Study identifies novel markers as key indicators of future renal failure in diabetes

January 19 2012

Andrzej Krolewski, M.D., Ph.D., is head of the section on genetics and epidemiology at Joslin Diabetes Center and an associate professor of Medicine at Harvard Medical School. Monika Anna Niewczas, M.D., Ph.D., is a research associate in the section on genetics and epidemiology at Joslin Diabetes Center and an Instructor in Medicine at Harvard Medical School. Credit: Stephanie McPherson

Scientists at Joslin Diabetes Center have identified two novel markers that, when elevated in the blood stream, can predict accurately the risk of renal (kidney) failure in patients with Type 1 and Type 2 diabetes. The findings have immediate diagnostic implications and can be used for the development of new therapies to prevent or postpone the progression of renal disease in diabetes.

In two studies published in the *Journal of the American Society of Nephrology*, the Joslin researchers found that high concentrations of Tumor Necrosis Factor Receptor 1 and 2 (TNFR1 and TNFR2) accurately predict the risk of renal function loss in Type 1 and in Type 2 diabetes ten years in advance. Currently available clinical tests cannot identify people at risk with that level of precision.

"These markers are excellent predictors of early and late renal function decline in patients with diabetes," says senior author Andrzej Krolewski, MD, PhD, section head of Genetics and Epidemiology at Joslin.", Our findings may improve clinical care for patients who are at risk of kidney damage."

Renal complications, also known as diabetic nephropathy, are one of the most life-threatening complications of diabetes. Over the course of many years, this damage frequently leads to end-stage renal disease, when the kidneys are no longer able to work at the level needed for everyday life. About a half million people in the United States have ESRD, which requires dialysis or kidney transplantation. Nearly 44 percent of these cases are due to diabetes. Currently, there is no accurate noninvasive test to identify patients at high risk of ESRD.

In one study, Krolewski and his colleagues followed 410 patients with Type 2 diabetes for eight to 12 years and found that those at risk of ESRD had elevated concentrations of TNFR1 and TNFR2 in their blood. That prompted them to investigate whether circulating TNFR1 and TNFR2 are also indicators of early renal function decline in Type 1 diabetes. Their subsequent study of 628 patients with Type 1 diabetes similarly found that those with high levels of TNFR1 and TNFR2 were at higher risk of early stages of renal function loss. Elevated levels of these protein receptors led to renal disease in diabetic patients, regardless of the presence or absence of other clinical characteristics that are considered important risk factors for diabetic nephropathy.

"High levels of these markers multiply the risk of developing kidney complications by three to five times," says Monika A. Niewczas, MD, PhD, a leading author of both studies and a research associate in Krolewski's group at Joslin, ". By analogy, she says, "high levels of TNFR1 and TNFR2 enable the prediction of renal failure ten years in advance, similar to the way high levels of cholesterol provide an early warning of increased risk of cardiovascular complications.

"Currently, one of the important problems in the clinical care of patients with diabetes is the lack of an accurate, noninvasive tool for the early identification of those at high risk of renal function loss," says Krolewski. A growing body of evidence indicates while high blood sugar contributes to renal injury in diabetes, certain inflammatory mechanisms are also involved.

At the beginning of the studies, the researchers measured several dozen inflammatory markers in more than a thousand subjects with diabetes, monitored these individuals, and collected data on whether their renal function declined and, more importantly, if they developed renal failure and required dialysis or transplantation. The researchers discovered that the effect of TNFR1 and TNFR2 on renal function was distinct from other markers or clinical measurements, such as blood pressure, albuminuria (a leak of large amount of albumin into urine) and glycated hemoglobin, which are currently evaluated in doctors' offices. The scientists do not know how or why TNF receptors contribute to the injury of the diabetic kidney, but preliminary data suggests that the effect of TNFR1 and TNFR2 expands beyond the simple effect of TNFα mediation.

"A diagnostic test to measure TNFRs in blood will be developed soon and available for patients," says Krolewski. "In the meantime, our findings suggest that mechanisms underlying the association between TNFRs and high risk of renal function decline may be a target for new

drug development."

More information: The articles, entitled "Circulating TNF Receptors 1 and 2 Predict ESRD in Type 2 Diabetes" and "Circulating TNF Receptors 1 and 2 Predict Stage 3 CKD in Type 1 Diabetes," will appear online on January 19, 2012, doi:10.1681/ASN.2011060628 and doi:10.1681/ASN.2011060627

Provided by Joslin Diabetes Center