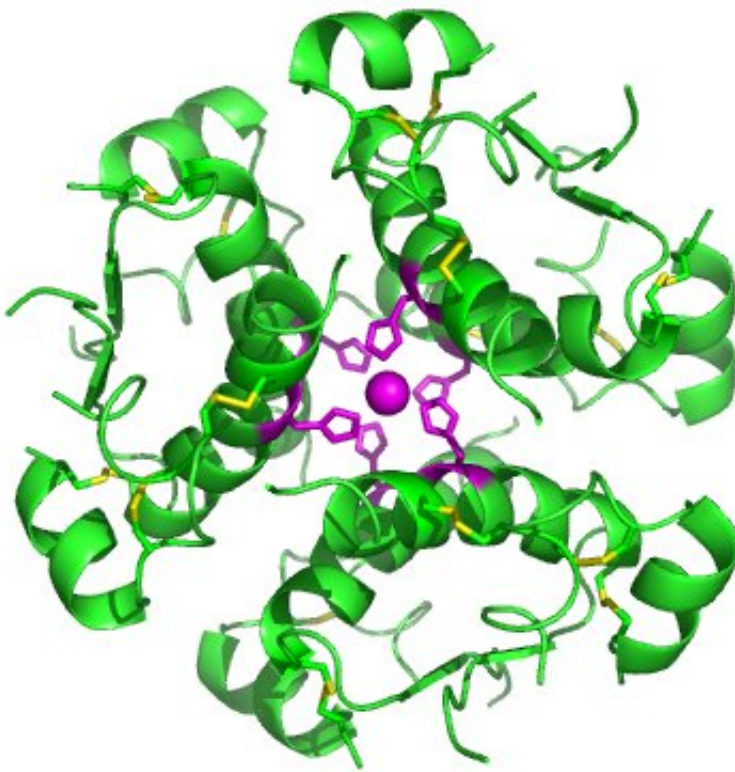


# New theory on how insulin resistance, metabolic disease begin

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High-resolution model of six insulin molecules assembled in a hexamer. Credit: Isaac Yonemoto/Wikipedia

Does eating too much sugar cause type 2 diabetes? The answer may not be simple, but a study published Sept. 26 in the *Journal of Clinical Investigation* adds to growing research linking excessive sugar

consumption—specifically the sugar fructose—to a rise in metabolic disease worldwide.

The study, conducted in mice and corroborated in human liver samples, unveils a metabolic process that could upend previous ideas about how the body becomes resistant to insulin and eventually develops diabetes.

The increasing prevalence of diabetes is considered a health epidemic as more than 29 million people in the U.S. have diabetes and another 86 million have pre-diabetes, according to the Centers for Disease Control and Prevention.

"There is still significant controversy as to whether [sugar](#) consumption is a major contributor to the development of diabetes," said senior author Mark Herman, M.D., assistant professor in the Division of Endocrinology, Metabolism, and Nutrition at Duke University School of Medicine.

"Some investigators contend that commonly consumed amounts of sugar do not contribute to this epidemic," Herman said. "While others are convinced that excessive sugar ingestion is a major cause. This paper reveals a specific mechanism by which consuming fructose in large amounts, such as in soda, can cause problems."

Insulin is a key hormone that regulates blood glucose after eating. Insulin resistance, when the body's metabolic tissues stop responding normally to insulin, is one of the earliest detectable changes in the progression to diabetes.

However, according to this study, the cause of insulin resistance may have little to do with defects in insulin signaling and might actually be caused by a separate process triggered by excess sugar in the liver that activates a molecular factor known as carbohydrate-responsive element-

binding protein, or ChREBP.

The ChREBP protein is found in several metabolic organs in mice, humans and other mammals. In the liver, it is activated after eating fructose, a form of sugar naturally found in fruits and vegetables, but also added to many processed foods including soft drinks. The study found that fructose initiates a process that causes the liver to keep making glucose and raising [blood glucose](#) levels, even as insulin tries to keep glucose production in check.

"For the past several decades, investigators have suggested that there must be a problem in the way the liver senses insulin, and that is why insulin-resistant people make too much glucose," Herman said. "We found that no matter how much insulin the pancreas made, it couldn't override the processes started by this protein, ChREBP, to stimulate glucose production. This would ultimately cause blood sugar and insulin levels to increase, which over time can lead to insulin resistance elsewhere in the body."

Herman is new to Duke and led the research over the past four years at Beth Israel Deaconess Medical Center at Harvard University with collaborators from the University of Massachusetts Medical School and Pfizer Inc.

To test their hypothesis, researchers studied mice that were genetically altered so their liver insulin signaling pathways were maximally activated—in other words, their livers should not have been able to produce any glucose.

The researchers found that even in these mice, eating fructose triggered ChREBP-related processes in the liver, causing it to make more and more glucose, despite insulin signals telling it to stop.

Previous studies have reported that high fructose diets can cause multiple metabolic problems in humans and animals, including insulin resistance and [fatty liver disease](#). Because most people found to be insulin-resistant also have fatty liver, many investigators have proposed that the fructose-induced fatty liver leads to liver dysfunction, which causes insulin resistance, diabetes and high risk for heart disease.

The new findings suggest fatty liver disease may be a red herring, Herman said. The likely cause of [insulin resistance](#) may not be the buildup of fat in the liver, as commonly believed, but rather the processes activated by ChREBP, which may then contribute to the development of both fatty liver and increased [glucose production](#).

Although much more research is required, the scientists believe they better understand a key mechanism leading to pre-diabetes and can now explore how to possibly interrupt that chain of events. ChREBP may not be the only pathway by which this happens, and the protein may also be activated in other ways, Herman said. But the study provides an important lead, he said.

"It gives us some insight into what may be happening early in diabetes," Herman said. "If we can develop drugs to target this process, this may be a way to prevent the process early in the development of the disease."

The finding could also help scientists one day diagnose metabolic disorders earlier on, potentially allowing patients to make changes to their diets and lifestyles sooner to prevent more serious complications.

As a medical doctor, Herman said the advice to patients remains the same: make sure you're not eating too much sugar, which often shows up on labels as sucrose (the main ingredient in beet and cane sugar) and high fructose corn syrup. Both sweeteners contain both glucose and fructose and are rapidly absorbed, he said.

In its naturally occurring form and quantity, fructose is not particularly harmful, Herman explained, because if you're eating an apple, for example, you're eating a relatively small amount of sugar and it's combined with other nutrients such as fiber that may slow its absorption.

"You could eat three apples and not get the same amount of fructose you might get from a 20-ounce sugar-sweetened beverage," he said. "The major sources of excessive fructose are in foods like sodas and many processed foods, which are foods most doctors would say to limit in your diet."

Provided by Duke University Medical Center

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