A panel of novel biomarkers representing different disease pathways improves prediction of renal function decline in type 2 diabetes

Michelle J Pena, Andreas Heinzel, Georg Heinze, Paul Perco, Bernd Mayer, Dick de Zeeuw, and Hiddo Lambers Heerspink

1 University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy & Pharmacology, Groningen, The Netherlands; 2 Emergentec Biodevelopment GmbH, Molecular Biology, Vienna, Austria; 3 Medical University of Vienna, Center For Medical Statistics, Informatics, and Intelligent Systems, Vienna, Austria

Introduction and Aims: Early detection of patients with type 2 diabetes at risk for diabetic kidney disease may be a key strategy for prevention and treatment of progressive renal damage. We aimed to identify a novel panel of biomarkers predicting eGFR decline in type 2 diabetes, using multiple biomarkers that represent different disease pathways speculated to contribute to the progression of diabetic kidney disease.

Methods: A systematic data integration approach was used to select biomarkers representing different disease pathways. Twenty-eight biomarkers were measured in 82 patients seen at an outpatient diabetes center in The Netherlands. Median follow-up was 4.0 years. We compared the cross-validated explained variation (R2) of two models to predict eGFR decline, the first including only established risk markers, and the second adding a novel panel of biomarkers on top of established risk markers. Least absolute shrinkage and selection operator (LASSO) was used for model estimation. The C-index was calculated to assess improvement in prediction of accelerated eGFR decline defined as <-3.0 mL/min/1.73m2/year.

Results: Patients’ average age was 63.5 years and baseline eGFR was 77.9 mL/min/1.73m2. The average rate of eGFR decline was -2.0 ± 4.7 mL/min/1.73m2/year. When modeled on top of established risk markers, the biomarker panel including matrix metallopeptidases (MMPs), tyrosine kinase (TEK), podocin (NPHS2), connective tissue growth factor (CTGF), tumor necrosis factor receptor-1 (TNFR1), sclerostin (SOST), monocyte chemotactic protein-1 (CCL2), chitinase-3-like protein 1 (YKL-40), and amino-terminal propeptide of C-type natriuretic peptide (NT-proCNP) improved the explained variability of eGFR decline (R2 increase from 37.7% to 54.6%; p=0.018) and improved prediction of accelerated eGFR decline (C-index increase from 0.835 to 0.896; p=0.008).

Conclusions: A panel of novel biomarkers representing different disease pathways of renal damage, including inflammation, fibrosis, angiogenesis, and endothelial function, improved prediction of eGFR decline on top of established risk markers in type 2 diabetes. The results of this study need to be validated in a large, prospective cohort to validate and assess its applicability in a broad type 2 diabetes population.