A novel urinary biomarker of type VI collagen formation and endotrophin is associated with loss of kidney function in patients with diabetic nephropathy

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BIOMARKERS

SO014 A NOVEL URINARY BIOMARKER OF TYPE VI COLLAGEN FORMATION AND ENDOTROPHIN IS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION IN PATIENTS WITH DIABETIC NEPHROPATHY

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INTRODUCTION AND AIMS: Diabetic nephropathy (DN) is the leading cause of CKD in the Western world. Around 50 percent of patients who have had diabetes for more than 20 years develop CKD. Glomerulosclerosis and tubulointerstitial fibrosis are histological features as DN progresses towards end-stage renal disease. Fibrosis is characterized by a dysregulated remodeling of the extracellular matrix (ECM). Collagen type VI (COL VI) is a crucial ECM molecule for the control of tissue organization. It is present at the interface of the glomerular basement membrane and interstitial matrix and its levels have been reported elevated in glomeruli of patients with glomerular diseases and in the mesangium of diabetic patients. During deposition of COL VI, a fragment is released, namely endotrophin (ETP). Endotrophin (ETP), has shown pro-fibrotic potential. We investigated the prognostic potential of COL VI formation and ETP for CKD progression by measuring baseline levels in urine and plasma from patients with DN.
METHODS: COL VI formation and ETP were measured using a novel enzyme-linked immunosorbent assay targeting the C-terminal end of the α3 chain of COL VI (Pro-C6). Patients with type 1 or 2 diabetes receiving renin angiotensin system inhibitors were included if they had serum creatinine concentrations between 1.3 to 3.5 mg/dl (or estimated glomerular filtration rate (eGFR) between 20 to 60 mL/min/1.73 m^2) or a 24-hour urine protein/creatinine ratio (PCR) $\geq$ 800 mg/g. Paired urine and plasma baseline samples from 99 DN patients who participated in a one year therapeutic clinical study (NCT01113801). Urinary Pro-C6 was normalized to urinary creatinine. The outcome of interest was change of eGFR (calculated with the MDRD formula) from baseline to 9 and 12 months.
RESULTS: Levels of Pro-C6 in both plasma and urine correlated with eGFR at baseline, 9 month, and 12 months (all $p<0.0001$). Moreover, urinary Pro-C6 correlated with change in eGFR at 9 and 12 months (both $p<0.01$). Whereas levels of Pro-C6 in urine correlated significantly with PCR ($p<0.0001$) no correlation between plasma Pro-C6 and PCR was observed ($p=0.99$). Urinary Pro-C6 was independently associated with decrease in eGFR at both 9 months ($r=-0.335$, $p<0.01$) and 12 months ($r=-0.358$, $p<0.01$) even after adjustment for eGFR and PCR. When patients were divided into quartiles based on their rate of eGFR change over 12 months, urinary Pro-C6 adjusted for baseline eGFR and PCR was able to separate the fastest progressing patients with an AUC of 0.732 ($p<0.001$).
CONCLUSIONS: We found a significant association between the Pro-C6 marker of COL VI formation and CKD progression in patients with DN, independent of baseline eGFR and proteinuria. Because the Pro-C6 assay cross-reacts with the matrikine endotrophin, these results might suggest a role for endotrophin in disease progression.