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Using Plasma Proteomics and Metabolomics for Biomarkers Detection to understand the Progression of Diabetic Kidney Disease

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Objectives : Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD) in Singapore. A steep estimated glomerular filtrate rate (eGFR) decline tends to be associated with poor survival outcomes. There is a lack of clinical markers to predict renal function decline in DKD. Here, we profiled molecular biomarkers including proteins and metabolites to help gain insights to DKD progression.
Methods : We recruited 227 patients with stage G2-G4 DKD (type-2 diabetes) from Nephrology Clinics at National University Hospital, Singapore. They were followed up for up to 3 years. Plasma samples were collected. Clinical information was captured through medical record and eGFR slopes were calculated. Using high-resolution mass-spectrometry, we profiled proteins and metabolites including amino acids, acylcarnitines and lipids. We identified proteins and metabolites that were associated with (i) eGFR slope and (ii) survival where the end-point is all-cause mortality and/or ESKD. Combining significant markers, we inferred a correlation network and used predictive analyses to identify signatures that separate patients with rapid kidney decline (eGFR slope< -5).
Results : We identified 54 proteins and 30 metabolites associated with eGFR slope after adjusting for age, gender, ethnicity, BMI, SBP, diabetes duration and baseline eGFR. Proteins negatively associated with eGFR decline were related to lysine degradation and ascorbate and aldarate metabolism. Proteins positively associated with eGFR decline were enriched in complements, tyrosine metabolism and glycolysis/gluconeogenesis-related pathways. Amongst which, 9 proteins and 9 metabolites were also associated with survival. Network analyses revealed protein clusters of fibrinogens (FGA, FGB, FGG), PGM1, AMBP, ADH4 and PARVB that were inversely correlated with eGFR slope. Sphingolipids including gangliosides (GM3 d18:1/16:0, d18:1/24:0 and d18:1/24:1), Hexosylceramides (Hex1Cer d18:1/22:0) and ceramide d18:1/20:0 were correlated with uACR and inversely correlated to eGFR slope.
Conclusions : Integrative analysis of plasma proteomics and metabolomics identifies prognostic biomarkers of renal function decline and provides insights into DKD progression.