# Team unlocks secrets of diabetes drug: How and why metformin needs to interact with insulin to be effective

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About 120 million people around the world with Type 2 diabetes – and two million in Canada – take the drug metformin to control their disease.

While doctors know metformin needs to interact with insulin to be effective, and that it can't lower blood sugar on its own, no one has been able to explain how and why this happens.

Researchers at McMaster University are the first to unlock that mystery with their discovery metformin works on fat in the liver. Their research is published in today's issue of the journal *Nature Medicine*.

"The key is that metformin doesn't work to lower blood glucose by directly working on the glucose. It works on reducing harmful fat molecules in the liver, which then allows insulin to work better and lower blood sugar levels," said Greg Steinberg, associate professor in the Department of Medicine of the Michael G. DeGroote School of Medicine.

He also holds the Canada Research Chair in Metabolism and Obesity and is a co-director of the Metabolism and Childhood (MAC)-Obesity Research Program. His research team included scientists in Alberta, Australia and Scotland.

Steinberg said that most people taking metformin have a fatty liver, which is frequently caused by obesity. "Fat is likely a key trigger for pre-diabetes, causing blood sugar to start going up because insulin can't work as efficiently to stop sugar coming from the liver."

In their detective work to uncover what causes fatty liver, the scientists studied mice that have a "genetic disruption" to a single amino acid in two proteins called acetyl-CoA carboxylase (ACC). These proteins, which are controlled by the metabolic sensor AMP-activated protein kinase, regulate fat production as well as the ability to burn fat.

Mice with the mutated proteins developed signs of fatty liver and pre-diabetes even in the absence of obesity.

"But what was really surprising was that when obese mutant mice were given metformin, the most common and inexpensive drug prescribed to Type 2 diabetics, the drug failed to lower their blood sugar levels," said Steinberg. "It indicates the way metformin works isn't by directly reducing sugar metabolism, but instead by acting to reduce fat in the liver, which then allows insulin to work better."

Morgan Fullerton, lead author of the study, added: "Unlike the majority of studies using genetic mouse models, we haven't deleted an entire protein; we have only made a very minor genetic mutation, equivalent to what might be seen in humans, thus highlighting the very precise way metformin lowers blood sugar in Type 2 Diabetes".

"This discovery offers a huge head start in finding combination therapies (and more personalized approaches) for diabetics for whom metformin isn't enough to restore their blood sugar to normal levels," said Steinberg.

**More information:** Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin, DOI: 10.1038/nm.3372

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