New treatment target for diabetic kidney disease

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(Medical Xpress) -- UC Davis investigators have shown that blocking a specific receptor pathway could slow or even prevent diabetic nephropathy - an often fatal complication of diabetes for which there are few good treatment options. Published online today (May 26) in the journal Arteriosclerosis, Thrombosis and Vascular Biology, the study is the first to clarify the role of the receptor - toll-like receptor 2, or TLR2 - in diabetes-associated kidney disease.

"Diabetic nephropathy is one of the most serious outcomes of diabetes and the most common cause of renal failure," said Ishwarlal Jialal, UC Davis professor of endocrinology, diabetes and metabolism and senior author of the study. "It is progressive and eventually requires chronic dialysis or transplant. But now we have a precise molecular target for treating this difficult disease."

Nephropathy, which affects about 30 percent of diabetics, becomes apparent between five and 25 years following a diabetes diagnosis. It occurs when high glucose - often with hypertension - overworks the kidneys' intricate blood filtration system, eventually causing that system to break down. It is typically diagnosed midway through the disease process, when the kidneys enlarge and protein appears in urine.

"We currently cannot fully predict why some people with diabetes, even some with well-controlled diabetes, get nephropathy while others do not," said Jialal, whose lab specializes in studying the role of inflammation in heart disease and diabetic complications. "Our goal is to
find a way to identify and stop it in its tracks at the earliest possible stages, well before dialysis is required."

TLRs are receptors of the innate immune system that provide protection from microbes and other pathogens. Previous research by Jialal and his team showed that diabetics have increased TLR activity and inflammatory markers in their immune systems, which was worse in patients with microvascular complications, especially nephropathy. Research by other teams showed that one receptor in particular - TLR2 - is expressed in higher amounts in kidney biopsies of patients with diabetic nephropathy.

"We wanted to find out if this receptor could have a causal link to nephropathy," said Sridevi Devaraj, UC Davis professor of pathology and lead author of the study. "We also wanted to take that work to the next step and see if we could identify a unique biomarker that could be used for early identification of the disease."

The team used mice lacking the gene for TLR2 to see if it had an effect on the development of nephropathy. They divided 80 mice into two groups: 40 were genetically deficient in TLR2 and 40 were wildtype mice with no genetic modifications. Type 1 diabetes was induced in both groups, and then all were tested for features of diabetic nephropathy, including inflammation markers, significantly elevated kidney weight and at least a tenfold increase albumin - a blood protein - in urine.

At 14 weeks, the wildtype mice progressed to nephropathy, while the TLR2-deficient mice did not. In addition, kidney tissue biopsies of the wildtype mice showed an abundance of TLR2 and an influx of pro-inflammatory macrophages that produced increasing amounts of critical biomediators such as interleukin-6 (IL-6) and monocyte chemotactic protein-1 (MCP-1). This outcome was not seen in the genetically deficient mice.
"Finding concentrations of TLR2 and inflammation in the kidney tissues shows that TLR2 truly could be linked with the disease process in nephropathy," said Jialal. "And showing that an absence of TLR2 protected kidneys from nephropathy strongly indicates that medications blocking TLR2 expression show great promise for preventing the disease."

Additional tests showed that cells known as podocytes and a protein known as podocin - both of which help maintain the filtration barrier in kidneys and prevent albumin loss - were deficient in diabetic mice. Because tissue biopsies to determine podocyte changes are not easily obtained, Jialal is conducting research to find out if a blood biomarker for podocin or other indicators of podocyte function is possible.

"If confirmed, this biomarker could serve as a novel indicator of the onset of nephropathy, giving physicians the chance to intervene before much permanent kidney damage occurs," said Jialal.

In future research, Jialal will examine if genetic deficiency of another important receptor known as TLR4 may also prevent the progression of diabetic nephropathy. He also hopes to procure inhibitors of both TLR2 and TLR4 to test in animal models and, if safe, in people with diabetes.

"Now that we have identified the absence of TLR2 as pivotal in preventing diabetic nephropathy along with a potential indicator of the onset of nephropathy, we are excited to further define the clinical potential of our work for humans," said Jialal.

**More information:** The study, "Knockout of Toll-Like Receptor-2 Attenuates Both the Pro-Inflammatory State of Diabetes and Incipient Diabetic Nephropathy," will appear in the August print issue of the journal.