Abnormal lactate metabolism linked to kidney injury in diabetic patients

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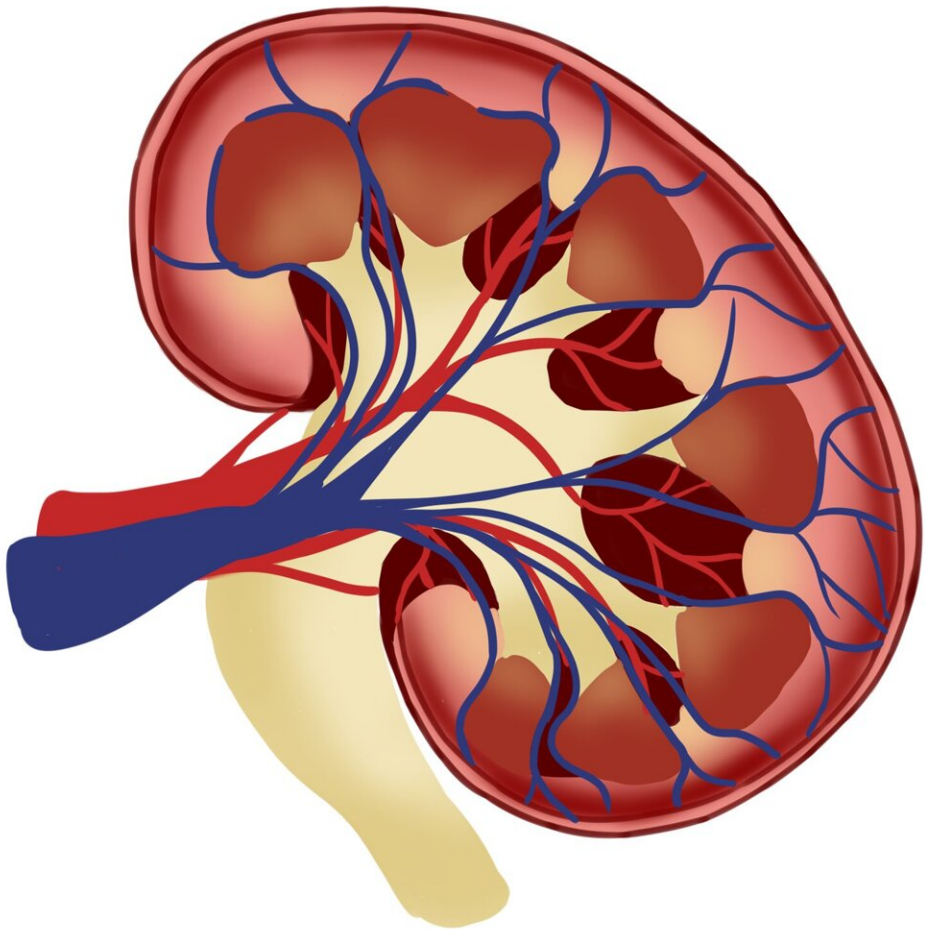

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Disrupted kidney metabolism is a key driver of progressive kidney injury in diabetic kidney disease (DKD), according to a new study led by scientists at Duke-NUS Medical School and Khoo Teck Puat Hospital in Singapore and Yokohama City University Graduate School of Medicine in Japan.

The findings, published in *Kidney International*, shed light on metabolic abnormalities associated with kidney damage in diabetes and point to potentially improved ways of detecting risk for kidney failure.

DKD is a major cause of kidney failure in Singapore where, on average, nine people are diagnosed with kidney failure every day—up to 40 percent of individuals with longstanding diabetes will eventually develop kidney disease.

This new study is part of the Diabetes Study in Nephropathy and other Microvascular Complications (DYNAMO), a global collaborative study involving clinicians and scientists from six countries and 25 institutions with the overall aim of reducing the prevalence of DKD.

The research team combined experiments conducted on a pre-clinical model with analysis of clinical data and samples from a Singaporean cohort of 230 patients with type 2 diabetes.

"We found abnormal metabolism resulting in accumulation of lactate, a by-product of cellular energy production, that appears to derive from impaired function of mitochondria in kidney tubule cells," said lead author Assistant Professor Kengo Azushima, a nephrologist with Yokohama City University Graduate School of Medicine and Duke-NUS. "Lactate levels were tightly linked with albumin in the urine, which is a marker of kidney damage, suggesting lactate may be a signal of distress caused by high levels of protein in the urine."

Treatment with angiotensin receptor blockers (ARBs), a common therapy for DKD, reversed metabolic abnormalities and prevented kidney injury in the pre-clinical model. Among the patients, those with the highest urinary lactate levels were at significantly increased risk of eventual kidney failure.

"Monitoring urinary lactate could help predict prognosis and guide management in diabetic kidney disease," said nephrologist Professor Thomas Coffman, a senior author of the study from the Duke-NUS Cardiovascular & Metabolic Disorders Program, and Lead Principal Investigator of DYNAMO. "Our findings indicate optimizing kidney energy metabolism may be important for slowing disease progression."

"By teasing out specific defects in renal energy pathways linked to diabetic kidney disease, this work brings us closer to precision interventions that tackle underlying disease drivers. I am hopeful future research can build on these insights to develop innovative prevention strategies," said co-senior author Associate Professor Lim Su Chi, Senior Consultant, Diabetes Center, Admiralty Medical Center, and Clinical Director, Clinical Research Unit, Khoo Teck Puat Hospital.

"This study provides new insights into mechanisms driving progressive kidney disease in diabetes," said Prof Coffman, who is also Dean of Duke-NUS. "It illustrates the strength of leveraging basic science approaches with human translational research to uncover mechanistic pathways underlying major health conditions like diabetic kidney disease."

The researchers plan follow-up studies to explore lactate itself as a possible cause of kidney injury. If successful, reducing kidney lactate generation or blocking its effects could suggest novel therapeutic approaches to prevent DKD.

More information: Azushima K, Kovalik JP, Yamaji T, et al, Abnormal Lactate Metabolism is Linked to Albuminuria and Kidney Injury in Diabetic Nephropathy. *Kidney International* (2023). DOI: 10.1016/j.kint.2023.08.006. www.kidney-international.org/a … (23)00565-3/fulltext