Metabolite in urine predicts diabetic kidney failure 5–10 years early: Oral therapeutic drug shows promise in mice

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Urine levels of adenine, a metabolite produced in the kidney, are predictive and a causative biomarker of looming progressive kidney

failure in patients with diabetes, a finding that could lead to earlier diagnosis and intervention, researchers from The University of Texas Health Science Center at San Antonio (also called UT Health San Antonio) reported in the *Journal of Clinical Investigation*.

The study results are significant because until now, the most important marker for kidney disease has been protein (or albumin) in the urine. Up to half of diabetes patients who develop kidney failure never have much protein in their urine. As 90% of patients with diabetes (more than 37 million patients in the U.S.) remain at increased risk despite low levels of albumin in their urine, this study has widespread consequences. It is the first study to identify these patients at an early stage by measuring this new causative marker in the urine.

The finding paves the way for clinic testing to determine—five to 10 years before kidney failure—that a patient is at risk, said the senior study author, Kumar Sharma, MD. Sharma is professor and chief of nephrology at UT Health San Antonio, where he is the founding director of the Center for Precision Medicine. He is also vice chairman for research in the Department of Medicine in the Joe R. and Teresa Lozano Long School of Medicine.

Importantly, the research team identified a small molecule that blocks the major pathway of endogenous adenine production in the body. This therapeutic drug reduced kidney adenine levels in mice with type 2 diabetes. "The drug protected against all the major aspects of diabetic kidney disease without affecting blood sugar," Sharma said. "The study is remarkable as it could pave the way to precision medicine for diabetic kidney disease at an early stage of the disease."

Findings consistent across diverse study populations

The researchers studied more than 1,200 patients with diabetes across

three international research cohorts. The Chronic Renal Insufficiency Cohort (CRIC) study included African American, Hispanic and Caucasian participants in the U.S. A separate study was in the American Indian population. The team also evaluated an Asian cohort of mostly Chinese, Asian Indians and Malay populations in a study based in Singapore.

"In each study there was the same pattern, that high urine adenine was associated with higher risk of kidney failure," Sharma said. "We are truly grateful for all the participants in this global study, and I would like to thank all of the investigators and research teams who were part of this collaborative effort."

Mapping the metabolites

UT Health San Antonio is one of few centers in the U.S. perfecting a technique called spatial metabolomics on kidney biopsies from human patients. This technique enables researchers to determine the locations of adenine and other small molecules in kidney tissues. The kidney biopsies were provided from academic centers throughout the United States as part of the Kidney Precision Medicine Project, a national collaborative and innovative program supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

"It's a very difficult technique, and it took us several years to develop a method where we combine high resolution of the geography of the kidney with mass spectrometry analysis to look at the metabolites," Sharma said.

Metabolites are small molecules that the body produces based on metabolism. They make cells go in a healthy way or in a disease pattern, Sharma said.

Adenine situated around kidney blood vessels

The team found endogenous adenine around scarred blood vessels in the kidney and around tubular-shaped kidney cells that were being destroyed. Endogenous substances are those that naturally occur in the body.

The finding that high levels of adenine were also associated with all-cause mortality in the study participants suggests that the metabolite is affecting other parts of the body, as well, Sharma said.

Many patients with diabetes know they're at risk of kidney disease, but if they don't have protein in their urine, they think they are protected, he said.

"They could be feeling a false sense of security that there is no kidney disease occurring in their body," Sharma said. "But in fact, in many cases it is progressing, and they often don't find out until the kidney disease is pretty far advanced. And at that time, it is much harder to protect the kidneys and prevent dialysis."

Once a patient needs dialysis, he or she must have a fistula or catheter placed and go on a dialysis machine three times a week, four hours at a time to clean the blood.

"The death rate is very high, especially in patients with diabetes," Sharma said. "There is about 40% mortality within five years in patients with diabetes and kidney failure."

A new type of therapy is needed

Although treatments to protect against diabetes and blood pressure are

improving, they only push the envelope a little bit, Sharma said, in that patients still have progressive kidney disease and kidney failure, but they are afforded more time before they reach that endpoint. The measurement of urine adenine is difficult; however, the team at the Center for Precision Medicine at UT Health San Antonio has developed a robust and sensitive method to measure urine adenine in patients.

"What we're hoping is that by identifying patients early in their course and with new therapies targeting adenine and kidney scarring, we can block kidney disease or extend the life of the kidney much longer," Sharma said.

More information: Kumar Sharma et al, Endogenous adenine mediates kidney injury in diabetic models and predicts diabetic kidney disease in patients, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI170341 www.jci.org/articles/view/170341

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