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A novel biomarker of laminin turnover is associated with mortality and disease progression in chronic kidney disease

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LG1M levels in serum and urine from a large prospective cohort of patients with high-risk CKD.

METHODS: A novel immunoassay targeting a specific MMP-9-generated neo-epitope fragment of LAMC1 (LG1M) was used to measure the fragment levels in urine and serum from 492 patients from the Renal Impairment in Secondary Care (RIISC) study, a prospective cohort of patients with high-risk CKD. Patients were monitored for a median follow-up time of 2.5 years. Progression of CKD was defined as a decline in eGFR of more than 30%, or starting renal replacement therapy as a definition of end-stage-renal disease (ESRD) within 12 months. Associations between LG1M levels in both serum and urine for progression of CKD were assessed by a multivariable logistic regression model with forward selection, while adverse outcomes were assessed by Kaplan-Meier and Cox regression analysis.

RESULTS: Forty-six patients (11%) of 411 patients who were alive and under follow-up at 12 months had progressed. During the study 102 patients developed ESRD and 65 patients died. Both urinary and serum levels of LG1M showed an inverse linear correlation with baseline eGFR (Spearman's correlation coefficient $r=-0.43$, $p<0.0001$ and $r=-0.17$, $p=0.0002$, respectively). Serum but not urinary LG1M levels were significantly associated with progression of CKD within 12 months ($p<0.01$), but were not included in the final model for prediction of whether the patients developed ESRD. Urinary LG1M levels were significantly associated with death; patients in the highest LG1M tertile were 4.5 ($p<0.0001$) times more likely to die than patients in the first tertile. Urinary LG1M levels were included in the final model for prediction of mortality (HR 1.25, 95% CI 1.04-1.51, $p=0.02$).

CONCLUSIONS: The novel biomarker LG1M reflecting glomerular basement membrane remodeling is associated with disease progression, development of ESRD, and mortality in high-risk CKD patients.

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A NOVEL BIOMARKER OF LAMININ TURNOVER IS ASSOCIATED WITH MORTALITY AND DISEASE PROGRESSION IN CHRONIC KIDNEY DISEASE

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INTRODUCTION AND AIMS: Patients with chronic kidney disease (CKD) have increased risk of progressing to end-stage renal disease (ESRD) and a high mortality rate. One of the major underlying causes of progression of renal failure is renal fibrosis, which is caused by dysregulated extracellular matrix (ECM) remodeling. The laminin $\gamma 1$ (LAMC1) chain is a constituent of the laminin types present in the glomerular basement membrane (GBM), and its turnover may be altered in CKD. Fragments of LAMC1 could quantify GBM turnover in human CKD and reflect pathological tissue changes. We developed an immunoassay targeting LG1M, a neo-epitope of LAMC1 generated by matrix metalloproteinases (MMPs). We then measured