortality, as were higher age, a past history of cardiovascular disease, diabetes, higher CRP, hyperparathyroidism, and hyperphosphatemia. Anemia, hypoalbuminemia, hypocalcemia, and low eGFR were also associated with mortality (Supplementary Table S2 online).

In multivariate analysis, suPAR was associated with mortality after correction for eGFR and the Framingham risk factors (age, gender, systolic blood pressure, current smoker, diabetes mellitus, cholesterol). (Table 3 and Supplementary Table S3 online). In the final model, suPAR was, however, not independently associated with overall mortality ($P = 0.08$), presumably owing to lack of power.

When looking at death due to cardiovascular cause only, high suPAR was significantly associated with a hazard ratio of 6.856 (2.880–16.320; $P = 0.00001$). Owing to the low number of events ($n = 17$), multivariate models for death due to cardiovascular cause have not been constructed.

suPAR and cardiovascular disease

Next, we explored the link between suPAR and cardiovascular disease in patients with mild-to-moderate CKD. During the study period, 76 patients had at least one cardiovascular event. We analyzed the time to first cardiovascular event (Supplementary Table S4 online for types of cardiovascular event). We observed a clear association between tertiles of suPAR and cardiovascular disease (Figure 3) ($P < 0.0001$). In univariate Cox analyses, high suPAR was directly associated with cardiovascular events, as were higher age, a past history of cardiovascular disease, diabetes, higher blood pressure, higher CRP, hyperparathyroidism, hyperphosphatemia, and proteinuria. Anemia, hypoalbuminemia, hypocalcemia, and low eGFR were also associated with cardiovascular disease (Supplementary Table S5 online).

In multivariate Cox analyses (Table 4 and Supplementary Table S6 online), the association between suPAR and cardiovascular events was independent after adjustment for kidney function and the Framingham risk factors. As we recently demonstrated that the eGFR is one of the strongest determinants of suPAR concentrations in patients with CKD,[16] we performed additional analyses testing the nontransformed eGFR, the log-transformed eGFR, and