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The role of Lactic Acidosis on Reneal Fibrosis and its dysfunction in DKD

Won-Ho Kim
질병관리청 국립보건연구원, Korea, Republic of

Diabetes characterized by hyperglycemia and insulin resistance is the most common cause of chronic kidney disease (CKD) however, the metabolic factors that promote diabetic renal failure including fibrosis are unclear. We investigated the metabolite changes in animal and human subjects with diabetic CKD (dCKD) and the role of lactate dehydrogenase A LDHA-mediated lactate production in renal fibrosis and dysfunction.
Streptozotocin (STZ; 60 mg/kg)-induced dCKD rats and clinical information and samples from dCKD patients (n=53) and healthy participants (n=16) were used. Diabetic renal fibrosis and dysfunction were closely associated with significant changes in the metabolites involved in the top-ranked functional pathways. Among them, lactate, a glycolysis end product, was significantly increased in STZ-induced
diabetic rats and dCKD patients. Increased lactate positively correlated with reduced Wilms' tumor-1 (WT-1) expression and increased LDHA expression, mitochondrial and oxidative damage, resulting in renal fibrosis. TGF-β1-mediated renal fibrosis depends on lactate production, which was significantly attenuated by inhibiting glycolytic and LDHA lactate regulatory pathways. dCKD patients showed a significant negative correlation between urinary lactate levels or LDHA expression and the estimated glomerular filtration rate (eGFR), which were closely associated with an increase in glycated hemoglobin (HbA1c).
In conclusion, increased renal or urinary lactate metabolites are associated with alterations in renal metabolic homeostasis and may serve as early predictive biomarkers for the progression of d CKD.