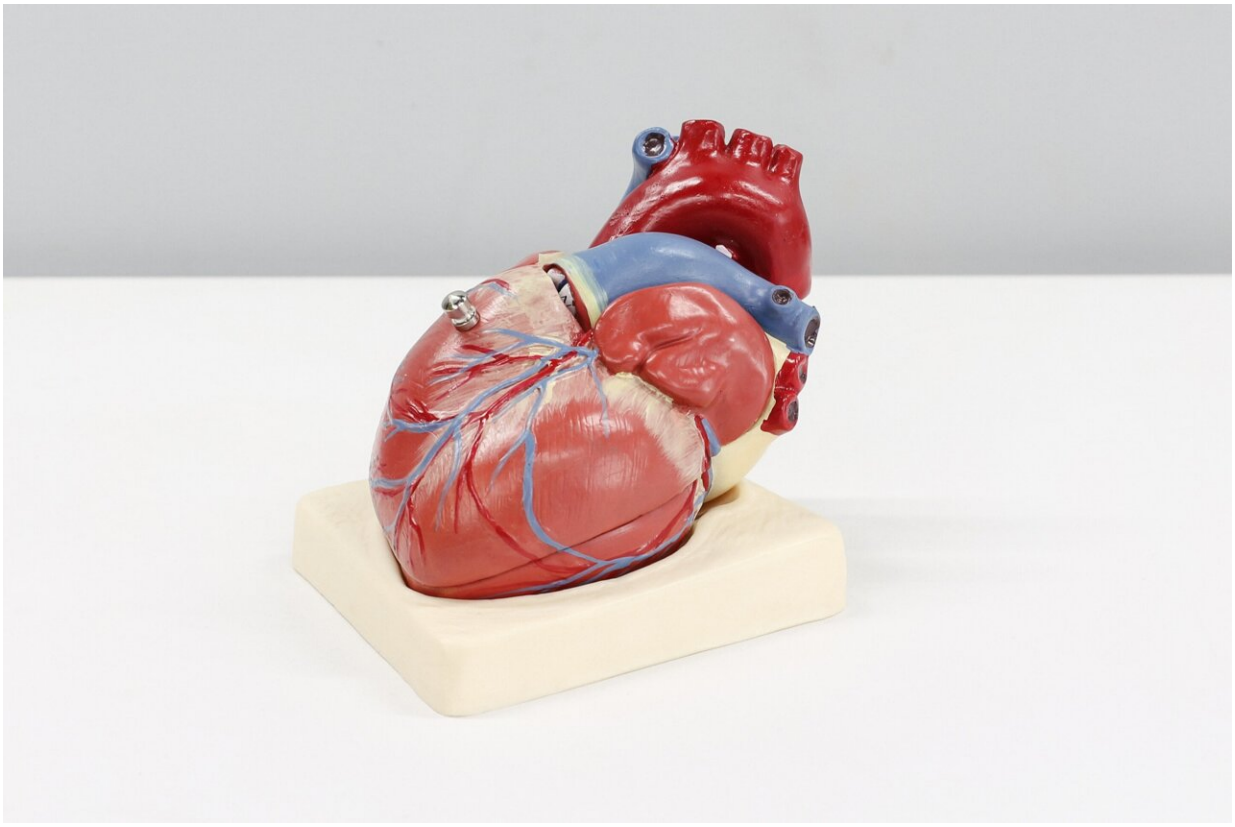
Drug could help diabetic hearts recover after heart attack

October 20 2021



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Researchers at the University of Oxford have identified a drug that could ultimately help improve heart function in people with diabetes who have heart attacks.

The drug, currently in clinical trials as a potential treatment for a form of anemia, could help diabetic hearts to recover and reduce their risk of developing heart failure, according to research funded by the British Heart Foundation published in the journal *Diabetes*.

During a heart attack blood supply to the heart is reduced or cut off, starving the heart of oxygen (hypoxia). In diabetes heart cells are less able to tolerate hypoxia and therefore die more quickly.

Now, the research team has found that a drug known as molidustat can increase levels of a protein that helps cells to adapt and survive after they are starved of oxygen. They hope that giving molidustat to people with diabetes will help their hearts to recover after a heart attack and reduce their risk of further complications, such as heart failure.

Molidustat, which is taken orally, is currently in phase III clinical trials for treating anemia in chronic kidney disease. It works by increasing levels of a protein called Hypoxia-Inducible Factor 1 (HIF). When oxygen levels fall HIF levels increase, causing it to activate its 'target' genes which help cells to adapt and survive. However, previous research has found that people with diabetes have lower levels of HIF in their heart cells.

When the researchers exposed human heart cells with insulin resistance, a characteristic of type 2 diabetes, to low levels of oxygen they found that the increase in HIF protein levels was much lower than in control cells without insulin resistance. But, when they treated the insulin resistant cells with molidustat, the researchers saw increased levels of the HIF protein and activation of its target genes.

Next the team investigated the impact of molidustat on heart function by exposing hearts from rats with and without type 2 diabetes to low levels of oxygen. The function of the diabetic hearts was significantly

decreased after the period of low oxygen. However, when these hearts were treated with molidustat their function recovered back to the level of those without diabetes.

HIF is also involved in healing processes that happen after a heart attack, such as the growth of new blood vessels, a process known as angiogenesis. New blood vessels grow to bypass the tissue that has died and ensure a good blood supply to the surrounding areas of the heart that have survived.

Angiogenesis is known to be reduced in diabetic hearts, and this is believed to be a critical step in the development of heart failure. When rats with type 2 diabetes were treated with molidustat the researchers saw increased levels of the signals involved in the growth of new blood vessels. They hope that molidustat treatment could help to improve blood supply to the heart after a heart attack in people with diabetes.

Dr. Lisa Heather, BHF Intermediate Research Fellow at the University of Oxford, said: "Even with optimal management, people with type 2 diabetes still have a higher risk of developing heart and circulatory diseases. They're then more likely than people without diabetes to develop heart failure after a heart attack.

"Despite this, there are no treatments available to help the diabetic heart recover after a heart attack. We're hopeful that we've identified a drug that can address this unmet need and improve outcomes for people with diabetes after a heart attack."

Professor Metin Avkiran, Associate Medical Director at the British Heart Foundation, said: "Heart and circulatory diseases are the leading cause of death in people with diabetes, a condition which affects nearly 5 million people in the UK.

"These promising results suggest that drugs which stabilize HIF could become a new treatment to reduce the risk of heart failure after a heart attack in people with diabetes. Further research is now needed to translate these early stage findings into clinical benefit."

More information: Maria da Luz Sousa Fialho et al, Activation of HIF1α Rescues the Hypoxic Response and Reverses Metabolic Dysfunction in the Diabetic Heart, *Diabetes* (2021). DOI: 10.2337/db21-0398

Provided by University of Oxford