Improved glucose control slows progression to end-stage renal disease in type 1 diabetes

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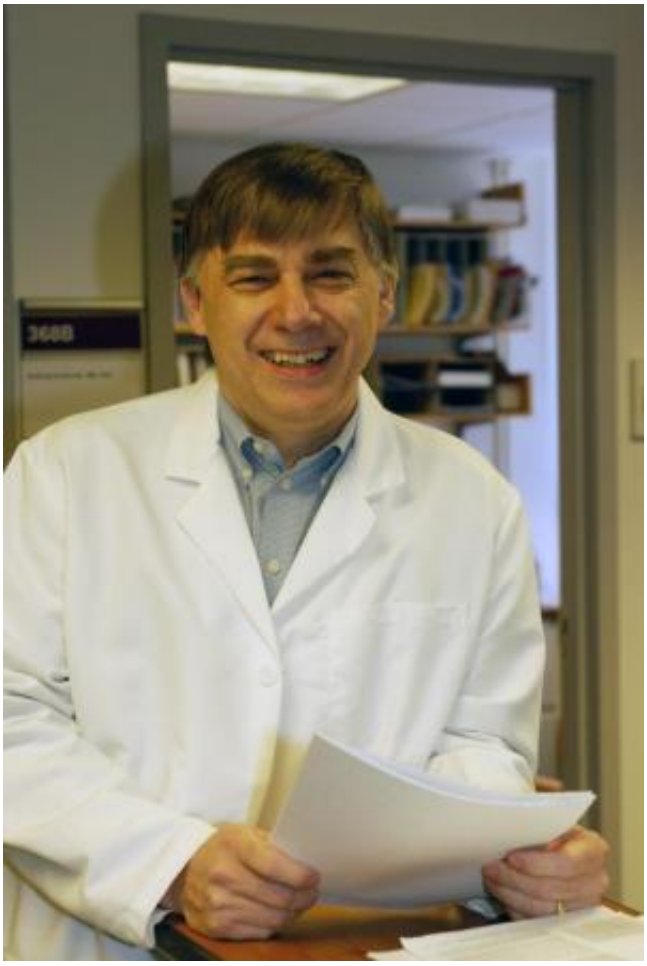

Andrzej Krolewski, M.D., Ph.D., is head of the Section on Genetics & Epidemiology at Joslin Diabetes Center, and associate professor of Medicine at Harvard Medical School. Credit: John Soares

People with type 1 diabetes who have developed kidney complications can slow the progression of their complications by improving control of their glycemic (blood glucose) levels over the long term.

This finding, which may change clinical practice at many institutions for this population, was drawn from a long-term observational study led by Andrzej Krolewski, M.D., Ph.D., head of Joslin Diabetes Center's Section on Genetics and Epidemiology.

Running for almost 20 years, the study showed that "you have to improve glycemic control for a long period of time to see this effect among these patients," emphasized Krolewski, who is also a professor of medicine at Harvard Medical School.

Published in the *Journal of the American Society of Nephrology*, the study followed a cohort of type 1 diabetes patients in the Joslin Clinic who had developed proteinuria. (Proteinuria is a potential kidney complication in which urine contains elevated amounts of protein; albumin is typically the most common protein found). The condition frequently leads to end-stage renal disease (ESRD), a life-threatening ailment that can only be treated with kidney dialysis or transplant.

The Joslin study began tracking kidney impairment among the patients in 1991 and followed them until 2011. As part of the study, researchers collected measurements of glycolated hemoglobin (HbA1c), which provides an indication of average blood glucose levels, for 279 patients.

All patients with type 1 diabetes produce little or none of the hormone insulin, and depend on insulin injections to stay alive. To maintain their health and minimize kidney problems and other complications, they must actively control their glycemic levels by paying attention around the clock to their blood glucose levels, diet and exercise. Endocrinologists generally recommend an HbA1c goal of 7.0% or below, but achieving

that level of control is difficult. The patients with proteinuria in the study were generally poorly controlled, with an average HbA1C of 9.3% before the study began.

Earlier investigations had suggested that achieving better glycemic control did not slow kidney complications for such patients. However, those studies were small and only extended for several years. In contrast, the Joslin research showed that those who lowered their HbA1C levels demonstrated a significantly lower risk of ESRD after a lag period of about five years. After 15 years, those with improved glycemic control had a cumulative risk of ESRD of 29% while those whose HbA1c increased or remained poor had a risk of 42%. There were no detectable differences between these two groups at the start of the study.

"The number of patients with diabetic kidney disease continues to grow at an epidemic rate throughout the rest of the world," said Robert Stanton, M.D., chief of the Kidney and Hypertension Section at Joslin and coauthor on the paper. "There is a great need to find new approaches and new treatments to both prevent development of diabetic kidney disease and to slow progression. This long-term study provides an important rationale to both patients and doctors to improve glycemic management in people with type 1 diabetes and kidney disease and to work very hard to maintain the glycemic control over many years."

Importantly, patients with proteinuria could substantially postpone severe outcomes from the disease without maintaining optimal HbA1c levels, Krolewski said. "We are talking about improving HbA1c from 11% to 9%, or 10% to 8%," he said, adding that earlier work by his lab indicated that levels of HbA1c below 8-9% may be sufficient to avoid kidney damage.

Down the road, Krolewski has high hopes for the emergence of "smart insulins," which have been modified to automatically release the

hormone once blood glucose levels rise above certain levels. When and if these drugs become available, he speculated, they might prove highly effective for slowing down progression to ESRD among this group of patients even if the drugs maintain higher than ideal glycemic levels.

Most people with type 1 diabetes will never proceed to ESRD, even if their glycemic control is far from perfect. Among the estimated 80,000 in the United States who have developed proteinuria, Krolewski said, about 10% are "rapid progressors" whose kidney function deteriorates completely within a few years.

Examining risk factors in developing kidney disease, researchers in his lab found in 2012 that high concentrations of the proteins TNFR1 and TNFR2 in blood accurately predict the risk of kidney function loss in both type 1 and type 2 diabetes 10 years in advance. This work has been licensed to EKF Diagnostics, a European firm now developing a commercial diagnostic test. Eventually, Joslin scientists hope, tests will identify diabetes patients at risk of impaired kidney function. Those patients then can be given special efforts to improve their glycemic control, and perhaps eventually also receive new combinations of drugs tailored to their condition.

Changes in clinical practice are usually driven by clinical trials, which compare results for multiple groups of patients who receive different treatments, rather than by observational investigations such as the Joslin proteinuria study. Krolewski noted, however, that a prospective clinical trial cannot be designed to address questions about effects of improved long-term glycemic control on progression to ESRD since it would not be ethically appropriate to purposely maintain a control group of patients with very high levels of blood glucose.

Other contributors to the study included Jan Skupien, James Warram and Adam Smiles from Joslin and Andrzej Galecki from the University of

Michigan.

This research was funded by JDRF as part of its program to develop therapies that progressively treat and reverse debilitating complications resulting from the impact of type 1 diabetes throughout the body. "These findings provide hope that long-term improvements in glucose control may alter the course of kidney disease in people with type 1 diabetes," said JDRF program director Helen Nickerson, Ph.D. "This reinforces the importance of improved glycemic control as we pursue novel therapies to slow or reverse loss of kidney function." The National Institutes of Health provided additional funding for the work.

Provided by Joslin Diabetes Center