

New source of liver disease in obesity caused by saturated fat, but not unsaturated fat

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In results published on October 19, 2015 in the [Journal of Lipid Research](#), a team of translational scientists at the Medical University of South Carolina (MUSC) report a new reason why non-alcoholic steatohepatitis (NASH) worsens in people who are obese.

The results may help prevent cirrhosis and [liver cancer](#), according to co-senior authors Kenneth D. Chavin, M.D., PhD, a [transplant surgeon](#) in the MUSC Health Department of Surgery, and Lauren Ashley Cowart, PhD, Associate Professor of Biochemistry and Co-Director of the MUSC Center of Biomedical Research Excellence in Lipidomics and Pathobiology.

NASH (also called non-alcoholic fatty liver disease) has become a major cause of [liver disease](#) requiring transplant. "In my 17 years of doing [liver transplants](#), it's gone from 4% of patients to around 20% of patients who get transplants because of NASH," says Chavin. "In 10-15 years, because of advances with Hepatitis C, it will probably become the number one reason why patients get transplants."

When excess dietary fats are consumed over time, fat deposits form in the liver and NASH can develop. Early-stage NASH is typically not associated with any physical symptoms; nearly 30% of people in the U.S. have it. Though [obesity](#) is correlated with the development of NASH, the team wanted to know exactly why NASH worsens to a stage requiring transplant in certain obese people.

"Obesity doesn't cause disease in every obese person and we don't understand why it does in some but not others," explains Cowart.

The team suspected that inflammation stemming from a lipid molecule called sphingosine-1-phosphate (S1P) might be responsible. They'd previously discovered in other organs that S1P is increased by excess dietary saturated fat.

Chavin took biopsies from human livers during transplant surgery and supplied them to Cowart, who determined the levels of sphingosine kinase 1, the enzyme that makes S1P. They found double the normal amount of sphingosine kinase 1 in livers of obese people with non-alcoholic steatohepatitis.

The team wanted more understanding of why S1P causes inflammation, but NASH has previously been difficult to mimic in the laboratory setting. They developed a new and highly improved preclinical model of NASH, wherein mice were fed on custom-designed diets of either high saturated fat or high unsaturated fat. Curiously, mice on each type of diet became obese, but only mice on the saturated fat diet developed inflammation and NASH-like pathology stemming from S1P. Taking the human and pre-clinical studies together, it's likely that saturated fat, but not unsaturated fat, raises S1P levels in obese people, and it's S1P that unleashes the inflammation that characterizes NASH.

Performing lipid studies in the laboratory is not easy—most biochemistry is water-based, and fat and water don't easily mix. The group relied on the MUSC Sphingolipidomics Core laboratory, one of only a handful of such facilities in the country capable of developing the new methods needed to examine S1P for their study. "Without lipidomics, we never would have understood that saturated fats activate this pathway," says Cowart. The team is working to identify the S1P receptors responsible for inflammation in NASH, with the ultimate goal

of designing treatments to prevent the need for a liver transplant in obese patients with NASH.

Does this work support the idea that it's the type of fat, but not all fat, that leads to health problems? After all, mice fed a high unsaturated fat diet still became obese but were metabolically healthy. "Because the unsaturated fat diet didn't cause NASH, it may provide a clue as to what actually links obesity to disease," says Cowart. "Even if it's difficult to lose weight, dietary modifications might prevent some disease associated with obesity."

Provided by Medical University of South Carolina

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