Trial suggests way to personalize heart health in diabetes

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Scientists at Joslin Diabetes Center have taken another step toward solving a long-standing puzzle about heart health in type 2 diabetes, with a finding that eventually may point towards more personalized patient

care.

People with type 2 diabetes, who are at least twice as likely to develop cardiovascular disease (CVD) as people without the condition, generally can reduce their risks by careful controlling their glycemic (blood glucose) levels.

But back in 2008, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial made a paradoxical finding, says Alessandro Doria, M.D., Ph.D., M.P.H., a senior investigator in Joslin's Section on Genetics and Epidemiology. Among people with diabetes and high risk of CVD, it found that those who achieved extremely tight glycemic control showed higher risks of fatal heart attacks than those who did not, he says.

Last year, Doria and his colleagues made progress toward explaining this surprising discovery by identifying two genetic variants associated with a threefold increase in CVD specifically among patients in ACCORD who underwent intensive glycemic control.

Now in a paper published in *Diabetes Care*, the Joslin team has linked one of these genetic markers with levels of a hormone known as glucagon-like peptide 1 (GLP-1), says Doria, senior author on the paper and an associate professor of medicine at Harvard Medical School.

ACCORD participants who carried the variant associated with increased cardiovascular mortality showed a significant drop in fasting levels of GLP-1 during 12 months of intensive glycemic control, he says. GLP-1 levels were instead stable or increased among patients who did not carry that variant.

The Joslin team began its analysis by measuring 65 biomarker molecules in the blood among 351 people in ACCORD. The researchers then

looked for an association between these biomarkers and the previously discovered genetic variants for CVD in the two arms of the study—one arm with intense glycemic control and the other arm with standard glycemic control. (The most common measurement for glycemic control is a "hemoglobin A1C" or HbA1C test, which reflects average blood glucose levels over several months. Those in the trial's intensive-control group sought to reduce their HbA1C levels below 6%, while those following standard guidelines aimed for HbA1C levels below 8%).

While the link between higher risks of fatal heart attacks and lower GLP-1 levels after 12 months of intensive glycemic control was unexpected, it fit with what is known about the hormone. "GLP-1 is produced by intestinal cells, and its main action is to stimulate insulin secretion from beta cells, but the hormone also has a beneficial effect on the heart and blood vessels that is independent from its action on insulin secretion," says Doria.

The U.S. Food & Drug Administration has approved several GLP-1 "agonist" drugs (injectable GLP-1-like molecules) for people with type 2 diabetes, Doria says. In addition to lowering blood glucose, these drugs have been shown to improve cardiovascular health of diabetic patients. An earlier class of drugs known as DPP4 inhibitors, given orally, aims to provide similar effects by preserving the hormone in the bloodstream.

If the latest Joslin study is confirmed by other research, it will suggest that people with diabetes eventually might be tested for the genetic risk marker associated with lower GLP-1 levels. This testing could be done relatively inexpensively, Doria says, and patients who carry this marker might be particularly good candidates for using GLP-1 drugs to improve their glycemic control.

Doria and his co-workers will follow up on their work with experiments in cells that help them understand how the genetic variant affects GLP-1

production.

Additionally, the scientists will analyze other ACCORD data to pursue other methods that might help to personalize heart health in type 2 diabetes. "The trial itself was concluded in 2009, but researchers continue to mine its data, which shows the deep benefits of carefully collected data sets and samples," Doria says.

Provided by Joslin Diabetes Center