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Type 1 diabetes and heart disease linked by inflammatory protein

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Type 1 (insulin-dependent) diabetes appears to increase the risk of heart disease, the leading cause of death among people with high blood sugar, partly by stimulating the production of calprotectin, a protein that sparks an inflammatory process that fuels the buildup of artery-clogging plaque. The findings, made in mice and confirmed with human data, suggest new therapeutic targets for reducing heart disease in people with type 1 diabetes. Led by Columbia University Medical Center (CUMC) researchers in collaboration with investigators at New York University and the University of Pittsburgh, the study was published today in the online edition of *Cell Metabolism*.

Diabetes is known to raise the risk for atherosclerosis, a disease in which fatty deposits known as plaque accumulate inside arteries. Over time, the arteries harden and narrow, leading to coronary artery disease and other forms of heart disease. Atherosclerosis is the leading cause of heart attacks, strokes, and peripheral vascular disease—collectively known as coronary heart disease, the leading cause of death in the United States.

Scientists have known that diabetes leads to atherosclerosis. The study shows that this is associated with increased circulating levels of inflammatory white blood cells (WBCs), which contribute to the build-up of plaque. "But exactly how diabetes causes white blood cells to proliferate and lead to heart disease has been a mystery," said study co-leader Ira J. Goldberg, MD, Dickinson W. Richards Professor of Medicine at CUMC.

In studies of mice with type 1 diabetes, Dr. Goldberg and his colleagues found that high blood sugar stimulates a type of inflammatory WBC known as neutrophils to release the protein calprotectin (also known as S100A8/9). The calprotectin travels to the bone marrow, where it binds to a cell-surface receptor called RAGE receptor, on common myeloid progenitor cells, which are involved in the production of various types of blood cells. This, in turn, leads to the proliferation of cells, known as granulocyte macrophage progenitor cells, which trigger the proliferation of even more neutrophils and of monocytes (another type of inflammatory WBC). Finally, these new WBCs enter the circulation and make their way to arterial plaques, fueling their progression.

The researchers also found that normalizing the mice's blood glucose dampened this pathway, leading to an overall decrease in inflammation.

To determine the relevance of these findings in humans, the researchers analyzed data from 290 patients in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, led by EDC Principal Investigator Trevor J. Orchard, who has been following people with diabetes for 18 years. Total WBC, neutrophil, and monocyte counts were all significantly associated with the development of coronary artery disease. The researchers also analyzed blood samples from a subgroup of EDC patients. Those who had developed coronary artery disease had significantly higher levels of calprotectin, compared with patients who had not developed coronary artery disease.

"The human data appear to fit with the animal data, in that both WBCs and calprotectin are associated with heart disease," said co-lead author Andrew J. Murphy, PhD, postdoctoral fellow in medicine at CUMC. The other lead author is Prabhakara R. Nagareddy, PhD, postdoctoral fellow at CUMC.

"Our findings point to the importance of controlling blood levels to limit

the production of inflammatory cells that drive atherosclerosis; they also suggest novel therapeutic strategies, such as inhibiting the production of calprotectin or preventing its binding to the RAGE receptor," said study co-leader Alan R. Tall, MD, the Tilden Weger Bieler Professor of Medicine at CUMC.

The CUMC team is currently studying how type 2 diabetes increases one's risk for heart disease.

More information: The paper is titled, "Hyperglycemia promotes myelopoiesis and impairs the resolution of atherosclerosis": dx.doi.org/10.1016/j.cmet.2013.04.001

Provided by Columbia University Medical Center

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