HIGH SOLUBLE UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR (sUPAR) AND THE RISK OF DEATH AND CARDIOVASCULAR (CV) EVENTS IN STAGE 2-5 CKD PATIENTS

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Introduction and aims

sUPAR is a multi-functional protein that regulates fibrinolysis and extracellular matrix (ECM) degradation, cell adhesion, migration and proliferation and is highly expressed in advanced atherosclerotic plaques. Circulating sUPAR predicted death, ischemic heart disease, heart failure and stroke in various studies the general population and in one study in CKD patients. Whether the predictive power for death and CV disease by sUPAR in the CKD population is independent of proteinuria and emerging risk factors in this population like ADMA and FGF23 is still unclear.

Methods

We measured plasma sUPAR levels (R&D ELISA) and a series of traditional and CKD-specific risk factors in 753 stage G2-5 CKD patients. Time to death and first cardiovascular event were analysed by multivariate Cox regression analysis adjusting for traditional risk factors and a large series of CKD-specific risk factors.

Results

sUPAR was gender-dependent and associated with lower GFR and higher proteinuria, older age, diabetes, higher systolic BP, C Reactive Protein (CRP), phosphate, PTH, FGF23, ADMA and lower Hb, 25-OH Vit.D and 1,25-OH Vit.D (all P<0.001) (Fig.1, Tab.1). Over a 31+10 months follow-up 42 patients died and 95 had a renal event. sUPAR was a strong predictor of the combined end-point death and cardiovascular events [HR (500pg/ml): 1.09 , 95%CI: 1.04-1.14] in a Cox's regression analysis adjusting for a large series of potential confounders including background cardiovascular disease, the GFR, proteinuria, age, gender, smoking, diabetes, systolic BP and anti-hypertensive treatment, phosphate, Hb, serum albumin, BMI, CRP, ADMA and FGF23 (Fig.2). Separate analyses of time to death and time to first CV event were both highly significant in crude and adjusted analyses (appropriately corrected by a shrinkage factor).

Figures

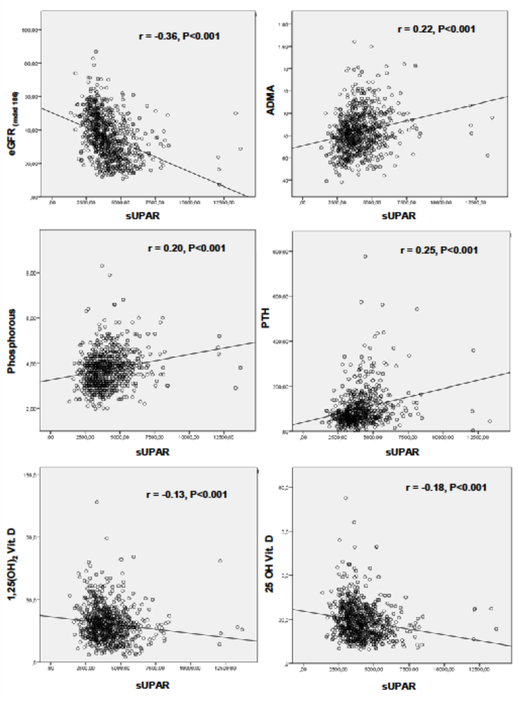

Fig. 1. Main baseline correlates of sUPAR

Variable	r	P
Age	r = 0.147	<0.001
Diabetes	r = 0.138	<0.001
Systolic BP	r = 0.177	<0.001
$eGFR_{(mdrd\ 186)}$	r = -0.363	<0.001
Proteinuria	r = 0.145	<0.001
C Reactive Protein	r = 0.137	<0.001
Haemoglobin	r = -0.174	<0.001
ADMA	r = 0.224	<0.001
1, 25 $(OH)_2$ Vit. D	r = -0.131	<0.001
25 OH Vit. D	r = -0.182	<0.001
FGF 23	r = 0.221	<0.001
Phosphorous	r = 0.199	<0.001
PTH	r = 0.245	<0.001

Tab. 1. Baseline correlates of sUPAR

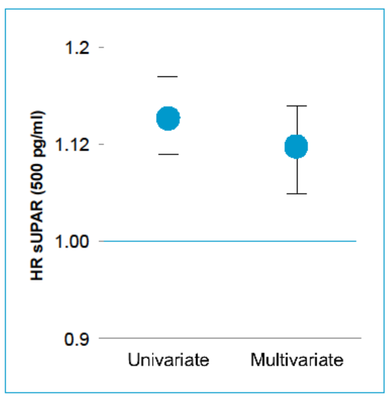

Fig. 2. Hazard ratio associated to sUPAR levels and 95% CI for the combined end-point all cause mortality/cardiovascular events.

Conclusions

Elevated sUPAR levels robustly predict incident cardiovascular events and death in CKD patients. These findings go along with biological knowledge documenting a strong role of sUPAR in atherosclerosis and support the contention that sUPAR is causally implicated in cardiovascular disease in CKD patients.

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