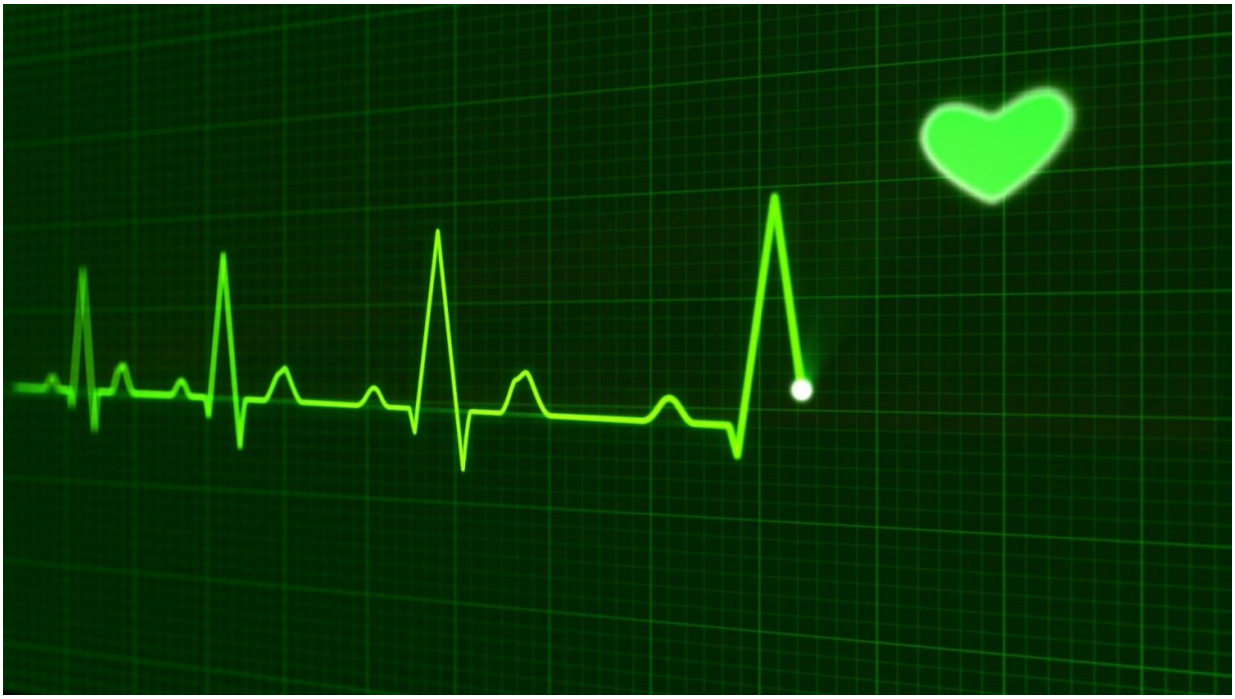
Medical Xpress

Autoimmunity-associated heart dilation tied to heart-failure risk in type 1 diabetes

April 6 2020



Credit: CC0 Public Domain

People with type 1 diabetes, particularly those with poor glycemic control, are at markedly increased risk for cardiovascular disease than the general population. Even more puzzling, in individuals with type 1 diabetes, many of the risk factors for cardiovascular disease do not line up with the known risk factors associated with type 2 diabetes.

Dr. Myra Lipes, Investigator in the Section on Immunobiology at Joslin Diabetes Center at Harvard Medical School, has been working for more than a decade to understand exactly what leads to such increase risk of cardiovascular disease in patients with type 1 diabetes and what can be done about it.

"Heart failure in particular has recently been recognized as an important complication of type 1 with national register-based studies showing tenfold increased risk of heart failure in individuals with poor glycemic control," says Dr. Lipes. "In addition, there's a higher case fatality rate in type 1 than type 2 diabetes, which suggests different mechanisms for heart failure might be involved in type 1 diabetes." Given the burden of heart failure in type 1 diabetes, the early identification of patients at particular risk is of importance.

New research from Dr. Lipes's lab at Joslin shows that in people with type 1 diabetes without known cardiovascular disease, the presence of autoantibodies against heart muscle proteins was associated with cardiac magnetic resonance (CMR) imaging evidence of increased volume of the left ventricle (the heart's main pumping chamber), increased muscle mass, and reduced pumping function (ejection fraction), features that are associated with higher risk of failure in the general population. This new study was published in *Circulation*.

Antibodies are normally produced by the immune system and circulate in the blood, playing in important role in the body's defense against infection. In autoimmune-prone people, the body misidentifies its own proteins as threats and attacks. This is what happens in type 1 diabetes—the immune system thinks pancreatic beta cells are invaders and destroys them. In these situations, antibodies are called autoantibodies. So, perhaps it's not too surprising that this complication of type 1 diabetes also involves a faulty immune response against the heart muscle cells.

Previous studies run by Dr. Lipes' group have shown that mouse models of type 1 diabetes developed dilated cardiomyopathy (weakened heart muscle) and early heart failure associated with the presence of autoantibodies directed against heart muscle proteins. Her group has also shown that poor glycemic control in patients with type 1 diabetes—but not in those with type 2 diabetes—was associated with cardiac autoimmunity. An unexpected finding was the similar cardiac autoantibody levels in the patients with type 1 diabetes, who were young adult and without diabetes complications, and a heart failure cohort with Chagas' cardiomyopathy, which is thought to be caused by chronic inflammation of the heart muscle ("myocarditis"), raising the possibility of a subclinical autoimmune-associated myocardial dysfunction in type 1 diabetes " says Dr. Lipes.

In this study, Lipes wanted to determine whether the dilated heart phenotype seen in mouse models and Chagas' patients was also present in people with type 1 diabetes who had these circulating autoantibodies. She and her team used data gathered from a participants involved in the post-Diabetes Control and Complications Trial (DCCT) Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study, and consisted of people who had type 1 diabetes for an average of 28 years. As part of this study, the participants had their heart imaged using CMR, the gold-standard noninvasive imaging technique for assessing heart structure and function.

"In the study, we measured autoantibodies to heart muscle proteins in blood samples taken from the time of CMR imaging in 892 EDIC participants without any known cardiovascular disease," says Lipes. "And then we examined where the presence of cardiac antibodies was associated with CMR evidence of myocardial dysfunction."

They found that although the recent A1c levels were similar in participants with and without cardiac autoantibodies, presence of cardiac

autoantibodies identified patients with worse glycemic control in the past, suggesting that cardiac autoantibodies are markers of long-term glycemic exposure. In addition, they found that the CMR scans from people with two or more of these autoantibodies showed dilated hearts. They sorted patients into categories based on numbers of circulating autoantibodies, which indicated that people with more of these specific autoantibodies had more pronounced changes to the heart. These findings were not weakened after adjusting for traditional cardiovascular risk factors, suggesting these changes were primarily due to cardiac autoimmunity.

They knew from previous research that the heart can have structural and functional changes related to the metabolic problems of diabetes itself; however, these relationships were relatively modest. For example, higher A1C levels were associated with slightly smaller left ventricle volumes that were not clinically significant. But this study suggests that higher A1C levels can trigger an additional autoimmune response that damages the heart in a different and more pronounced way that leads to enlargement and worse function, features that are known to be associated with a high risk of heart failure.

"This points to a novel process involving the heart and linked to poor glycemic control in type 1 diabetes," says Lipes.

Because cardiac autoantibodies can be detected in simple blood test, this research opens a new avenue for detecting the potential for heart failure in patients with type 1 diabetes.

"Given the high burden of heart failure in type 1 diabetes, cardiac antibodies may enable the early identification of people at higher risk of developing heart failure," says Lipes. "And, of course, understanding the underlying cause of heart failure is important since it could lead to targeted therapeutic approaches to improve outcomes in these patients."

More information: Giovane R. Sousa et al, Cardiac Autoimmunity Is Associated With Subclinical Myocardial Dysfunction in Patients With Type 1 Diabetes Mellitus, *Circulation* (2020). DOI: 10.1161/CIRCULATIONAHA.119.044539

Provided by Joslin Diabetes Center