Genes influence response to glycemic control as a preventive therapy for cardiovascular complications in type 2 diabetes

September 19 2016

Credit: CC0 Public Domain

Genes play a role in how people with type 2 diabetes at high risk of cardiovascular disease risk respond to intensive glycemic control as an

intervention to prevent the disease. That is the major finding of a Joslin-led study which was published online on August 15 in *Diabetes Care*.

"This is the first time that we have found predictors of cardiovascular disease mortality associated with intensive glycemic control," says lead author Alessandro Doria, M.D, Ph.D., M.P.H., Senior Investigator in the Section on Genetics and Epidemiology and Director of the Genetics Core at Joslin Diabetes Center and Associate Professor of Medicine at Harvard Medical School.

Cardiovascular disease is the major cause of health problems and mortality in people with type 2 diabetes, who have a two to four times higher risk of the disease than people without diabetes. Preventing coronary artery disease is a major focus of diabetes treatment and research.

One recent nationwide study, Action to Control Cardiovascular Risk in Diabetes (ACCORD) investigated whether intensive glycemic control (which aims at a target A1C level of less than 6 percent) of type 2 diabetes is an effective intervention for cardiovascular disease compared to standard therapy (which aims for an A1C level of 7-7.9 percent).

ACCORD had surprisingly inconsistent results: intensive glycemic control reduced the risk of myocardial infarction and major cardiovascular events but also resulted in an increase in cardiovascular mortality. To identify a possible cause for these outcomes, Joslin scientists and collaborators at the Universities of Virginia and North Carolina initiated a genome-wide association study (GWAS) of ACCORD participants in the intensive control group. "We wanted to find out if there was a way to take advantage of the benefits of glycemic control while avoiding increased mortality," says Dr. Doria.

The study identified two genetic markers associated with a threefold

increase in cardiovascular disease among patients undergoing intensive as opposed to standard glycemic control. The two markers were considered together to create a genetic risk score (GRS) to calculate cardiac disease risk among study participants.

Participants with the lowest score (20 percent of the ACCORD population) derived the greatest benefit from the intensive therapy, experiencing a significant reduction in both fatal and nonfatal cardiovascular events. Those with an intermediate score (50 percent of participants) derived some benefit, experiencing a reduction in nonfatal events but not cardiovascular mortality. For participants with the highest score (30 percent of participants), the therapy had negative effects, resulting in a major increase in cardiovascular deaths without a decrease in nonfatal events.

To further validate these findings, genetic analysis was performed on participants in the Joslin Kidney Study in Type 2 Diabetes, who had good glycemic control but not as intensive as the ACCORD participants. Despite the study differences, similar results were found: subjects with the lowest GRS received the greatest benefit from glycemic control. Subjects with high GRS had neutral rather than detrimental effects, perhaps because of the less stringent glycemic control.

These genetic markers have the potential to identify patients who are likely to benefit from intensive glycemic control of cardiac complications and those who will derive harm from it. "We are always striving to offer personalized medicine to patients with diabetes. We have been trying to find markers to direct diabetes treatment and we now have genetic markers that offer that possibility," says Dr. Doria.

Testing of two genetic markers is readily available and inexpensive. However, before these findings can be used in clinical practice, they must be confirmed in additional studies. Dr. Doria hopes that publication

of this study will spur researchers to conduct genetic analysis of participants in other diabetes trials to provide more evidence to support study results.

In addition to the two genetic markers, the study identified 22 other genetic variants with a less conclusive association than the two genetic markers with intensive glycemic control and cardiac outcomes. Dr. Doria and Joslin researchers are currently investigating those variants in Joslin Kidney Study participants. They are also looking into the mechanisms that enable the two genetic markers to influence patient outcomes which could lead to the development of new interventions to prevent cardiovascular disease in diabetes.

More information: Hetal S. Shah et al. Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Control in Type 2 Diabetes: Findings From the ACCORD Clinical Trial, *Diabetes Care* (2016). dx.doi.org/10.2337/dc16-0285

Provided by Joslin Diabetes Center