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Study may explain how exercise improves heart function in diabetics

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A detailed study of heart muscle function in mice has uncovered evidence to explain why exercise is beneficial for heart function in type 2 diabetes. The research team, led by scientists at the Johns Hopkins University School of Medicine, found that greater amounts of fatty acids used by the heart during stressful conditions like exercise can counteract the detrimental effects of excess glucose and improve the diabetic heart's pumping ability in several ways. The findings also shed light on the complex chain of events that lead to diabetic cardiomyopathy, a form of heart failure that is a life-threatening complication of type 2 diabetes.

The study, described in an article published online on July 17, 2012 in the journal *Diabetes*, was conducted in a mouse model of type 2 diabetes, and focused on the exchange of energy within heart muscle cells. The researchers looked at the impact of glucose and fatty acids, which are different types of "fuel" that provide energy to the cells—and how those affect heart muscle function.

"Our work offers a new view of the role of fatty acids in diabetic hearts under stress, and suggests potential new therapies to improve heart function," says Miguel Aon, Ph.D., assistant professor of medicine at the Johns Hopkins University School of Medicine and a senior author of the study article. "It has been commonly assumed that fatty acids were detrimental to heart muscle function, but our study showed the opposite to be true in the diabetic heart."

The researchers studied models of intact mouse hearts from both normal and diabetic mice, and also were able to isolate the mitochondria—the tiny energy drivers within cells—from the mouse hearts. The heart relies on energy from mitochondria to produce beats.

Specially bred diabetic mice have long been used successfully to study human diabetes because the disease in the tiny mammals mimics the disorder in humans. For example, both mice and people with diabetes have an excess amount of glucose circulating in their blood because of impaired insulin function, and they are generally overweight or obese.

In their experiments, the researchers "fed" the normal and diabetic hearts excess glucose and stimulated the hearts to beat faster by bathing them in a hormone-like substance, isoproterenol, which acts like the body's natural catecholamine, activated when a person is under stress or participating in high levels of physical activity. While the normal hearts were able to handle the increased glucose load and pump normally, the diabetic hearts could not contract or relax enough to keep up with the load and pump normally.

Next, the scientists repeated the experiments by feeding twice the usual amount of fatty acids to the normal and the diabetic hearts. "We found that the function of the normal heart did not change, but to our surprise, the diabetic hearts improved to the level of the normal hearts," says Nazareno Paolocci, M.D., Ph.D., assistant professor of medicine at the Johns Hopkins University School of Medicine and co-author of the study.

Aon says fatty acids appear to improve the exchange of energy within cells and also help the heart to resist the negative effects of reactive oxygen species (ROS). These molecules have a positive role in signaling within cells, but too much ROS can cause oxidative stress, damaging or even killing cells.

The researchers found that the fatty acids also counteracted impairments in the function of diabetic hearts caused by too much glucose.

When we overeat, the excess energy is stored as fat, leading to being overweight or obese, which increases the risk of type 2 diabetes. When people chronically put on weight, the fat accumulates inside cells and becomes toxic, crowding out the other functions of the cells. Aerobic exercise, such as brisk walking, jogging, biking and swimming, has long been known to modify the negative impact of diabetes on heart muscle.

Aerobic exercise breaks up stored fatty acids to provide more fuel to the heart, and this study demonstrates that additional fatty acids can be good for the diabetic heart when it needs to beat faster, Aon says.

Another key finding of the study relates to understanding why people with type 2 diabetes develop cardiomyopathy—a form of heart failure. "Over time, if the heart muscle is not receiving enough energy, the mechanical and electrical functions required to produce a normal heartbeat become impaired, which leads to cardiomyopathy," says Aon. "In our study, we were able to show a cause-and-effect relationship between dysfunction of the mitochondria—the energy-producing components of cells—and the heart's mechanical and electrical functions, which helps to explain why people with type 2 diabetes develop cardiomyopathy," he says.

To counteract the damaging chain of events, the researchers added glutathione, an important antioxidant, to the diabetic mouse heart cells, and that greatly improved their mechanical function. Researchers also found that increasing the exposure of the heart muscle cells to fatty acids raised the amount of naturally occurring glutathione. So, the scientists conclude that glutathione or similar compounds could be a new avenue of treatment for people with type 2 diabetes.

"Now that we have shed light on why exercise can improve heart function in people with type 2 diabetes," says Aon, "the next step is figuring out how to harness that knowledge to prevent heart damage from diabetes, especially among those people who cannot bring their blood sugar levels under good control."

Provided by Johns Hopkins University School of Medicine