Medical Xpress

Research could explain why some obese people develop diabetes while others don't

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For years, scientists have known that someone who is thin could still end up with diabetes. Yet an obese person may be surprisingly healthy.

Now, new research led by scientists at the University of Utah College of Health, and carried out with an international team of scientsts, points to an answer to that riddle: accumulation of a toxic class of fat metabolites, known as ceramides, may make people more prone to type 2 diabetes.

"Ceramides impact the way the body handles nutrients," says the study's senior author Scott Summers, Ph.D., also chairman of the University of Utah Department of Nutrition and Integrative Physiology. "They impair the way the body responds to insulin, and also how it burns calories."

In the study, published on Nov. 3 in *Cell Metabolism* online, the

researchers show that a buildup of ceramides prevents the normal function of fat (adipose) tissue.

When people overeat, they produce an excess of fatty acids. Those can be stored in the body as triglycerides or burned for energy. However in some people, fatty acids are turned into ceramides.

"It's like a tipping point," Summers said.

At that point, when ceramides accrue, the adipose tissue stops working appropriately, and fat spills out into the vasculature or heart and does damage to other peripheral tissues. Until now, scientists didn't know how ceramides were damaging the body.

The three-year project found that adding excess ceramides to human fat cells, or mice, caused them to become unresponsive to insulin and develop impairments in their ability to burn calories. The mice were also more suceptible to diabetes as well as fatty liver disease.

Conversely, they also found that mice with fewer ceramides in their adipose tissue were protected from insulin resistance, a first sign of diabetes. Using genetic engineering, researchers had deleted the gene that converts saturated fats into ceramides.

The findings indicate that high ceramides levels may increase diabetes risk and low levels could protect against the disease.

The trend may also hold true in people. In fact, among patients in Singapore receiving gastric bypass surgery, ceramide levels predicted who had diabetes better than obesity did. Even though all of the patients were obese, those who did not have type 2 diabetes had less ceramide in their adipose tissue than those who were diagnosed with the condition.

The scientists think this could mean that some people are more likely to convert calories into ceramides than others. "That suggests some skinny people will get diabetes or fatty liver disease if something such as genetics triggers ceramide accumulation," said Bhagirath Chaurasia, Ph.D., assistant professor at the University of Utah and the lead author of the study.

As a result of the new research, the scientists are now searching for genetic mutations that lead to people's predisposition to accumulating ceramides, developing obesity and type 2 diabetes.

Summers notes that some Asian countries have a higher diabetes rate than the United States even though the obesity rate is relatively low. "Some people are just not made to deal with dietary fat," says Summers. "It's not just how much you eat, because some people can eat a lot and they just store all the fat effectively and remain healthy."

Adipose tissue exists as three types. White adipose tissue is considered the "bad" kind, because it predominately stores fat. Brown adipose tissue burns fat to generate heat. Beige adipose tissue is a variety of white fat that can change to brown when the body needs to produce heat or create energy.

Based on their research, the scientists propose that as ceramides build up, the tissue loses the characteristics of brown fat, effectively becoming more white. This sets off a sequence of events that can lead to disease.

Summers previously published research in 2007 proving that the inhibition of ceramide synthesis in rodents prevented the development of fatty liver disease and diabetes. He is now working to develop drugs to target that issue.

"By blocking ceramide production, we might be able to prevent the

development of type 2 diabetes or other metabolic conditions, at least in some people," Chaurasia said. Knowing how problematic ceramide accumulation is inside adipose tissue will help researchers focus on that specific problem.

More information: Adipocyte Ceramides Regulate Subcutaneous Adipose Browning, Inflammation, and Metabolism; *Cell Metabolism* online Nov. 3, 2016 DOI: 10.1016/j.cmet.2016.10.002

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