Researchers find new cause of cardiac damage after heart attack in type 1 diabetes

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After people with type 1 diabetes have a heart attack, their long-term chance of suffering even more heart damage skyrockets. But the reason has long puzzled scientists. Now researchers at Joslin Diabetes Center have identified the misstep that sparks this runaway chronic damage and a promising way to block it.

"The problem arises from autoimmunity, a condition that people with type 1 diabetes already have ," says Myra A. Lipes, M.D, investigator in the Section on Immunology at Joslin and principal investigator of a study published in the June 13 edition of the journal *Science Translational Medicine.*

In the current work, Lipes and her team identified the factor that triggers an autoimmune response against cardiac muscle tissue following a heart attack. Furthermore, they developed a way to selectively stop it. They also showed the presence of a similar process in human patients, opening the door for possible ways to improve outcomes of patients with type 1 diabetes after myocardial infarction.

Their research focused on type 1 diabetes, for which cardiovascular disease accounts for 65□□% of deaths. Compared with the general population, people with type 1 diabetes are 13 times more likely to die of heart disease.

The researchers suspected the reason went beyond known factors associated with elevated glucose levels and abnormal metabolism.

Indeed, people with type 1 or type 2 diabetes are at elevated risk for heart disease because high blood glucose damages blood vessels. But the reason for particularly poor outcomes following a heart attack in patients with type 1 was mysterious.

They discovered that part of the answer stems from the heart itself. In all myocardial infarctions, with or without the presence of diabetes, an array of inflammatory signals gushes from the injured heart muscle and starts the repair process. "We tend to think of the inflammatory response as bad, but it also can be good," Dr. Lipes says. "It is critical for helping the heart heal and forming a good scar."

By contrast, this process is a "double-edged sword" in patients who are autoimmune-prone. Autoimmunity is the root cause of type 1 diabetes, in which the immune system mistakenly destroys the body's insulin-producing cells of the pancreas.

The Joslin studies show a similar error—this time directed to heart tissue—occurs in patients with type 1 diabetes following a heart attack. In this syndrome, cells of the immune system infiltrate the heart muscle and misinterpret myosin, the main structural protein of heart muscle, as being a foreigner.

A runaway attack is launched, called chronic cardiac autoimmunity. It never turns off, increasingly damaging the heart over time. It causes myocarditis (inflammation of the heart muscle), leading to cardiomyopathy (thinning and weakening of the heart muscle) and heart failure.

In the laboratory arm of the Joslin study, researchers studied a mouse model of human type 1 diabetes. They discovered that a form of myosin, alpha-myosin, triggers the development of autoimmunity after a heart attack. In fact, this autoimmune signal temporarily emerges after

myocardial infarctions in people in the general population, but normally the body is able to turn it off.

In most people with type 1 diabetes, however, the immune system is not capable of turning this response off. An intervention is needed to stop the onslaught on the heart. In this study, the researchers were able to block the autoimmune response by inducing immune tolerance to alpha-myosin. These studies therefore provide a pathway for future interventions to specifically protect the heart.

In the clinical portion of the study, they focused on type 1 diabetes patients who had survived a heart attack. Using a panel of newly developed blood tests, they were able to detect cardiac autoantibodies in 15 of 18 (83%) patients. Using noninvasive cardiac magnetic resonance imaging techniques, they were able to confirm the presence of myocardial inflammation in a patient who tested positive for cardiac myosin autoantibodies. These findings indicated that the same process found in type 1 diabetes-prone mice also occurs in patients with type 1 diabetes. In addition, they point to the potential role for using these autoantibody tests for more widespread screening to detect this newly discovered syndrome in other patients with type 1 diabetes.

"With these laboratory and patient studies, we now have a roadmap for future research and a promising antigen target for developing future interventions to help people with type 1 diabetes following heart attack," Dr. Lipes says. "Our findings also may have broader implications, possibly improving outcomes after heart attack in patients with other autoimmune disorders."

Provided by Joslin Diabetes Center

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