ROLE OF CIRCULATING ADAM17 ACTIVITY IN CHRONIC KIDNEY DISEASE

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INTRODUCTION AND AIMS: Several substrates for ADAM17 have been identified, including TNF-α, epidermal growth factor receptor (EGFR) ligands, L-selectin, vascular cell adhesion molecule 1 (VCAM-1) and angiotensin converting enzyme (ACE2). We now have studied circulating ADAM17 in chronic kidney disease (CKD) patients from the NEFRONA cohort study.

METHODS: 2032 patients without history of CV disease from an observational and multicenter study (NEFRONA project) divided in two groups: non-dialysis CKD stage 3-5 patients (CKD3-5, n=1463) and control patients (CONT, n=569) were studied. Baseline circulating ADAM17 activity was analyzed using a fluorimetric assay in plasma samples. ADAM17 levels according to presence of plaques, hypertension, age, smoking and treatments with ACE inhibitors or angiotensin II receptor blockers (ARBs) at baseline were studied. Increased serum creatinine and dialysis requirement after 24 months of follow-up depending on basal circulating ADAM17 activity were also studied. Logistic regression analysis was used to identify predictors of increasing serum creatinine and risk of dialysis requirement.

RESULTS: Circulating ADAM17 activity was significantly increased in CKD3-5 patients as compared to CONT. In CONT group, patients with plaques or patients on ACEi and ARBs therapy had increased ADAM17 activity as compared to those without plaques or therapy. Hypertension was also associated with higher ADAM17 activity in CKD3-5 patients. Smokers in both groups showed increased ADAM17. Baseline circulating ADAM17 activity was higher in patients with a 30% increase in serum creatinine levels after 2 years (p<0.05). Circulating ADAM17 activity was also higher in patients that needed dialysis after 2 years, in comparison with patients that maintained kidney function (p<0.05). In the multivariate model, after adjusting by age, diabetes, smoking and gender, increased circulating ADAM17 activity and age were independent predictors of increasing serum creatinine, whereas increased circulating ADAM17 activity, gender and age were independent predictors of dialysis requirement.

CONCLUSIONS: Circulating ADAM17 activity was increased in CKD. Smoking, presence of plaques and ACEi or ARBs therapies were associated with increased ADAM17 in CONT. Smoking and hypertension were associated with higher levels of circulating ADAM17 activity in patients in CKD3-5. Circulating ADAM17 activity was also increased in patients that doubled serum creatinine and/or patients that need dialysis therapy being an independent predictor of worsening renal function.